Ischemic stroke: Diagnostics and treatment of acute Ischemic stroke

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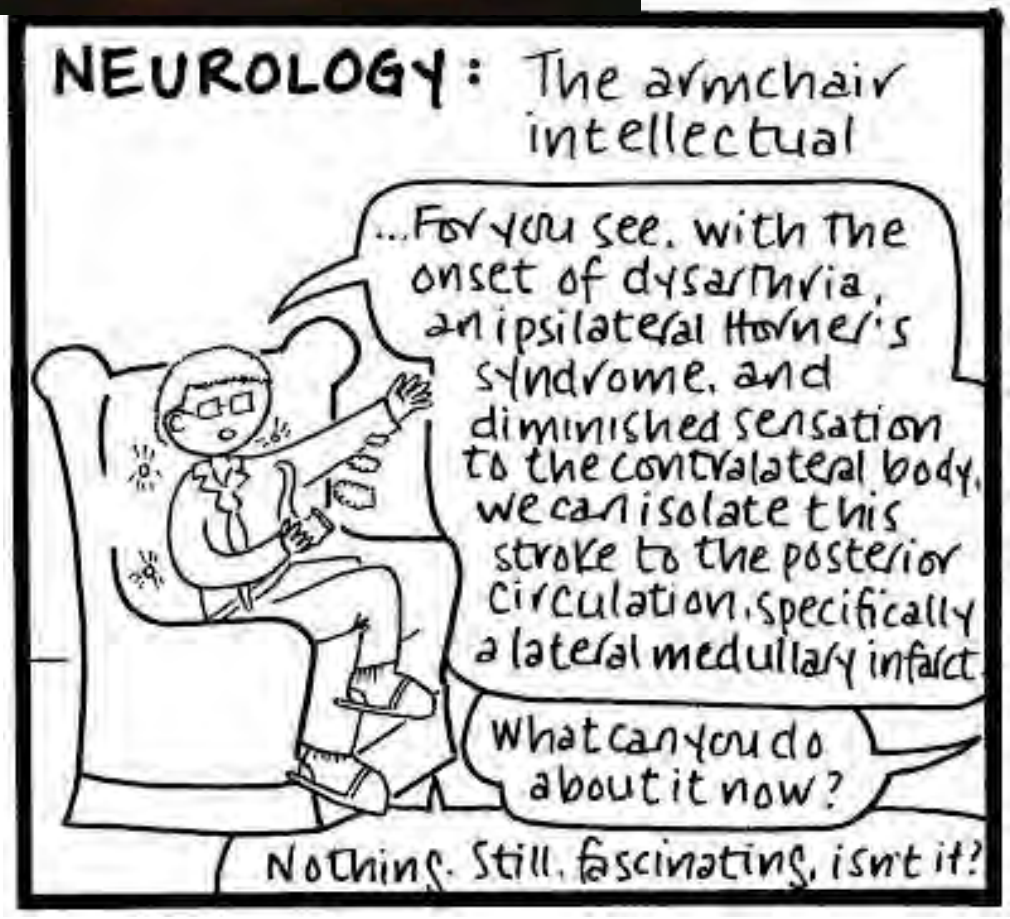
11.04.2019


NEUROLOGY: The armchair intellectual
...For you see, with the onset of dysarthria, an ipsilateral Horner's syndrome, and diminished sensation to the contralateral body, we can isolate this stroke to the posterior circulation, specifically a lateral medullary infarct.
What can you do about it now?
Nothing. Still, fascinating, isn't it?

Stroke : Time lost is brain lost

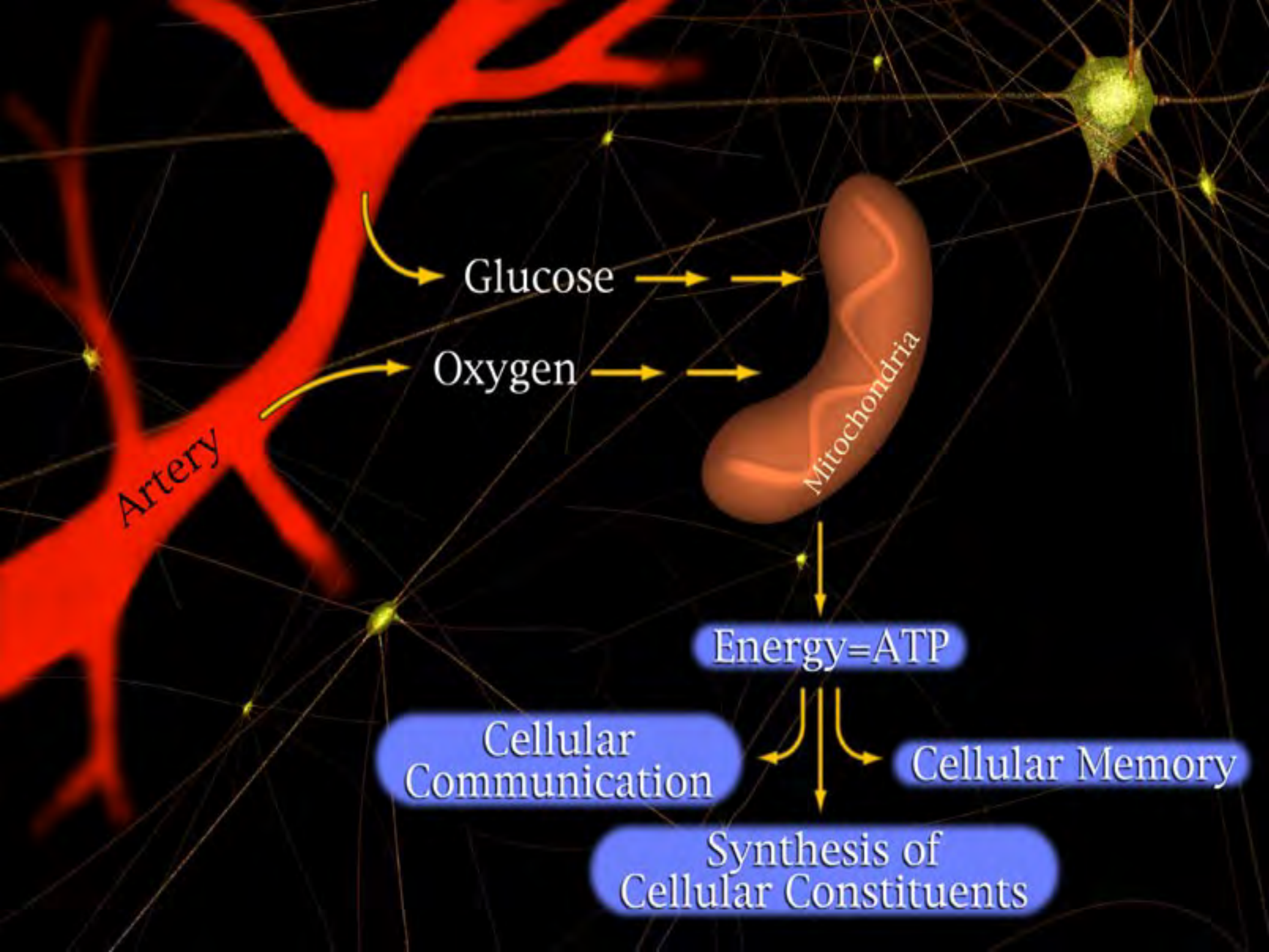
WHY?

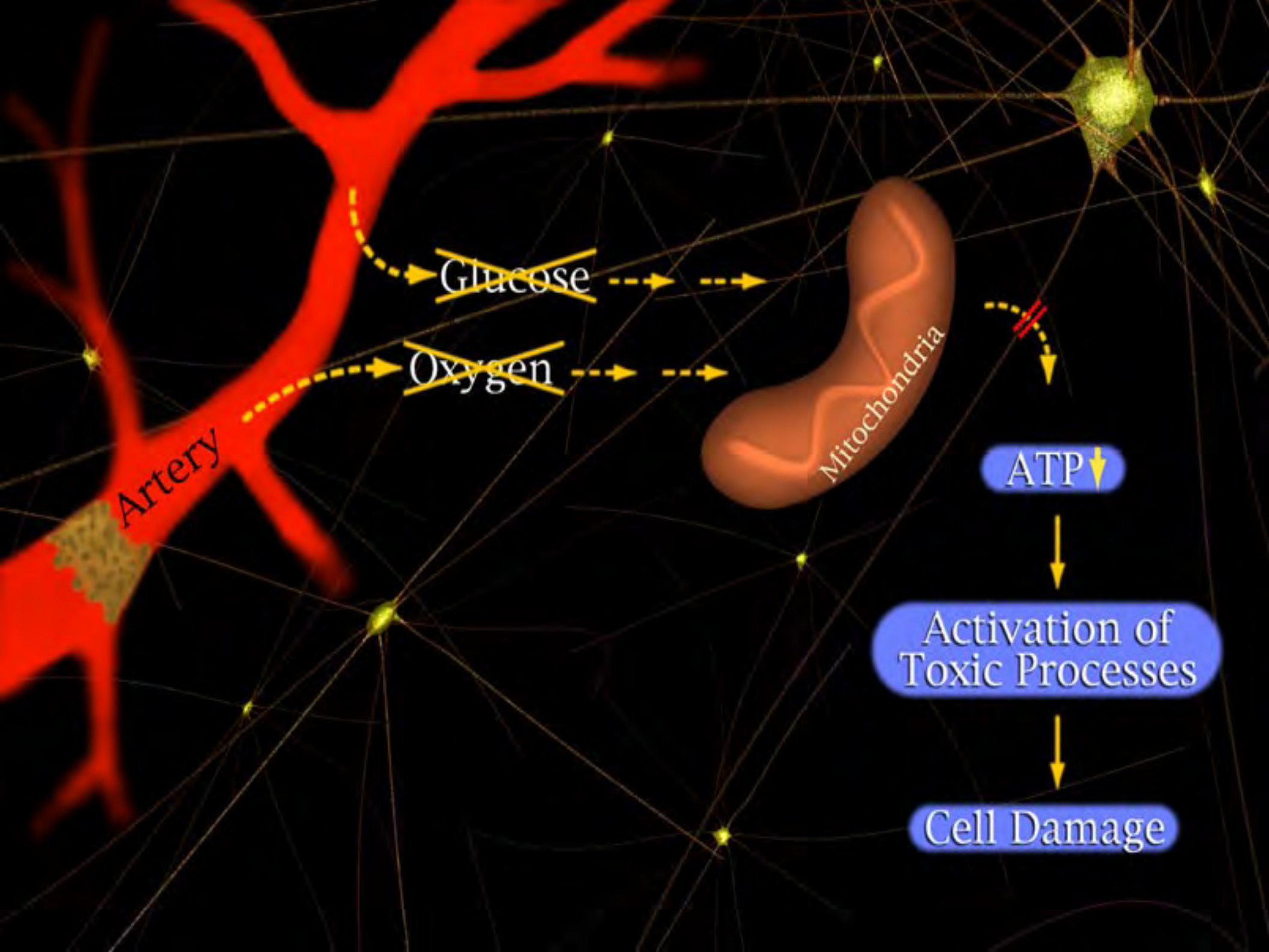
- Lots of evidence based treatment options
  - Thrombolysisi for ischemic stroke
  - Endovascular treatment of ischemic stroke
  - Secondary prevention
  - Prevention of complications

Ischemic Stroke – basic facts

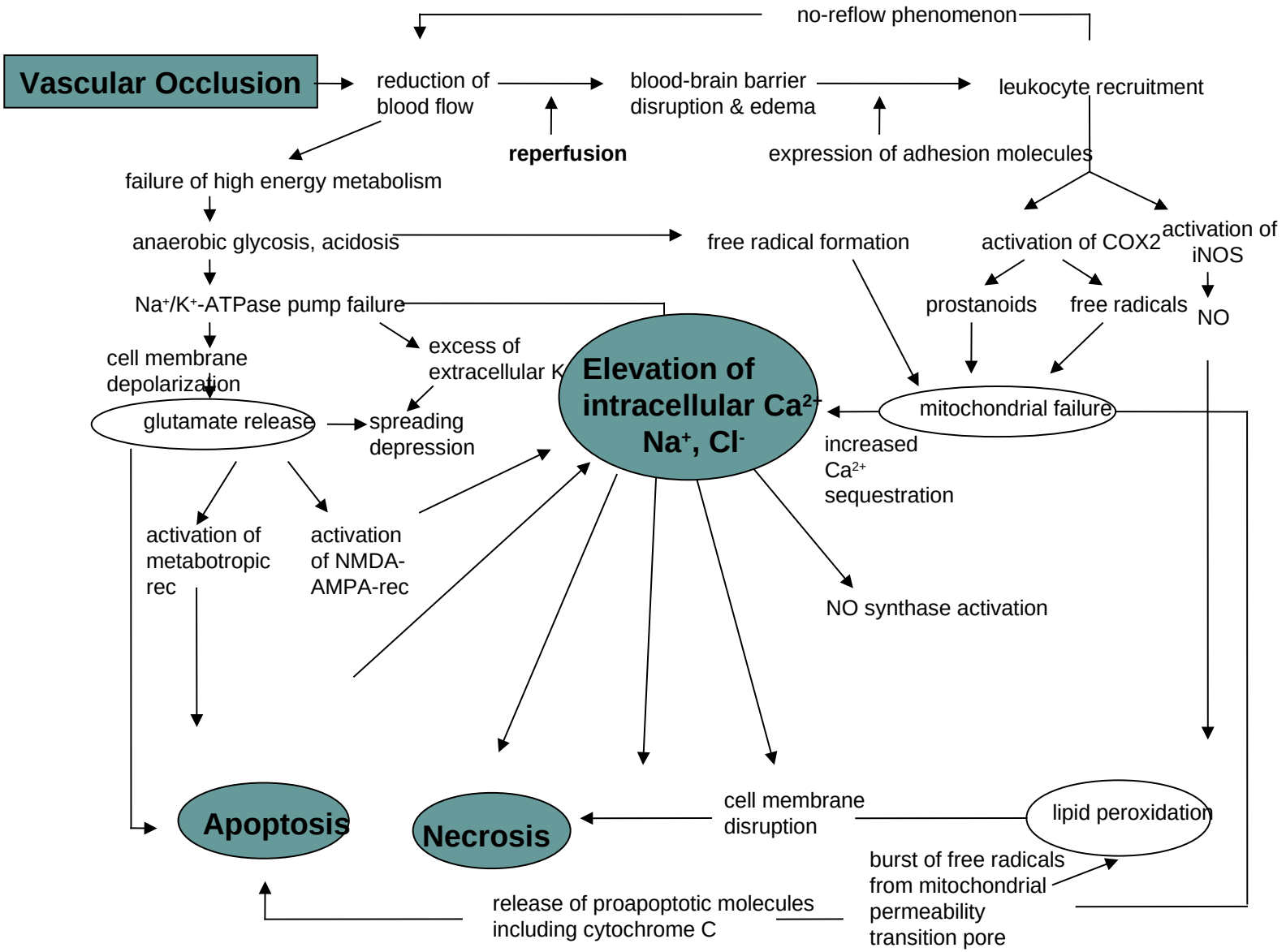
- Brain – ONLY 2% of body weight, BUT 15% of heart minute volume; 20% of O_2 supply
- Energy source - glucose: 95% aerobic, 5% anaerobic
  - short time anaerobic
  - tight balance: O_2 and glucose supply (! glu < 2.3 mmol/l)

- Not sufficient – damage, ion changes, depolarization of cell membranes etc.
- reversible / irreversible


Glucose
Oxygen
Artery
Mitochondria
Energy=ATP
Cellular Communication
Cellular Memory
Synthesis of Cellular Constituents


Glucose
Oxygen
Artery
Mitochondria
ATP
Activation of Toxic Processes
Cell Damage

Pathophysiology



Cerebral Blood Flow

- Perfusion pressure = MABP - ICP
- CBF = PP / Vessel resistance (Autoregulation)
  - 60-80 ml / 100 g / min

- Ischemic region → acidosis → local vasodilatation
  - therapeutic systemic vasodilatation - ↓ CBF in ischemic region even more - ↑ CBF in healthy tissue
- Depolarization, acidosis – cytotoxic edema, later vasogenic edema (BBB) →

  ↑ ICP → ↓ PP → ↓ CBF

- Ischemic / Infarct Threshold
  - differs among brain regions and cell types

Ischemia or Infarct

- Remaining CBF, O_2 / glucose supply + DURATION
  - **Ischemia** (functional damage)
    - CBF drop to 1/3-1/4 (20 ml -15 ml / 100 g / min) – reversible neurological deficits, when CBF normalizes – OK (TIA)
  - **Infarct** (tissue damage)
    - CBF drop to 10 ml / 100 g / min – duration of some minutes

Tissue fate

- PET – CBF, $CMRO_2$, OEF
  - autoregulation (↑CBV to maintain CBF)
  - oligemia (↓CBF, ↑OEF to maintain $CMRO_2$)
  - ischemia (↓CBF, ↓$CMRO_2$, ↑OEF)
  - irreversible injury (very low CBF and $CMRO_2$)

- PET in experimental MCAO by Heiss et al
  - 1h – pattern 3 widely
  - 4h – pattern 4 in the central ischemic zone, pattern 3 peripherally
  - 24h – nearly completely pattern 4, ↑correlation with postmortem infarct size

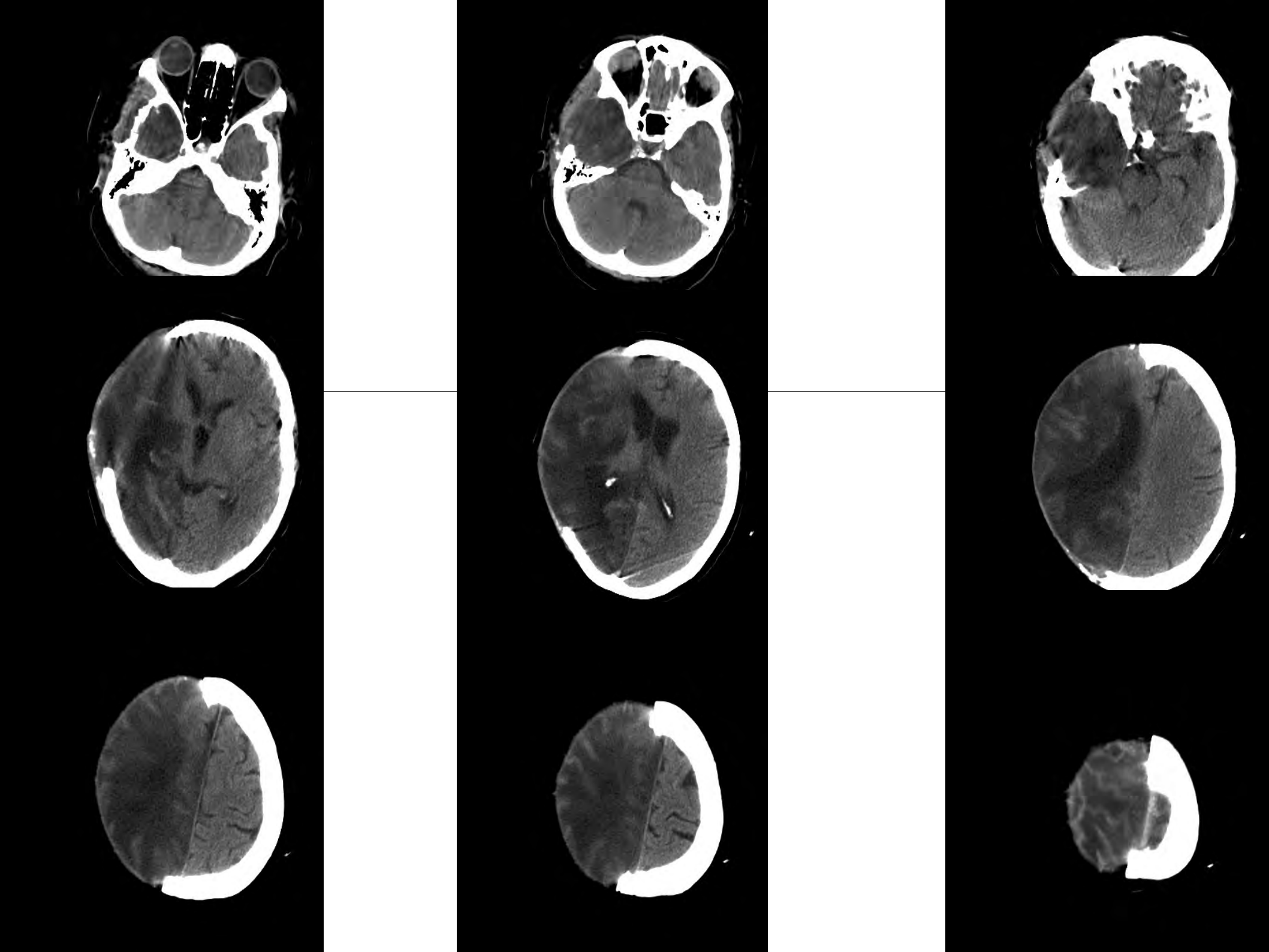
What to save?

- Salvaging ischemic tissue that is NOT irreversibly injured
- Capability of responding with appropriate and timely therapies

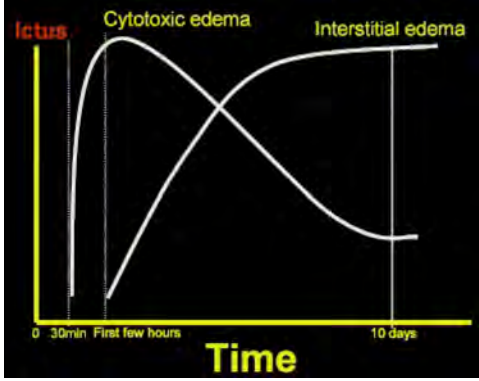
- Discrepancy between the histopathology (neuronal necrosis) and the time window for successful intervention -

  - “Irreversible ischemic injury” NOT Infarction:

    Focal ischemic tissue no longer capable of recovery –
    precedes the pathological identification of infarction by a wide time margin



Acute hypoxia



- cytotoxic edema within minutes
  - swelling of the cellular elements (neurons, glia, endothelial cells): failure of ATP-dependent ion (sodium and calcium) transport
  - rapid accumulation of sodium within cells → water follows (osmotic equilibrium)
  - ↑ intracellular Ca^{2+} activates PLs → release of arachidonic acid -ROC

- vasogenic edema within the next hours to days
  - ↑ extracellular fluid volume due to ↑ permeability of brain capillaries' endothelial cells to macromolecular serum proteins (e.g., albumin)

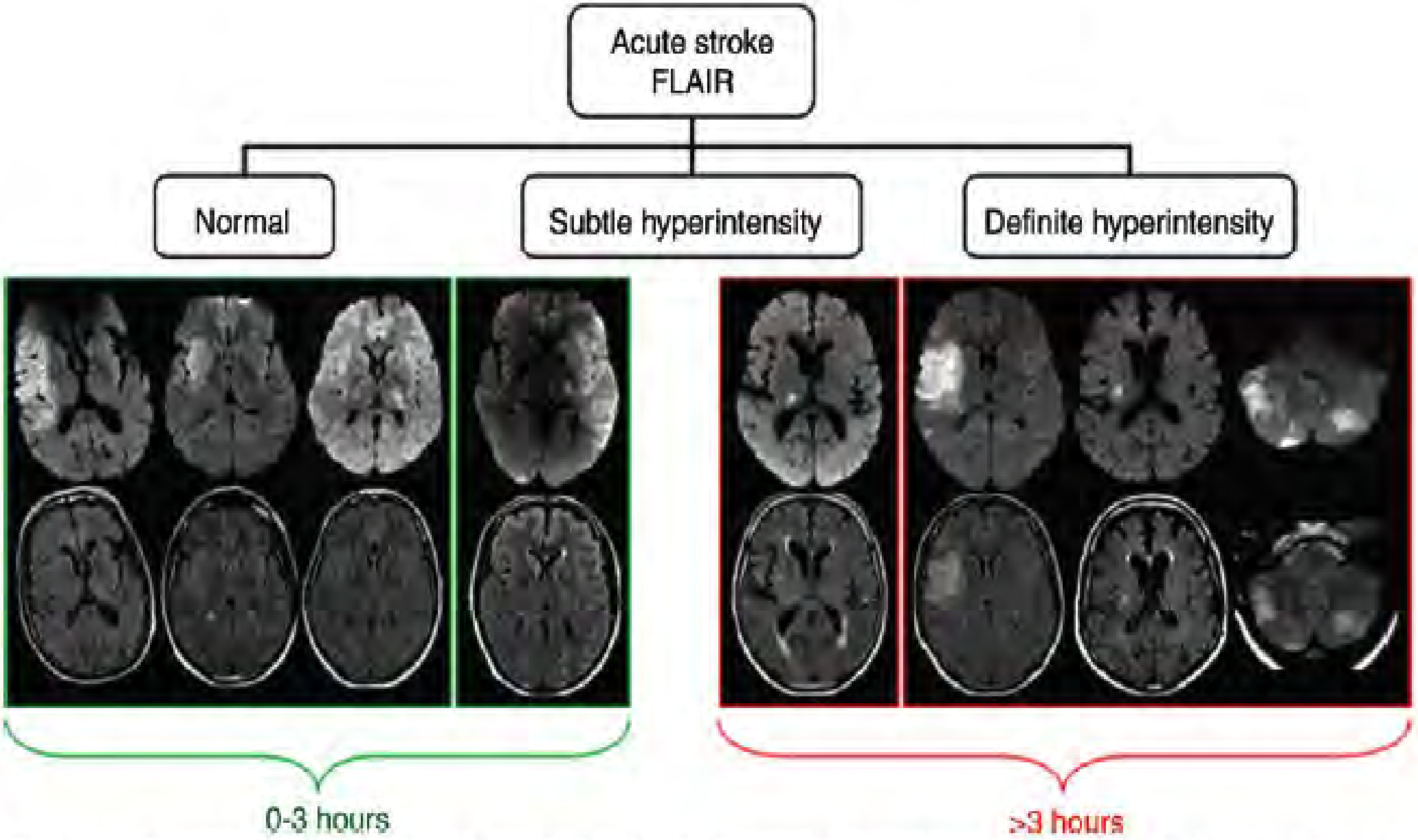


Figure 4: Diagrammatic presentation of the qualitative classification algorithm used to assign patients to the hyperacute group.

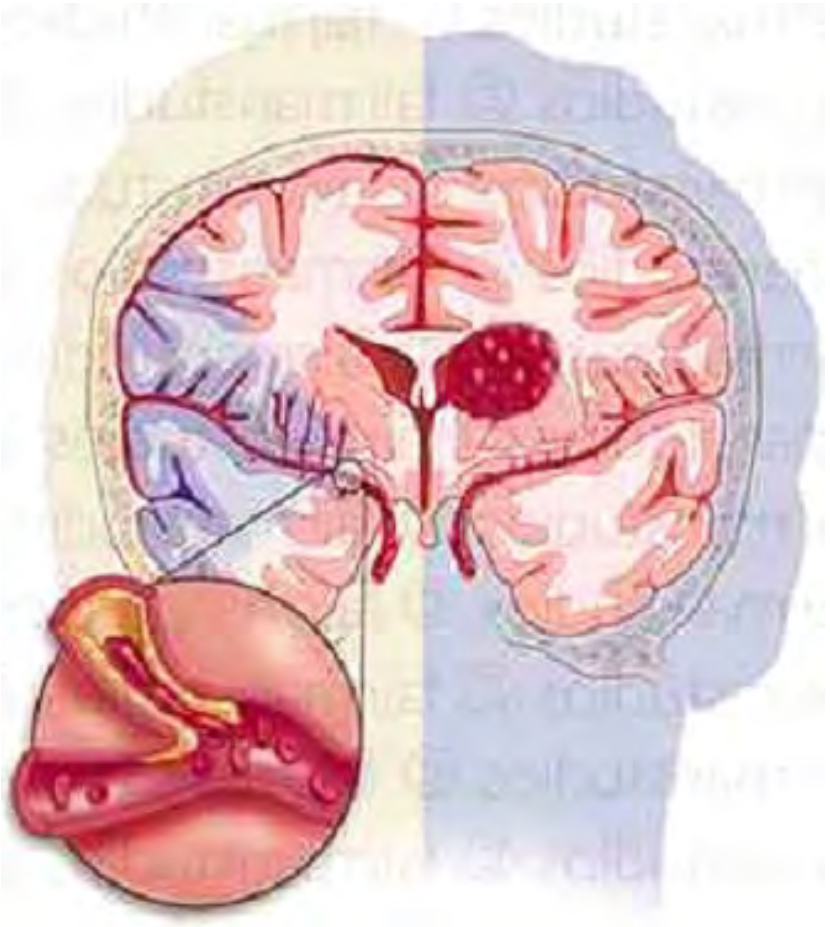
Stroke definition

The Stroke Council of the American Heart Association/American Stroke Association:

The consensus statement defines a central nervous system infarction as brain, spinal cord, or retinal cell death attributable to ischaemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury.

Stroke definition

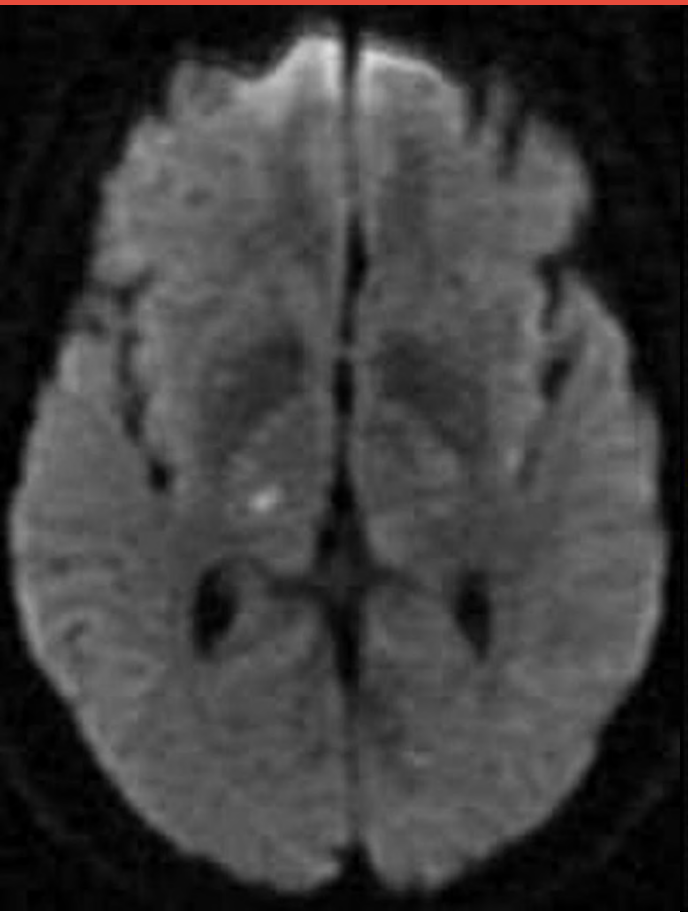
- **Ischaemic stroke**
- **Intracerebral haemorrhage**
- **Subarachnoid haemorrhage**



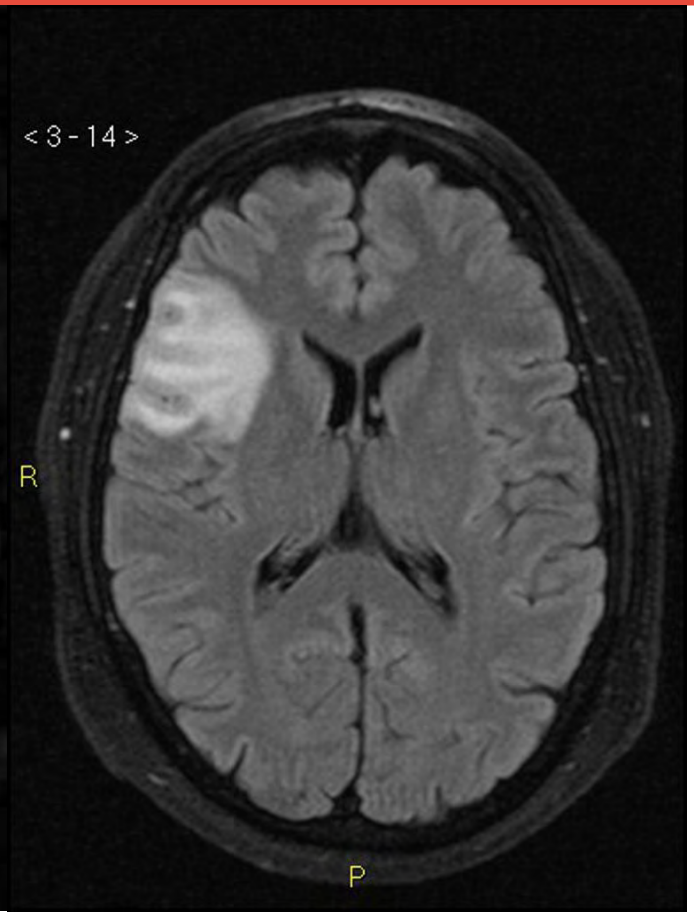
Stroke epidemiology

- One in six people suffers a stroke.
- Third leading cause of death.
- Important cause of long-term disability.
- Globally the incidence has grown by 15.8% between the year 2005 and the year 2015 from approximately 4.7 million to 5.4 million cases per year.
- Number one cause of disability among adults
- 1-y survival ~ 75% (worse than that for AMI or cancer)
- Third most expensive disease after schizophrenia and dementia
- Life-time cost of one stroke is ~ $70 000- $100 000
- Absorbs 5-6 % of health care and social-service budget
- Most common reason for in-hospital care days (~ 2 million days/year in Finland)
- 14 000 strokes in Finland and 500 000 strokes in USA annually

Diagnostics of acute Ischemic stroke



Case courtesy of Dr Roberto Schubert, Radiopaedia.org, rID: 14098



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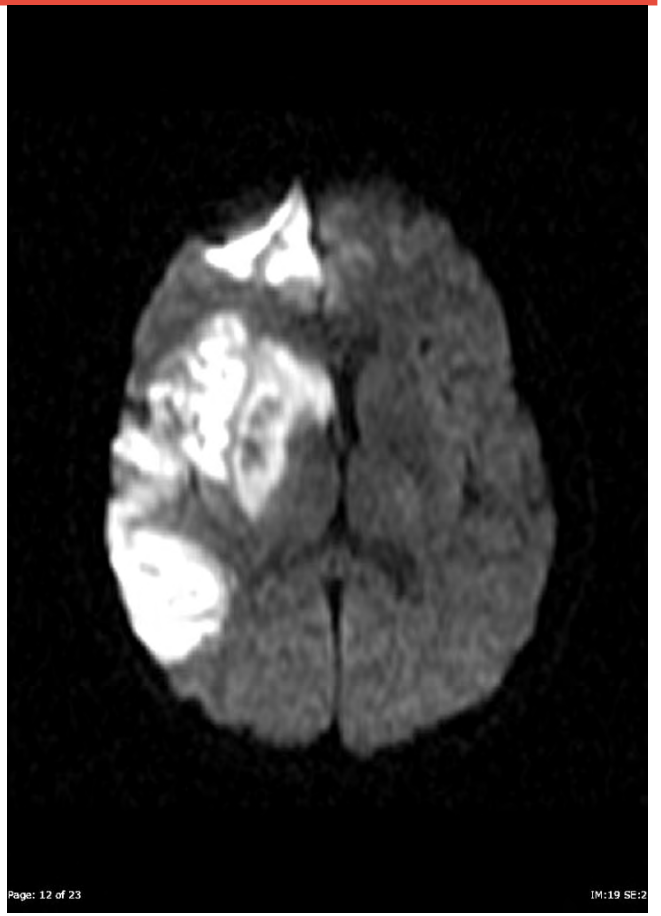

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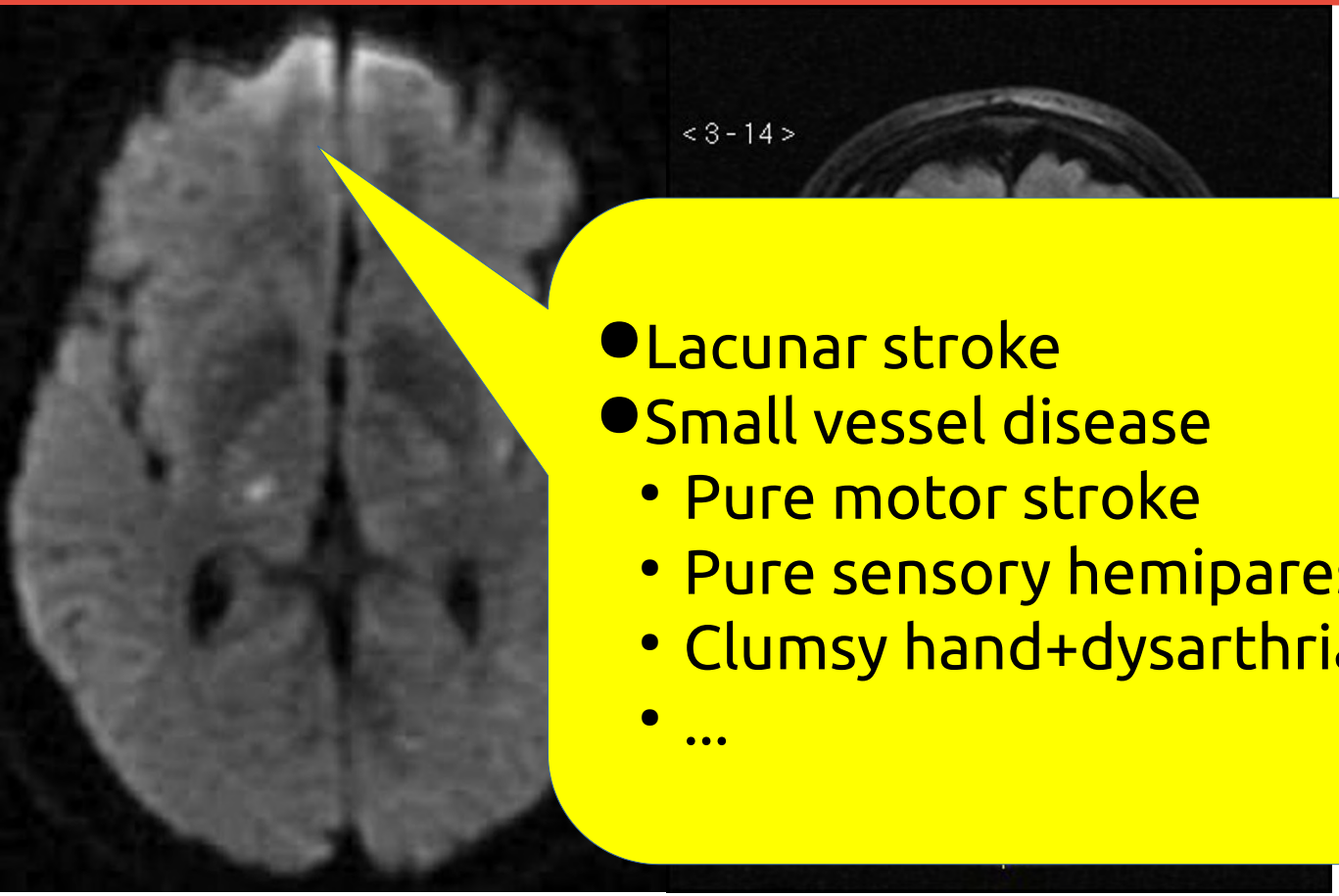
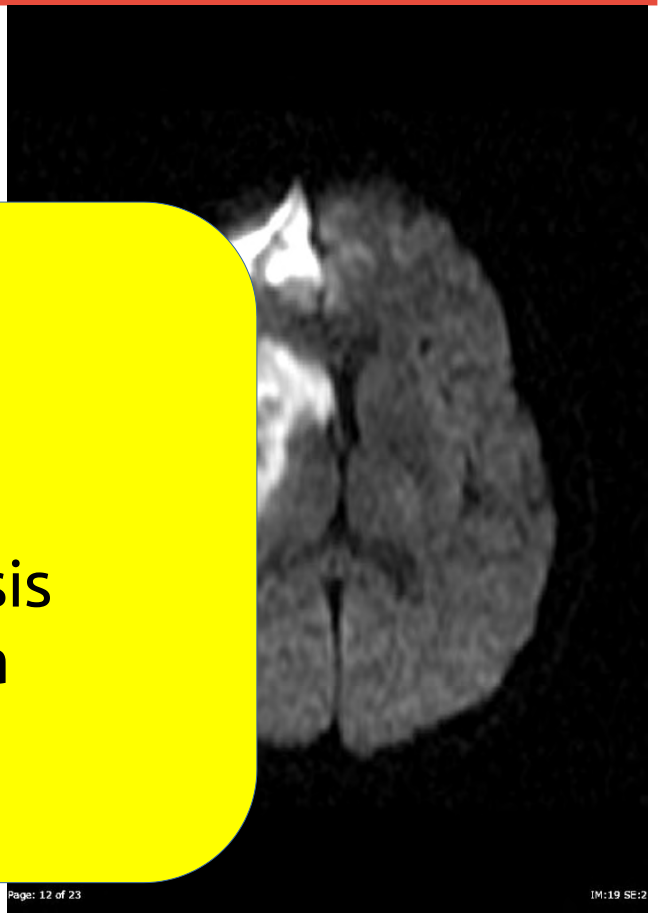
Diagnostics of acute Ischemic stroke



- Lacunar stroke
- Small vessel disease
  - Pure motor stroke
  - Pure sensory hemiparesis
  - Clumsy hand+dysarthria
  - ...



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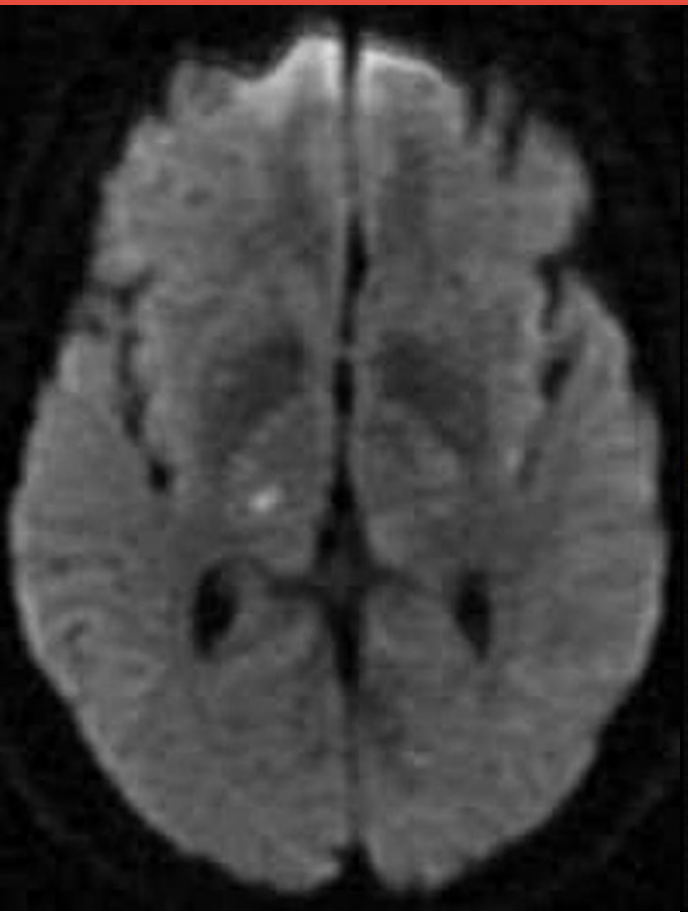
Diagnostics of acute Ischemic stroke



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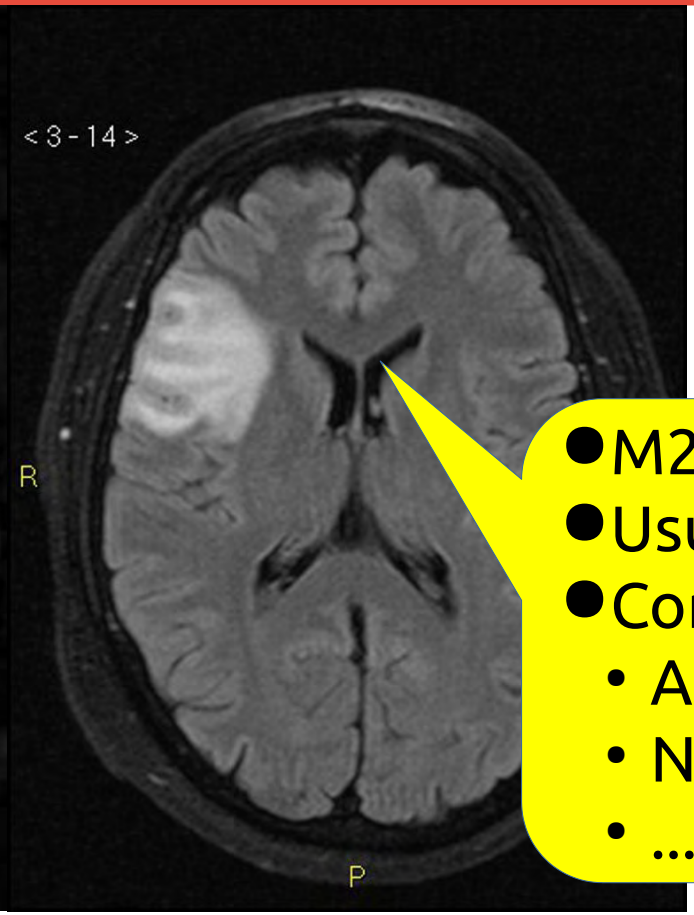

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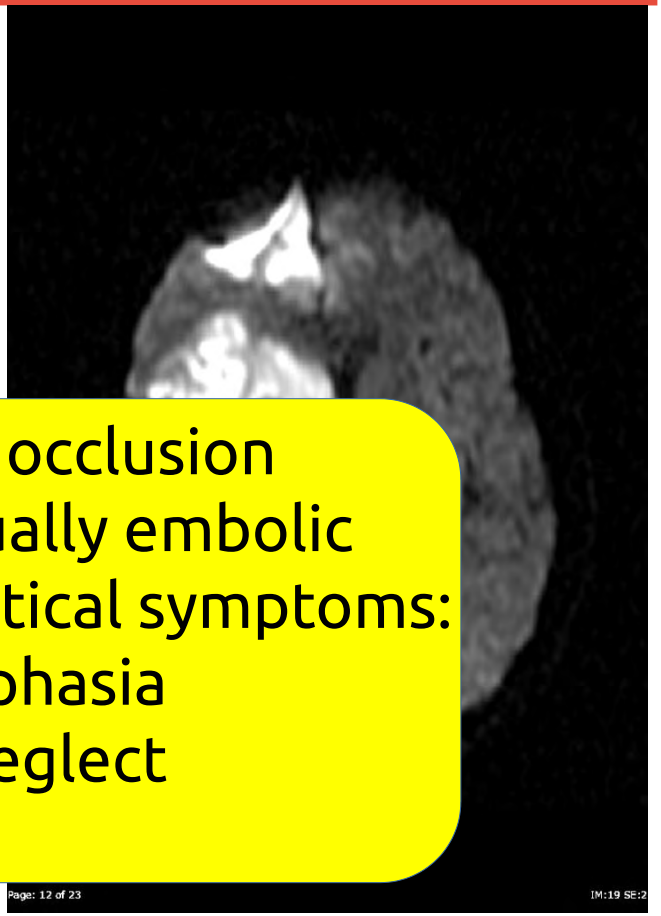

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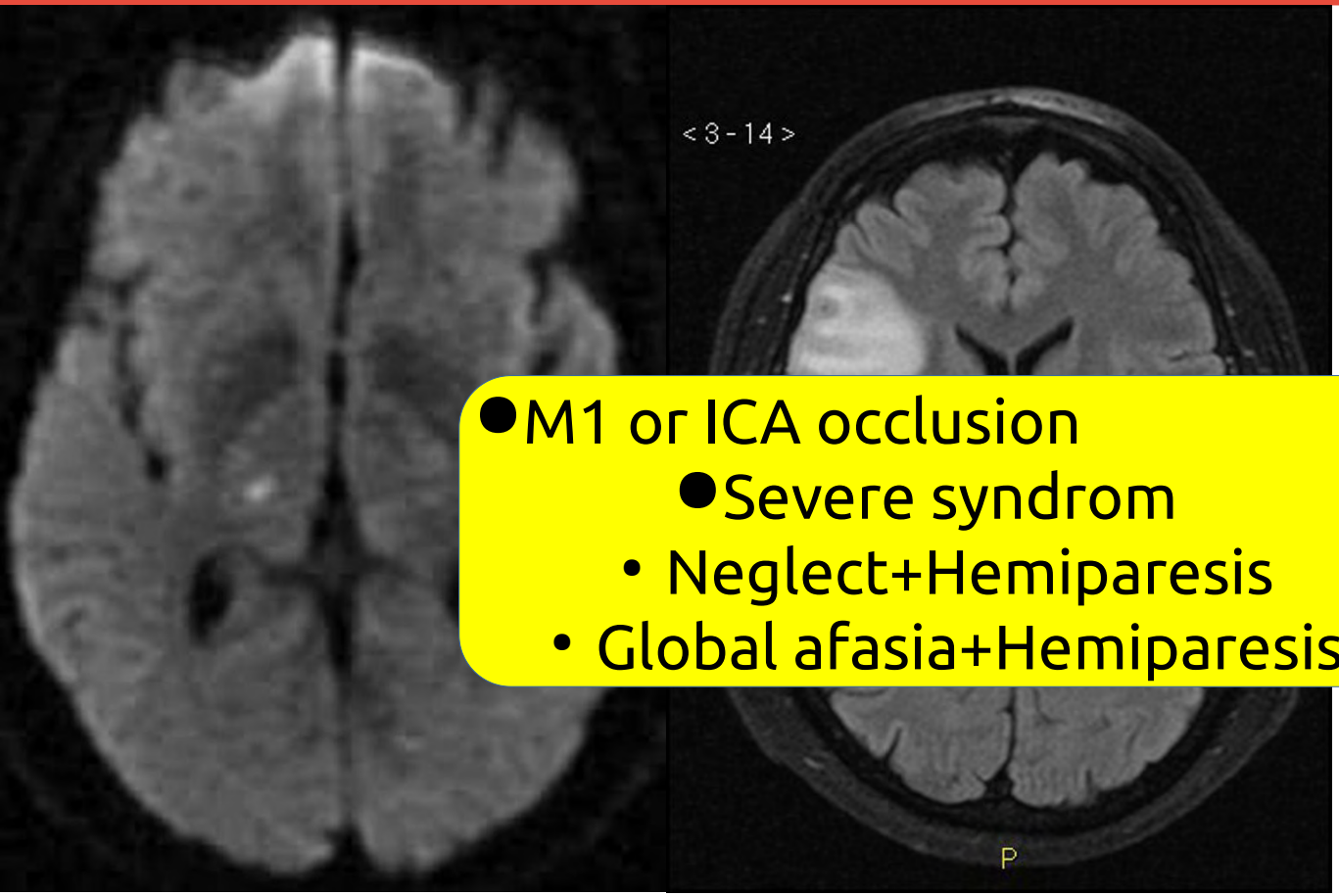
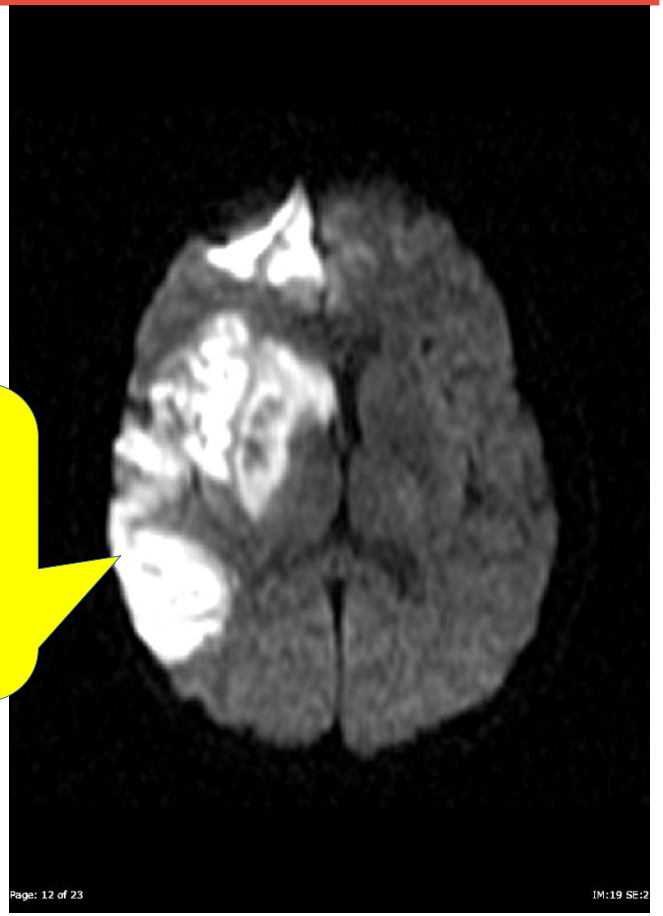
- M2 occlusion
- Usually embolic
- Cortical symptoms:
  - Aphasia
  - Neglect
  - ...

Diagnostics of acute Ischemic stroke



- M1 or ICA occlusion
  - Severe syndrom
    - Neglect+Hemiparesis
    - Global afasia+Hemiparesis



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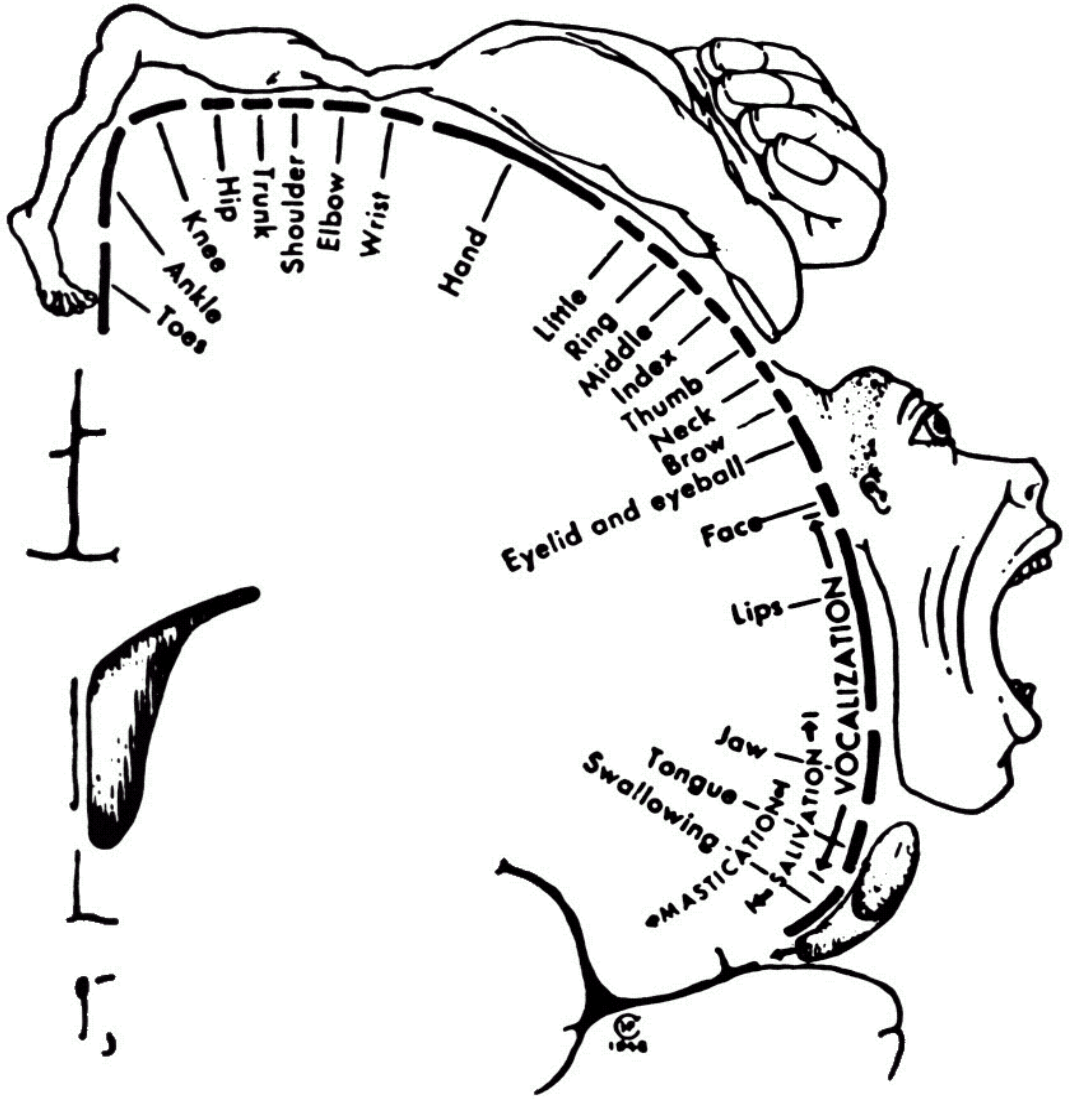
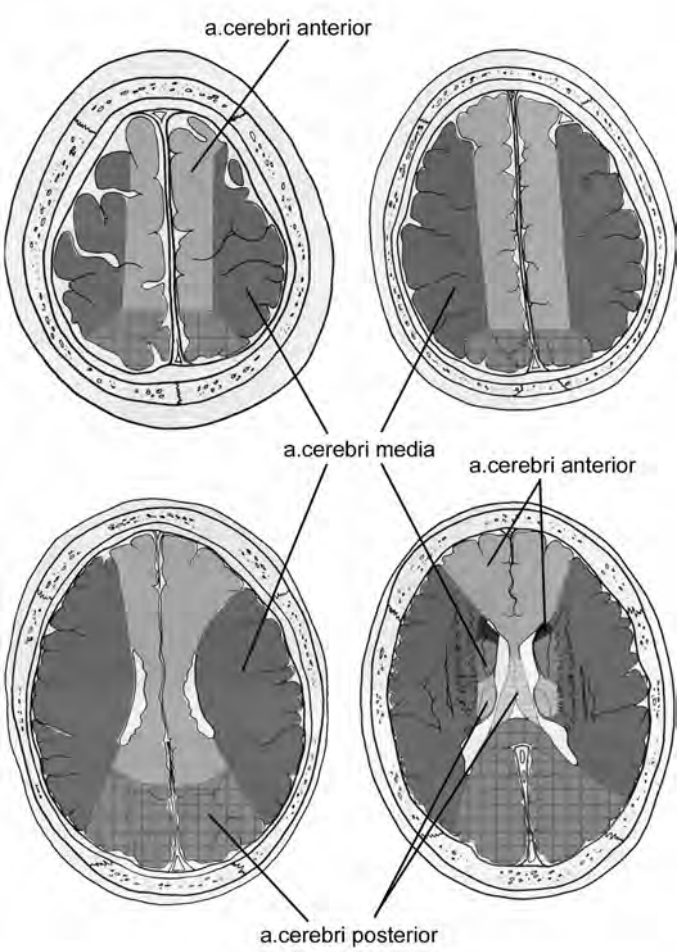
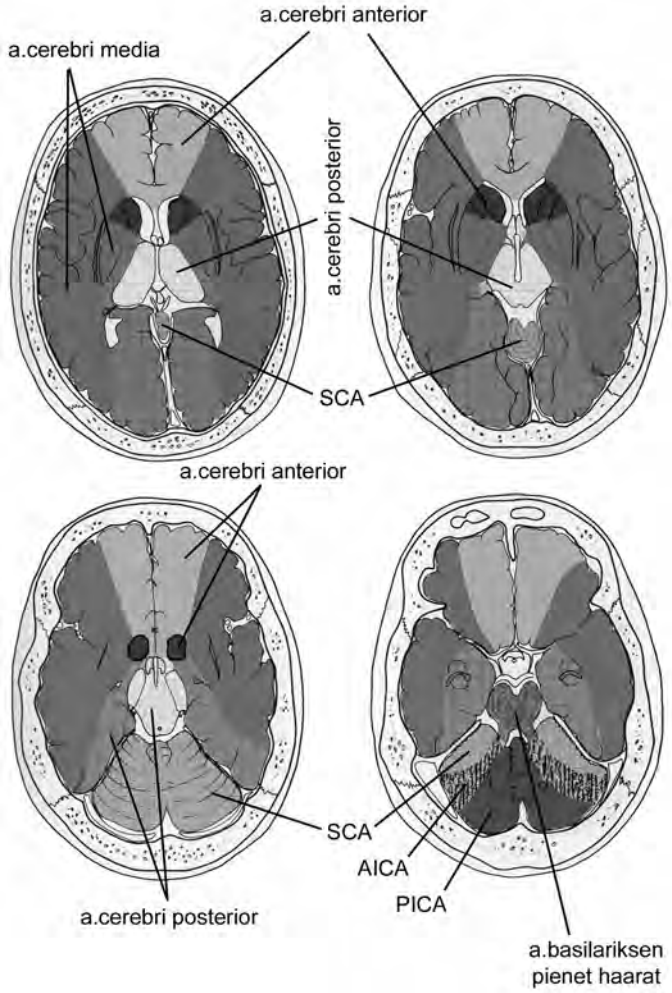
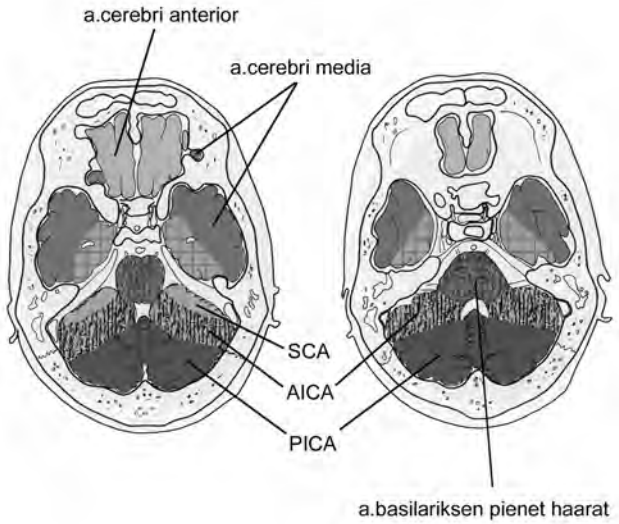
Diagnostics of acute Ischemic stroke



Diagnostics of acute Ischemic stroke







SCA=a.cerebellaris superior
AICA=a.cerebellaris inf. anterior
PICA=a.cerebellaris inf. posterior

Diagnostics of acute Ischemic stroke

Stroke symptom or not?

- **Epileptic seizure**
- **Tumor**
- **Encephalitis**
- **Meningitis**
- **Multiple sclerosis**
- **Migaine**

Diagnostics of acute Ischemic stroke

Stroke symptom or not?

- **Epileptic seizure**
- Tumor
- Encephalitis
- Meningitis
- Multiple sclerosis
- Migaine

- Uncontrollable jerking movements of the arms and legs?
- Gaze deviation – which side?
- Bloodpressure?
- Witnessed?

Diagnostics of acute Ischemic stroke

Stroke symptom or not?

- Epileptic seizure
- **Tumor**
- Encephalitis
- Meningitis
- Multiple sclerosis
- Migaine

- Uncontrollable jerking movements of the arms and legs?
- Longer history of symptoms?
- Headache?
- Known malignant disease?

Diagnostics of acute Ischemic stroke

Stroke symptom or not?

- Epileptic seizure
- Tumor
- **Encephalitis**
- Meningitis
- Multiple sclerosis
- Migaine

- Elevated temperature /fever?
- Travel-anamnesis?
- Seizures?
- Signs of infection?
- Immunodeficiency?

Diagnostics of acute Ischemic stroke

Stroke symptom or not?

- Epileptic seizure
- Tumor
- Encephalitis
- **Meningitis**
- Multiple sclerosis
- Migaine

- High fever?
- Travel-anamnesis?
- Drowsyness, confusion
- Signs of infection?
- Muscle pain?
- Severe headache?
- Stiff neck?

Diagnostics of acute Ischemic stroke

Stroke symptom or not?

- Epileptic seizure
- Tumor
- Encephalitis
- Meningitis
- **Multiple sclerosis**
- Migaine

- Slow development?
- Yonger patient?

Diagnostics of acute Ischemic stroke

Stroke symptom or not?

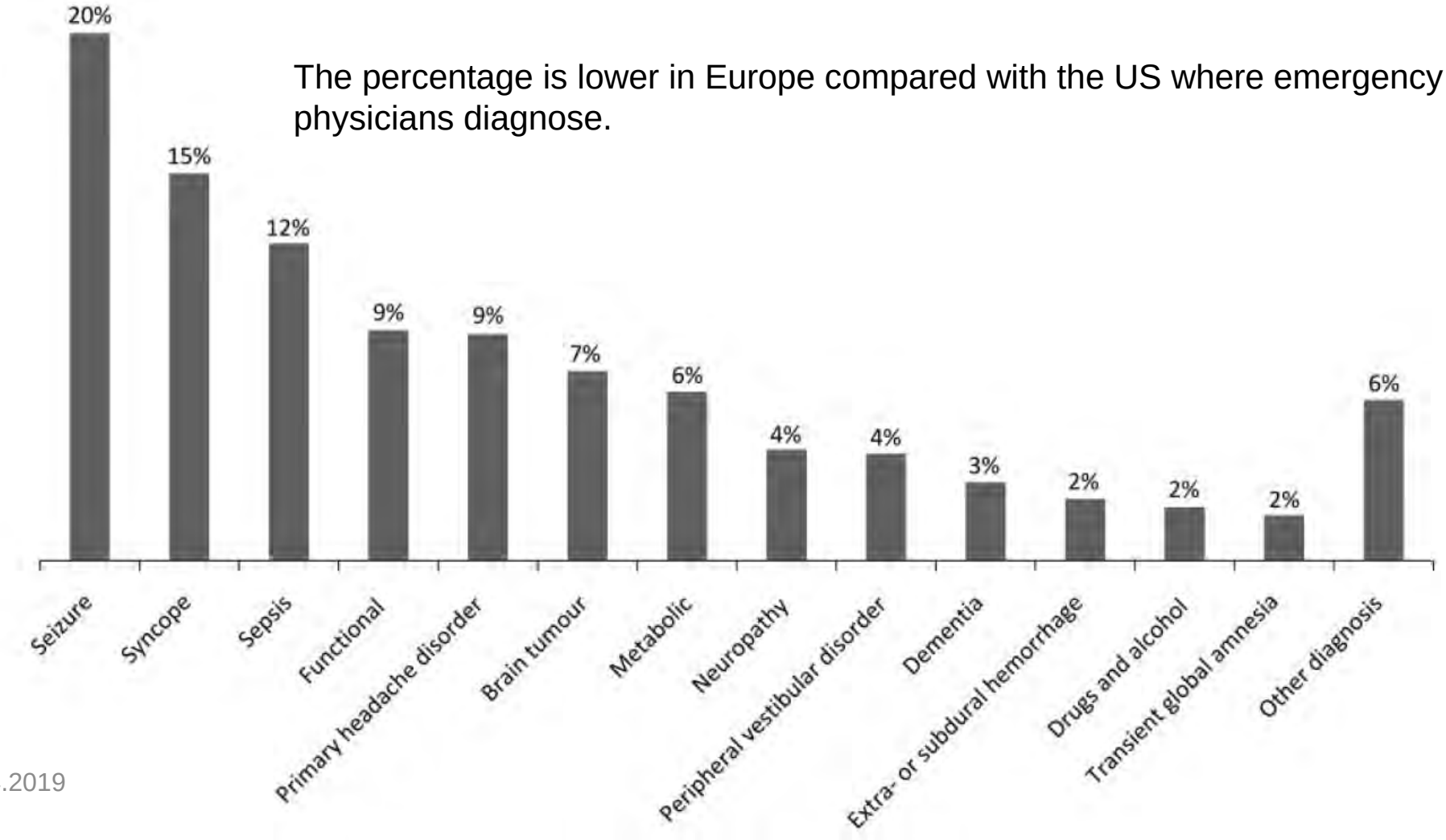
- Epileptic seizure
- Tumor
- Encephalitis
- Meningitis
- Multiple sclerosis
- **Migaine**

- Sometimes difficult to distinguish!

MIGAINE

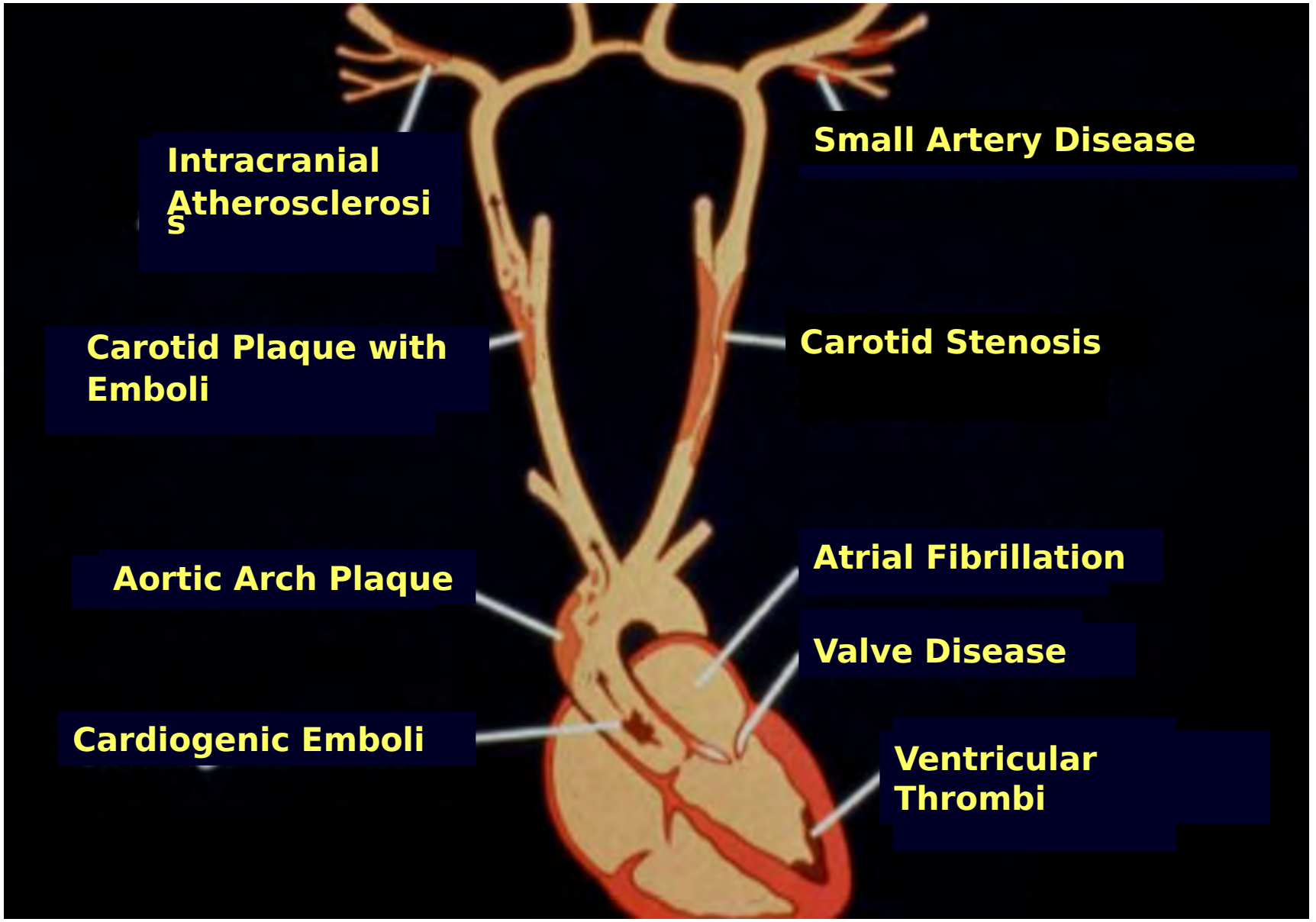
STROKE-MIMIC

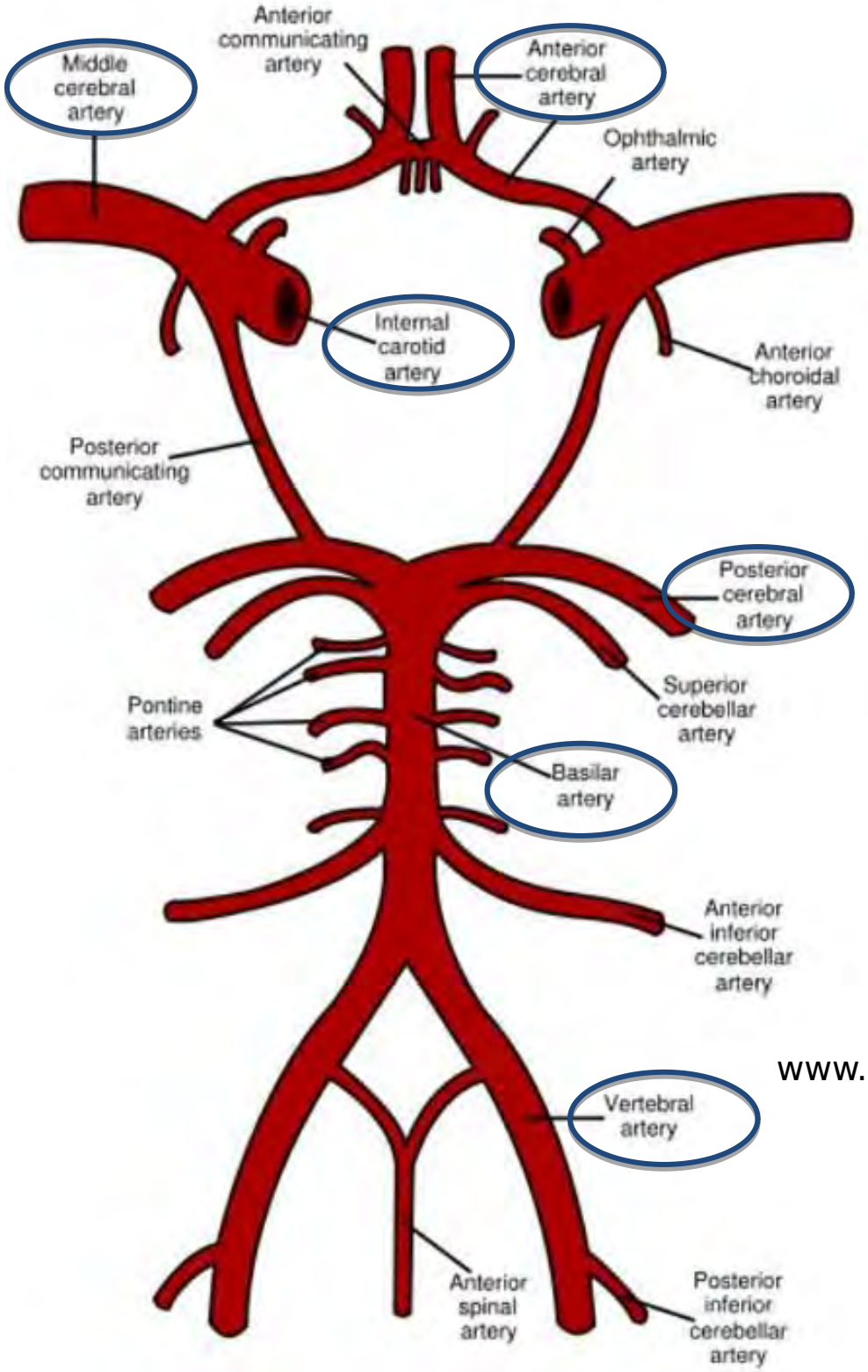
- Stroke mimics in patients with clinical signs of stroke

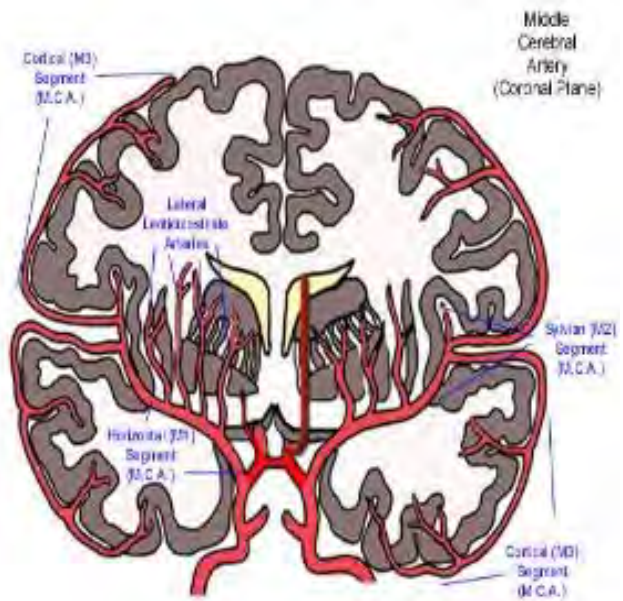


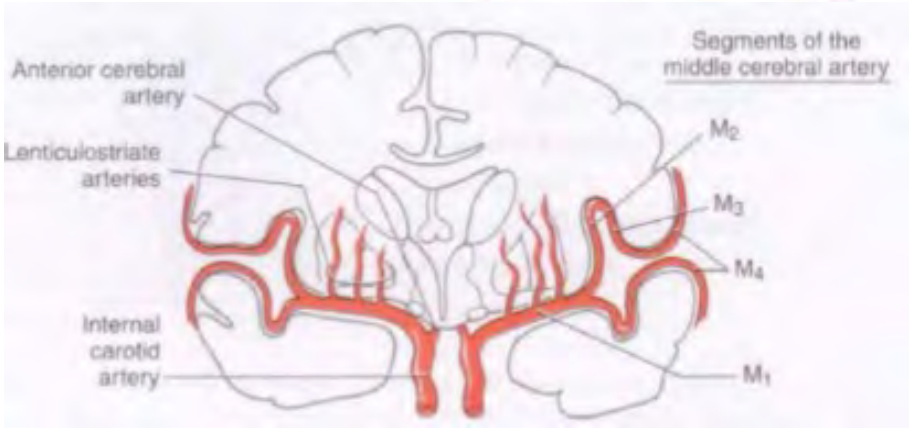
The percentage is lower in Europe compared with the US where emergency physicians diagnose.

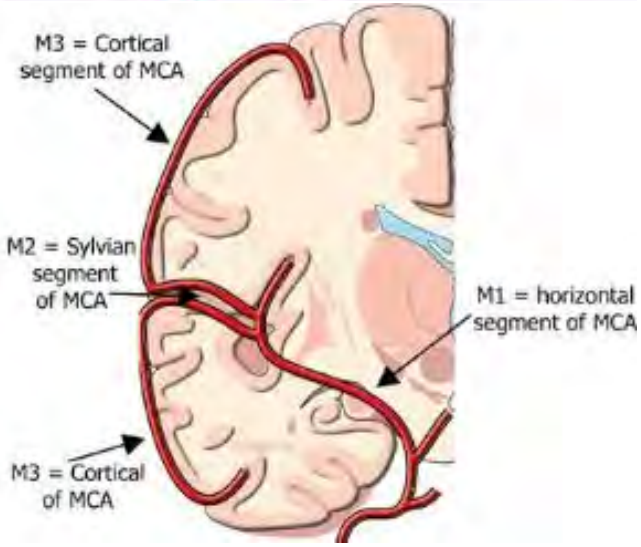
Stroke is *not* one disease











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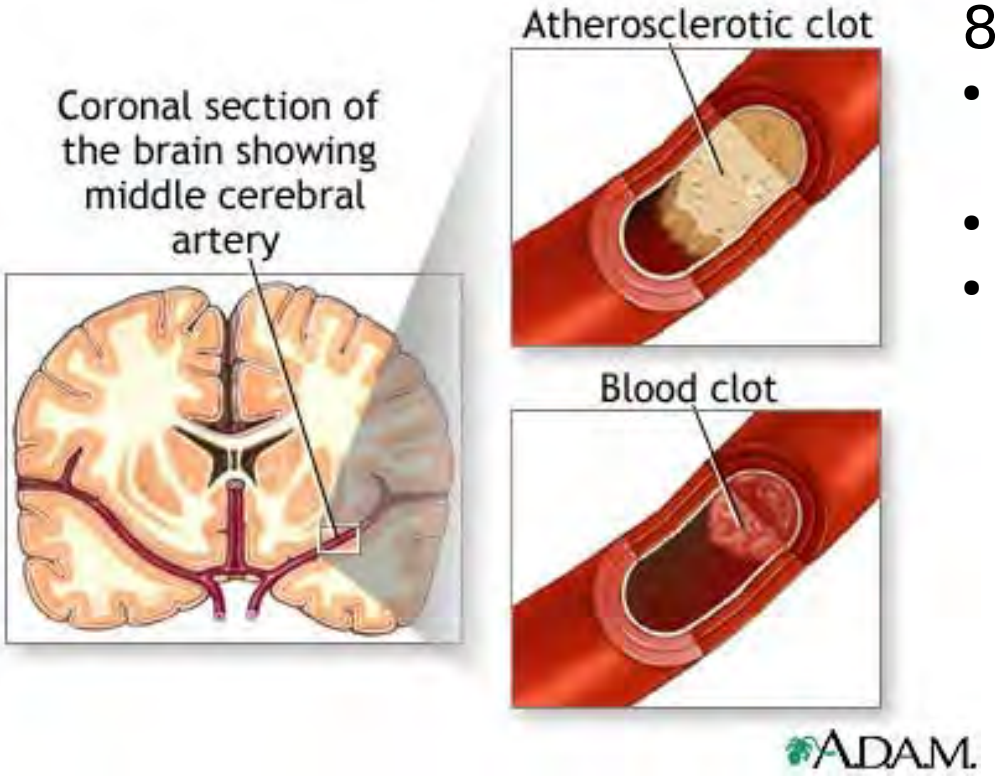
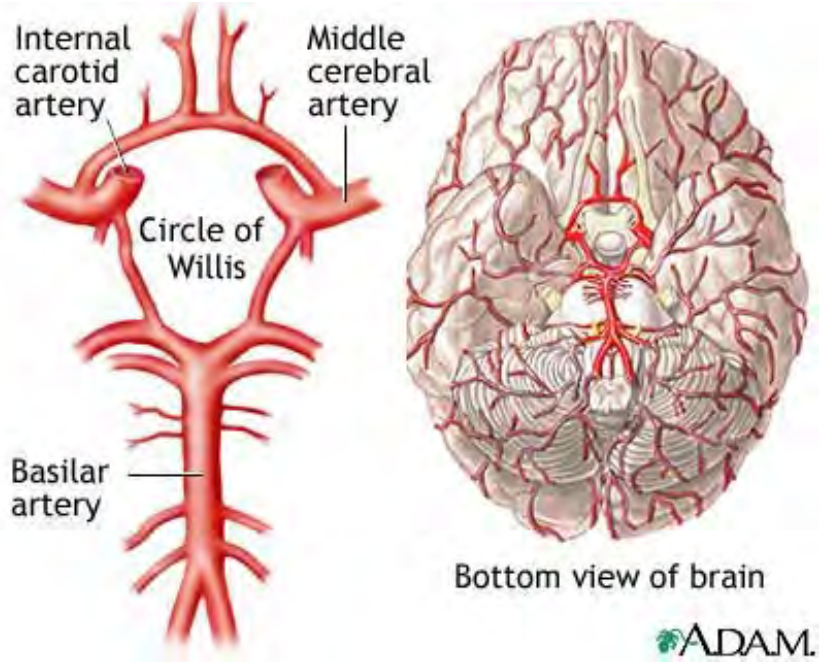
Ischemic stroke



80% of all strokes

- atherosclerosis (extra-, intracranial)
- cardioembolism
- lacunar stroke



TOAST

1. Large-artery disease
2. Cardioembolic
3. Small-artery disease
4. Other etiology
5. Undetermined cause
   - (a) More than 1 probable/possible etiology,
   - (b) no etiologic factor despite adequate search,
   - (c) etiologic studies incomplete

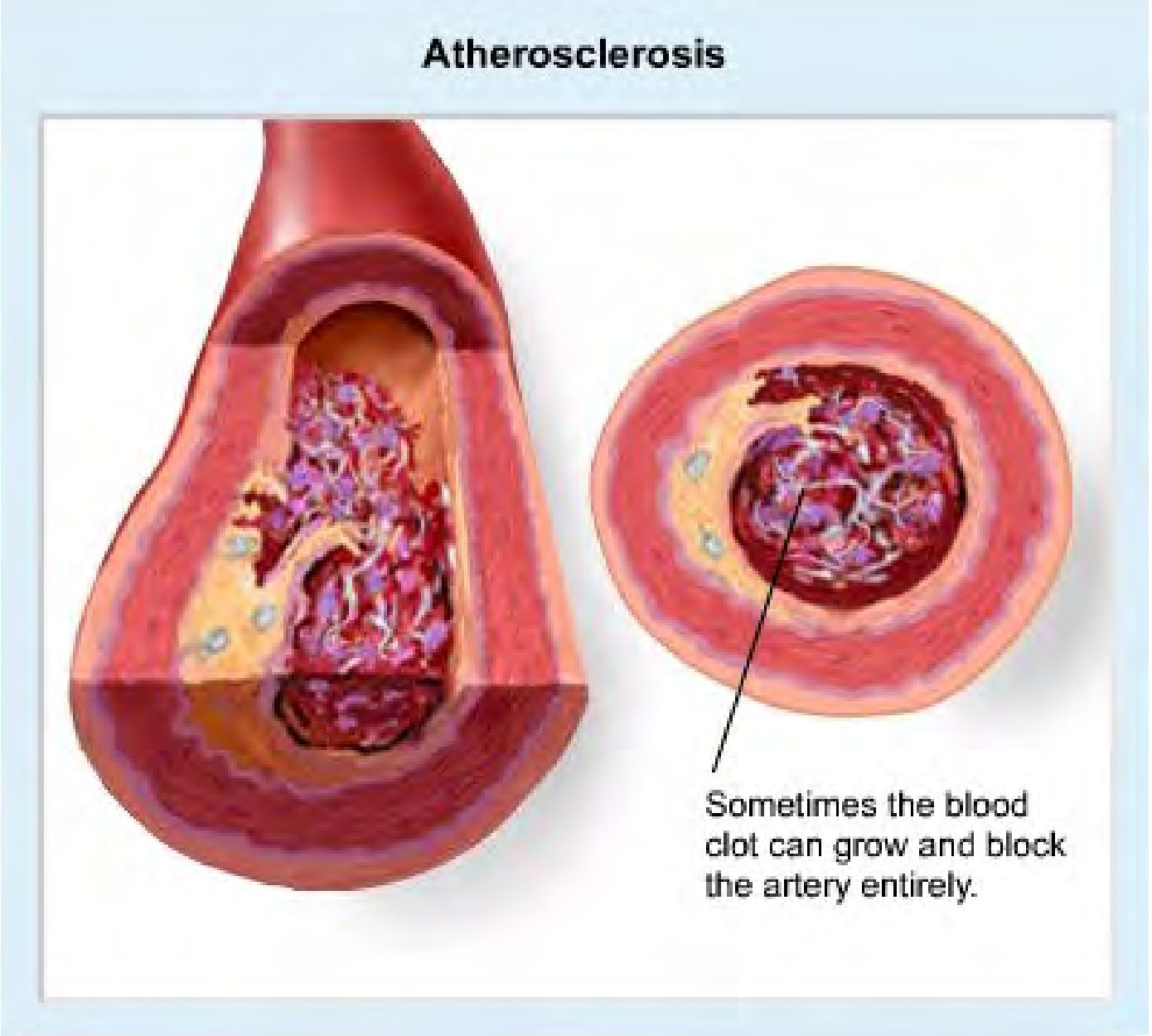
TABLE 1. TOAST Classification of Subtypes of Acute Ischemic Stroke

Large-artery atherosclerosis (embolus/thrombosis)*
Cardioembolism (high-risk/medium-risk)*
Small-vessel occlusion (lacune)*
Stroke of other determined etiology*
Stroke of undetermined etiology
a. Two or more causes identified
b. Negative evaluation
c. Incomplete evaluation

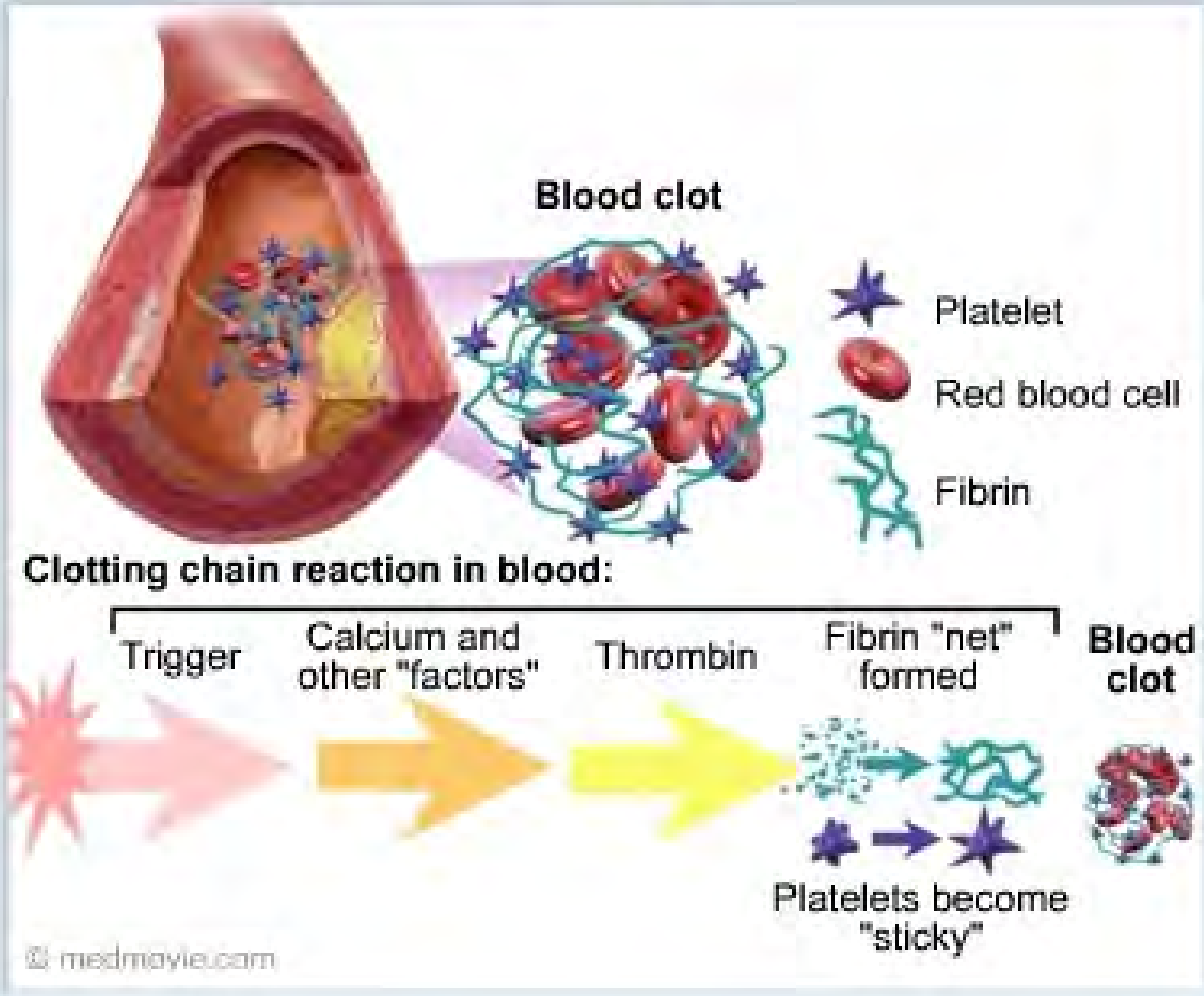
TOAST, Trial of Org 10172 in Acute Stroke Treatment.
*Possible or probable depending on results of ancillary studies.

0. Stroke mimic
1. Suurten suonten ateroskleroosi
2. Kardioembolia ja aortasta lähtevä tromboembolia
3. Pienten suonten tauti
4. Muu määritelty syy (sitä yleisempiä mitä nuorempi potilas)
4.1 Ei-ateroskleroottiset ei-inflammatoriset vaskulopatiat (esim. dissekaatio)
4.2 Ei-ateroskleroottiset inflammatoriset vaskulopatiat (esim. vaskuliitit)
4.3 Hematologiset häiriöt ja hyytymishäiriöt
4.4 Vasospastiset tilat (esim. RCVS)
4.5 Monogeeniset taudit
4.6 Aineenvaihduntasairaudet
4.7 Muut harvinaiset syyt
5. Syy epäselvä
5.1 Kaksi tai useampaa syytä
5.2 Selvittelyt kattavat, syy jää epäselväksi
5.3 Selvittelyt vajaat, syy jää epäselväksi

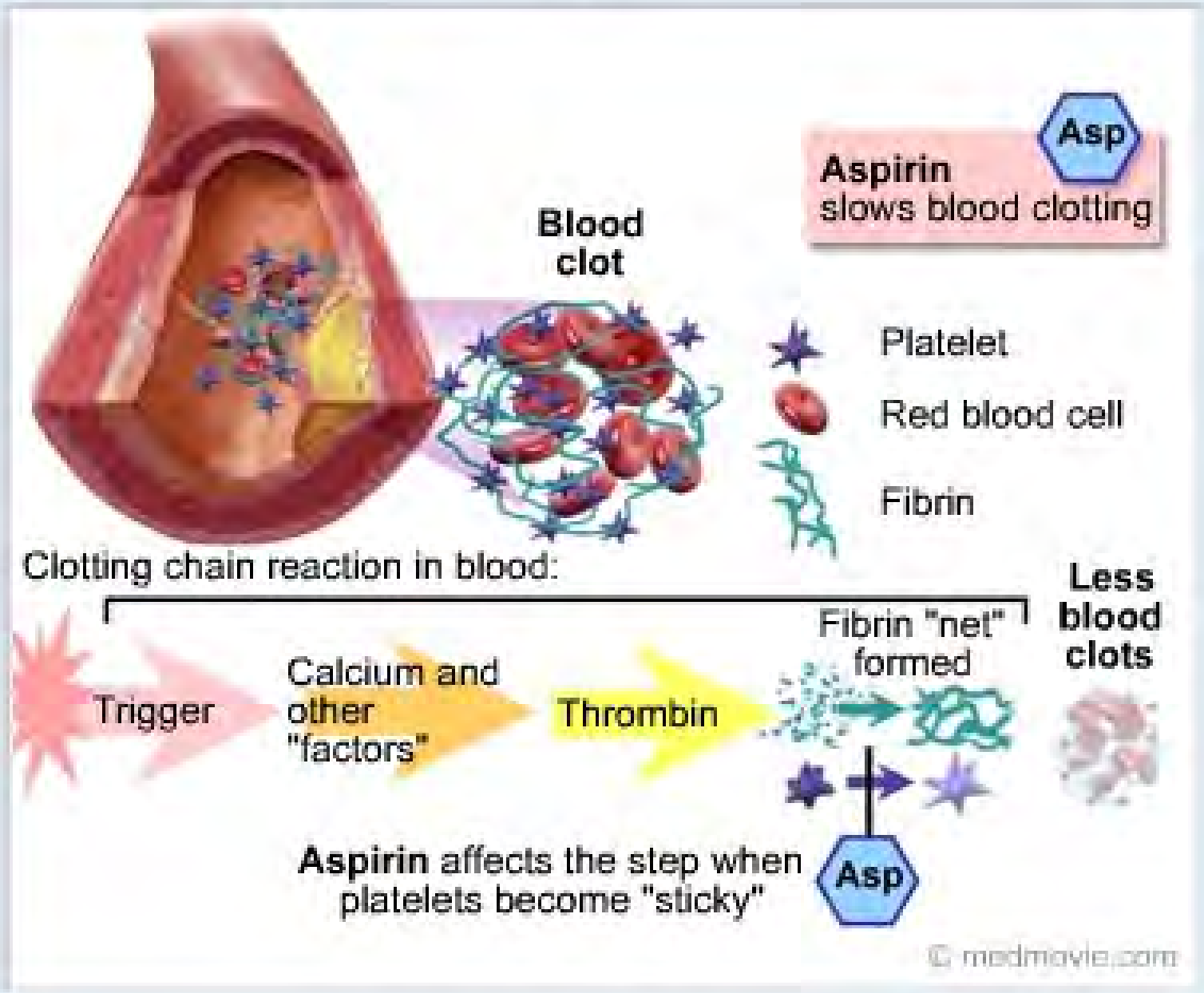
ATHEROSCLEROSIS



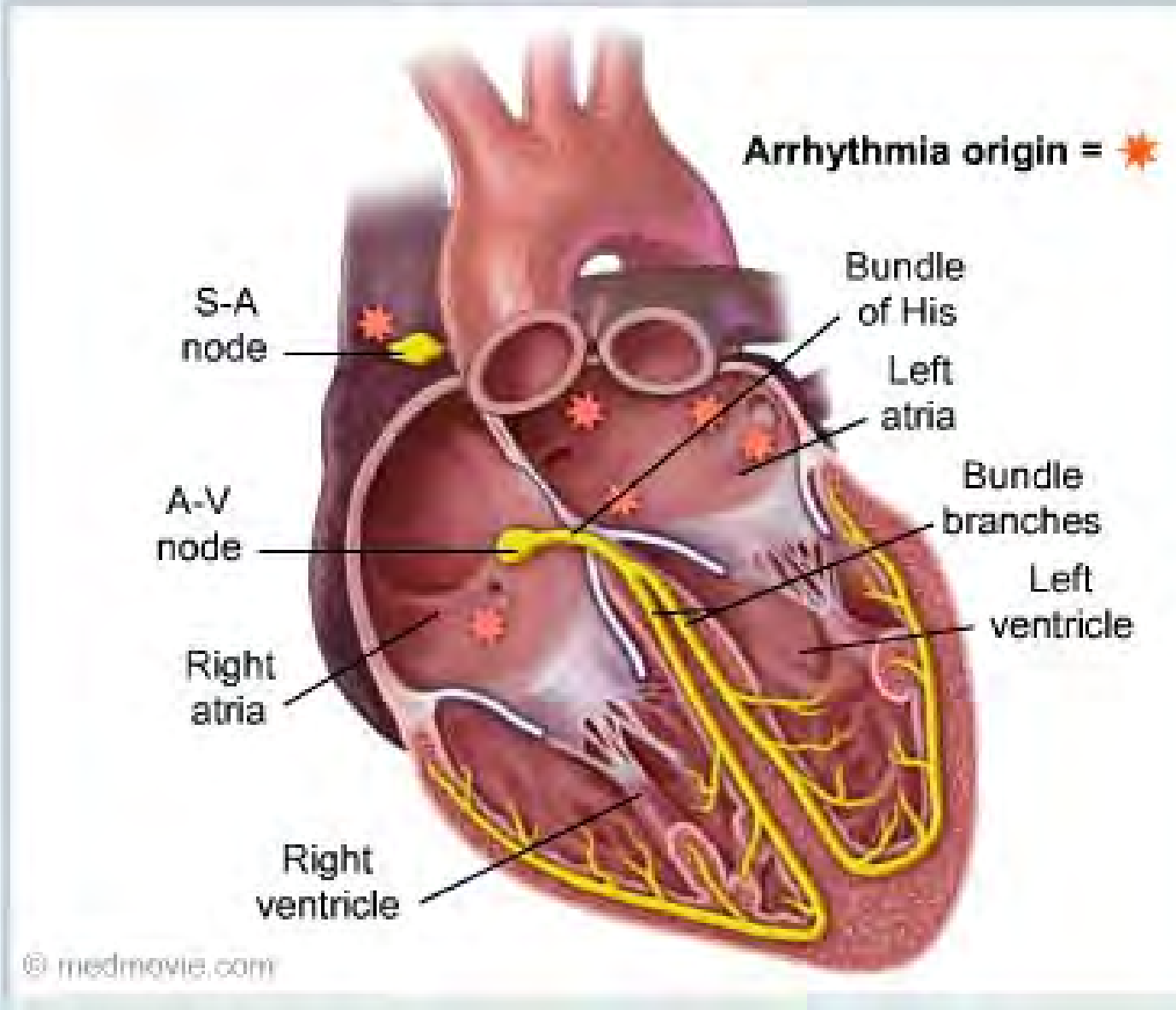
Thrombosis


Blood clot
Platelet
Red blood cell
Fibrin
Clotting chain reaction in blood:
Trigger
Calcium and other "factors"
Thrombin
Fibrin "net" formed
Blood clot
Platelets become "sticky"
© medmovie.com

Aspirin


Asp
Aspirin
slows blood clotting
Blood clot
Platelet
Red blood cell
Fibrin
Clotting chain reaction in blood:
Trigger
Calcium and other "factors"
Thrombin
Fibrin "net" formed
Less blood clots
Aspirin affects the step when platelets become "sticky"
Asp
© medmovie.com

Atrial Fibrillation



Risk factors TOAST I & III

- … for atherosclerosis and narrowing of the arteries and for SVO
  - High blood pressure
  - Tobacco use and Smoking
  - Diabetes
  - High cholesterol
  - Heavy alcohol use
  - Cocaine abuse
  - Family history of stroke
  - Increasing age

Risk factors TOAST II

- … for strokes caused by blood clots (emboli) that develop in the heart
  - Man-made or infected heart valves
  - Inflammation of the inside lining of the heart chambers and heart valves (endocarditis)
  - A heart muscle that is not beating strongly or regularly -- this may cause blood to stay in the heart area, leading to a clot. The clot can break off and travel to the brain
  - Irregular heart rhythms such as atrial fibrillation
  - Congenital heart defects, such as patent foramen ovale, which is a flap like opening between the chambers of the heart (may not cause any symptoms until a stroke occurs)

Risk factors TOAST IV

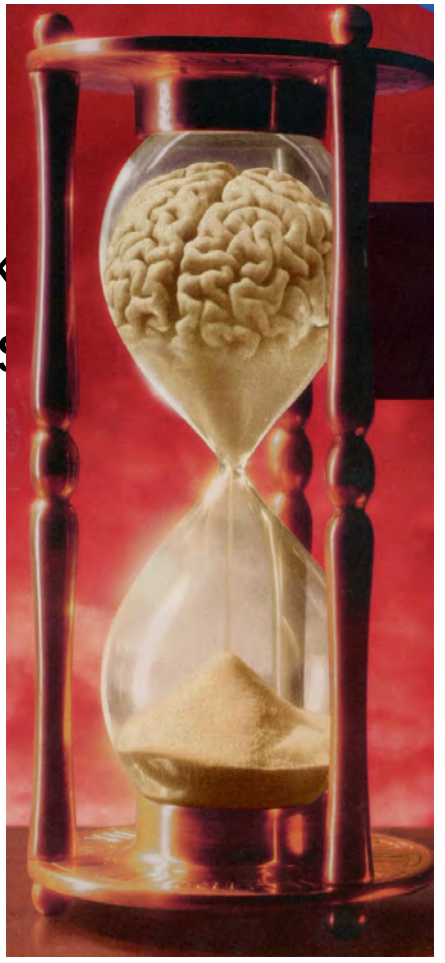
- … that can make the blood more likely to clot
  - Birth control pills can increase the chance of blood clots, especially in women who smoke and who are older than 35
  - Blood clotting disorders
  - Cancer
  - Rheumatoid arthritis, systemic lupus erythematosus, vasculitis, and ulcerative colitis
  - Pregnancy -- women have a higher risk of stroke during pregnancy and the weeks immediately after pregnancy

Risk factors TOAST IV

- … for stroke secondary to carotid dissection
  - Marfan syndrome or fibromuscular dysplasia
  - Injury to the neck from trauma or during a medical procedure such as an arteriogram

TIME IS BRAIN-QUANTIFIED-1

- Time is money (Benjamin Franklin)
- Time is muscle (acute myocardial infarction)
- Time is brain emphasizes that human brain tissue is rapidly and irretrievably lost as strok progresses and that therapeutic intervention must be emergently pursued



TIME IS BRAIN-QUANTIFIED-2

- The average volume of human forebrain is 1020 mL excluding CSF space
- Average final volume of a supratentorial brain infarction is 54 mL (5.3 % of brain vol)
- Total number of neurons 130 billions (cerebellar granular neurons 109, neocortical neurons 21.5 billions)
- Number of synapses in human neocortex approx. 150 trillion
- Total length of myelinated fibers is 135 000 km
- The neocortex loses ~31 million neurons per year in normal aging
- PET and MRI studies give evidence of persisting penumbra for 8 to 12 hours

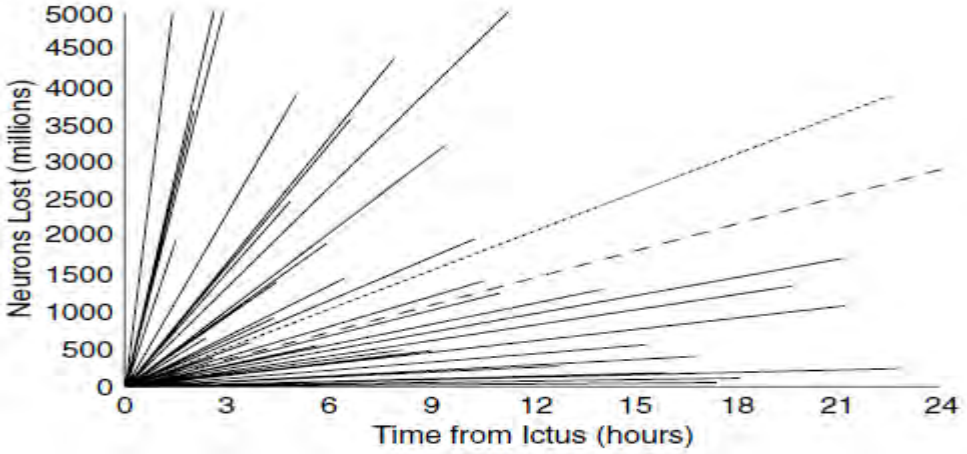
TIME IS BRAIN-QUANTIFIED-3

	NEURONS LOST	SYNAPSES LOST	FIBERS LOST
PER STROKE	1.2 billion	8.3 trillion	7140 km
PER HOUR	120 million	830 billion	714 km
PER MINUTE	1.9 million	14 billion	12 km

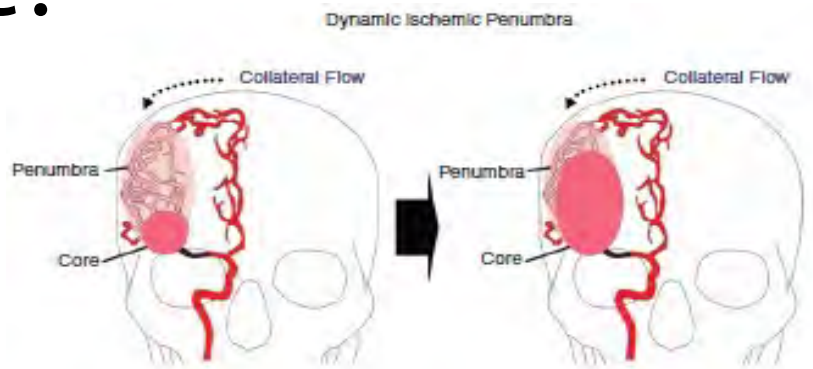
Estimated pace of neural circuitry loss in typical large vessel supratentorial acute ischemic stroke

Time is brain, but has each patient has his own time?

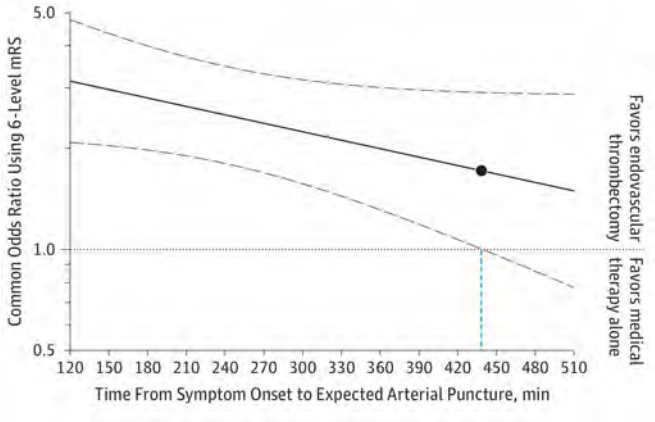
”1.8 million neurons are lost every minute”
Saver JL (2006) Time is brain–quantified. Stroke 37:263-266



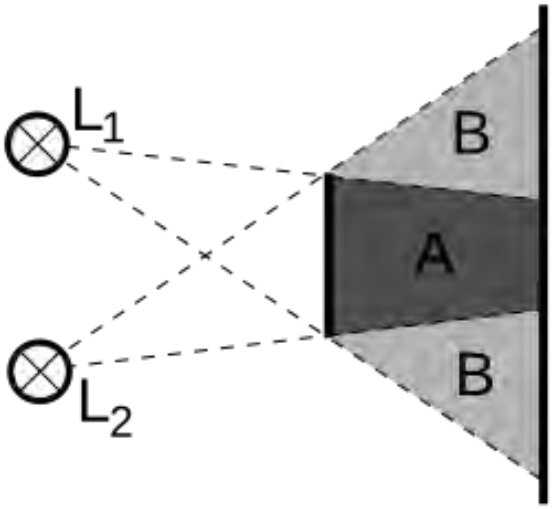
Hakimelahi R, Copen WA, Yoo AJ et al (2010) Time is brain, but each patient has his own time. European congress of radiology, Vienna, Austria doi: 10.1594/ecr2010/C-2615



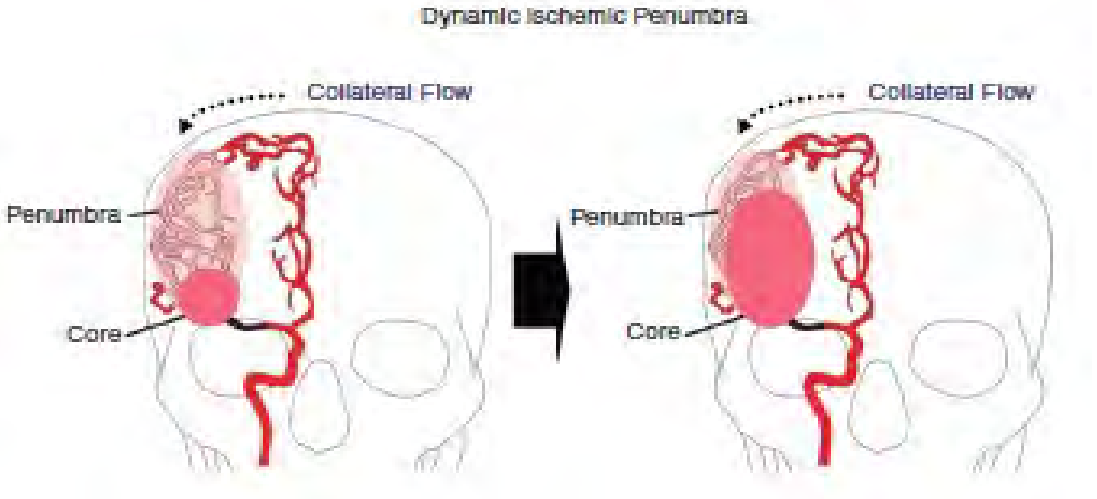
A Odds ratio for less disability at 3 mo in endovascular thrombectomy vs medical therapy alone groups by time to treatment



Penumbra: Time is brain, but has each patient has his own time?



(A) Umbra / varjo
(B) Penumbra / puolivarjo



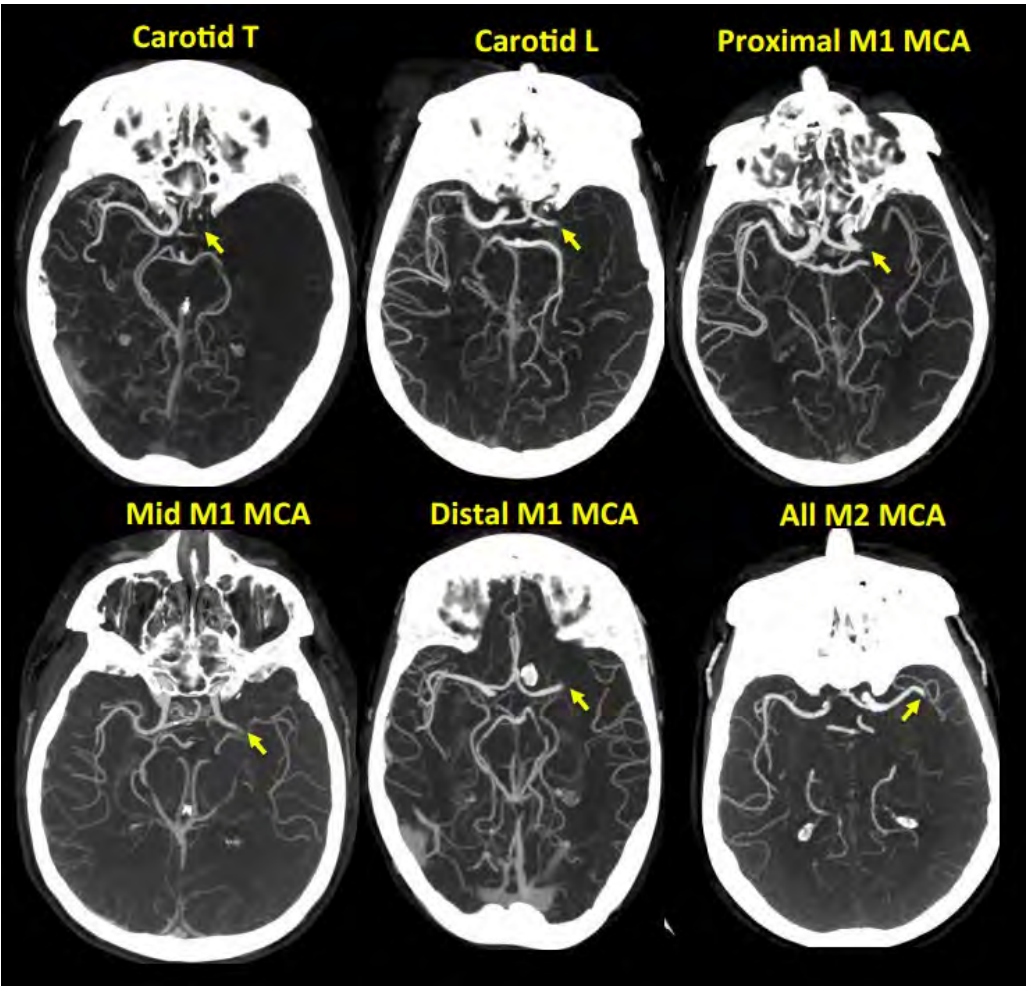
Aivoalue jossa verenkierto sen verran alentunut, että neuronit eivät toimi (neurologinen puutosoire) mutta pysyvä vaurio ei ole vielä kehittynyt.

- Mikäli pystytään verenkiertoa palauttamaan, puutosoire häviää ja infarkti ei synny.
- Mikäli verenkiertoa ei palauteta, kudos infarktoituu.

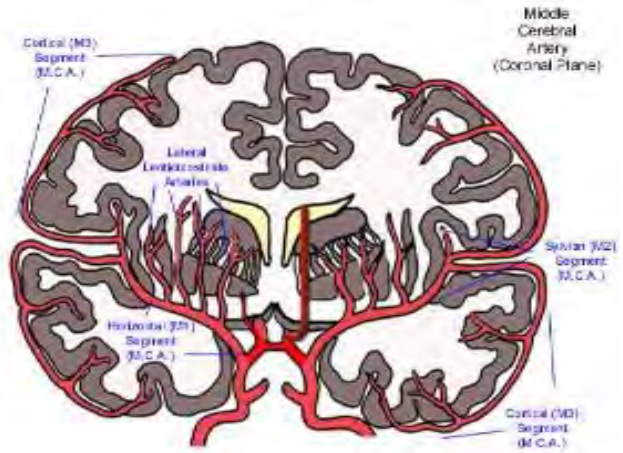
How to pick a suitable patient for endovascular treatment?

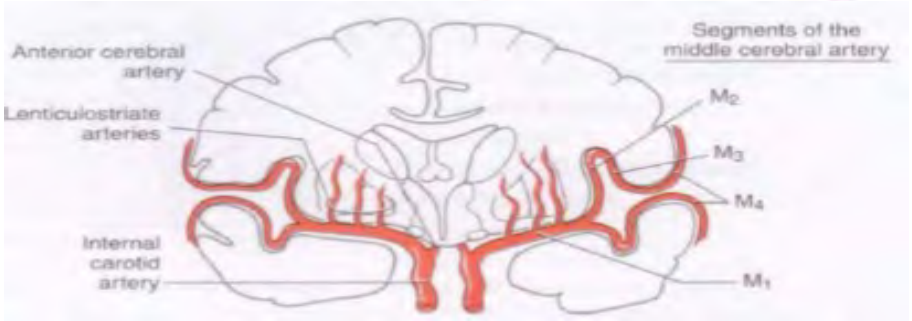
- Large vessel occulsion
- **Enough salvageable braintissue left**

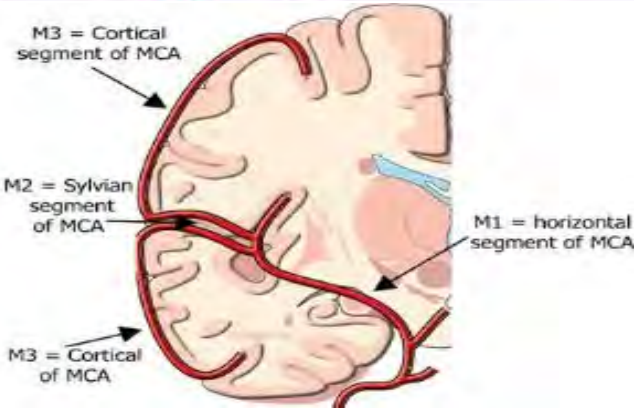
- How to determine?

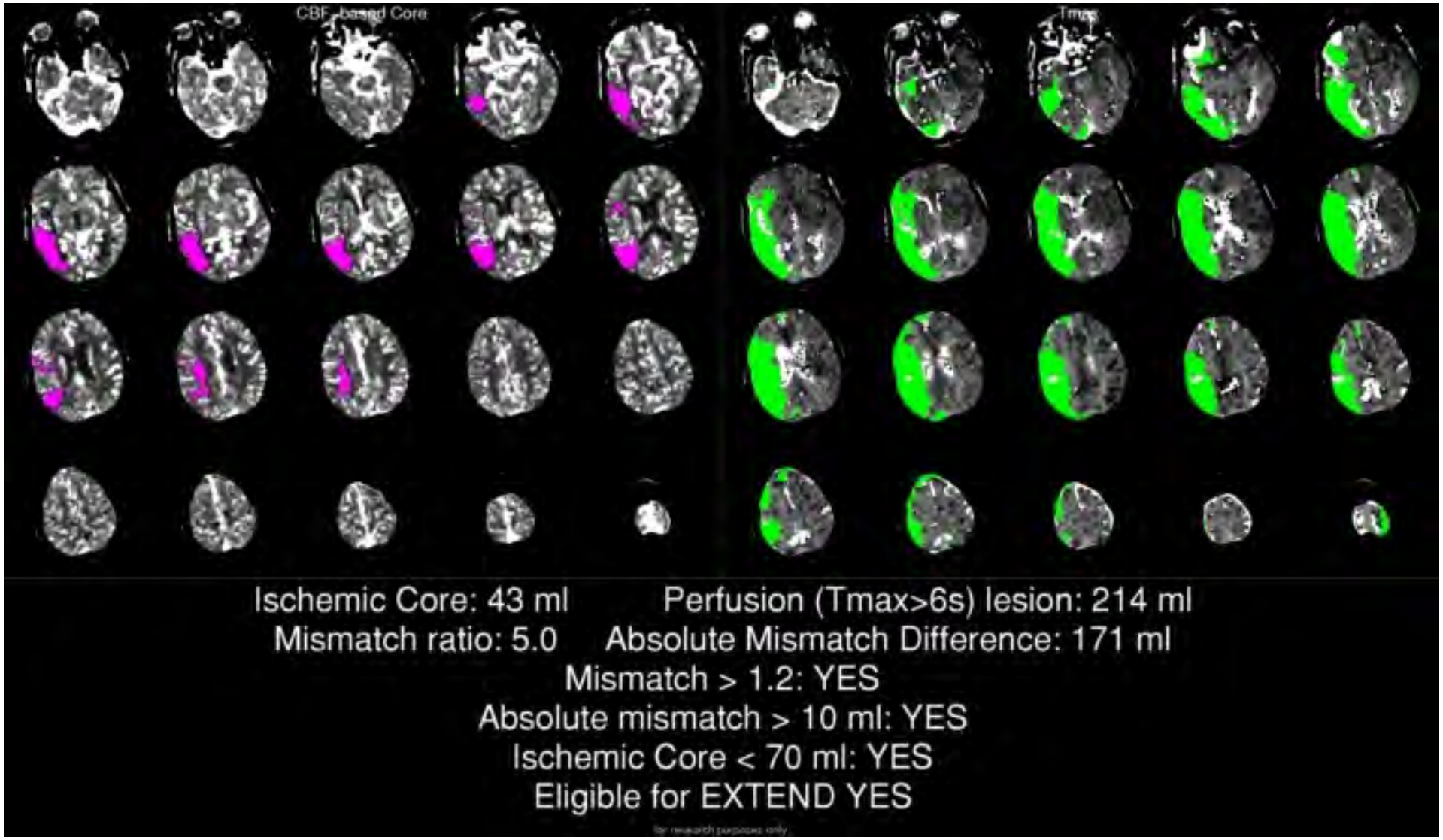


www.radiopaedia.org

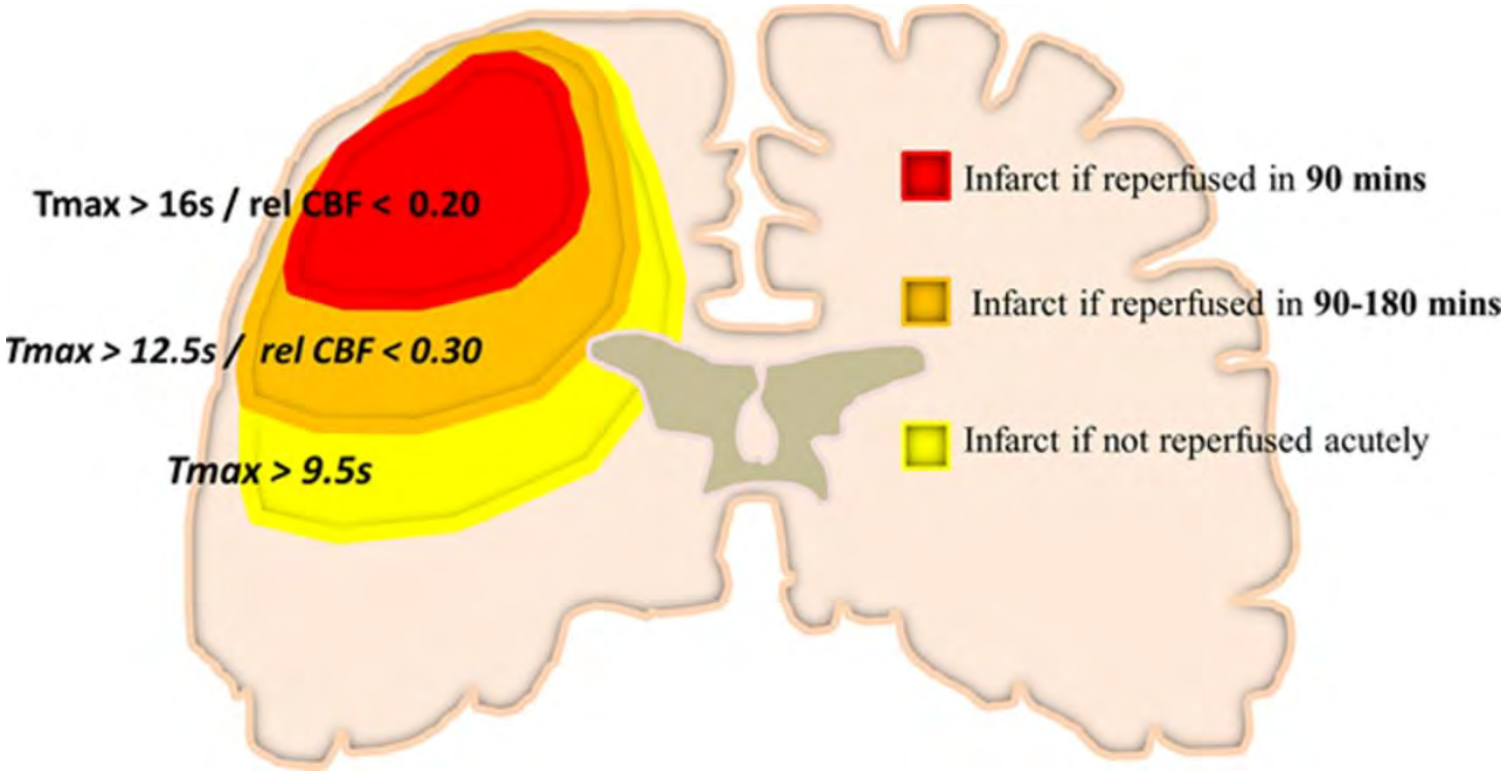






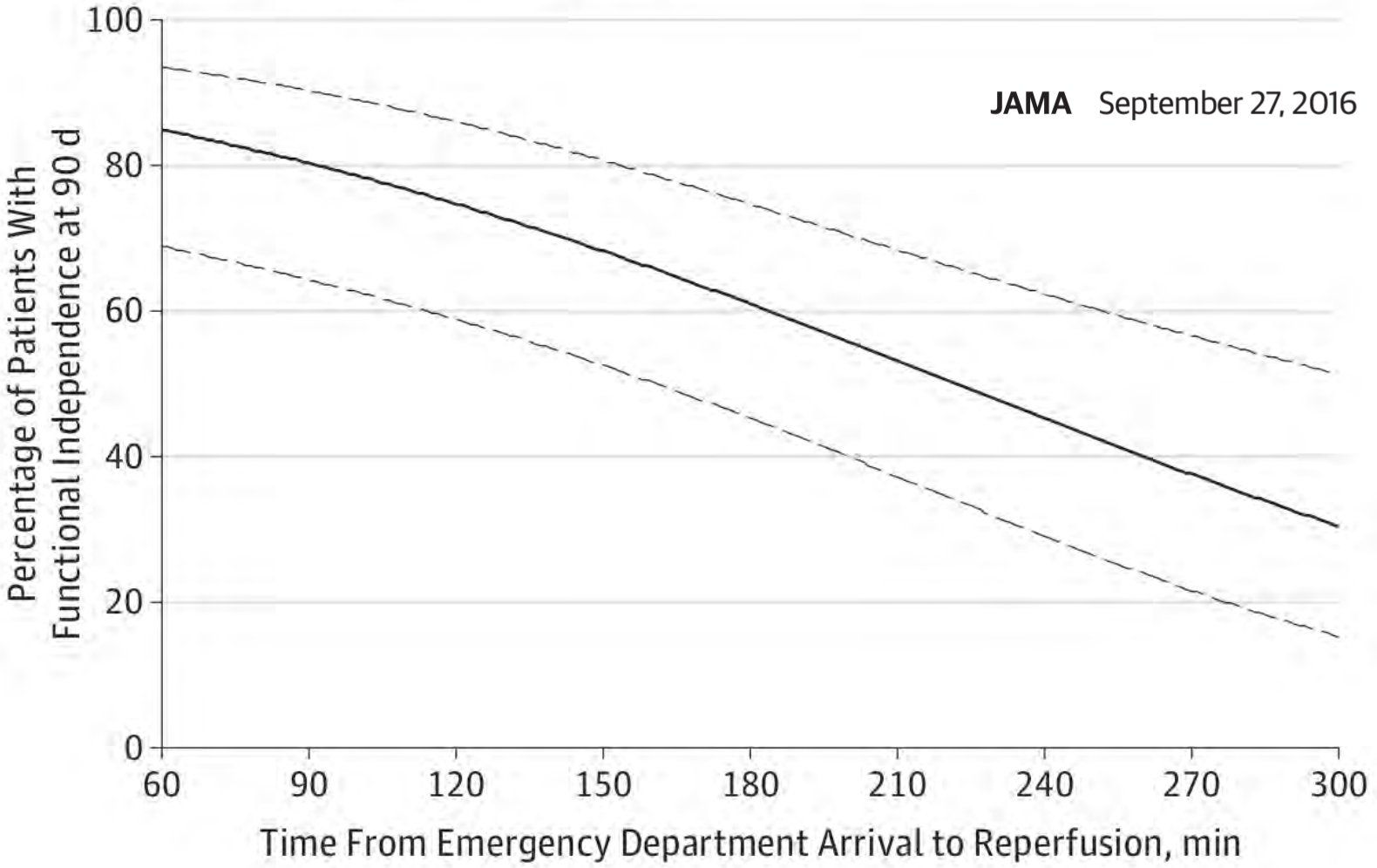

CBF -based Core
Tmax
Ischemic Core: 43 ml
Perfusion (Tmax>6s) lesion: 214 ml
Mismatch ratio: 5.0
Absolute Mismatch Difference: 171 ml
Mismatch > 1.2: YES
Absolute mismatch > 10 ml: YES
Ischemic Core < 70 ml: YES
Eligible for EXTEND YES
for research purposes only

Hypothetical model for time-based computed tomographic (CT) perfusion thresholds derived from the study.



Christopher D. d'Esterre et al. Stroke. 2015;46:3390-3397

A Functional independence (mRS 0-2) by time from emergency department arrival to actual substantial reperfusion

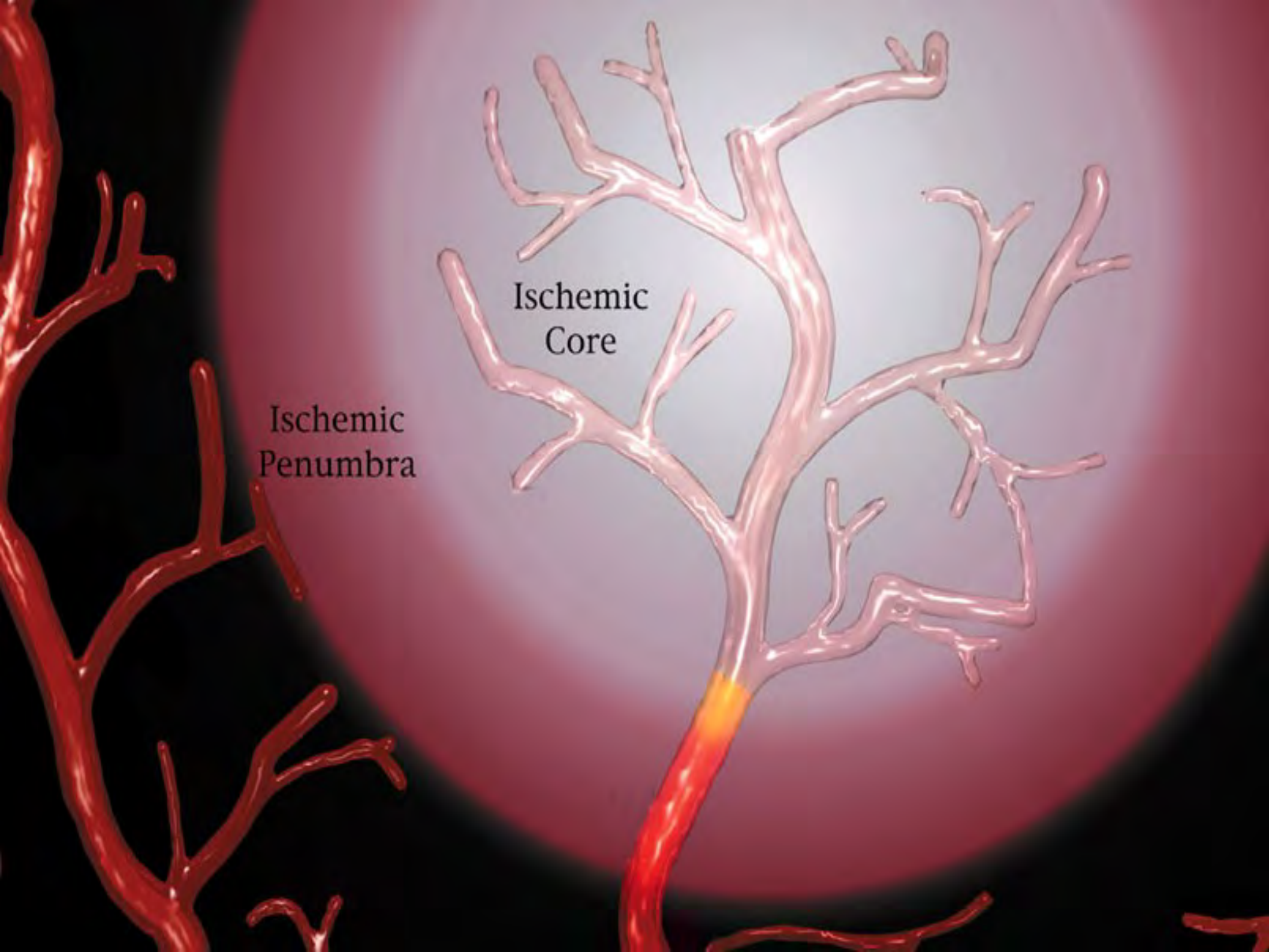


Stroke : Time lost is brain lost

Penumbra concept

- Regions with CBF < 10-15 ml / 100 g / min – rapid evolution to irreversible injury – 1h or less – the ischemic core

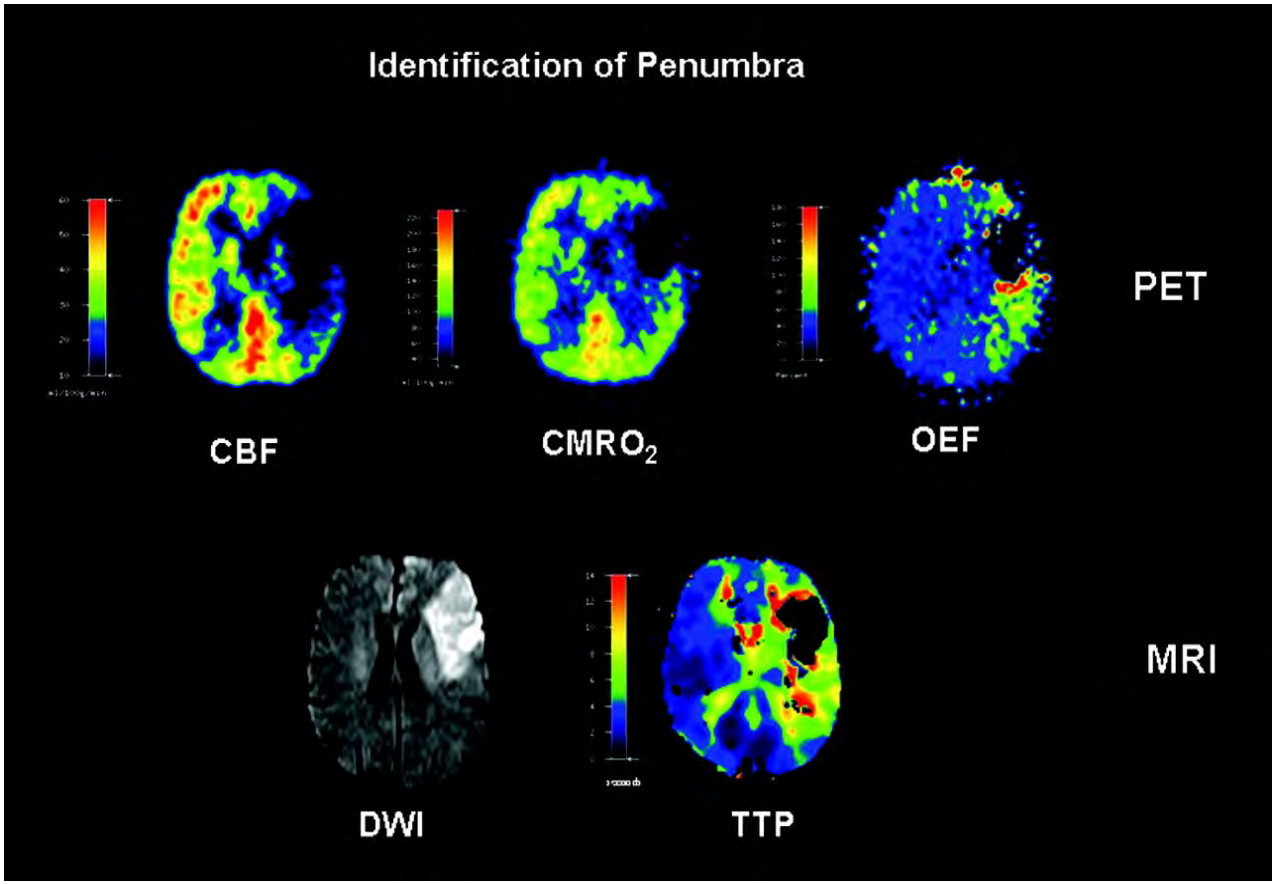
- Regions with CBF 15-35 ml / 100 g / min – evolution slower – many hours – penumbra – fundamentally reversible – evolves over time, depending on
  - duration and magnitude of perfusion deficit
    - even 15 ml / 100 g / min can become infarct
  - collateral blood flow
  - temperature, glucose, acidosis


Ischemic
Core
Ischemic
Penumbra

Penumbra Identification

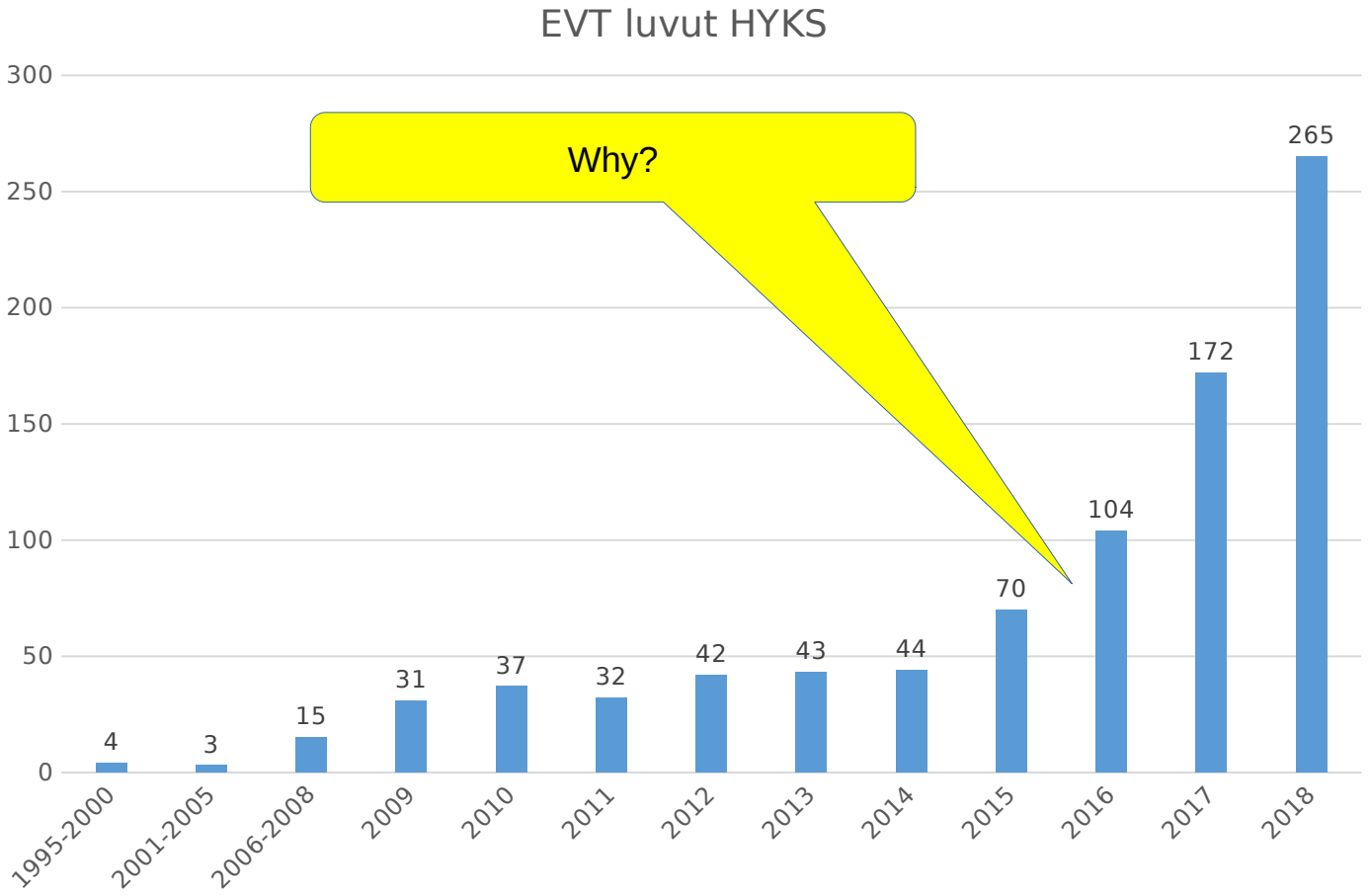
- The penumbra: hypoperfusion (↓CBF),preserved CMRO2, and ↑OEF

- Correspondence to the PWI/DWI mismatch

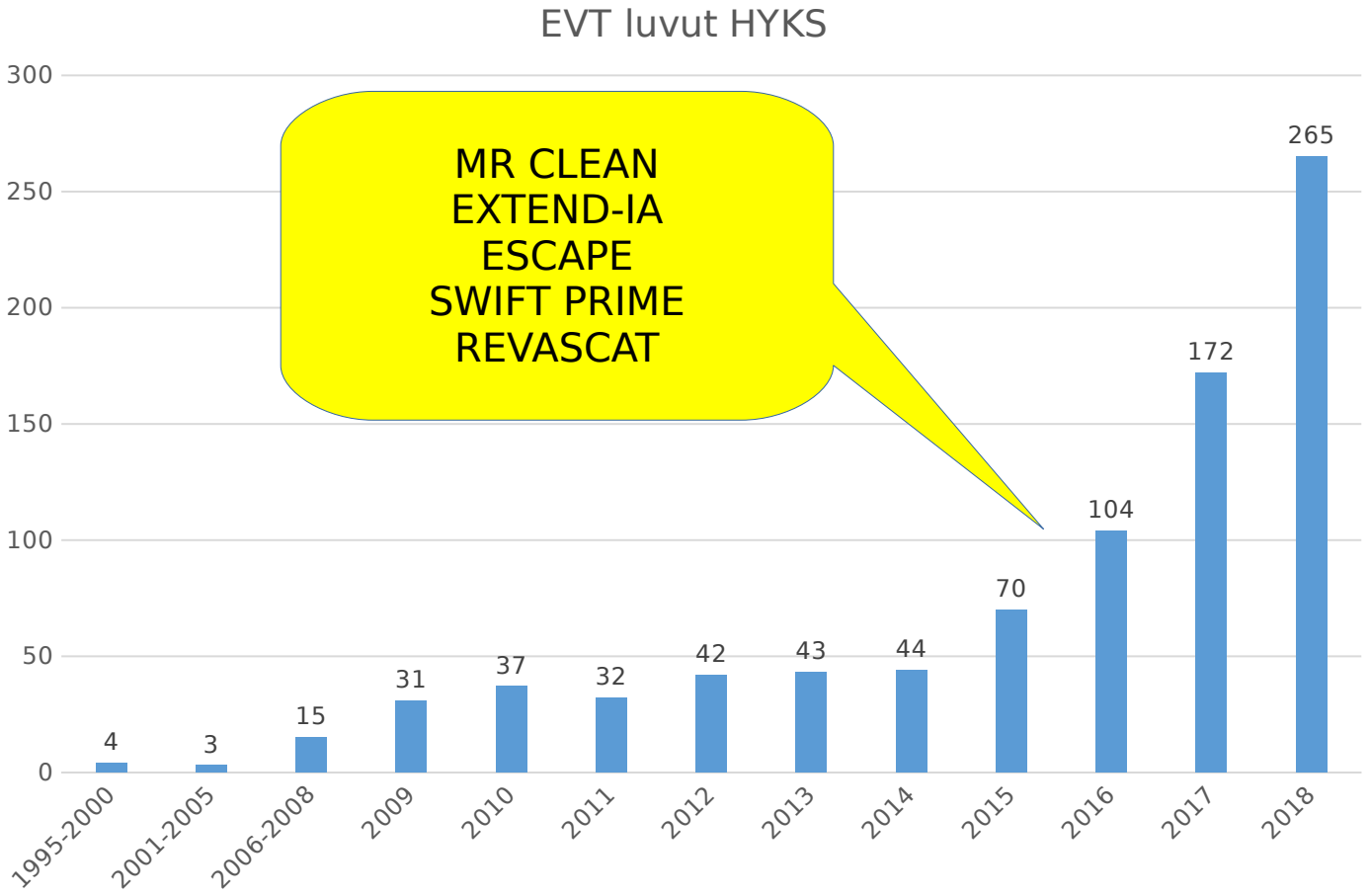


W-D Heiss: Stroke 2004; 35:2671-2674

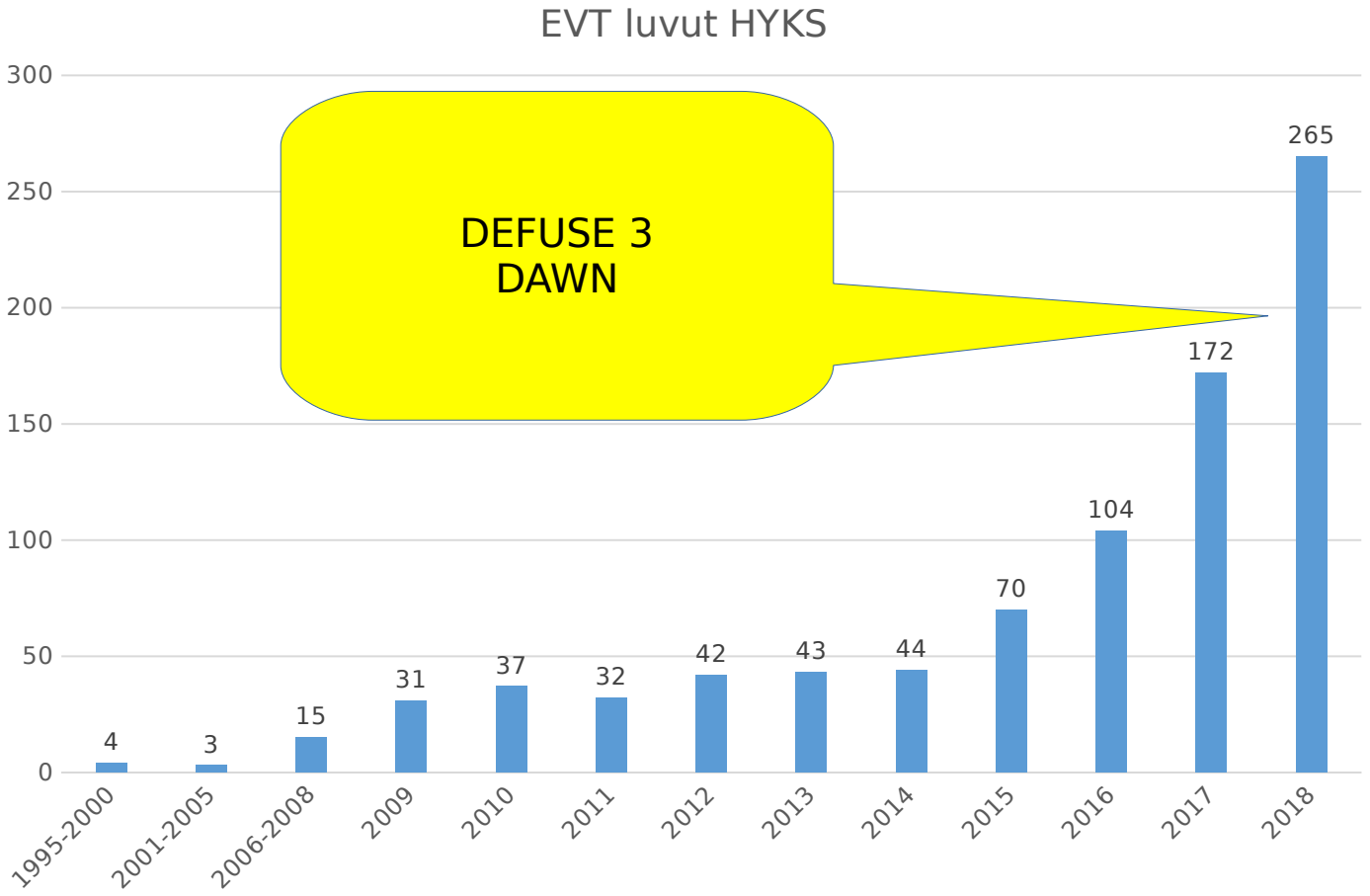
Endovascular treatment of stroke at our hospital



Endovascular treatment of stroke at our hospital



Endovascular treatment of stroke at our hospital



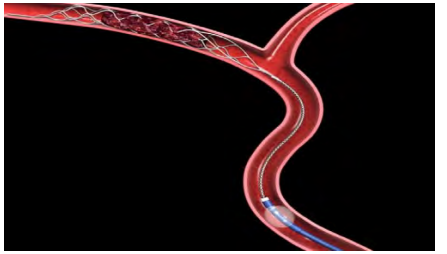
Endovascular treatment of ischemic stroke

NNT: 3-7 (0-6 h after onset)

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

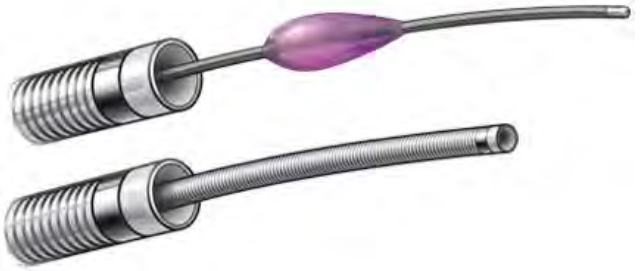
NNT: 2.8-4 (6-24 h after onset)

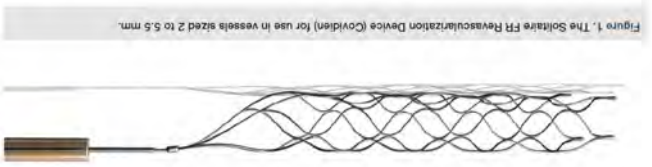
DAWN, DEFUSE 3

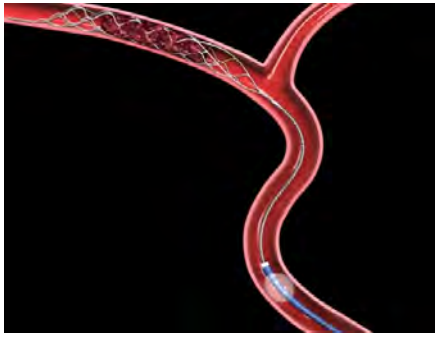


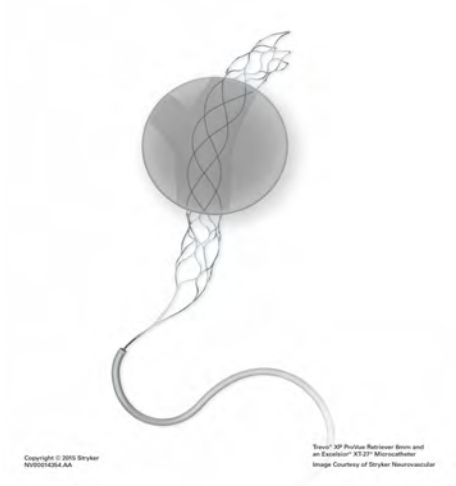
Endovascular treatment of stroke

- Coil retrievers
  - Merci
- Aspiration devices
  - Penumbra
- Stentrievers
  - Trevo
  - Embotrap
  - Capture



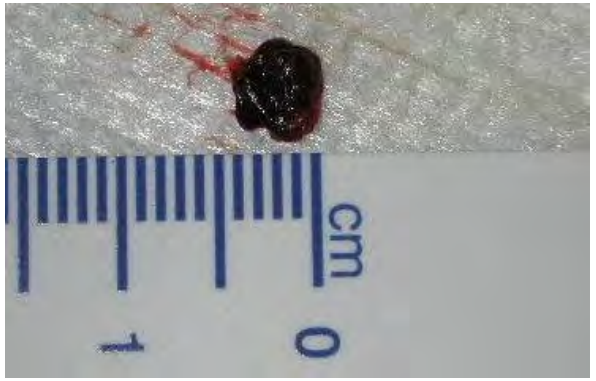






Typical Clots Retrieved

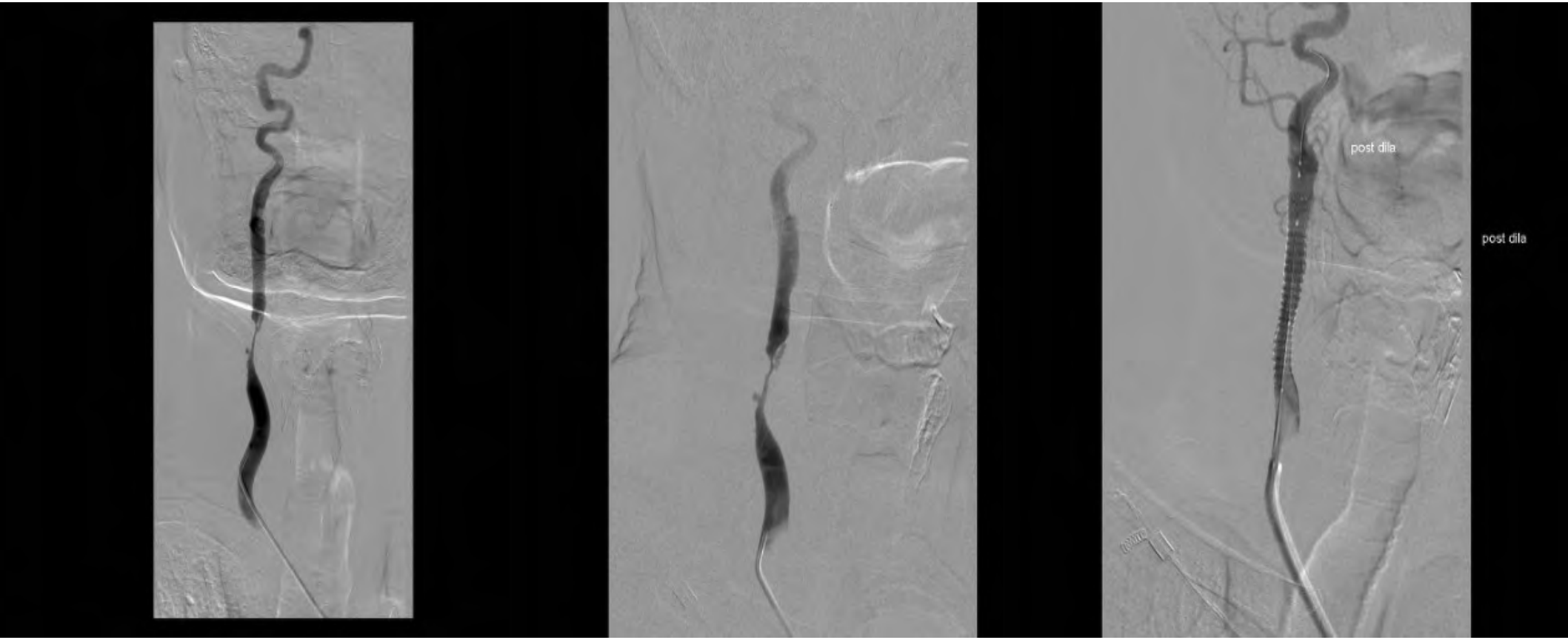
ICA occlusion
History of atrial fibrillation



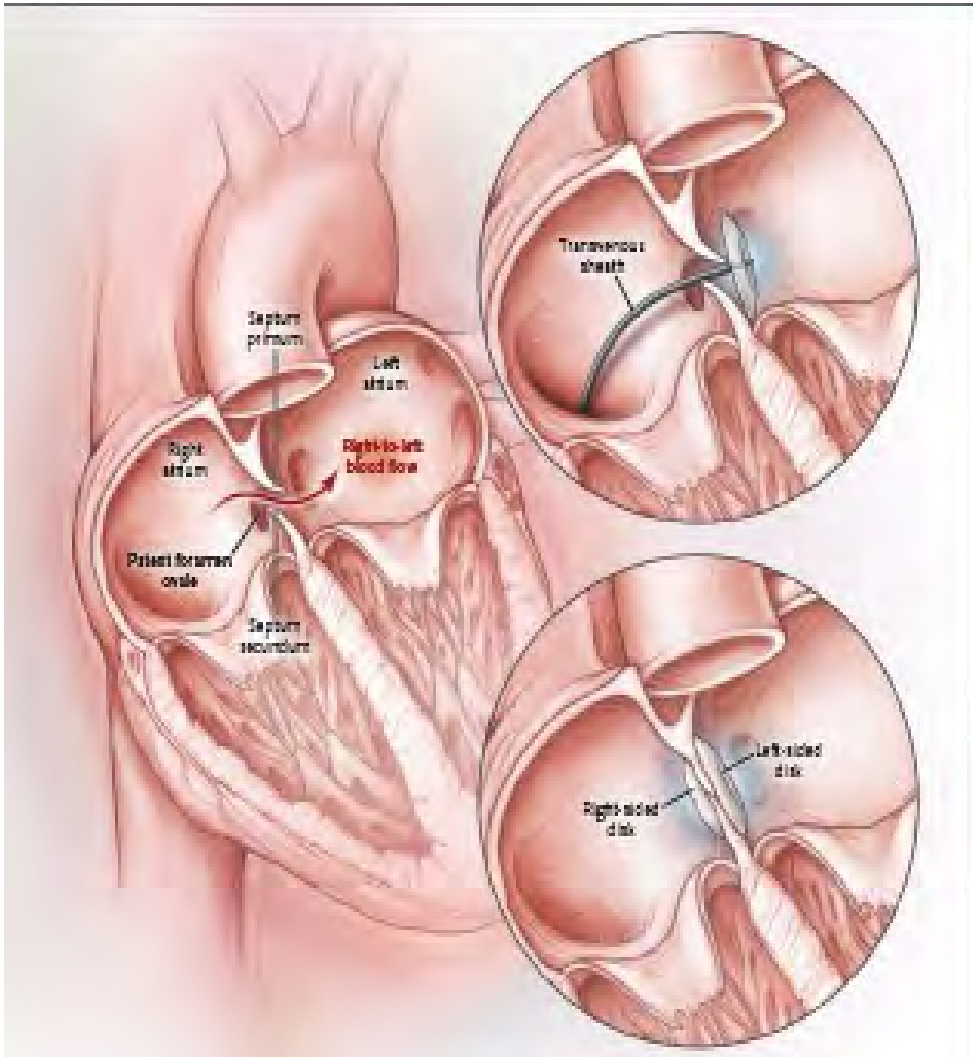
MCA occlusion
History of atrial fibrillation
Failed IV t-PA

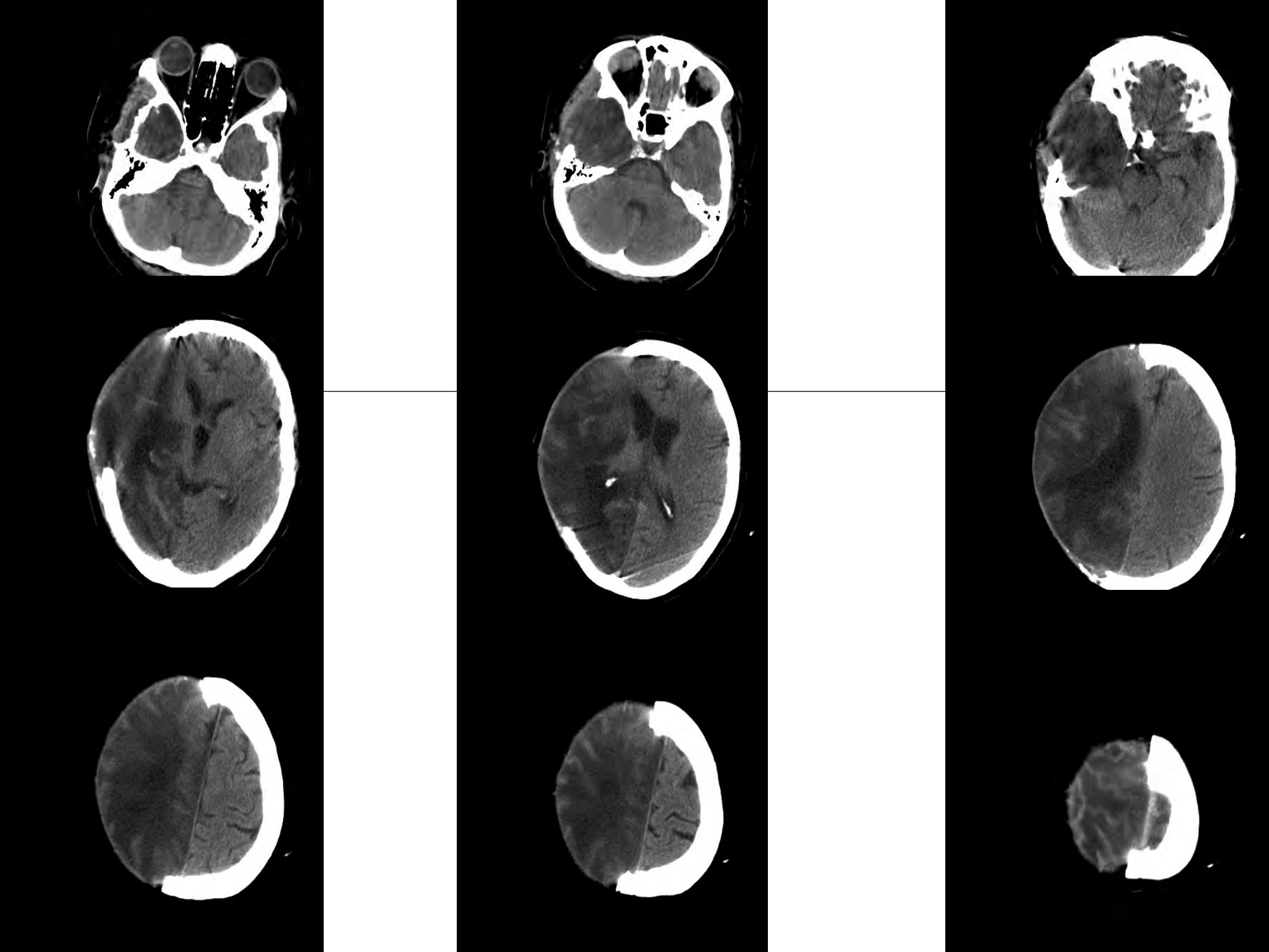
Basilar occlusion

Carotid stenting

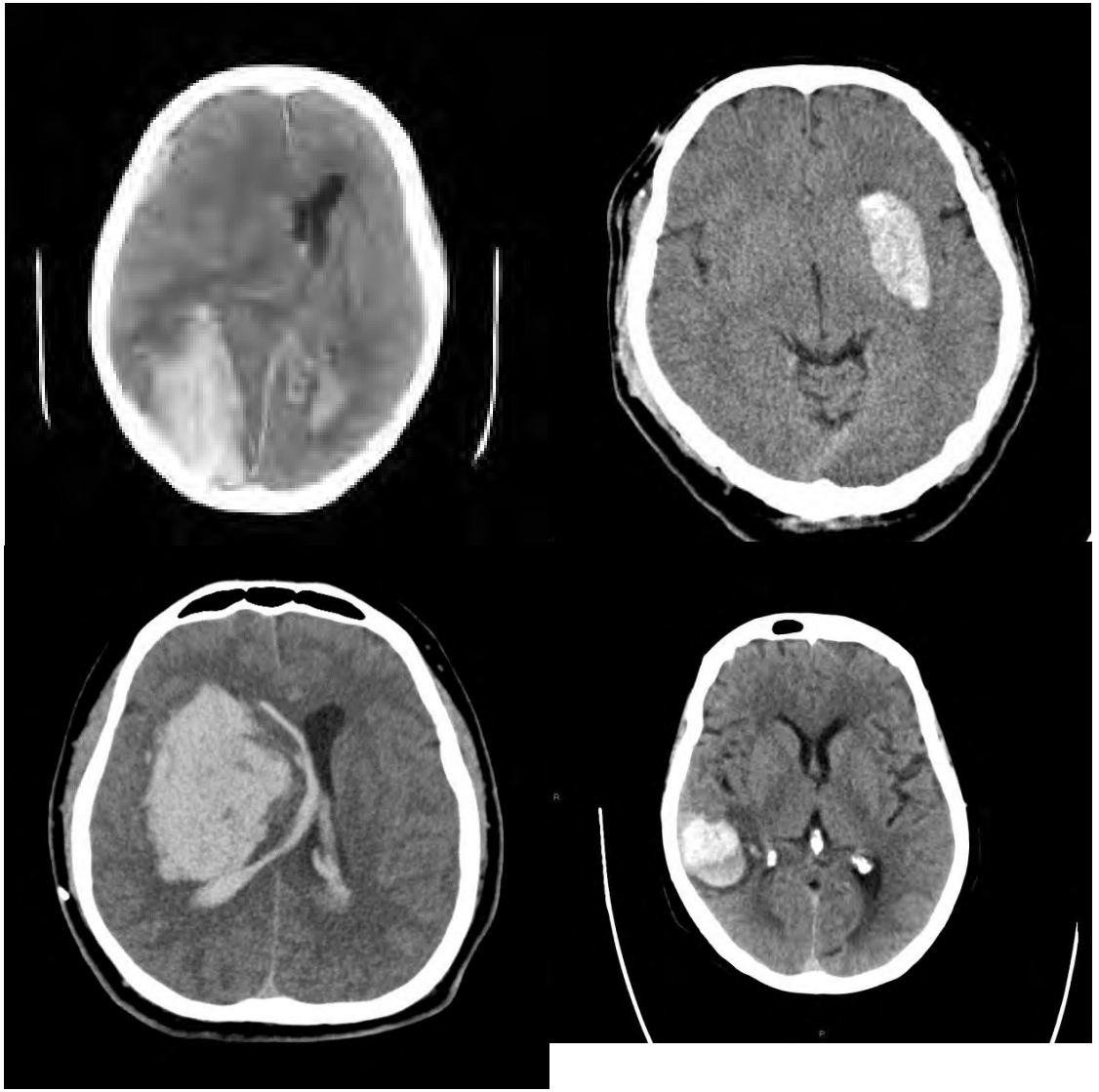


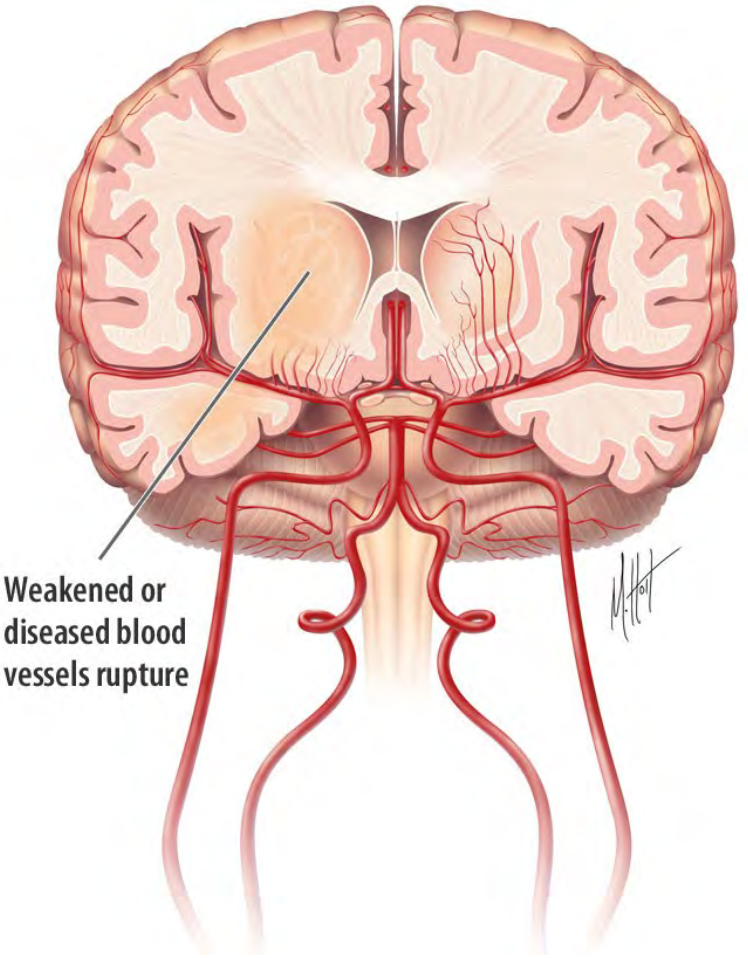
Closure of PFO



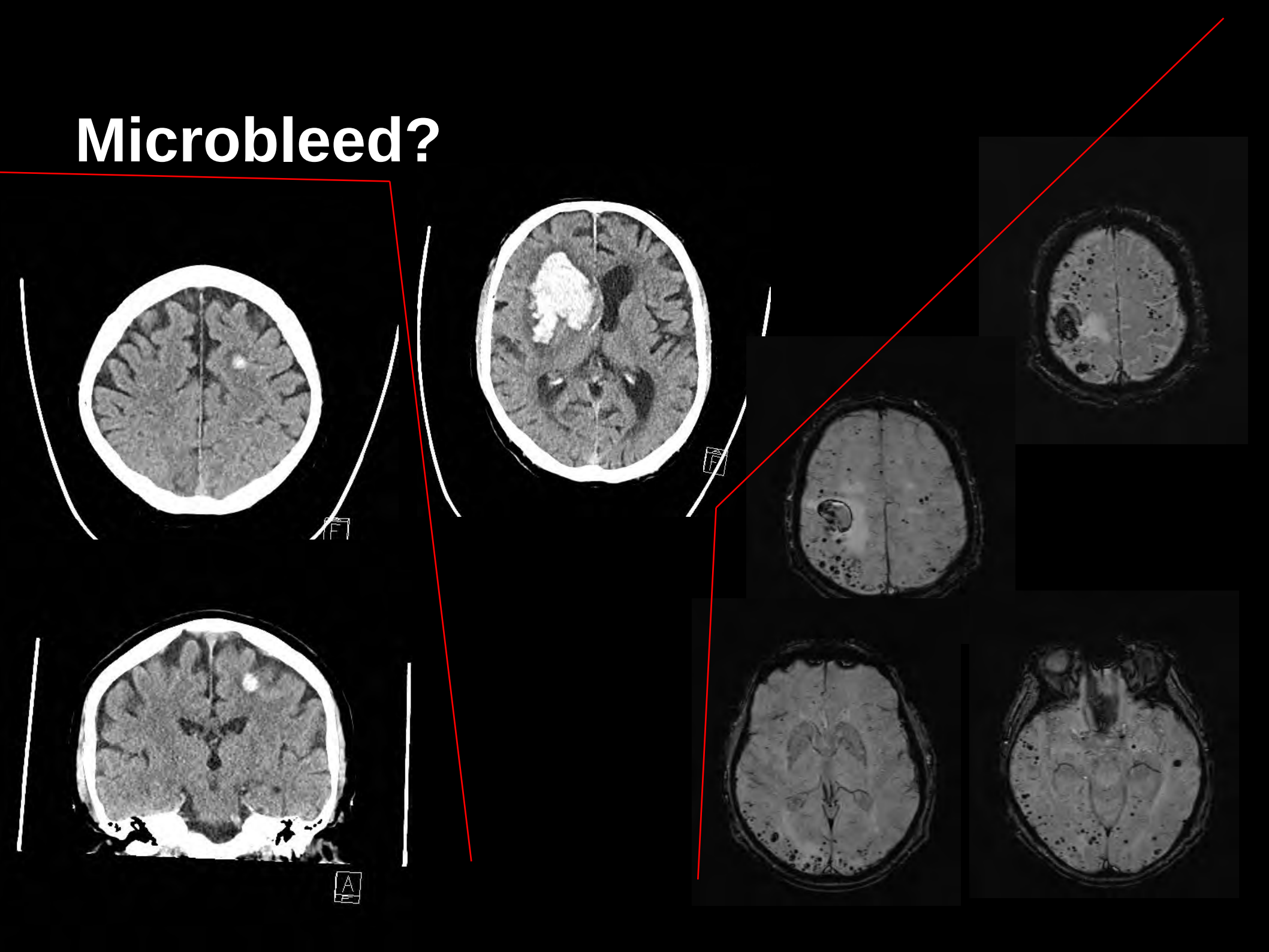


ICH

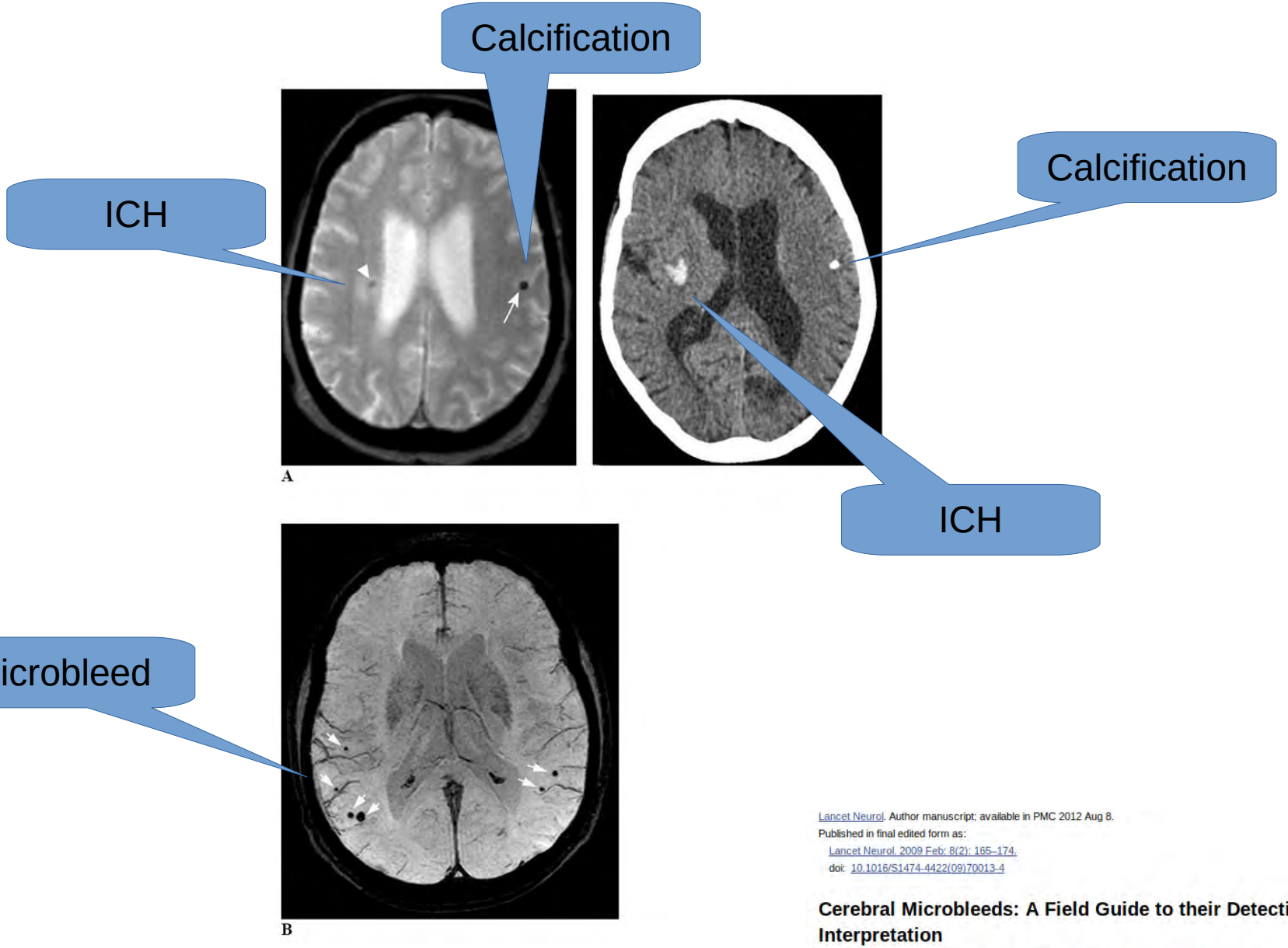




Microbleed?



What is a microbleed?



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Lancet Neurol. 2009 Feb; 8(2): 165–174.
doi: 10.1016/S1474-4422(09)70013-4

PMCID: PMC3414436
NIHMSID: NIHMS348039

Cerebral Microbleeds: A Field Guide to their Detection and Interpretation

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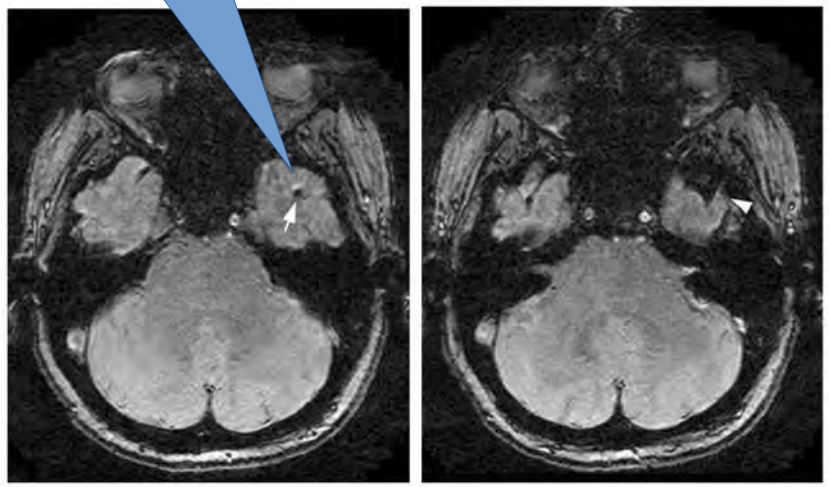
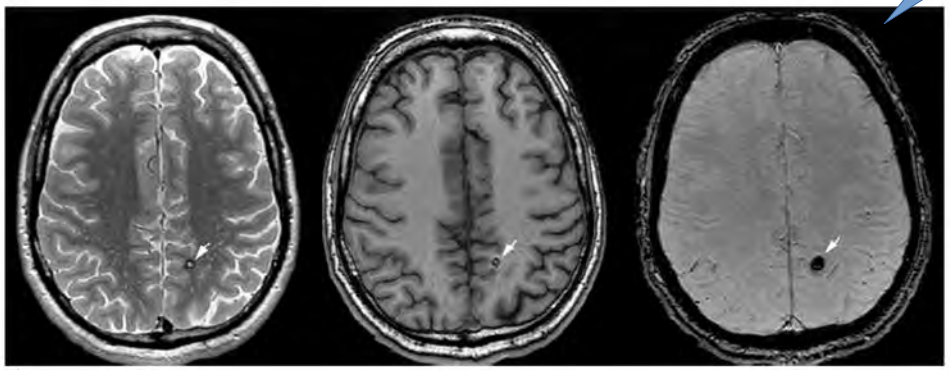
Microbleed?

Artifact



C

Cavernoma



D

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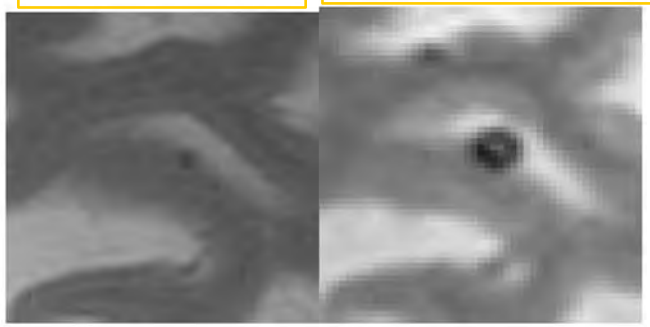
Definition of a microbleed

T2 fast SE

T2*-weighted MRI

Blooming effect (larger area of signal void)

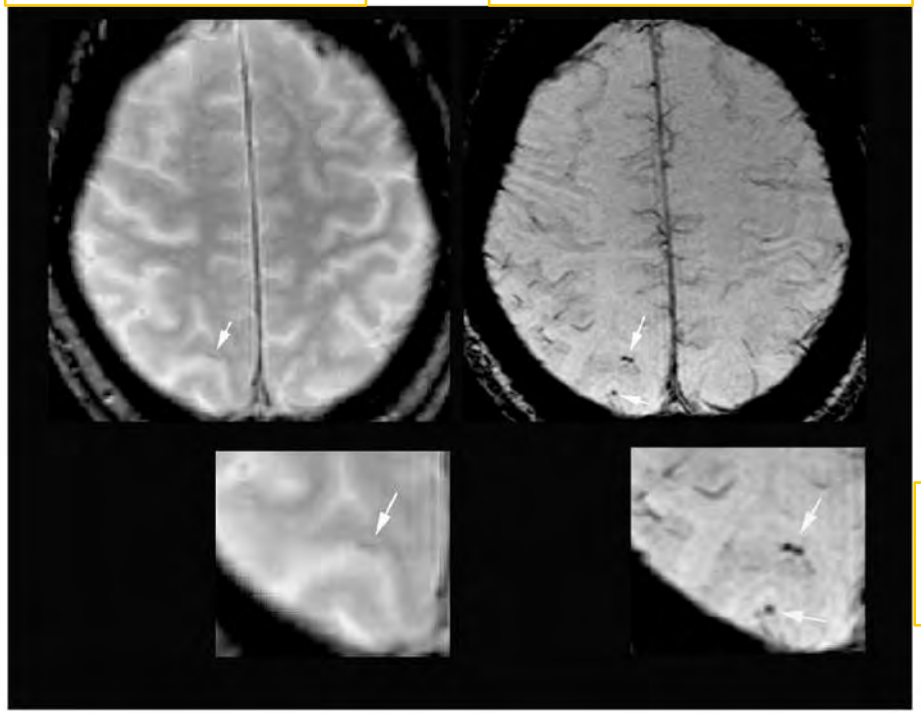
Ringing artifact as an area of high signal within the signal void.



A

Conventional 2D sequence T2*-weighted MRI (TR/TE 775/20, flip angle 25°, voxel size 0.5×0.5×5 mm3)

Accelerated 3D T2*-weighted MRI sequence (TR/TE 45/31, flip angle 13°, voxel size 0.5×0.5×0.8 mm3).



B

Magnifications of matching brain regions

The 3D T2*-weighted MRI image demonstrates three CMB in lobar locations (white arrows) that are not or barely discernible on the 2D T2*-weighted MRI image.

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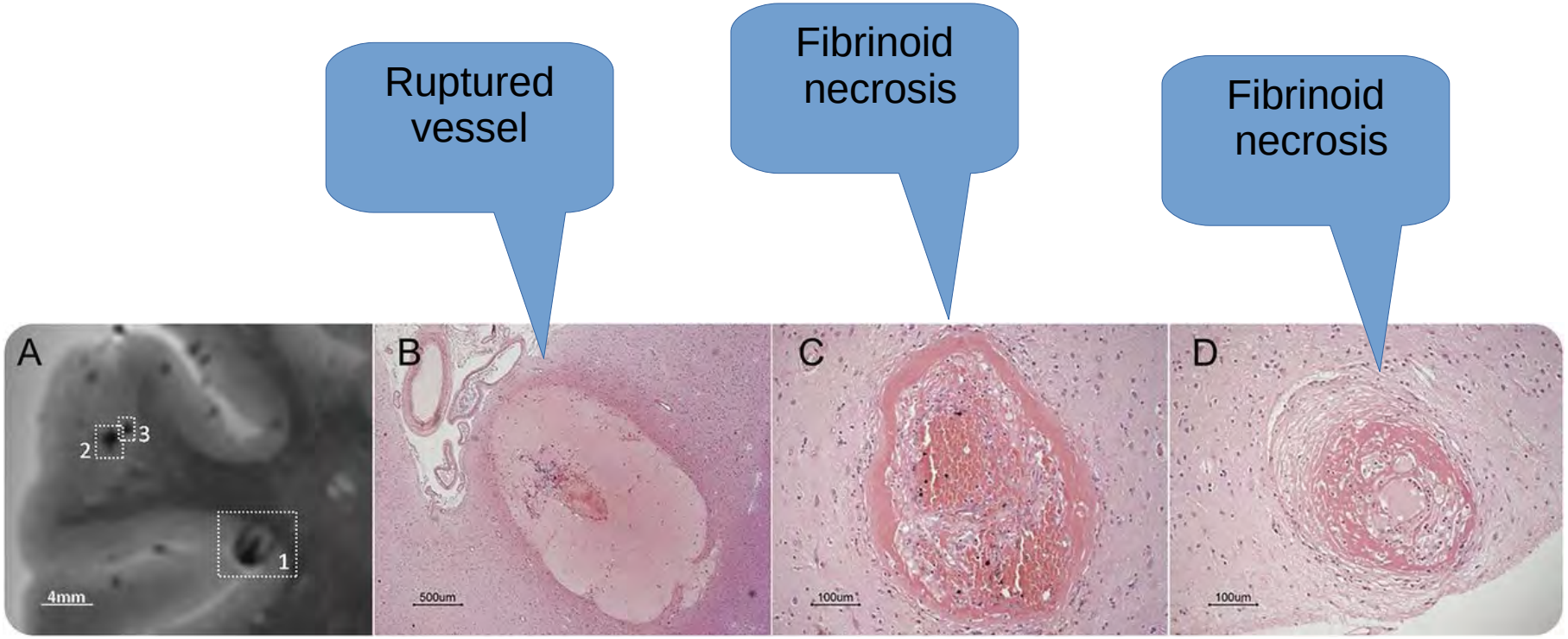
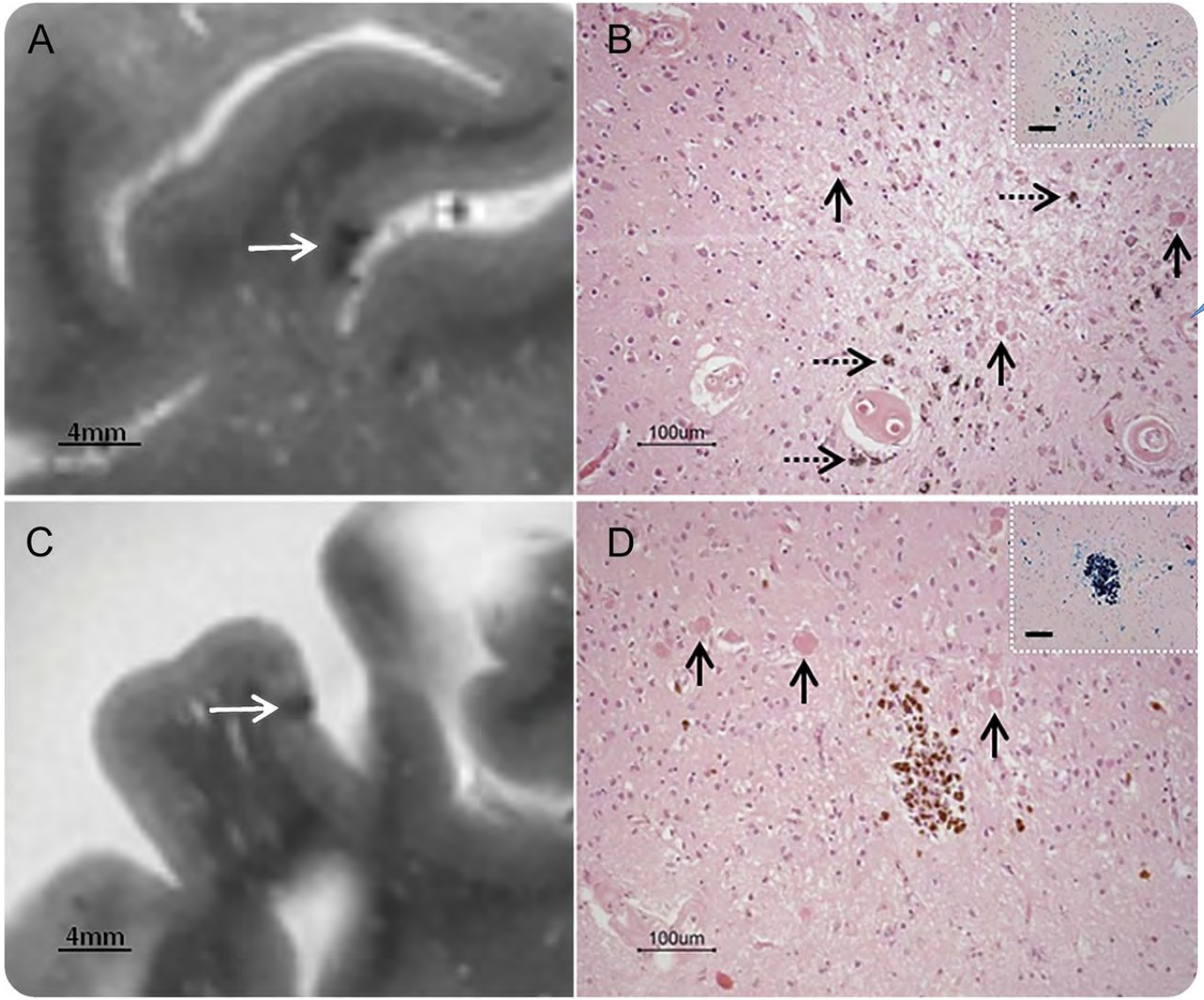
Figure 2 MRI-observed microbleeds in cerebral amyloid angiopathy correspond to hemorrhages and vasculopathies



Susanne J. van Veluw et al. Neurology 2016;86:867-871

Figure 3 Presence of chronic ischemic tissue injury underlying MRI-observed microbleeds in cerebral amyloid angiopathy



Hemorraginen mikroinfarkti

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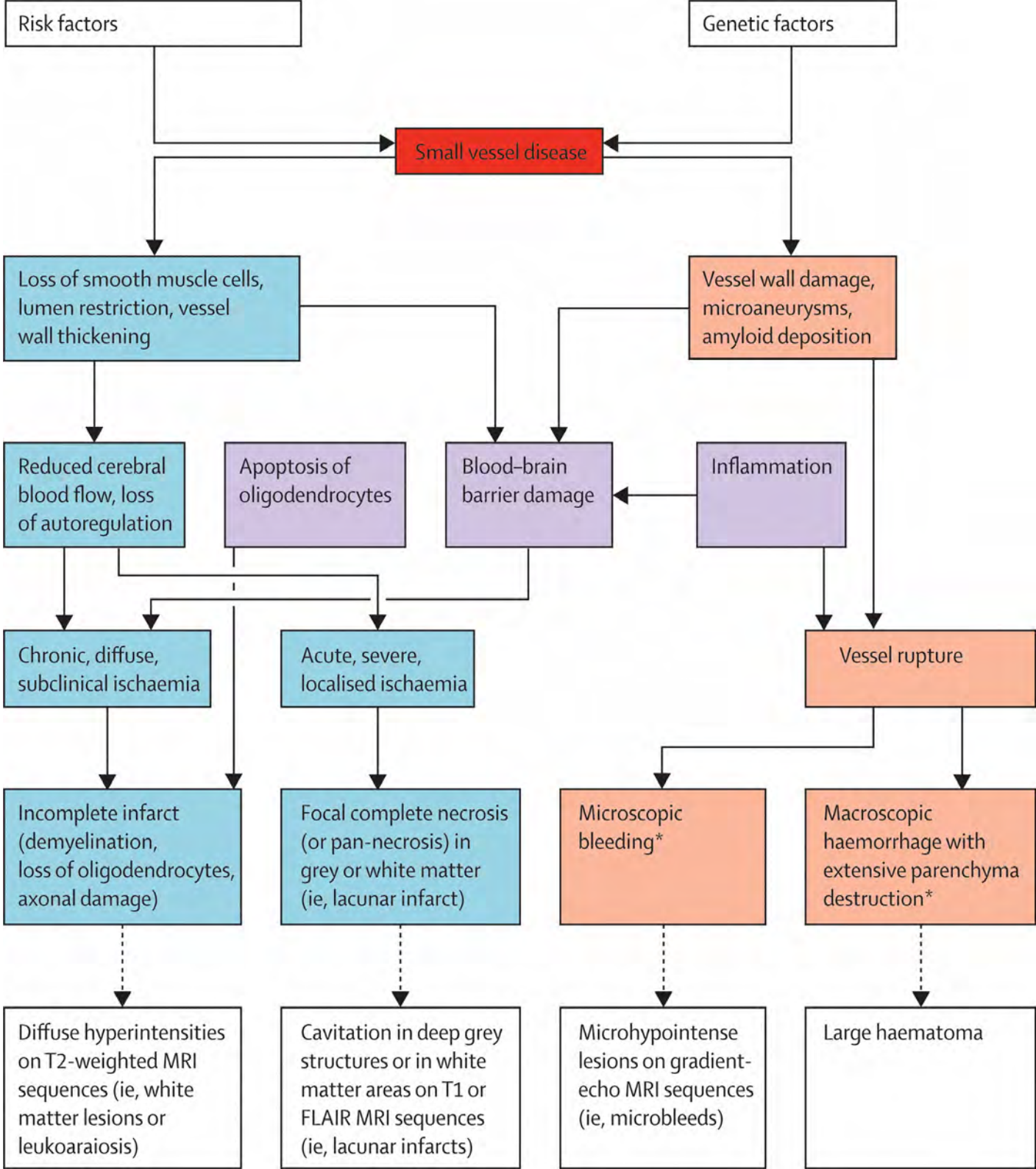
AMERICAN ACADEMY OF NEUROLOGY



L. Pantoni

Lancet Neurology,
Volume 9, Issue 7, July 2010,
Pages 689–701

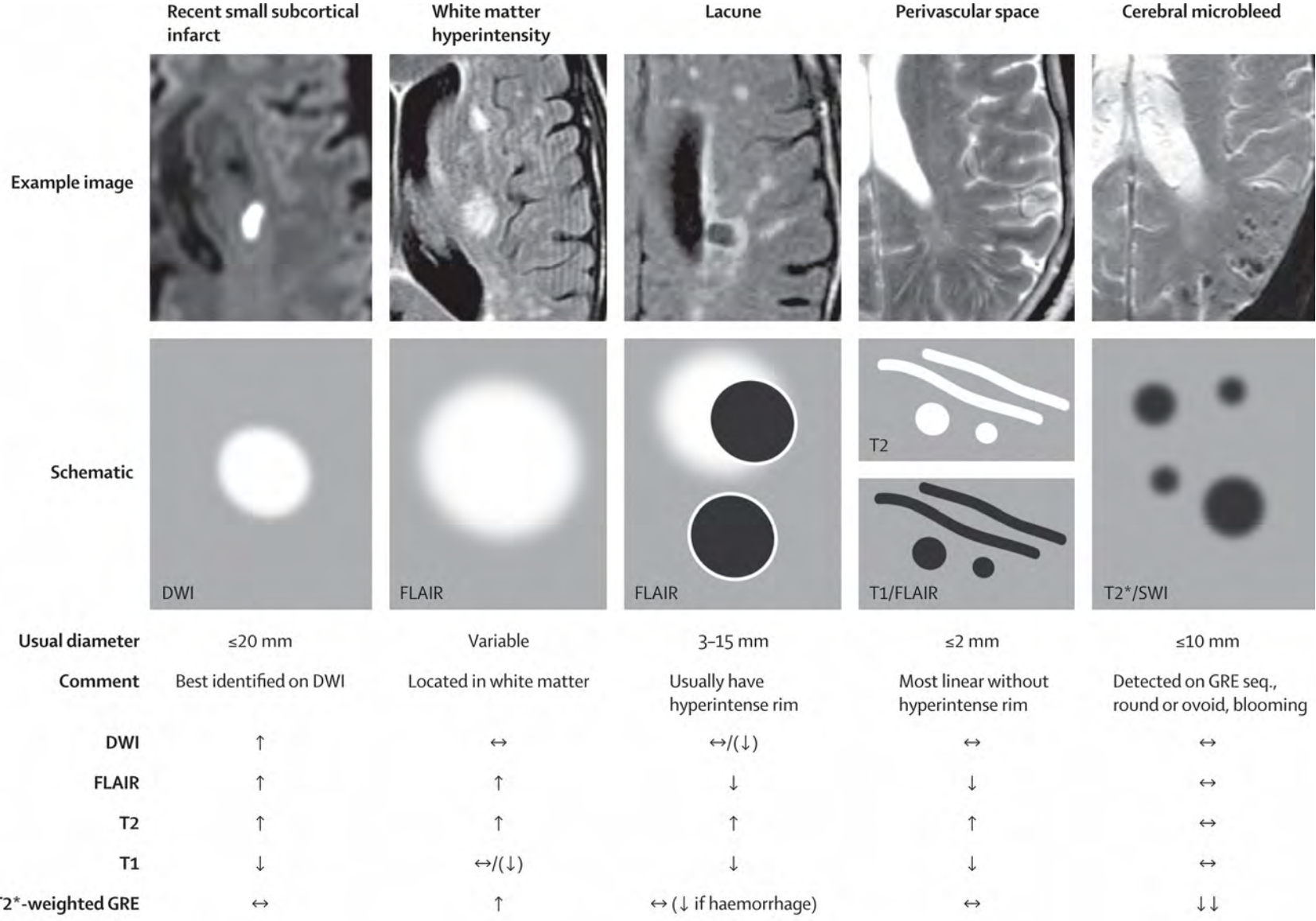


Figure 1 Variable fates of lesions related to small vessel disease and the convergence of acute lesions with different causes but similar late appearances on MRI Arrows indicate possible late fates of acute MRI findings. Blue arrows indicate common fates ...

Joanna M Wardlaw , Eric E Smith , Geert J Biessels , Charlotte Cordonnier , Franz Fazekas , Richard Frayne , Richa...

Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration

The Lancet Neurology, Volume 12, Issue 8, 2013, 822 - 838

Treatment of acute Ischemic stroke

- **Primary prevention**
- **Stroke treatment**
- **Secondary prevention**

Treatment of acute Ischemic stroke

- **Primary prevention**
- **Stroke treatment**
  - Acute tretment (clot removal)
  - Acute treatment (neuroprotection and limitation of infarct growth: stroke unit care)
  - Prevention of complications (stroke unit care)
  - Rehabilitation
- **Secondary prevention**