Stroke

Sudden onset of symptoms and signs of focal or global (coma) neurological impairment, lasting more than 24 hrs, due to presumed vascular origin

TIA : focal impairment with complete recovery within 24 hrs (usually within 2 hrs)

Clinical, experimental, and imaging data have shown that the 24-hour criterion is inaccurate in suggesting an absence of brain injury and often results in uncertainty about what to do when a TIA occurs.

NEW DEFINITION

a TIA is a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than **one hour**, and **without evidence of acute infarction**. The corollary is that persistent clinical signs or characteristic imaging abnormalities define infarction — that is, stroke

(N Engl J Med 2002;347:1713-1716).

TABLE 1. FEATURES OF THE CURRENT AND PROPOSED DEFINITIONS OF TRANSIENT ISCHEMIC ATTACK.

CURRENT, TIME-BASED DEFINITION*	PROPOSED, TISSUE-BASED DEFINITION†
Based on an arbitrary 24-hour time limit	Based on the presence or absence of a biologic end point
Suggests transient ischemic symptoms are benign	Indicates that transient ischemic symptoms can cause permanent brain injury
Promotes diagnosis on the basis of the temporal course rather than pathophysiology	Encourages use of neurodiagnostic tests to identify brain injury and its cause
Fosters delays in interventions for acute cerebral ischemia	Facilitates rapid interventions for acute brain ischemia
Inaccurately predicts the presence or absence of ischemic brain injury	More accurately reflects the presence or absence of ischemic brain injury
Diverges from the distinction between angina and myocardial infarction	Consistent with the distinction between angina and myocardial infarction

*A transient ischemic attack is a sudden focal neurologic deficit lasting for less than 24 hours, of presumed vascular origin, and confined to an area of the brain or eye perfused by a specific artery.

†A transient ischemic attack is a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction.

THEREFORE

The development of symptoms of acute brain ischemia constitutes a medical emergency and transient symptoms do not exclude the possibility of associated brain infarction.

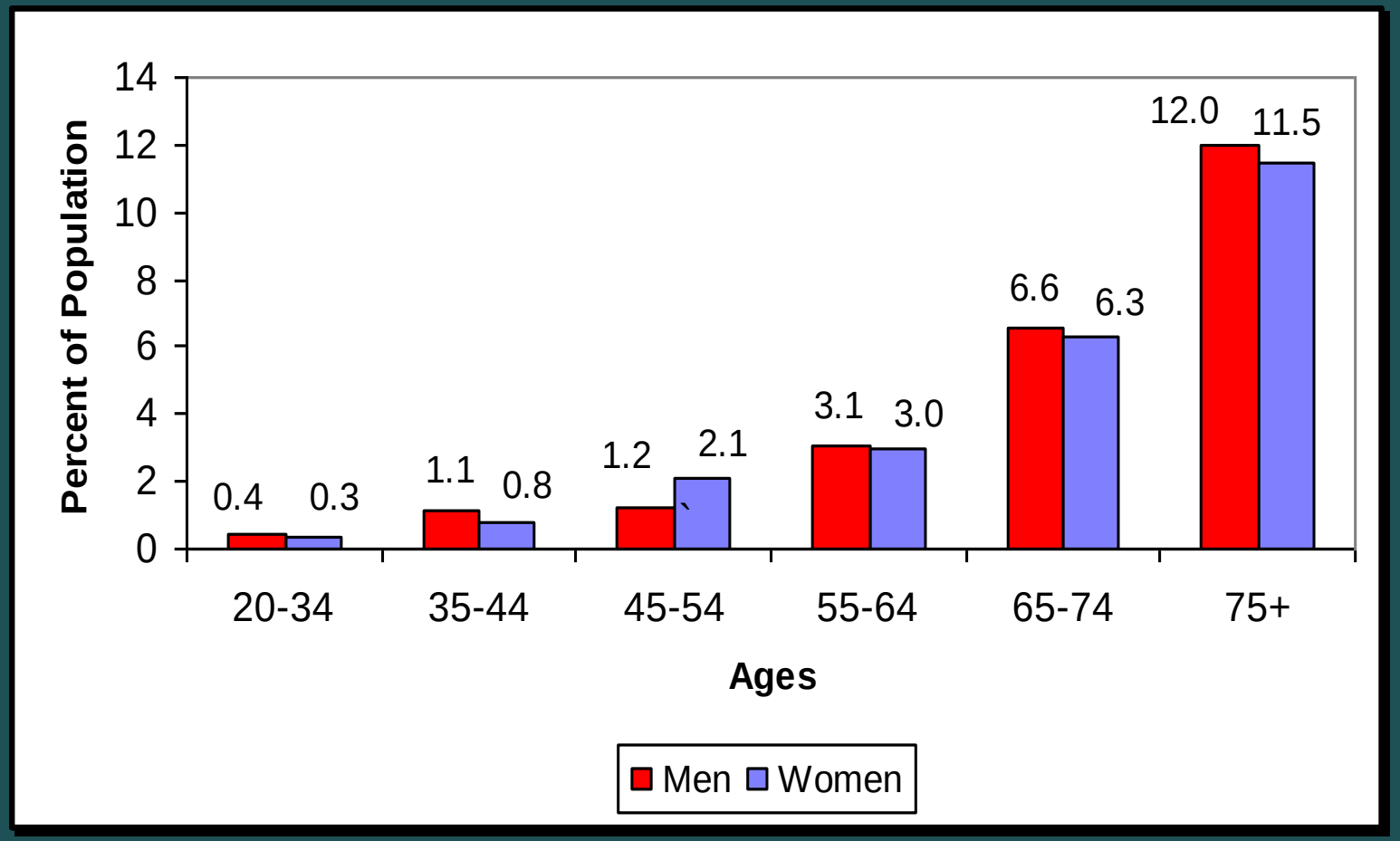
TIME=BRAIN

Epidemiology

- In Italy stroke is the third cause of death
- It is the first cause of invalidity
- 200.000 new strokes/year
- 1 million stroke patients

FACT: Prevalence of stroke in the US is 5.7 million people
15-30% of stroke victims are permanently disabled.

Prevalence of Stroke by Age and Sex



Source: CDC/NCHS and NHLBI.

What are the risk factors for ischemic stroke?

Risk Factors for Ischemic Stroke

Risks that cannot change

- Age
- Gender
- Heredity/Ethnicity
- Some mutations:

(**CBS MELAS Ehlers-Danlos Marfan CADASIL Amyloid Angiopathy-APP)**

Risks that can be controlled or treated

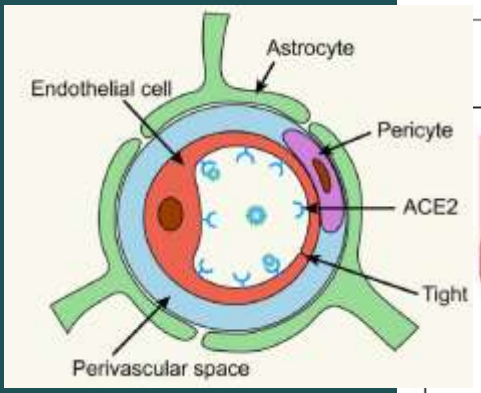
- High Blood Pressure
- Smoking
- Diabetes Mellitus
- Prior TIA
- Atrial Fibrillation
- Other Heart Disease
- Carotid Artery Disease or atherosclerosis in another arterial bed
- Certain blood disorders
- Sickle Cell Disease
- Hypercholesteremia
- Hyperhomocysteinemia
- Physical Inactivity, Obesity
- Excessive alcohol
- Illicit drugs
- Infections

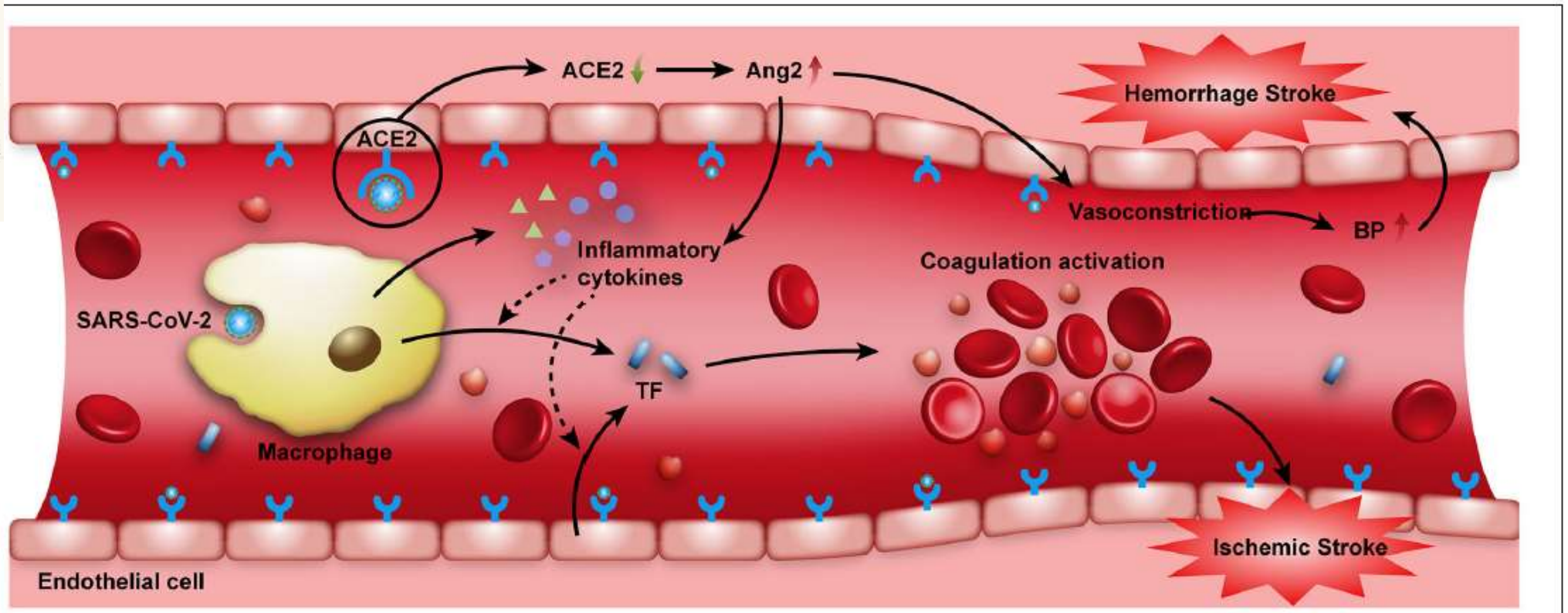
frontiers in Neurology

REVIEW
published: 27 October 2020
doi: 10.3389/fneur.2020.571996

COVID-19 Associated Ischemic Stroke and Hemorrhagic Stroke: Incidence, Potential Pathological Mechanism, and Management

Zilan Wang[1†], Yanbo Yang[1†], Xiaolong Liang[2], Bixi Gao[1], Meirong Liu[3], Wen Li[4],





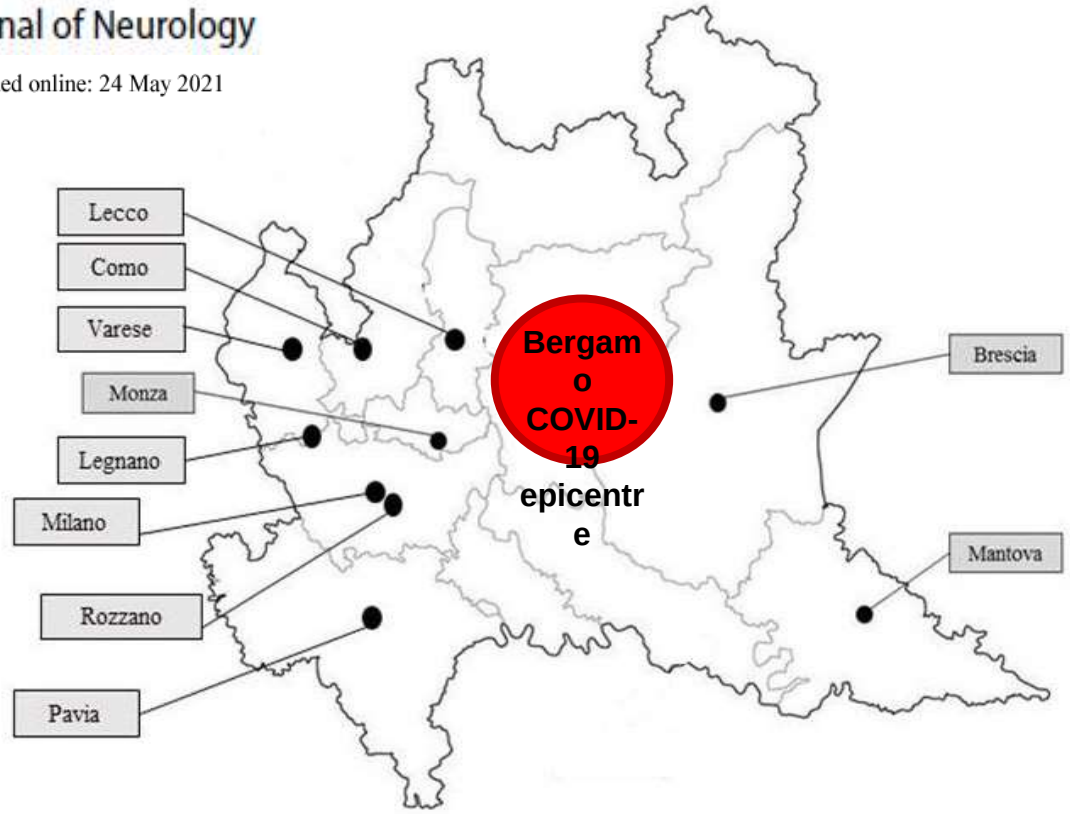
SARS-CoV-2 infection and acute ischemic stroke in Lombardy, Italy

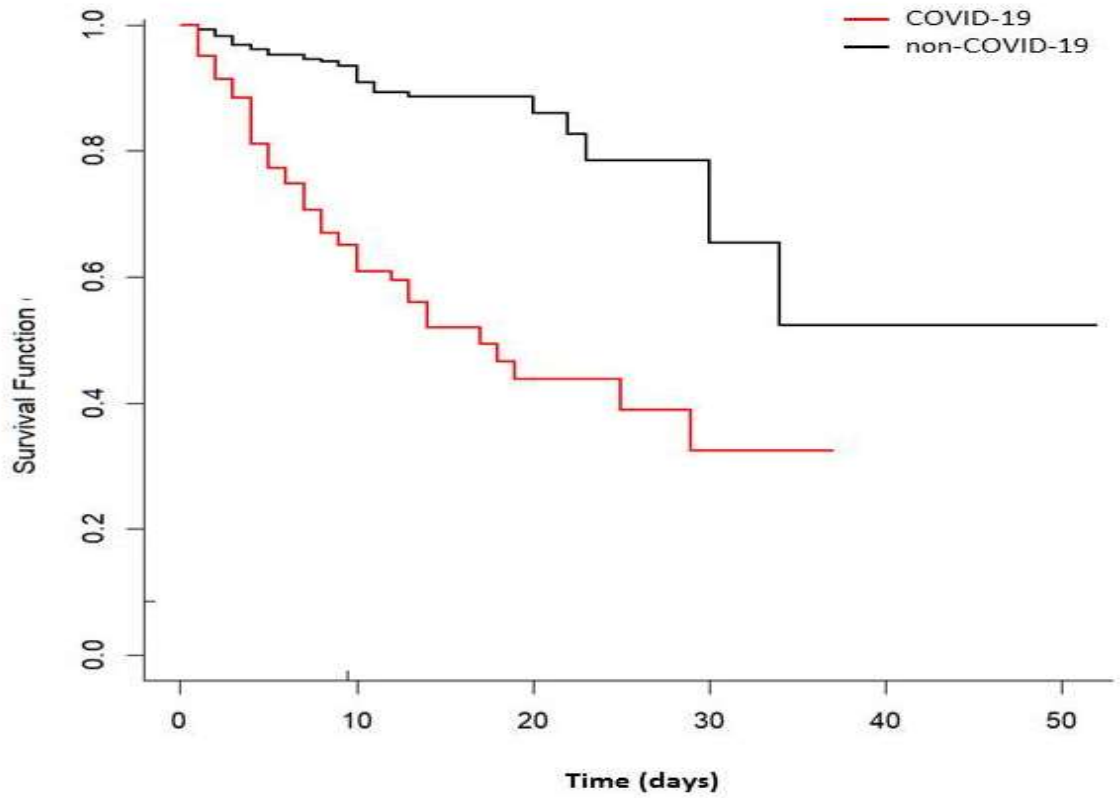
Alessandro Pezzini[1] · Mario Grassi[2] · Giorgio Silvestrelli[3] · Martina Locatelli[1,4] · Nicola Rifino[5,6] · Simone Beretta[5,6] · Massimo Gamba[7] · Elisa Raimondi[8] · Giuditta Giussani[9] · Federico Carimati[10] · Davide Sangalli[11] · Manuel Corato[12] · Simonetta Gerevini[13] · Stefano Masciocchi[1] · Matteo Cortinovis[1] · Sara La Gioia[14] · Francesca Barbieri[3] · Valentina Mazzoleni[1] · Debora Pezzini[1] · Sonia Bonacina[1] · Andrea Pilotto[1] · Alberto Benussi[1] · Mauro Magoni[7] · Enrico Premi[7] · Alessandro Cesare Prelle[8] · Elio Clemente Agostoni[9] · Fernando Palluzzi[2] · Valeria De Giuli[4] · Anna Magherini[3] · Daria Valeria Roccatagliata[3] · Luisa Vinciguerra[4] · Valentina Puglisi[4] · Laura Fusi[15] · Susanna Diamanti[5,6] · Francesco Santangelo[5,6] · Rubjona Xhani[15] · Federico Pozzi[15] · Giampiero Grampa[15] · Maurizio Versino[10] · Andrea Salmaggi[11] · Simona Marcheselli[12] · Anna Cavallini[16] · Alessia Giossi[4] · Bruno Censori[4] · Carlo Ferrarese[5,6] · Alfonso Ciccone[3] · Maria Sessa[14] · Alessandro Padovani[1] on behalf of the STROKOVID group

Journal of Neurology

Published online: 24 May 2021

- Sudio retrospettivo-prospettico di pazienti consecutivi con **ictus ischemico acuto ammessi ai 10 Stroke Hubs** tra **8 Marzo e 30 Aprile 2020** (7 settimane)
- **1013 pazienti: 160 COVID - 863 non-COVID**





frontiers in Neurology

CASE REPORT
published: 10 February 2021
doi: 10.3389/fneur.2021.622130

Case Report: Concomitant Massive Cerebral Venous Thrombosis and Internal Iliac Vein Thrombosis Related to Paucisymptomatic COVID-19 Infection

Simone Beretta[1,2,3], Fulvio Da Re[1,2,3], Valentina Francioni[2], Paolo Remida[4], Benedetta Storti[2], Lorenzo Fumagalli[1], Maria Luisa Piatti[1], Patrizia Santoro[1], Diletta Cereda[1], Claudia Cutellè[2], Fiammetta Pirro[2], Danilo Antonio Montisano[2], Francesca Beretta[2], Francesco Pasini[2], Annalisa Cavallero[5], Ildebrando Appollonio[1,2,3] and Carlo Ferrarese[1,2,3]*

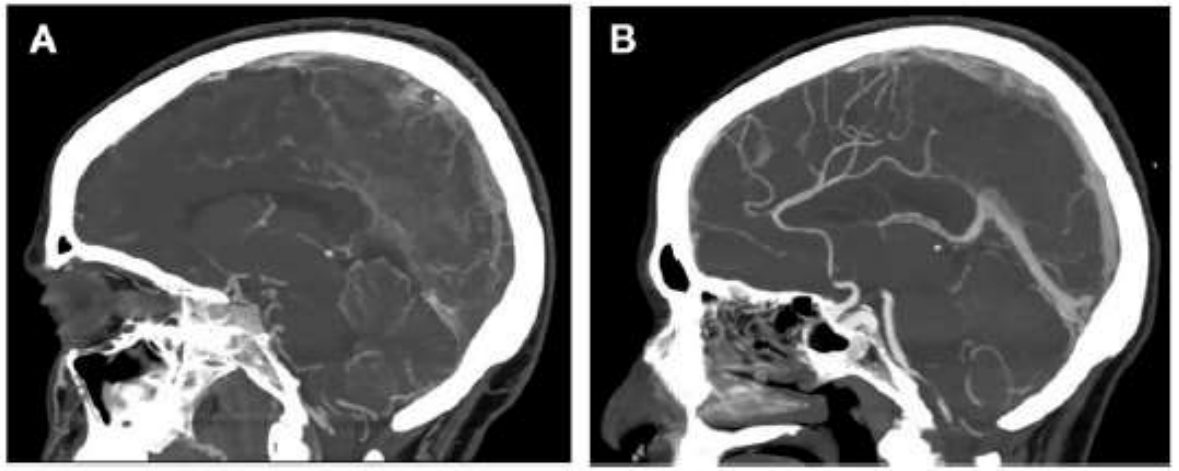
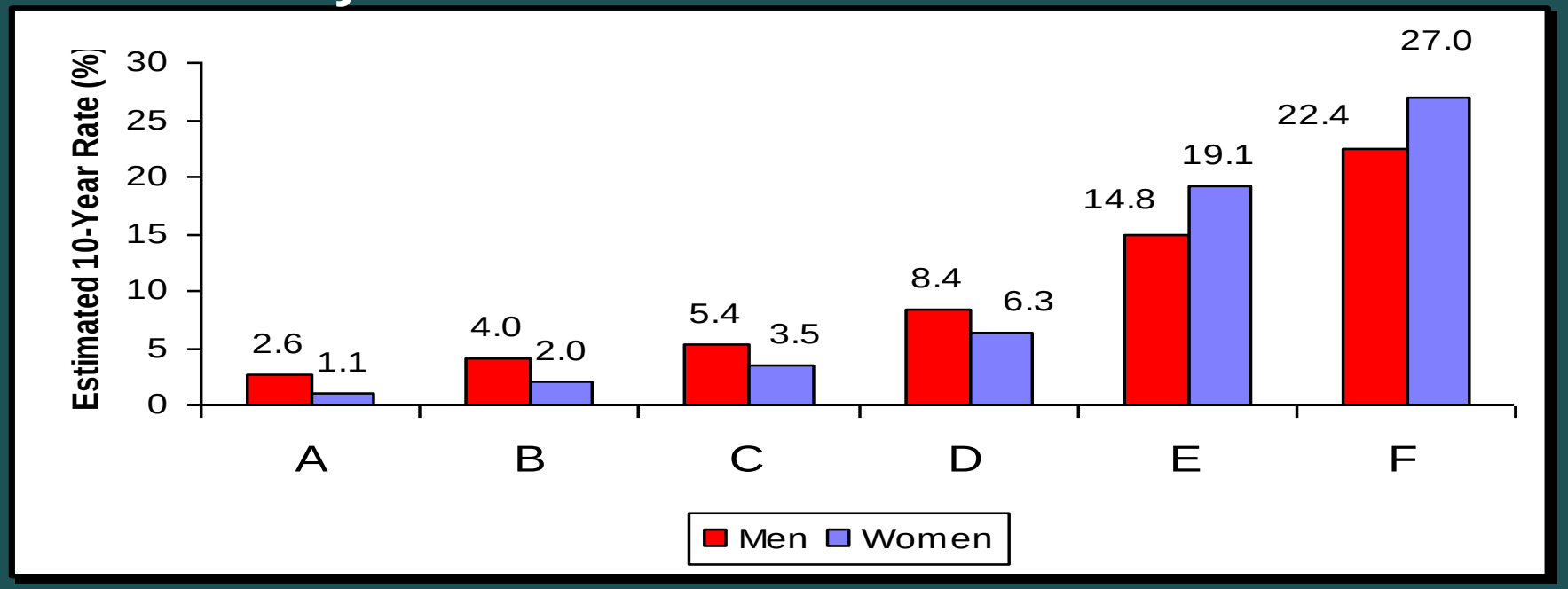


FIGURE 1 | CT cerebral venography showing massive cerebral venous thrombosis associated with COVID-19 infection. **(A)** At admission. **(B)** After 3 weeks of anticoagulation therapy.

Estimated 10-Year Stroke Risk in 55-Year-Old Adults According to Levels of Various Risk Factors - Framingham Heart Study



	A	B	C	D	E	F
Systolic BP	95-105	130-148	130-148	130-148	130-148	130-148
Diabetes	No	No	Yes	Yes	Yes	Yes
Cigarettes	No	No	No	Yes	Yes	Yes
Prior Atrial Fib.	No	No	No	No	Yes	Yes
Prior CVD	No	No	No	No	No	Yes

Source: Stroke 1991;22:312-318.

Estimates of Vascular Event Rates for Persons With Various Features of Atherothrombotic Cerebrovascular Disease

Cerebrovascular Features	Annual Probability(%) Stroke	Vascular Death
General elderly male population	0.6	-------
Asymptomatic carotid disease	1.3	3.4
Transient monocular blindness	2.2	3.5
Transient ischemic attack	3.7	2.3
Minor stroke	6.1	3.2
Major stroke	9.0	3.5
Symptomatic carotid stenosis >70%	15	2.0

Stroke. 1997;28:1507-1517.

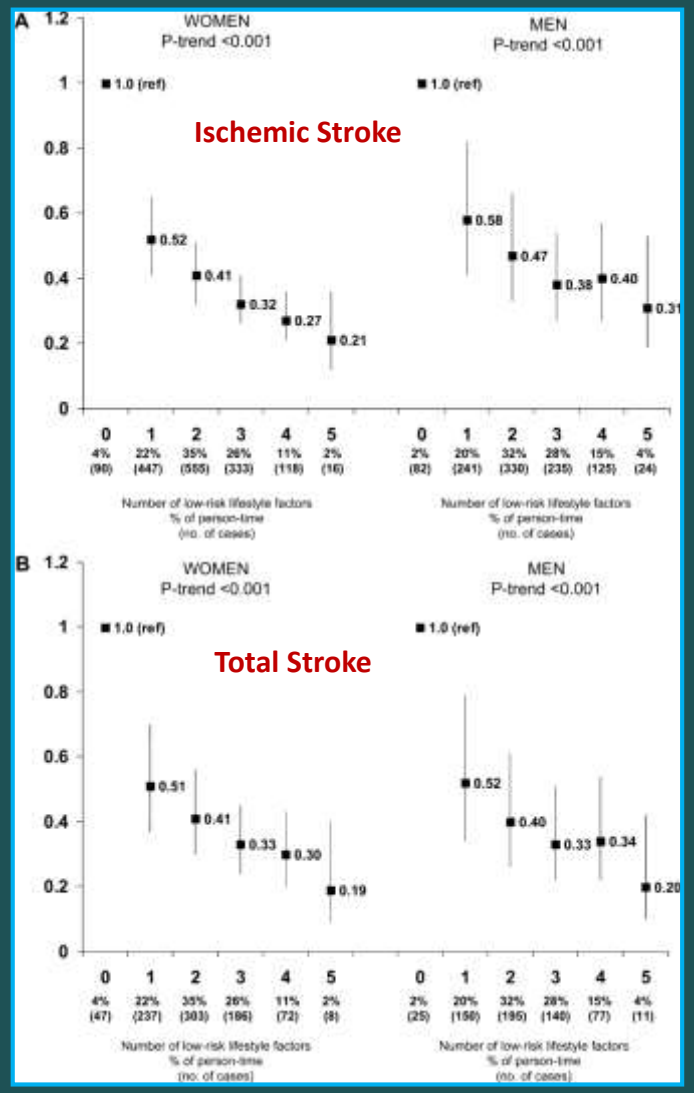
RF Control: Impact on Stroke Prevention

- >750,000 strokes annually in the US
- Preventable strokes
  - Hypertension 369,000
  - Hypercholesterolemia 150,000
  - Tobacco Use 91,500
  - Atrial Fibrillation 47,000
  - Heavy Alcohol Use 35,200

STROKE PREVENTION

A healthy lifestyle can reduce risk of stroke by up to 80%

Data from 43685 men from Health Professionals Follow-up Study and 71243 women from Nurses' Health Study



	Total Stroke	Ischemic Stroke
RR by all 5 low-risk factors (95% CI)*		
Women	0.21 (0.12–0.36)	0.19 (0.09–0.40)
Men	0.31 (0.19–0.53)	0.20 (0.10–0.42)

Definition of low risk lifestyle study factors

Smoking: not currently smoking
Physical activity: 30 min/d of moderate or vigorous activity
Diet: diet score in top 40% of each cohort distribution
Moderate alcohol consumption: at least 5 g/d with upper limit of 15 g/d for women and 30 g/d for men
Optimal weight: BMI < 25 kg/m2 during midlife

ONLY 2% OF THE SUBJECTS IN THE STUDY WERE AT LOW RISK FOR ALL 5 FACTORS

Chiuve et al. Circulation 2008; Gorelick et al. Circulation 2008

Stroke Mechanisms

ISCHEMIA

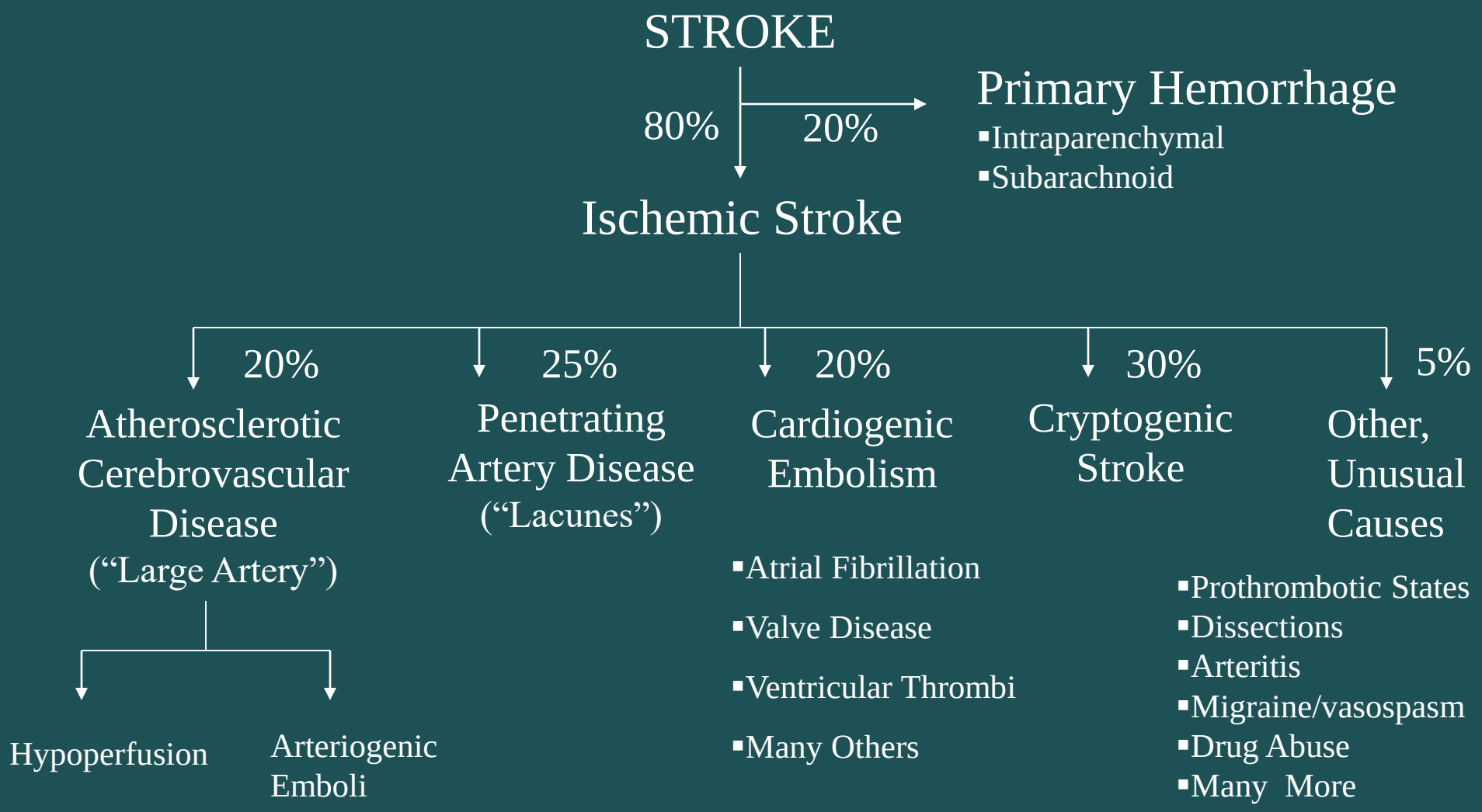
1. Thrombosis (60%)
2. Embolism (20%)
3. Decreased Systemic Perfusion

HEMORRHAGE

4. Intracerebral Hemorrhage (12%)
5. Subarachnoid Hemorrhage (8%)

Common Stroke Mechanisms

The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy



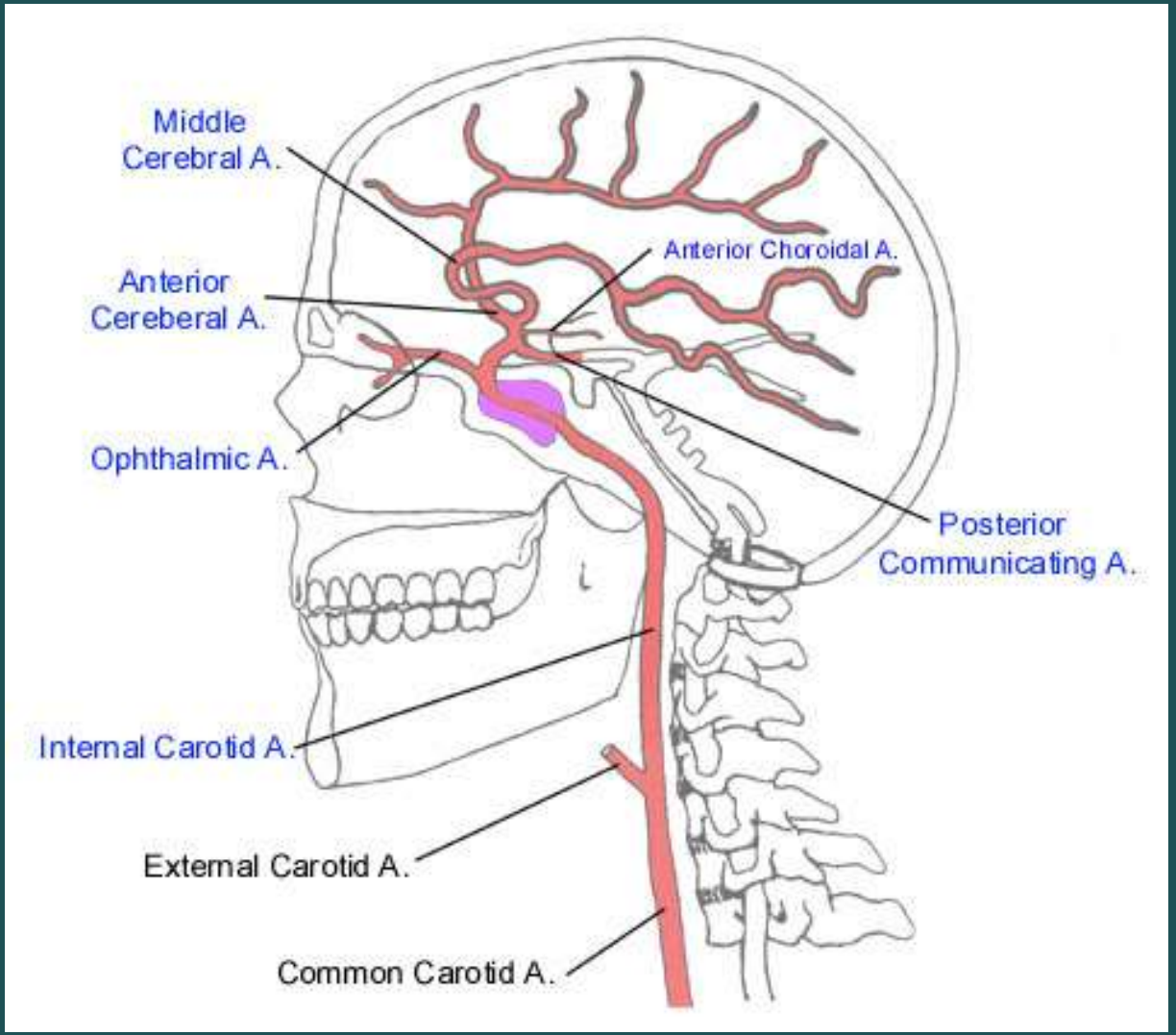
Goal of History and Physical Is to Localize Lesion and Its Vascular Supply

Knowing the location of the lesion and its vascular supply allow you to begin to speculate on the underlying pathophysiology as different stroke mechanisms characteristically affect certain cerebral vessels.

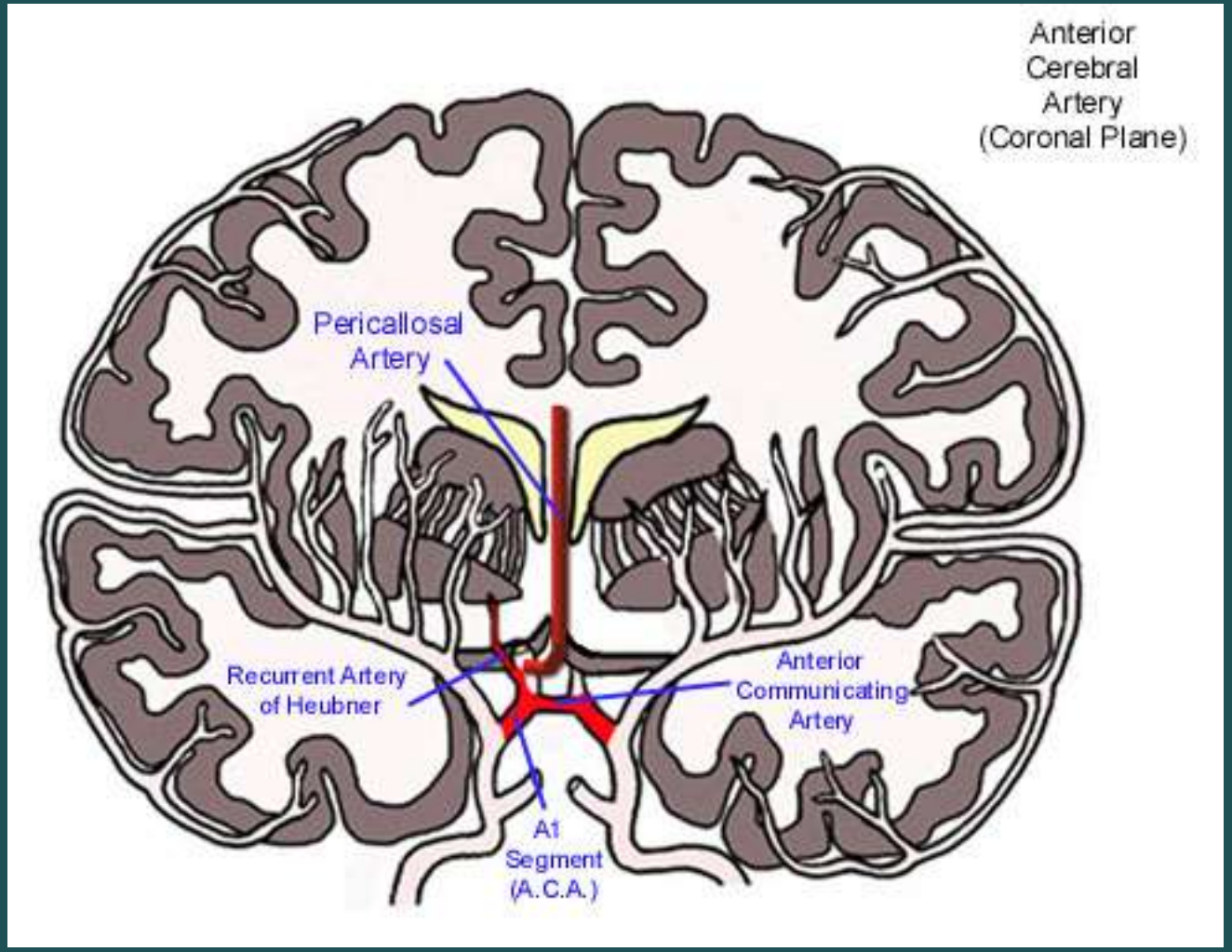
Blood Supply of the Brain

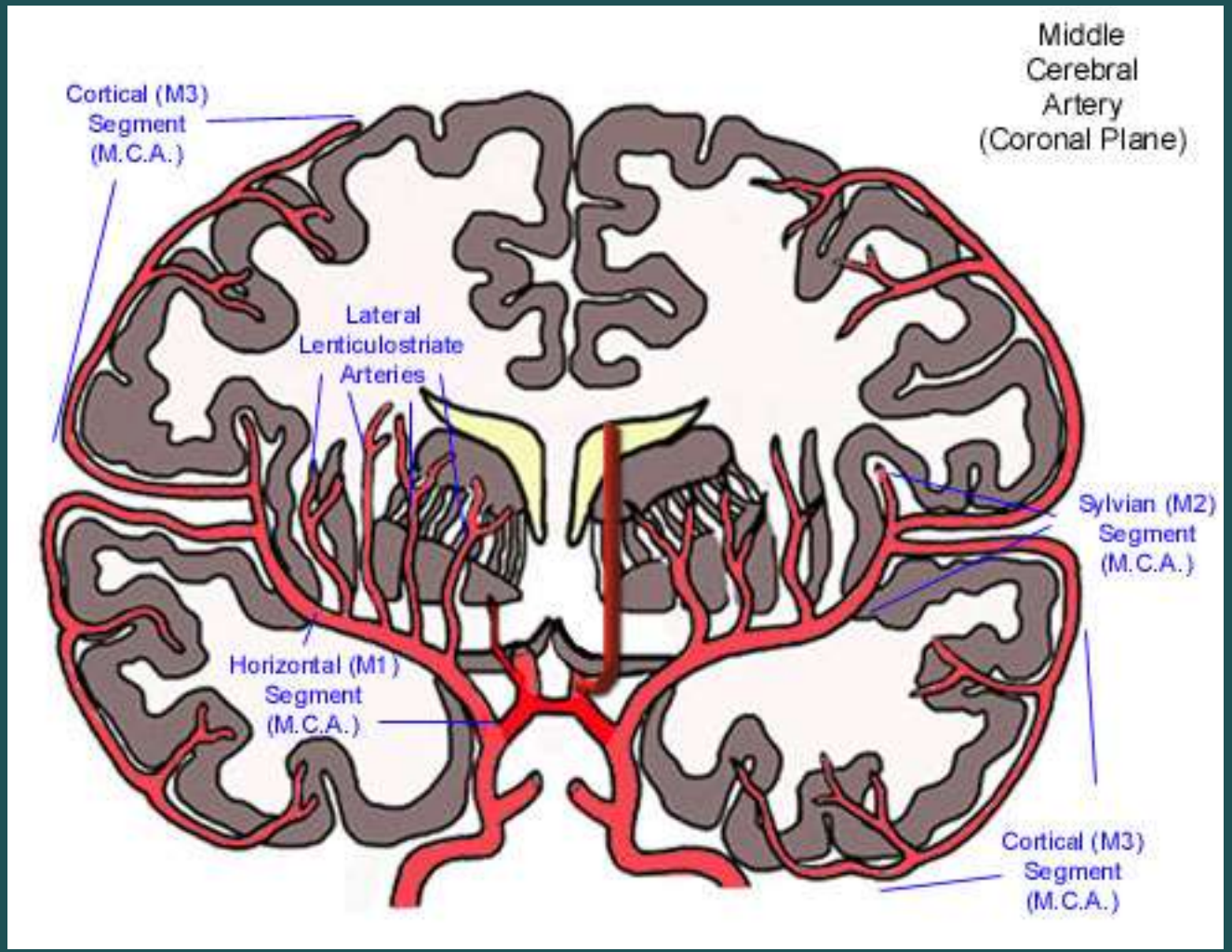
Anterior Circulation: Two ICAs which divide into ACA and MCA. Each ICA supplies roughly two fifths of the brain by volume.

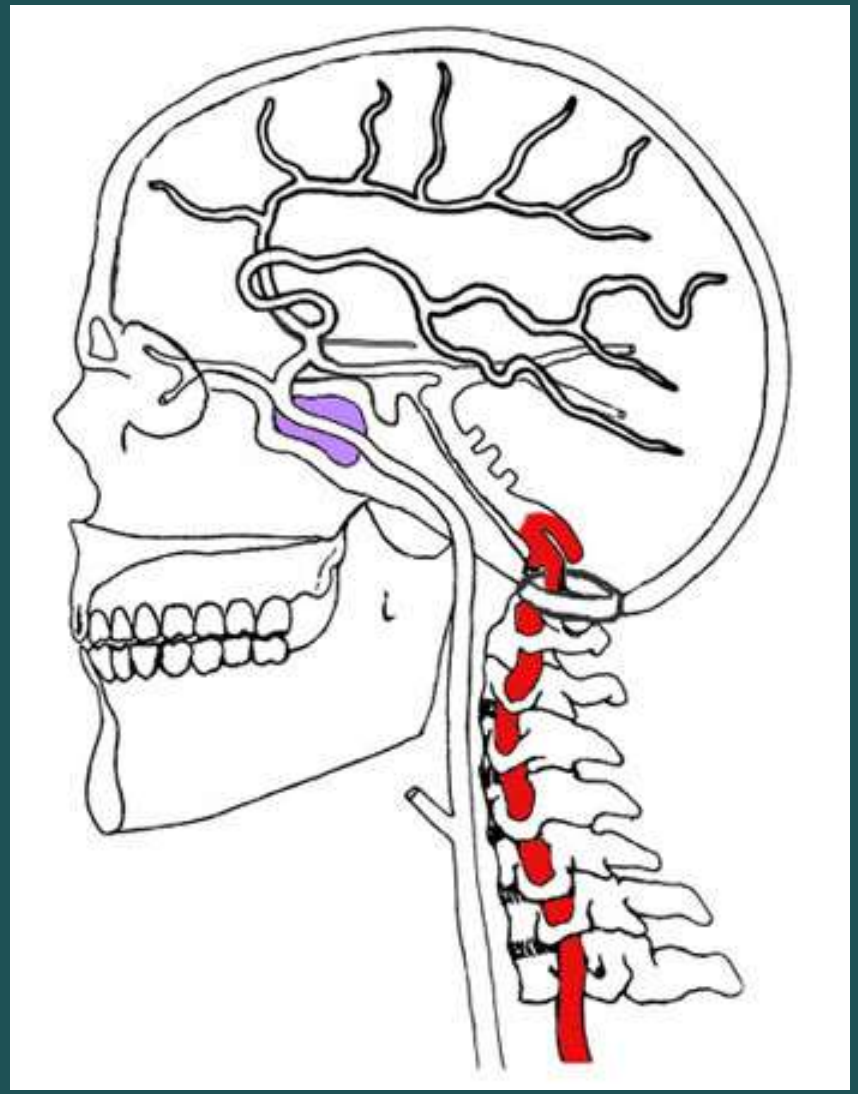
Posterior Circulation: Two Vertebrals which join to form the Basilar which then forms PCAs. The posterior circulation supplies roughly one fifth of the brain.



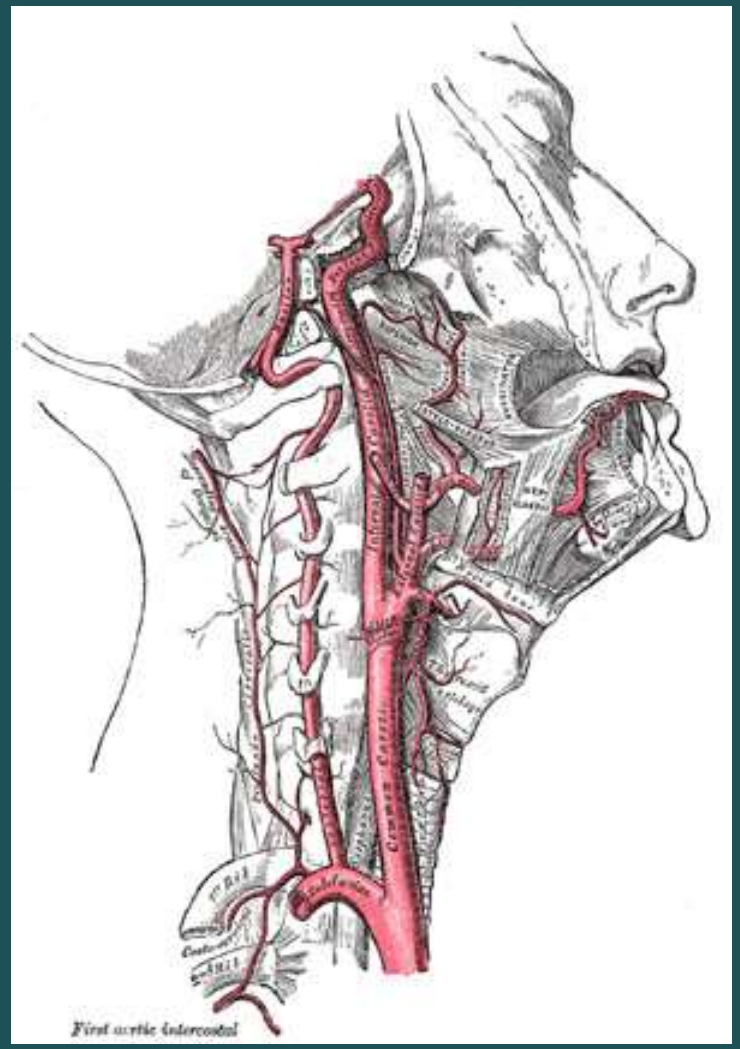
Source: Loyola University Neurovascular Tutorial

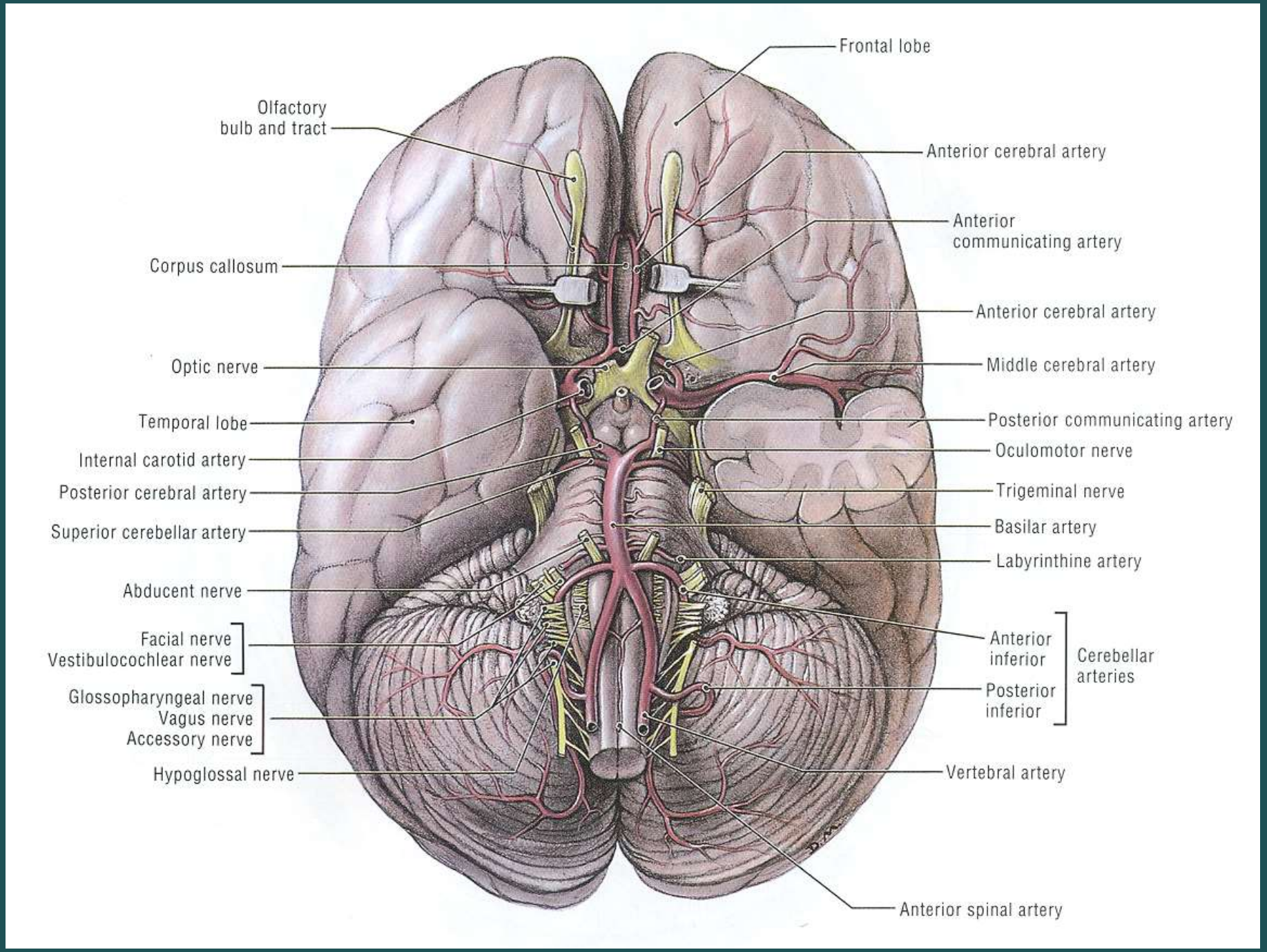

Anterior
Cerebral
Artery
(Coronal Plane)
Pericallosal
Artery
Recurrent Artery
of Heubner
Anterior
Communicating
Artery
A1
Segment
(A.C.A.)

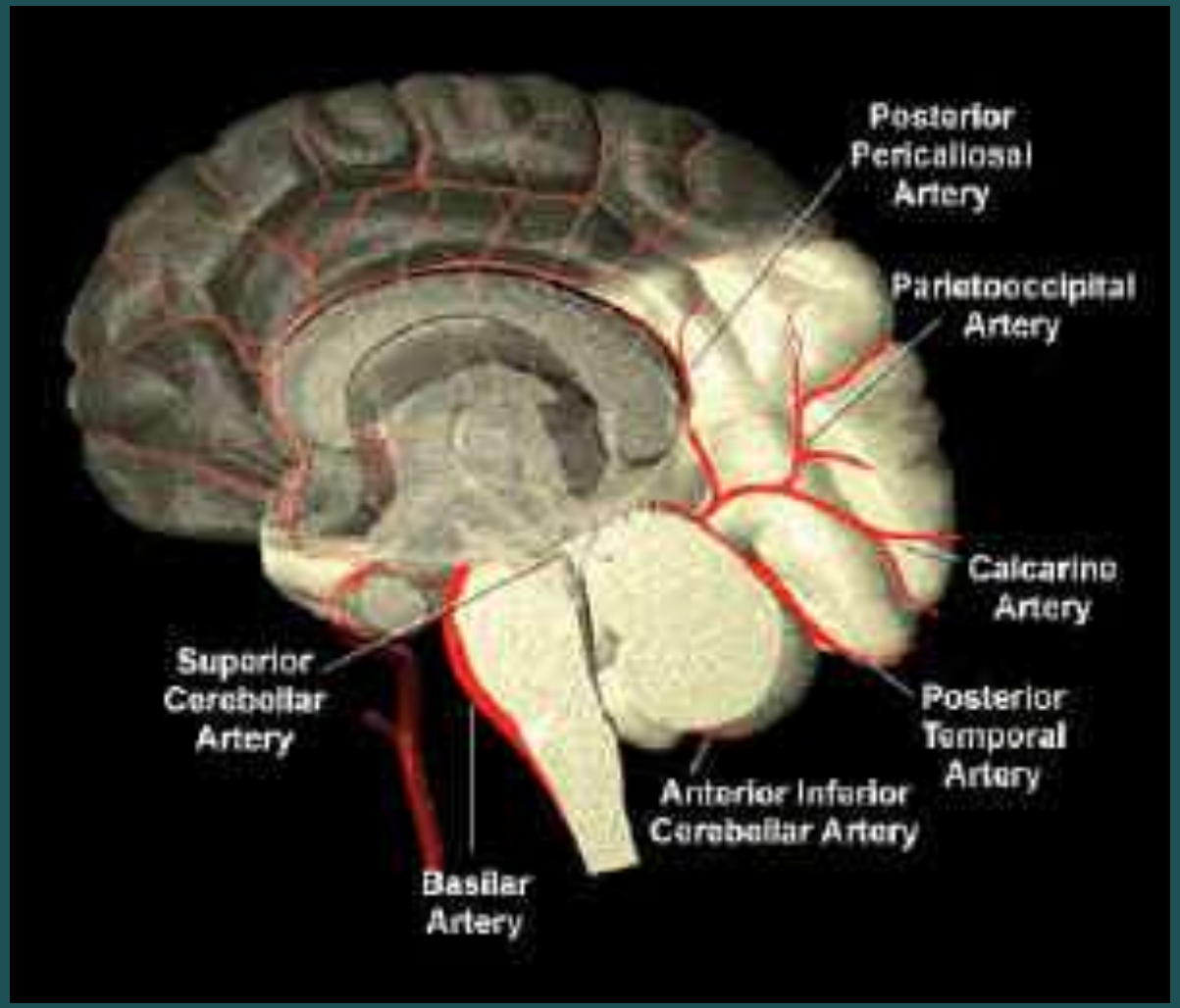

Middle Cerebral Artery (Coronal Plane)
Cortical (M3) Segment (M.C.A.)
Lateral Lenticulostriate Arteries
Sylvian (M2) Segment (M.C.A.)
Horizontal (M1) Segment (M.C.A.)
Cortical (M3) Segment (M.C.A.)



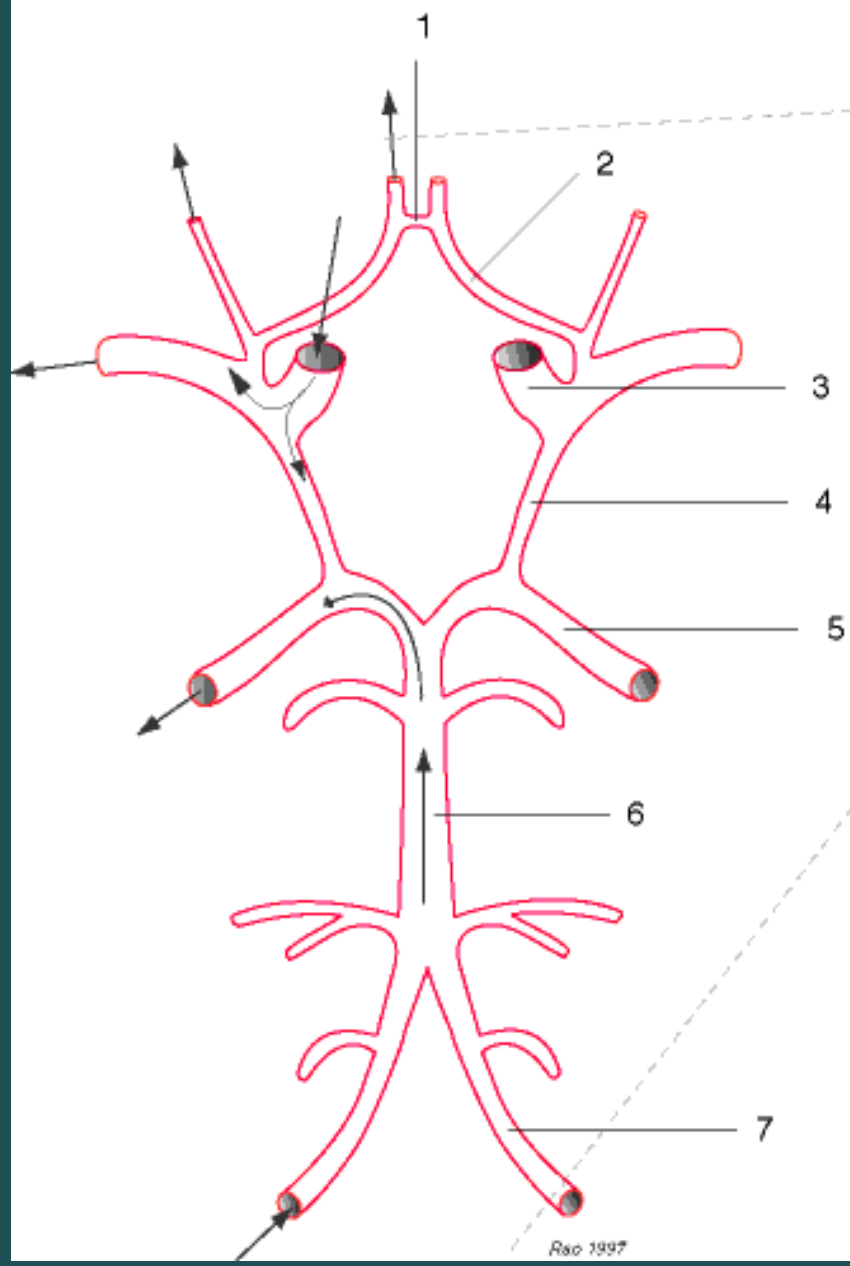
Four Divisions of the Vertebral Artery

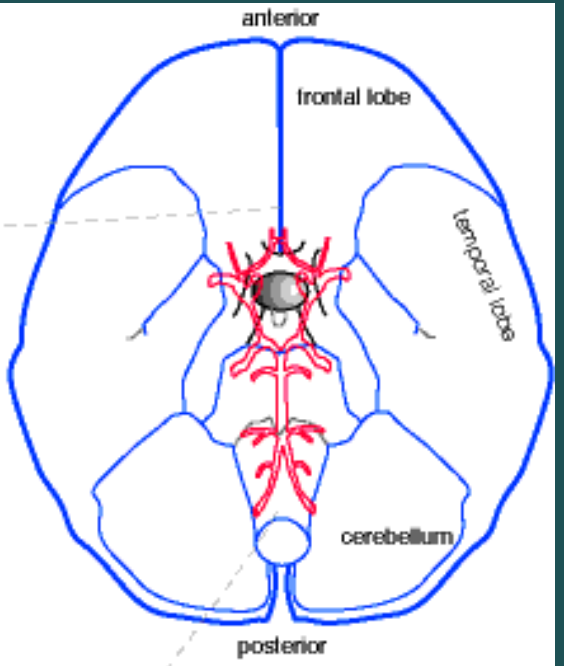



Frontal lobe
Olfactory bulb and tract
Anterior cerebral artery
Anterior communicating artery
Corpus callosum
Anterior cerebral artery
Optic nerve
Middle cerebral artery
Temporal lobe
Posterior communicating artery
Internal carotid artery
Oculomotor nerve
Posterior cerebral artery
Trigeminal nerve
Superior cerebellar artery
Basilar artery
Labyrinthine artery
Abducent nerve
Facial nerve
Vestibulocochlear nerve
Anterior inferior
Cerebellar arteries
Glossopharyngeal nerve
Vagus nerve
Accessory nerve
Posterior inferior
Hypoglossal nerve
Vertebral artery
Anterior spinal artery


Posterior
Pericallosal
Artery
Parietooccipital
Artery
Calcarine
Artery
Superior
Cerebellar
Artery
Posterior
Temporal
Artery
Anterior Inferior
Cerebellar Artery
Basilar
Artery

The Arterial Circle of Willis





Inferior view of the brain

Arteries of the Circle of Willis*

1. Anterior communicating*
2. Anterior cerebral*
3. Carotid
4. Posterior communicating*
5. Posterior cerebral*
6. Basilar
7. Vertebral

Most common sites of stenosis

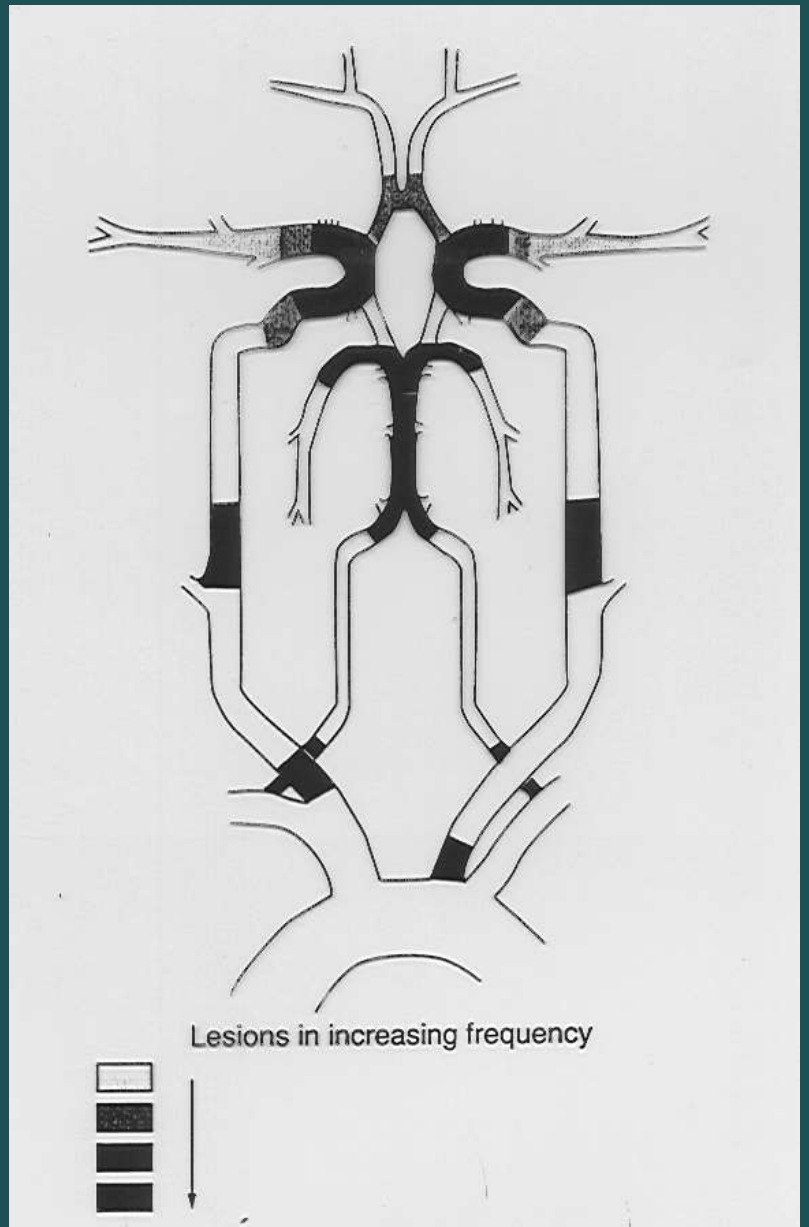


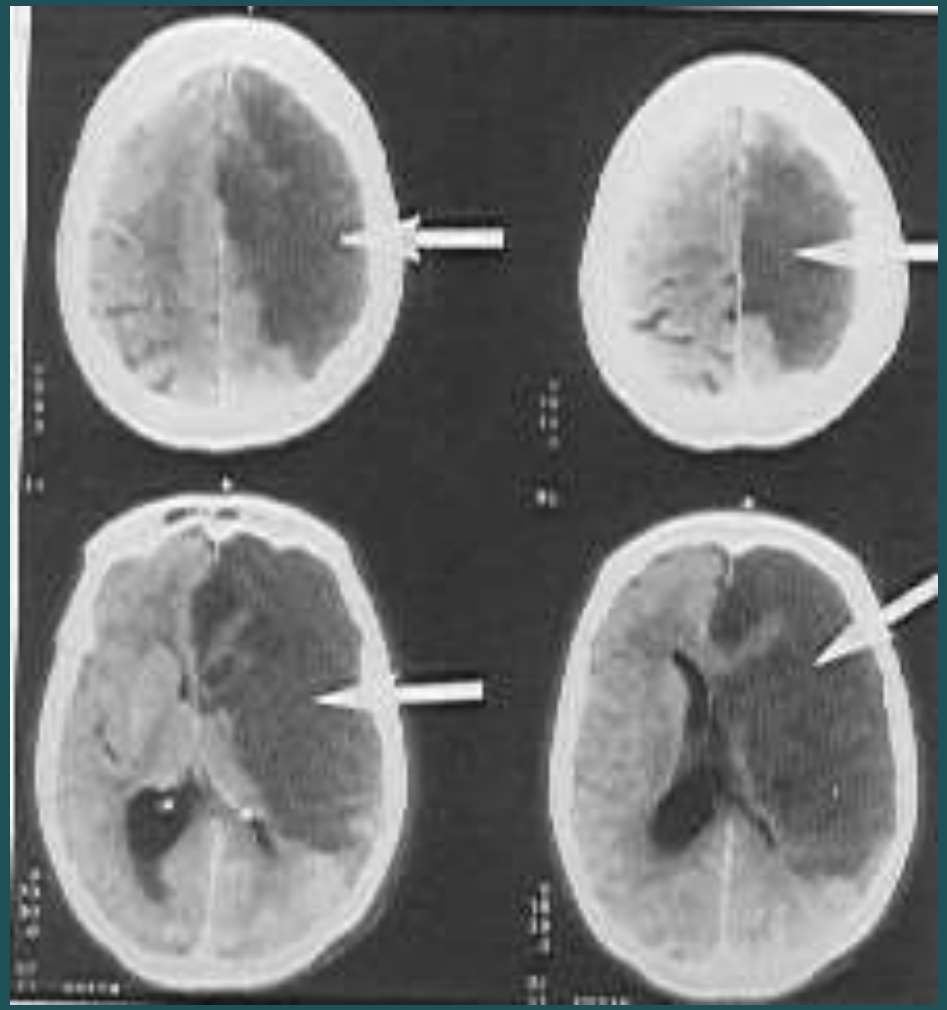
Figure 17.2 Distribution of lesions in the carotid territory.

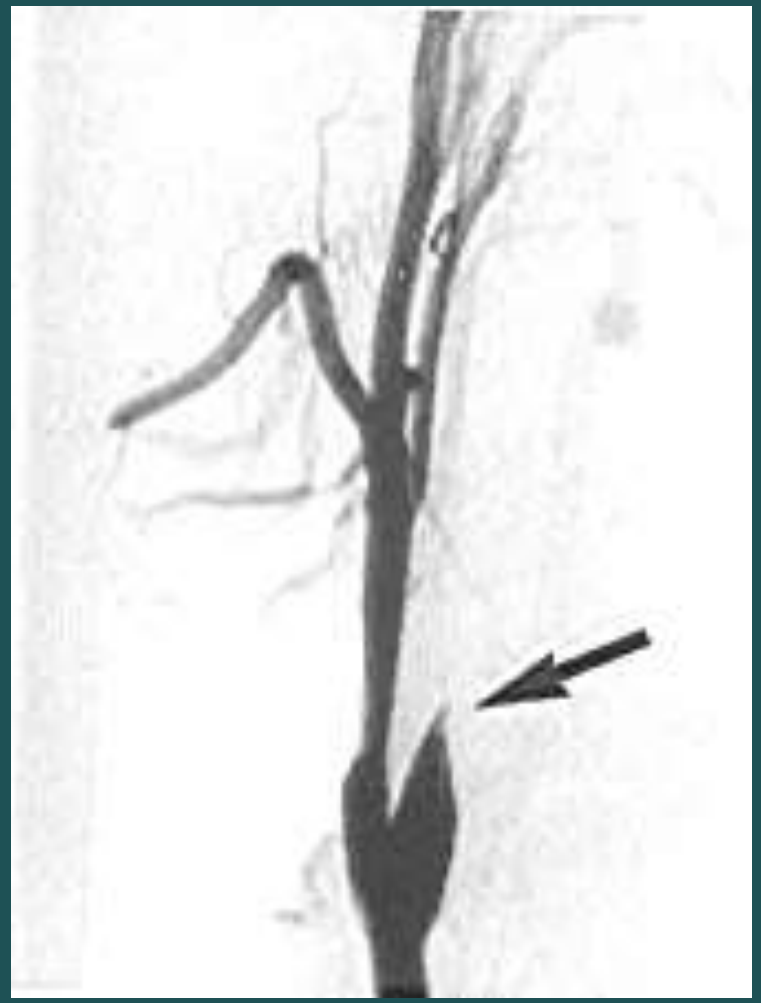
Lacunar Stroke

- Perforant branches of main arteries (MCA, ACA, PCA, Basilar)

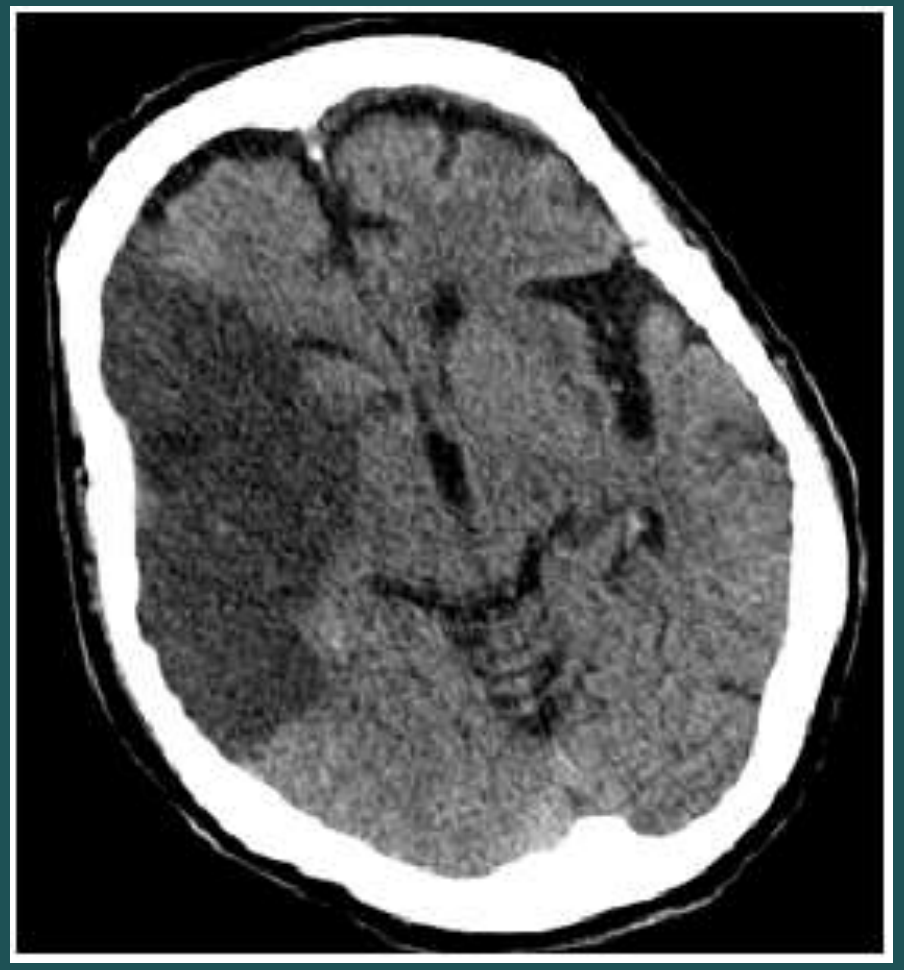
- Small lesions involving:
  - Basal ganglia
  - Thalamus
  - Internal capsule
  - Brainstem
  - Cerebellum

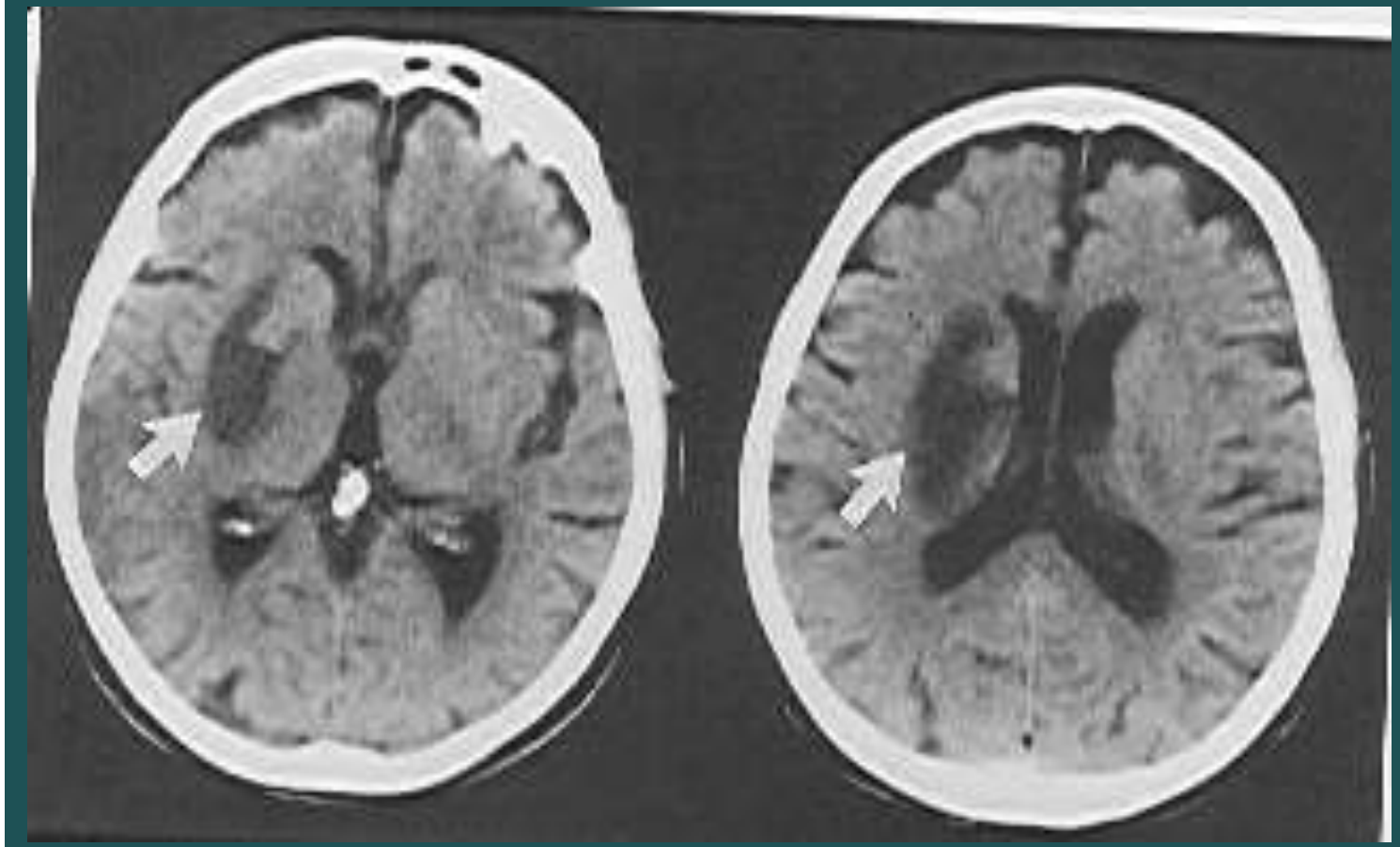
Stroke from sudden occlusion of internal carotid artery





Stroke from MCA occlusion



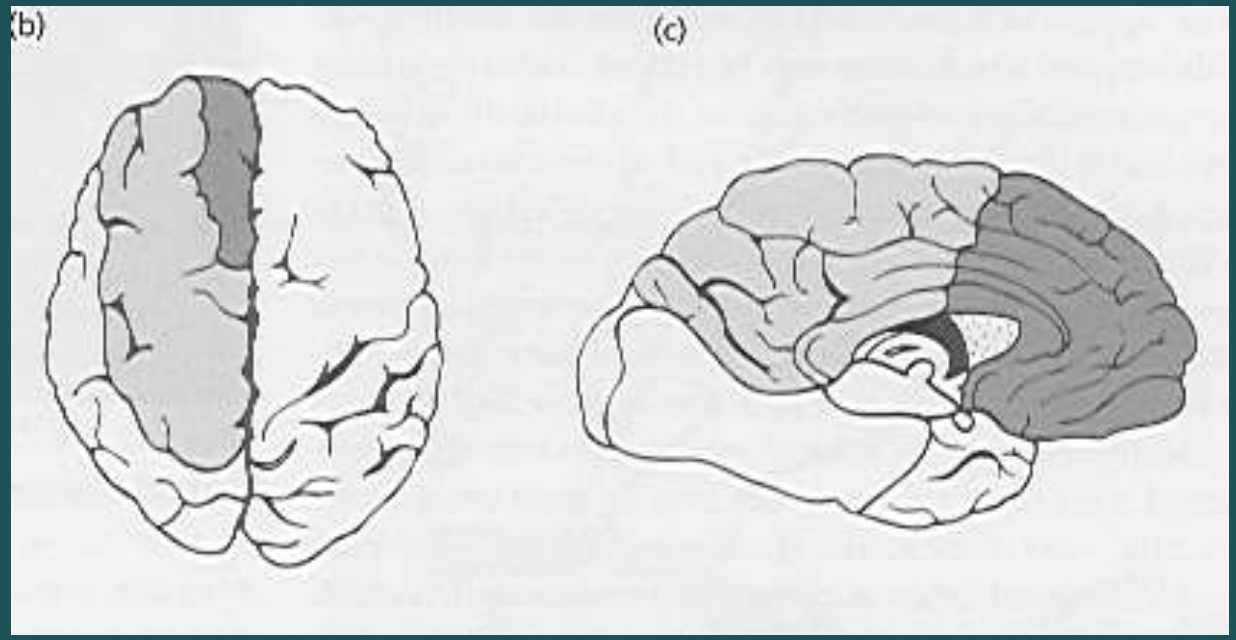


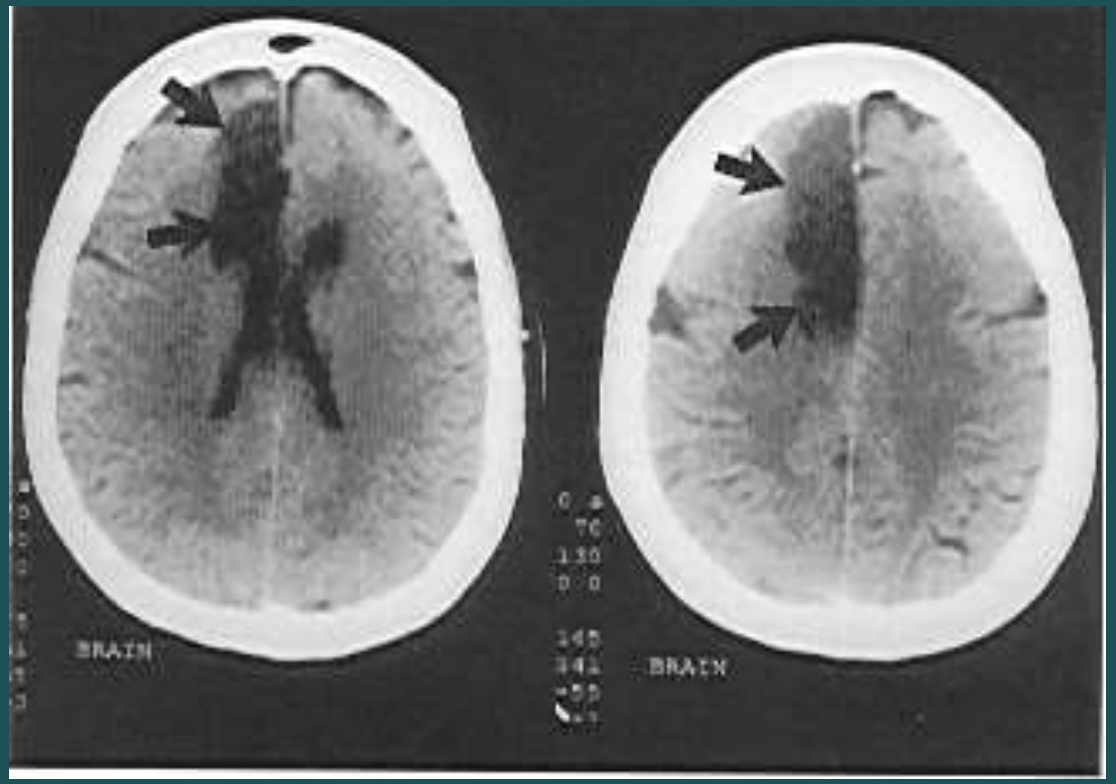
MCA occlusion: clinical features

- **Hemiplegia**
- **Hemianesthesia**
- **Hemianopsia**
- **Gaze paralysis**

Left	Right
Aphasia	Anosognosia
Gerstmann Syndrome:	Neglect
Acalculia-agraphia-digital agnosia	Emiasomatognosia
-confusion R/L	Apraxia

ACA Stroke





ACA Stroke: clinical features

- Controlateral leg and foot paresis
- Abulia
- Echolalia
- Urinary incontinence

Vertebrobasilar Stroke

basilar artery

Bilateral pons ischemia

Clinic:

- Tetraparesis
- Cranial nerve paralysis
- Coma
    - High mortality

Vertebrobasilar stroke – PICA: (Wallenberg syndrome)

Omolateral signs:

- Facial pain
- Ipoesthesia
- Reduced corneal reflex
- Horner S.
- Disphagia
- Cerebellar signs

Controlateral signs:

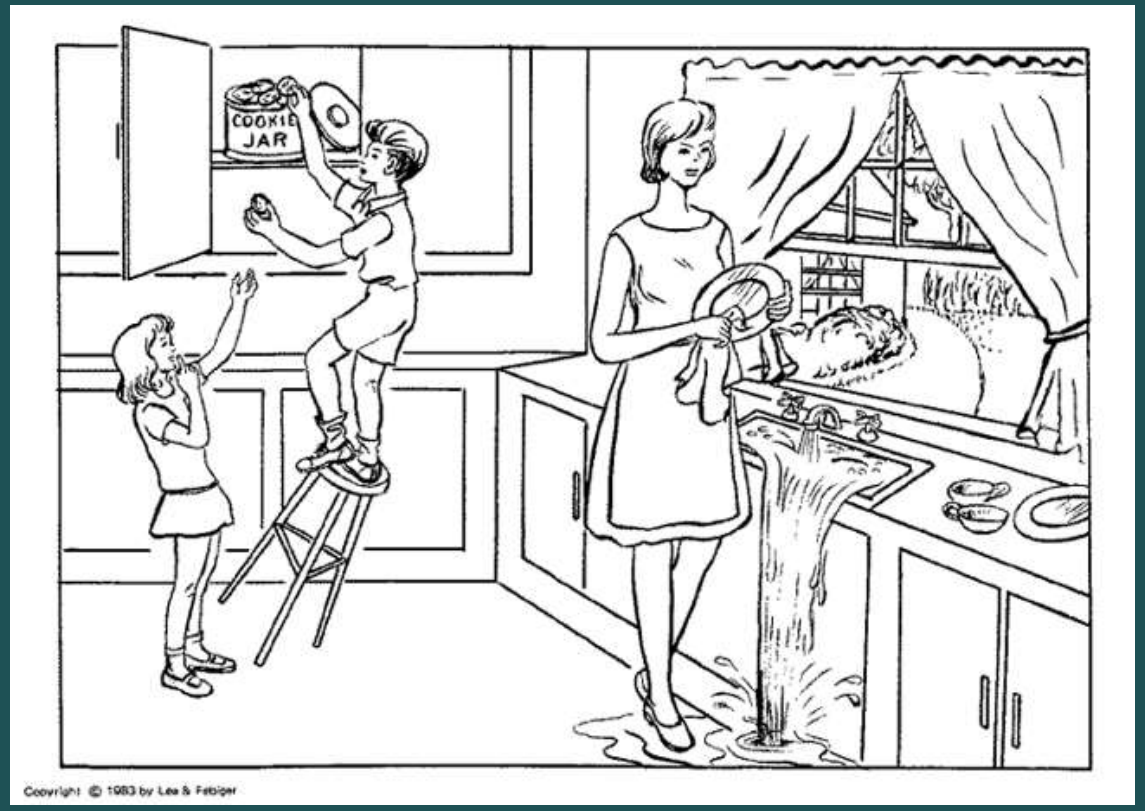
- Hypoesthesia of trunk and limbs

General symptoms:

- Vertigo, nausea, vomiting
- Nistagmus, ataxia

PCA stroke

- Controlateral hemianopsia
- Alexia
- Optic ataxia
- Simultaneoagnosia



What Else Could It Be?

Stroke Mimics

- Abcess
- Subdural and Epidural Hematomas
- Tumors
- Giant aneurysms
- Vascular malformations (AVMs)
- Hypertensive Encephalopathy
- Encephalitis/cerebritis
- Seizure/Todd's paralysis
- Migraine
- Metabolic-Hypoglycemia/Hyperglycemia
- Cerebral venous thrombosis
- Psychogenic
- Deficit from previous stroke made worse by general medical condition

What Will You Ask to patient or family?

- Exact time of onset or last time the patient was last seen at baseline
- History of seizures? Any seizure activity prior to onset of symptoms
- Migraine headaches
- Trauma or neck injury in the preceding days
- Recent illnesses
- Vomiting, change in level of consciousness
- Allergies
- Medications
- Associated symptoms (?chest pain)

What to Do on Exam?

- Vital Signs: especially notice BP
- Cardiac, vascular, extremity examination
- Directed and focused neurologic exam based on history - NIHSS

NIH Stroke Scale – focuses on 5 major areas

- Level of consciousness
- Visual function
- Motor function
- Sensation and neglect
- Cerebellar function

NIHSS is easily performed, reliable and valid. It is strongly associated with outcome with and without thrombolytics, and can predict those patients likely to develop hemorrhagic complications from thrombolytic use.

What Else to Ask

ALL stroke patients should get immediate

- CBC with platelets
- Bedside glucose
- PTT, PT (INR)
- Chem
- EKG, continuous cardiac monitoring
- IV access, 0.9% NS (no glucose)
- Troponin
- CXR

What's the Cardiac Workup for?

- Not infrequently, patients with acute cerebral ischemia have concomitant acute myocardial ischemia

- In addition cardiac evaluation helps determine etiology of the cerebral event

- Several small studies have shown that patients with TIA and stroke have a high prevalence of asymptomatic CD. These studies suggest that 20% to 40% of stroke patients may have abnormal tests for silent cardiac ischemia.

- 2% to 5% of patients with acute ischemic stroke have fatal cardiac-related events in the short term after stroke.

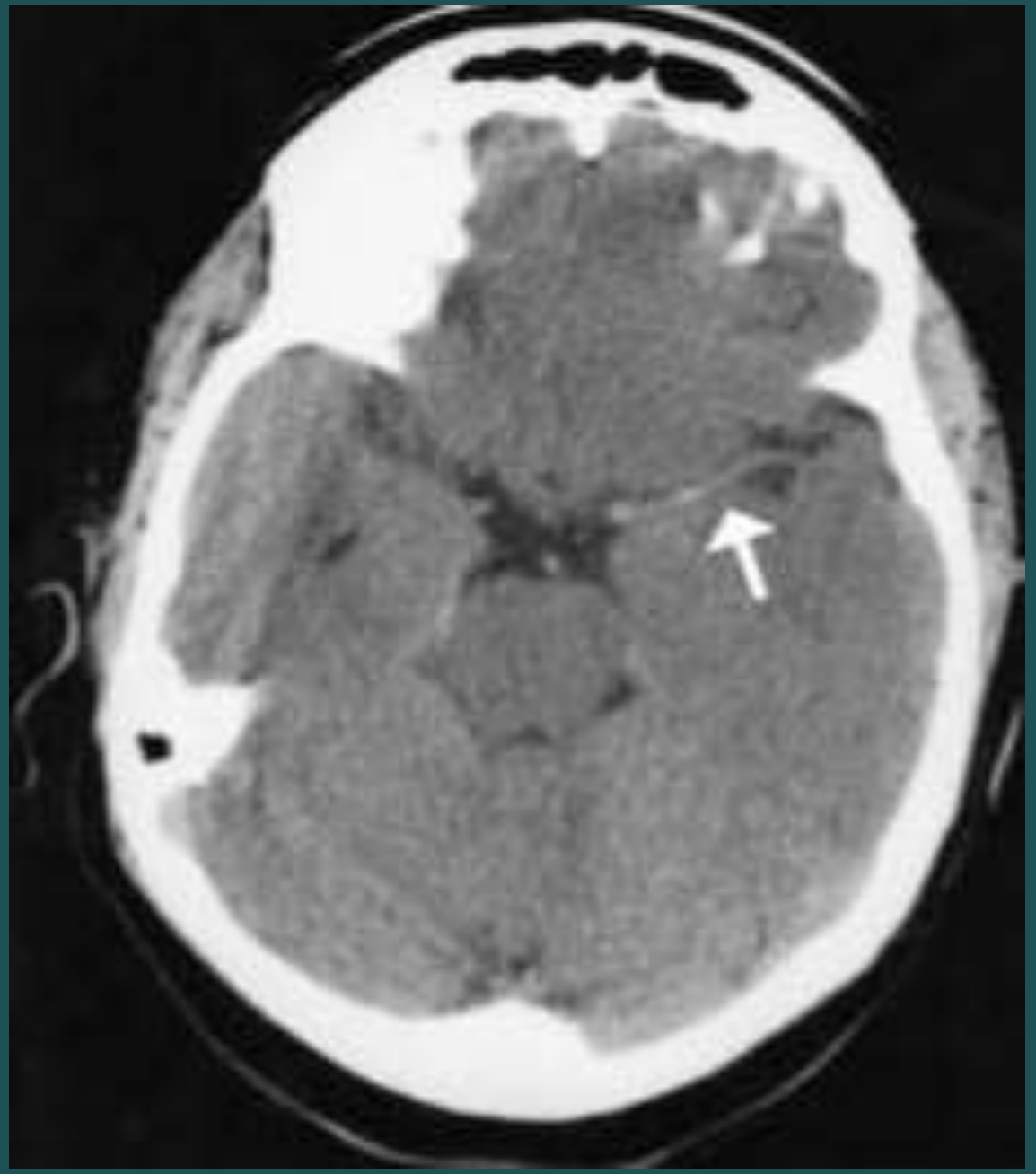
Circulation. 2003;108:1278.

Quickly Narrow the Differential With Imaging

When presented with acute onset neurological dysfunction, stroke should always be on your differential and one of the first goals in the evaluation is:
differentiating hemorrhagic stroke from ischemic stroke

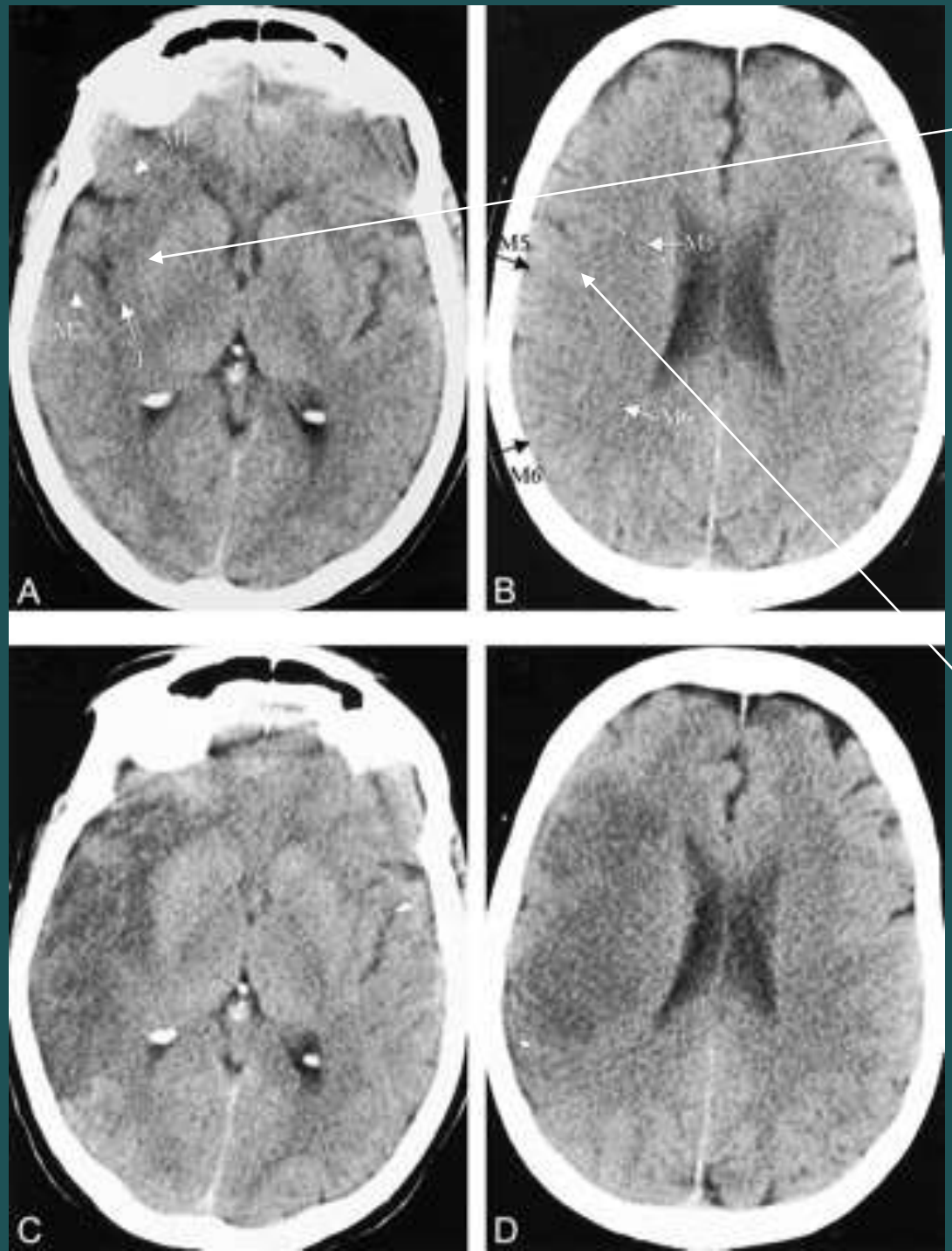
All patients, with few exceptions should undergo STAT cranial imaging. In other words:
GET A NON-CONTRAST HEAD CT (MRI if available STAT).

Normal CT: exclusion of hemorrage



Early signs:

Hyperdense MCA Sign



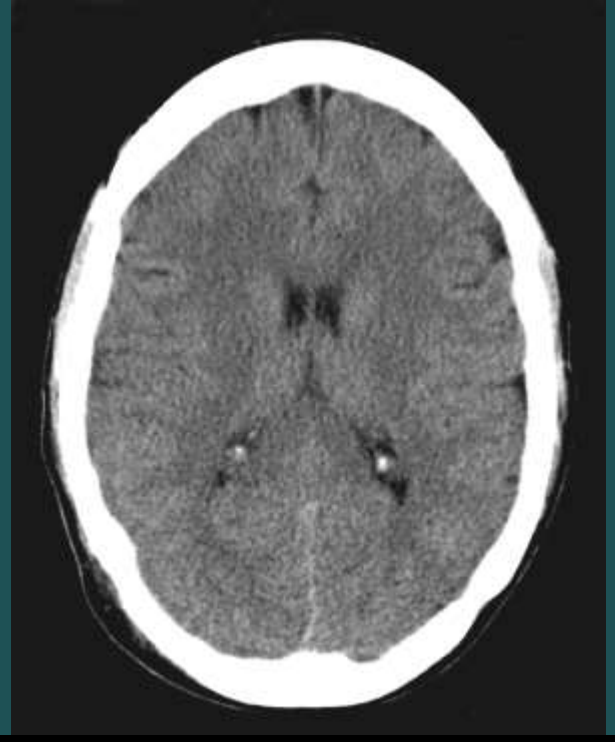
Insular Ribbon Sign

CT at 6 hrs

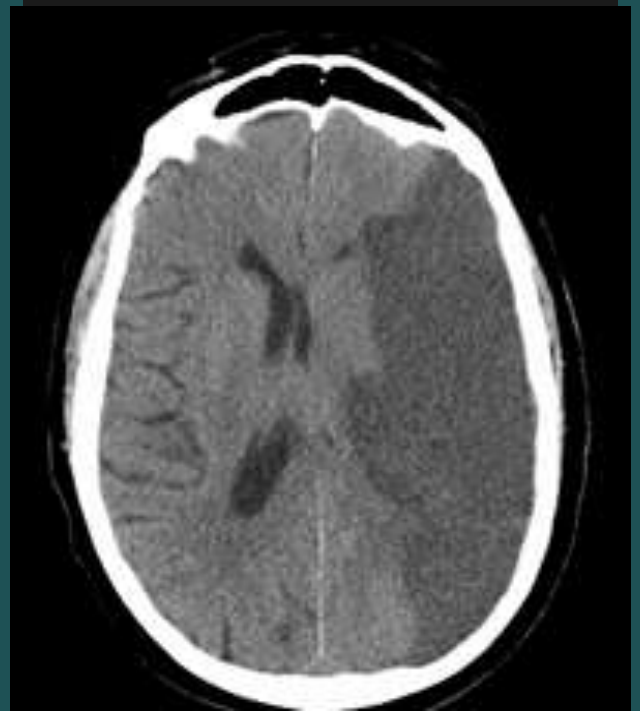
Loss of Gray-White Junction

CT at 48 hrs

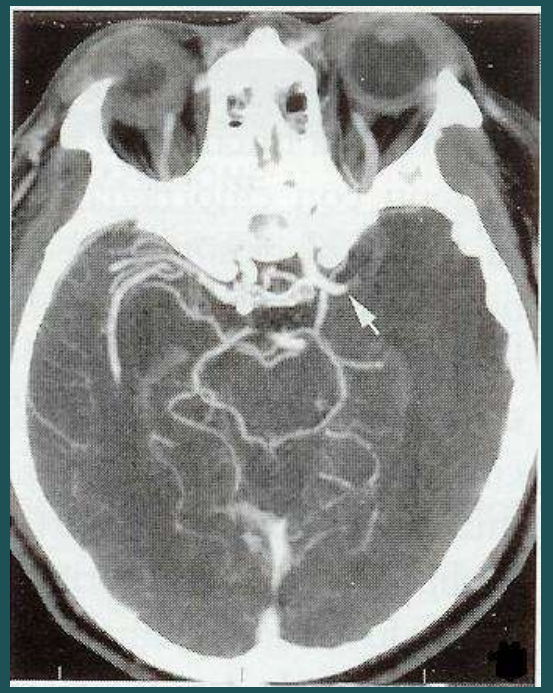
CT at 6 hrs

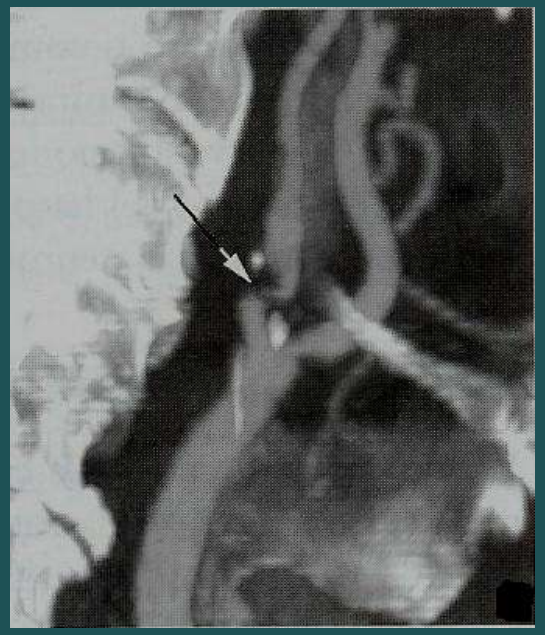


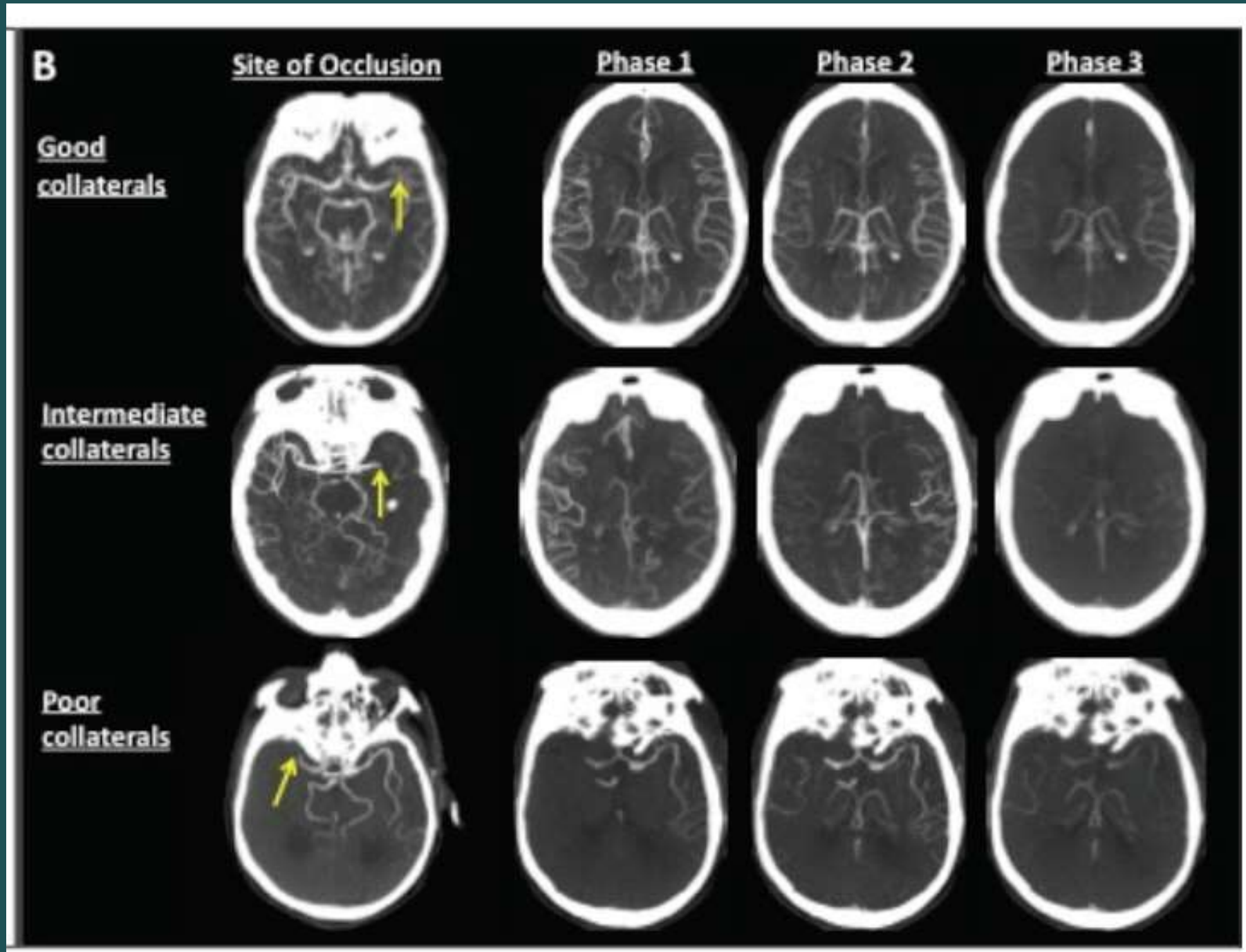
CT at 48 hrs



Angio-CT

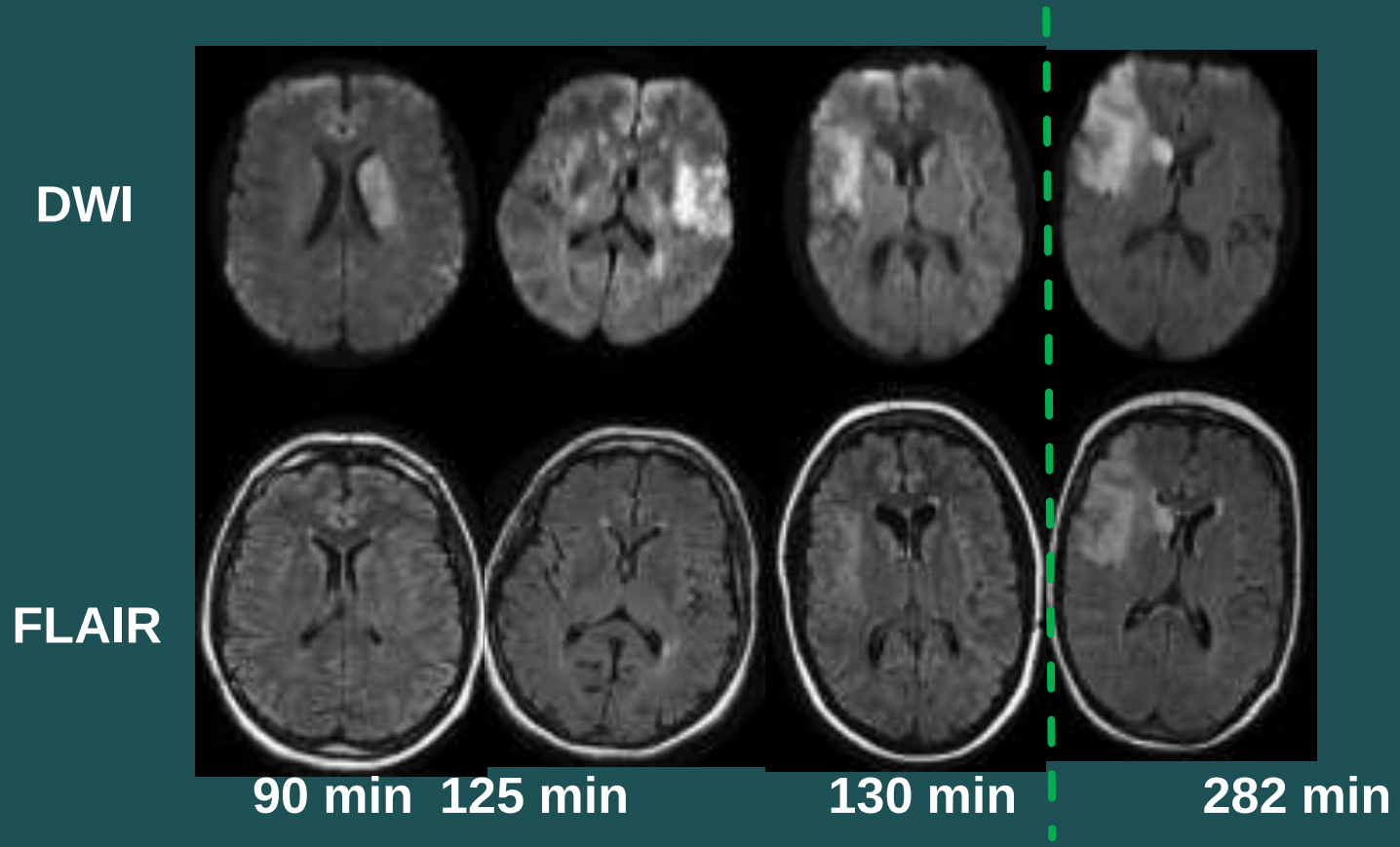




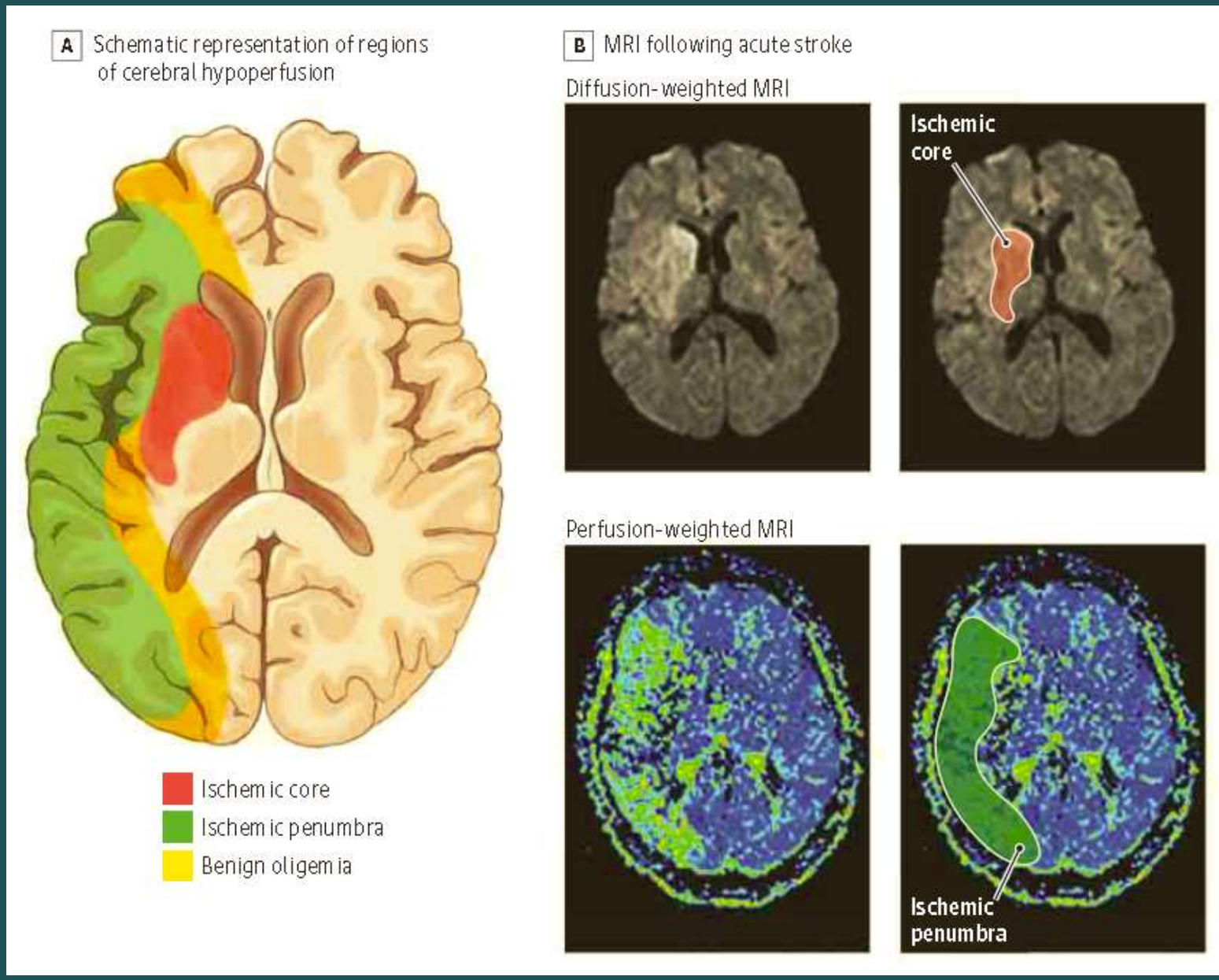

B
Site of Occlusion
Phase 1
Phase 2
Phase 3
Good collaterals
Intermediate collaterals
Poor collaterals

MRI utility:

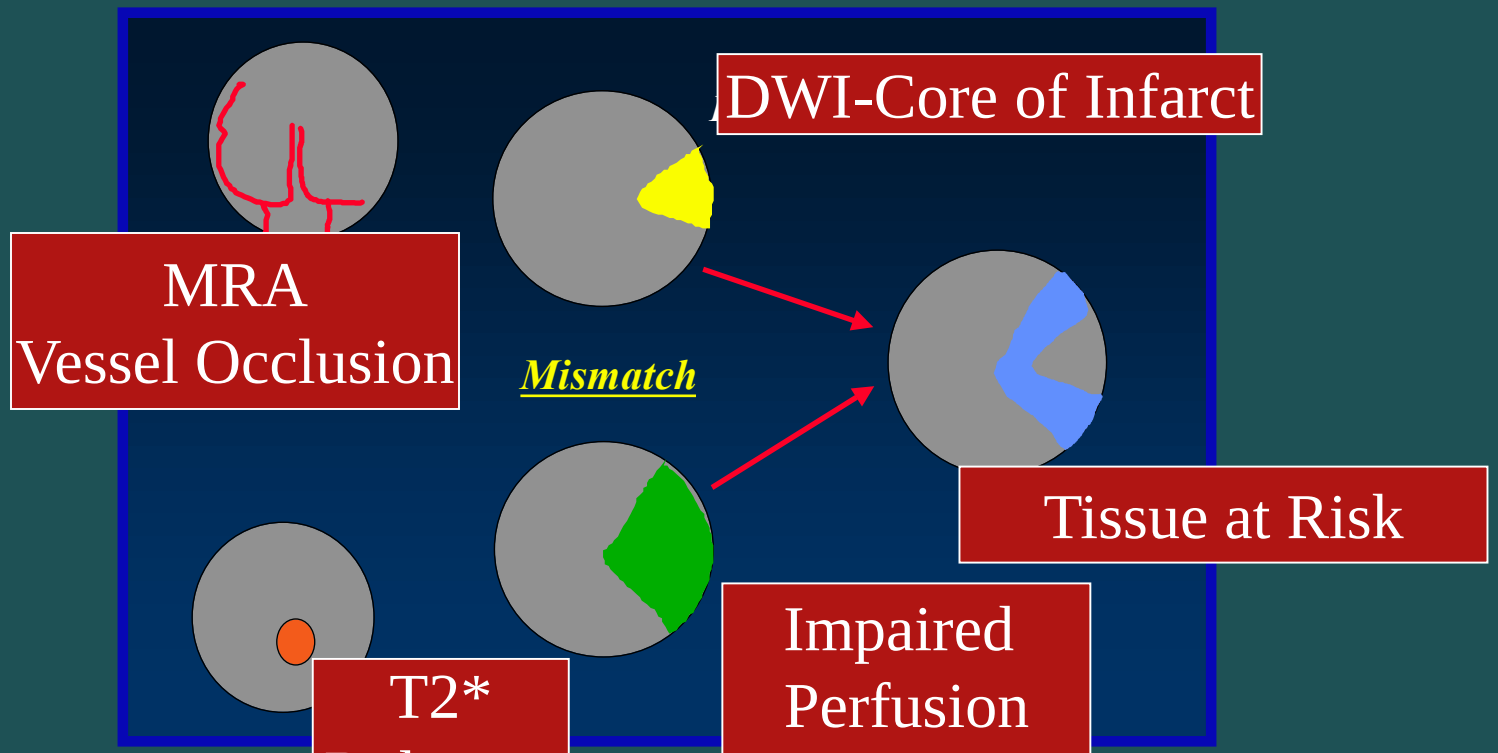
Positive DWI, Negative FLAIR identifies Strokes < 4.5 hours old



Thomalla et al. Ann Neurol. 2009.

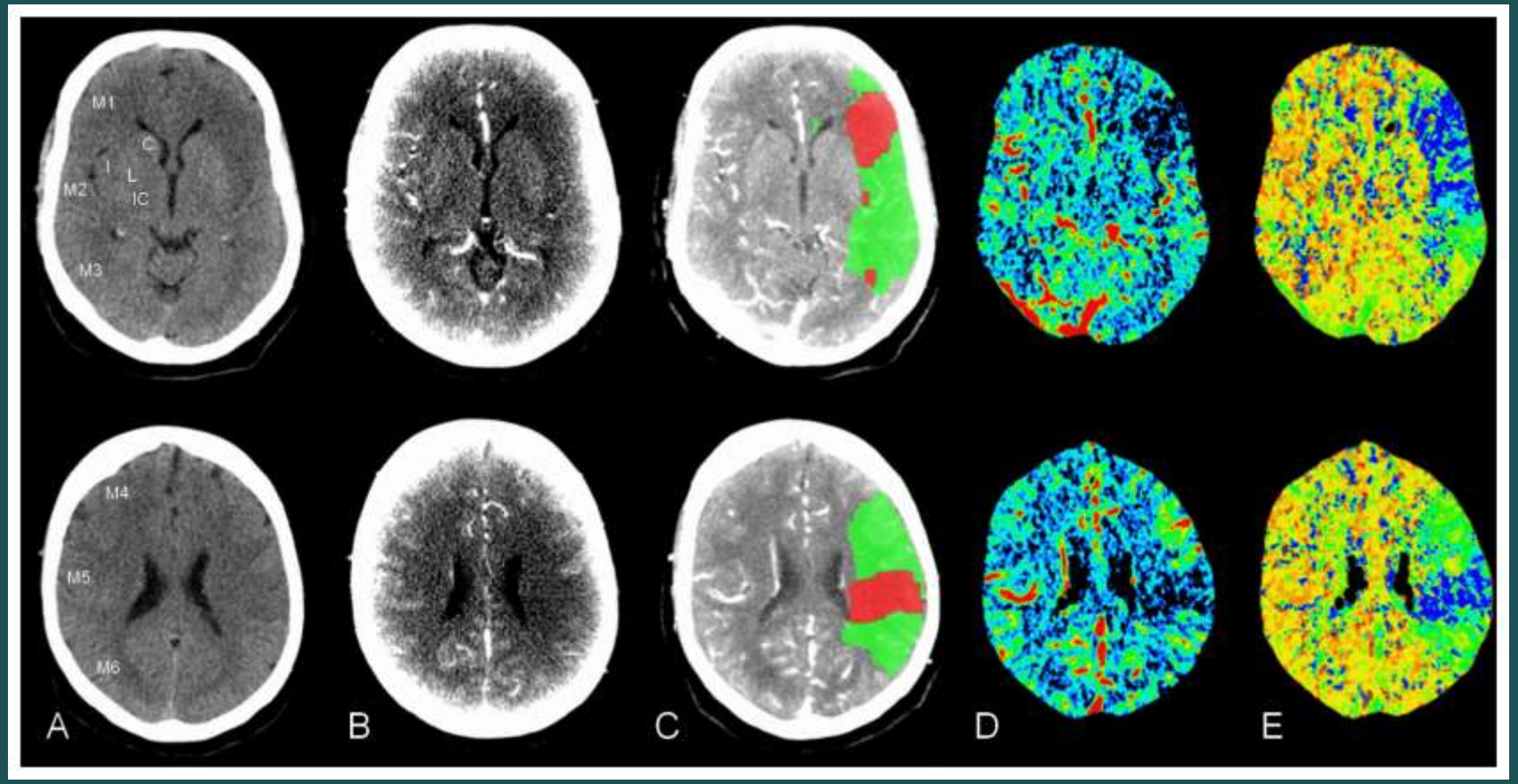

A Schematic representation of regions of cerebral hypoperfusion
Ischemic core
Ischemic penumbra
Benign oligemia
B MRI following acute stroke
Diffusion-weighted MRI
Ischemic core
Perfusion-weighted MRI
Ischemic penumbra

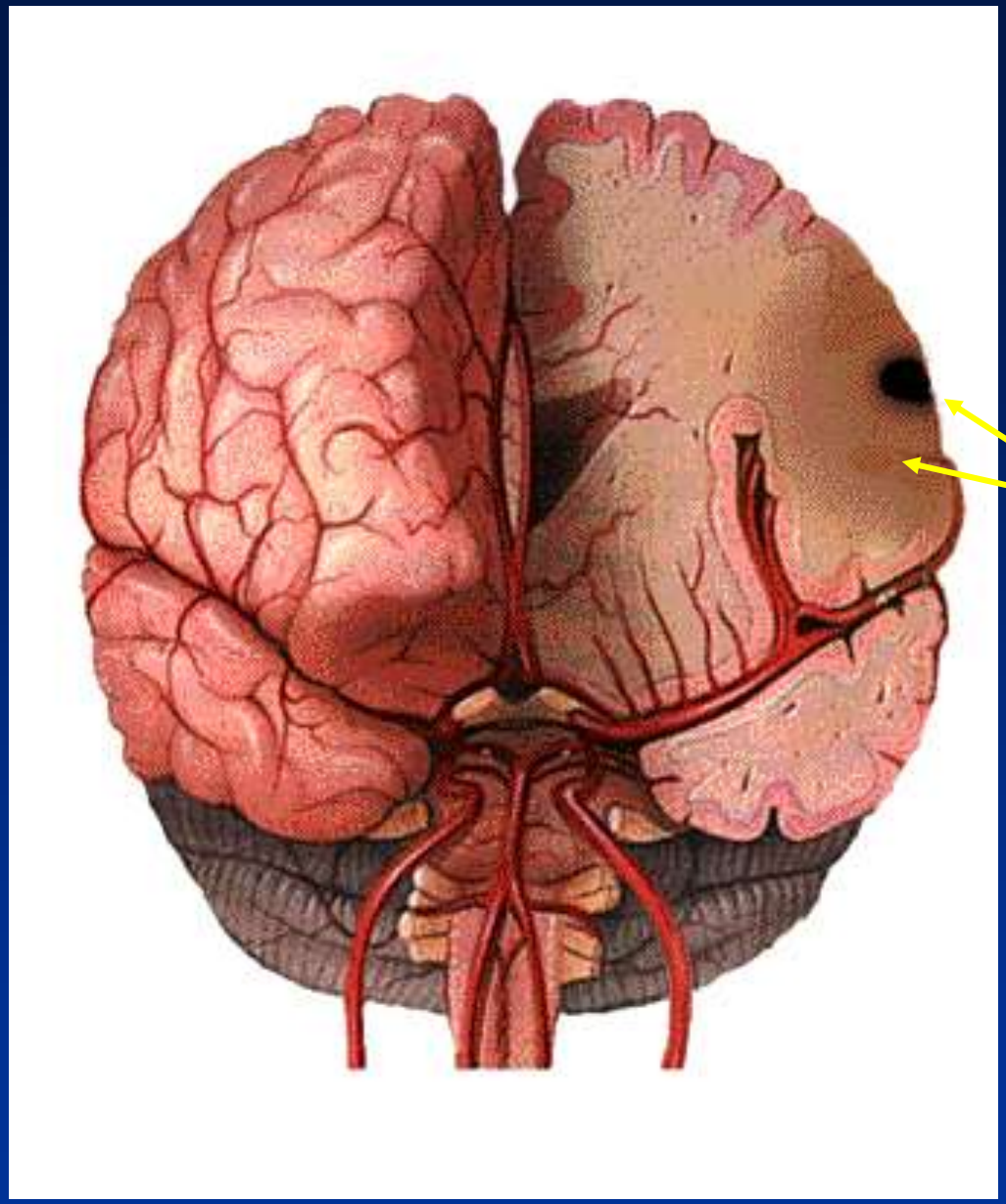
MRI-Mismatch Concept

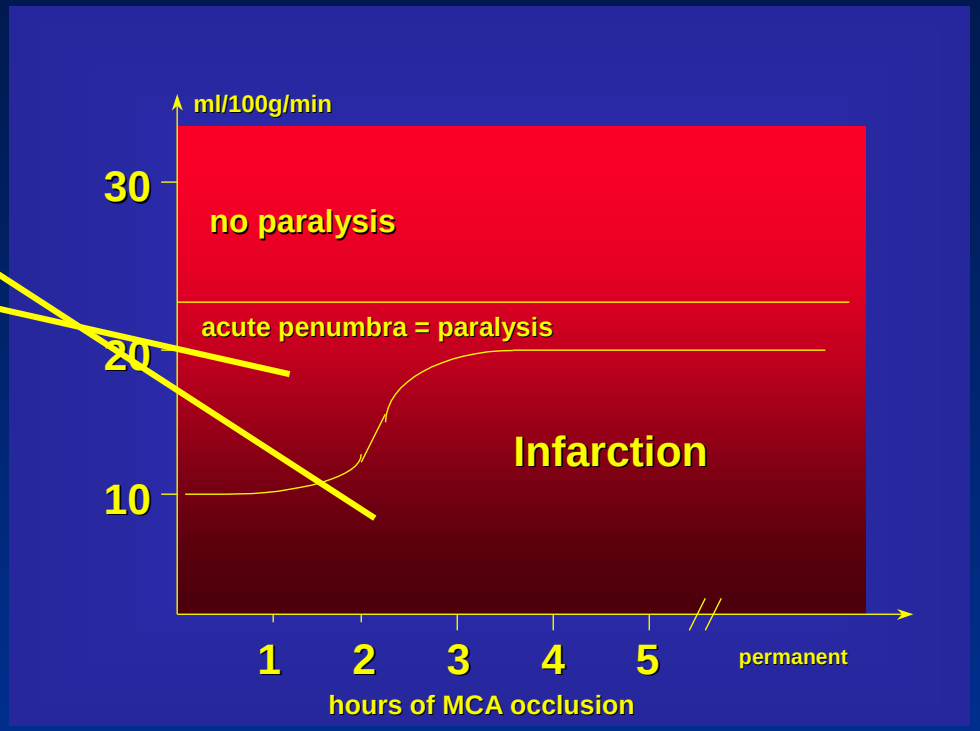


Jansen ea, Lancet 1999

Perfusion CT






ml/100g/min
30
no paralysis
acute penumbra = paralysis
20
Infarction
10
1
2
3
4
5
permanent
hours of MCA occlusion

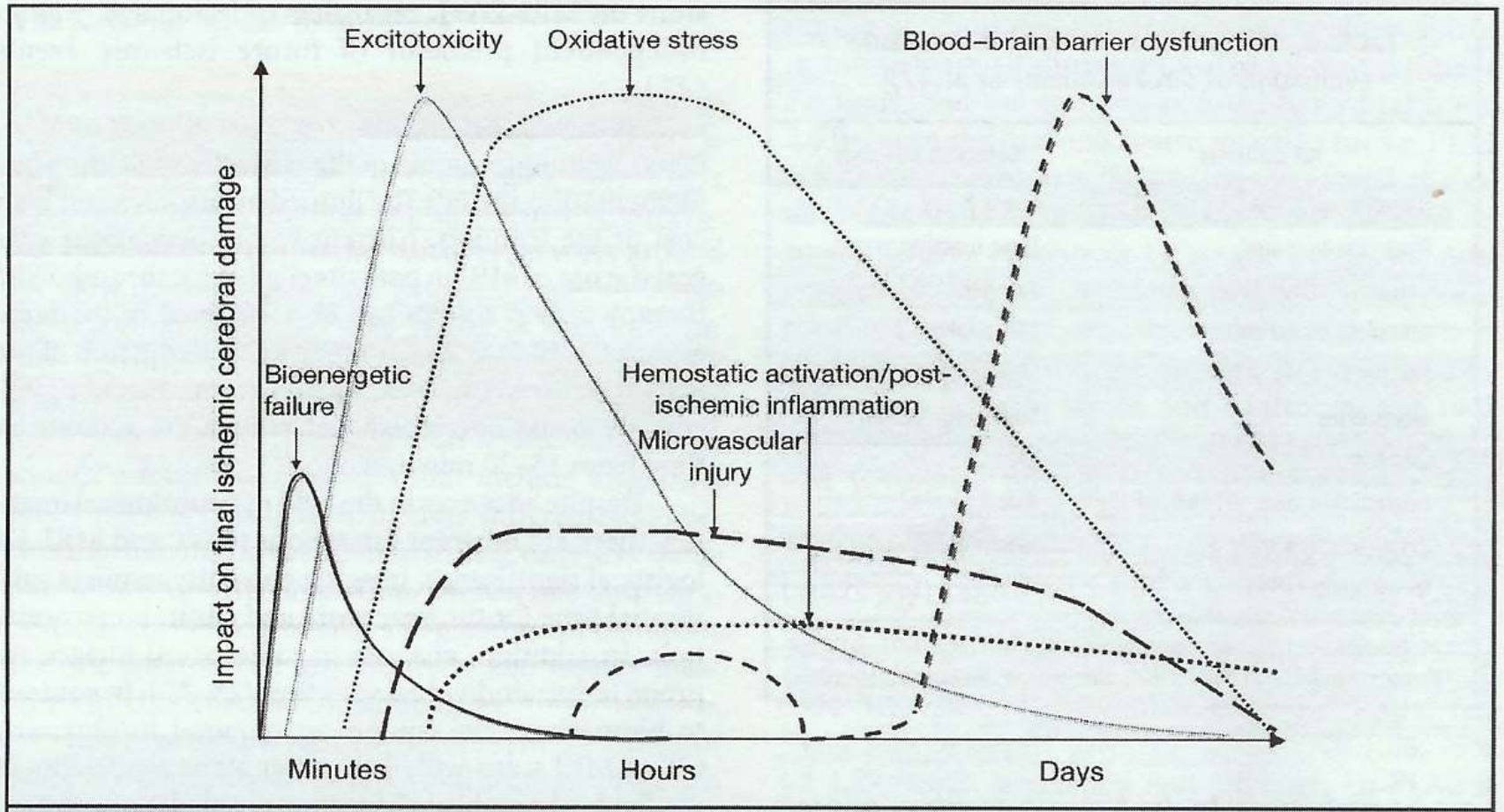
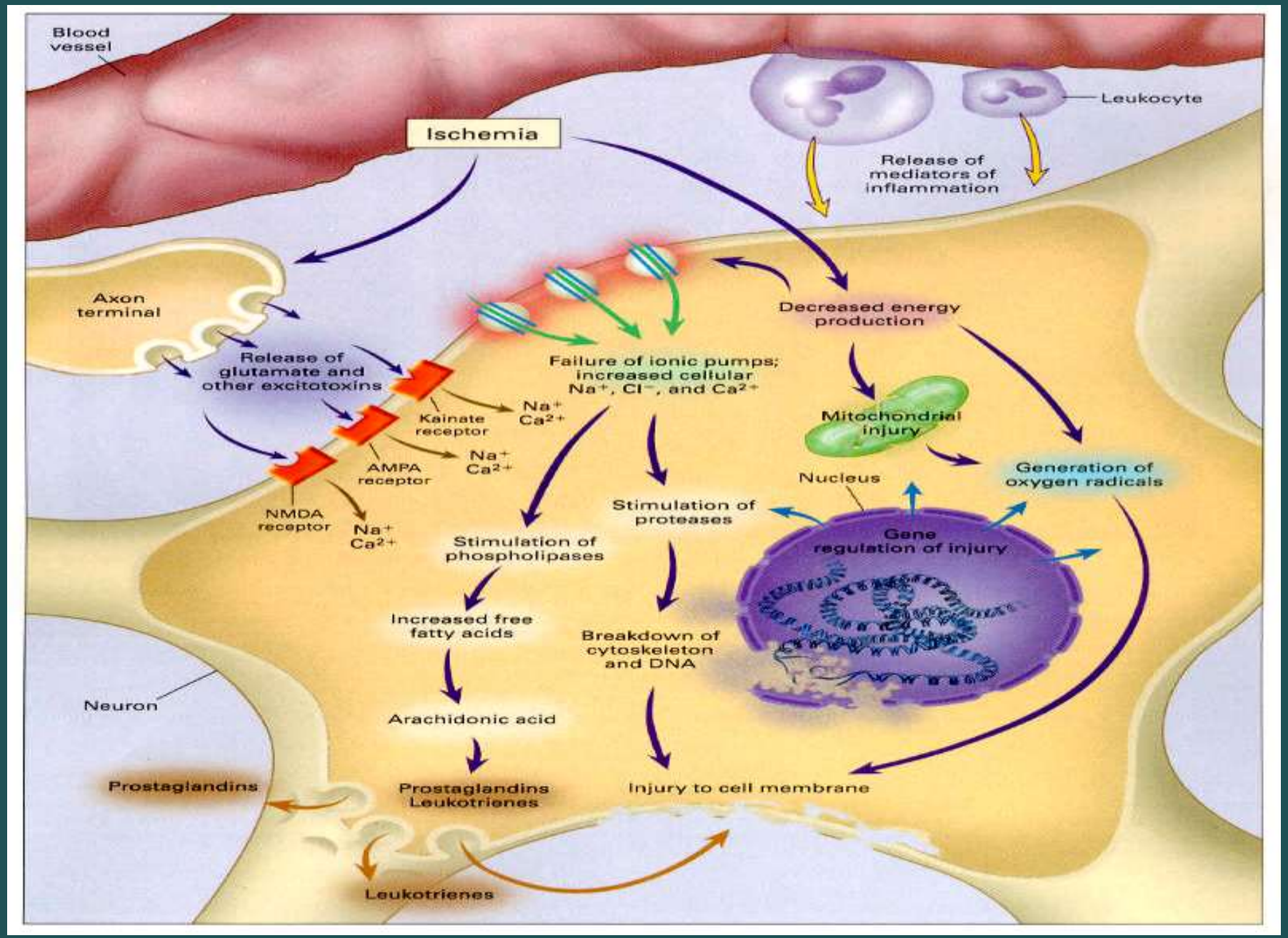


Fig. 1. Timing of events in the ischemic cascade.

Adapted from [Brouns and De Deyn *(8)*]; reprinted with permission from Elsevier.

Brouns, Clin Neurol Neurosurg 2009

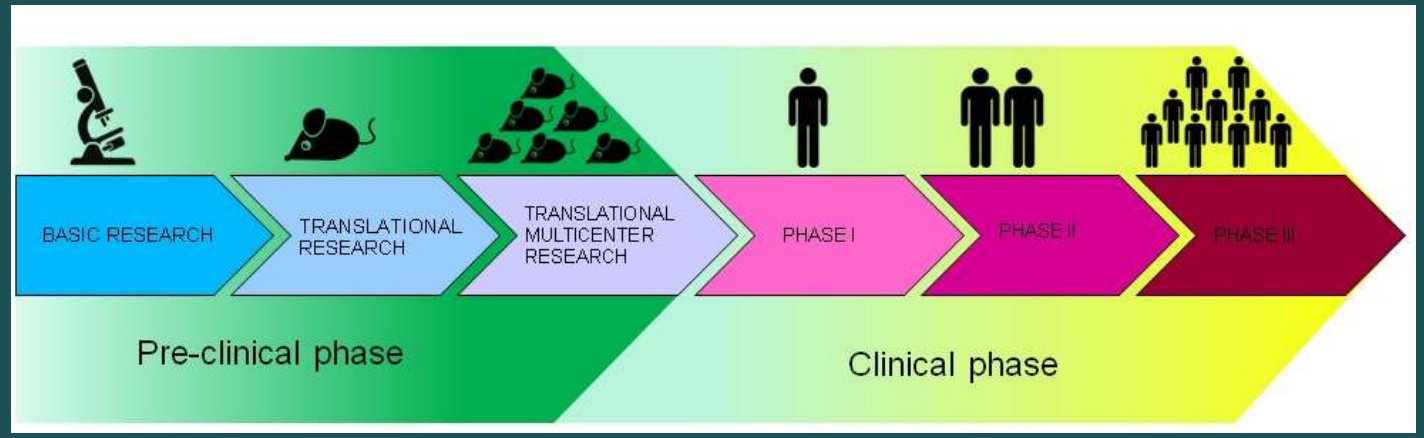

Blood vessel
Leukocyte
Ischemia
Release of mediators of inflammation
Axon terminal
Release of glutamate and other excitotoxins
Kainate receptor
AMPA receptor
NMDA receptor
Na^+ Ca^{2+}
Failure of ionic pumps; increased cellular Na^+, Cl^-, and Ca^{2+}
Decreased energy production
Mitochondrial injury
Generation of oxygen radicals
Nucleus
Gene regulation of injury
Stimulation of proteases
Stimulation of phospholipases
Increased free fatty acids
Arachidonic acid
Breakdown of cytoskeleton and DNA
Neuron
Prostaglandins
Prostaglandins Leukotrienes
Injury to cell membrane
Leukotrienes

Laboratorio di Ricerca Sperimentale sullo Stroke

Dipartimento di Medicina e Chirurgia
Università degli Studi di Milano Bicocca

Aims

- ✓ Developing new therapeutic approaches for neuroprotection in acute ischemic stroke
- ✓ Carring out translational projects (from bench to bedside)
- ✓ Build robust multicenter preclinical and clinical trials through a nation wide network of laboratories and Stroke Units



Laboratorio di Ricerca Sperimentale sullo Stroke

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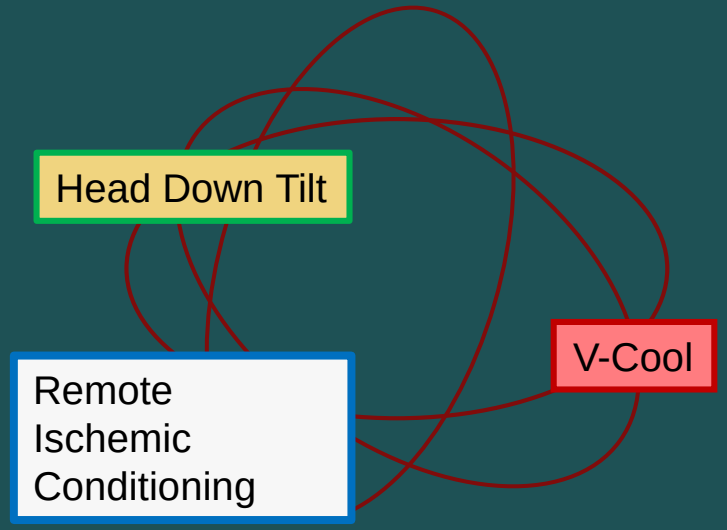
Experimental rat model of acute stroke

Rat model of transient middle cerebral artery occlusion (tMCAO)

Rat model of hemorrhagic stroke



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*

First recanalization therapy

IV t-PA FDA approved for use in acute ischemic stroke < 3 hours from onset in 1996. As compared with patients given placebo, patients treated with t-PA were at least 30 percent more likely to have minimal or no disability at three months on the assessment scales.

The Use of IV t-PA

Eligibility

- Age 18 or older
- Clinical diagnosis of ischemic stroke causing a measurable neurological deficit
- Time of symptom onset well established to be less than 4.5 hrs before treatment would begin

Contraindications

- Evidence of intracranial hemorrhage on pretreatment CT
- Clinical presentation suggestive of SAH, even with normal CT
- Active internal bleeding
- Known bleeding diathesis, including but not limited to:
  - Platelet count < 100,000/mm^3
  - Patient has received heparin within 48 hours and has an elevated aTT (greater than upper limit of normal for laboratory)
  - Current use of oral anticoagulants or recent use with an elevated prothrombin time > 15 seconds
- Within 3 months any intracranial surgery, serious head trauma, or previous stroke
- On repeated measurements, systolic blood pressure greater than 185 mmHg or diastolic blood pressure greater than 110 mmHg at the time treatment is to begin, and the patient requires aggressive treatment to reduce blood pressure to within these limits
- History of intracranial hemorrhage

Warnings

- Only minor or rapidly improving stroke symptoms
- History of GI or Urinary tract hemorrhage within 21 days
- Recent arterial puncture at a noncompressible site
- Recent lumbar puncture
- Abnormal blood glucose (<50 or >400 mg/dL)
- Post myocardial infarction pericarditis
- Patient was observed to have a seizure at the same time the onset of stroke symptoms were observed

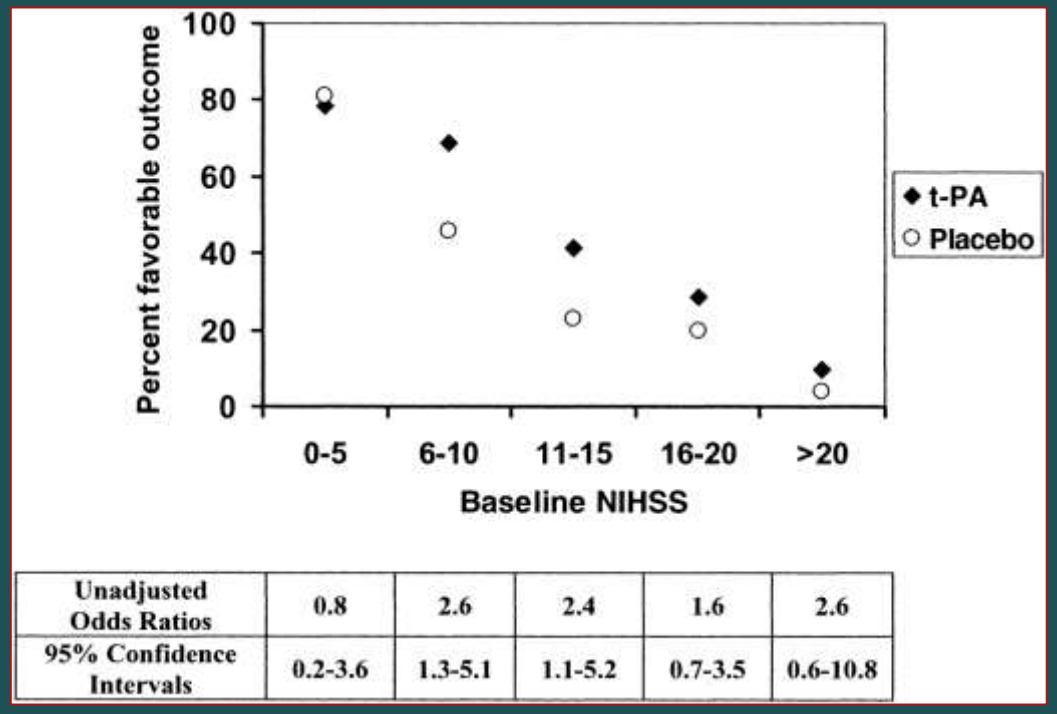
You write to administer t-PA at 0.9mg/kg (max 90mg) infused over 60 minutes with 10% of the dose administered as a bolus over 1 minute.

You ensure that BPs have been consistently less than 185/110 prior to administration.

You also make sure that no other antithrombotics or anticoagulants will be given in the next 24 hours and write for a Head CT in 24 hours.

You also write orders for SU admission as you know the patient will need close BP monitoring over the next 24 hours per NINDS protocol to maintain BP<180/105.

r-TPA limits



Unadjusted Odds Ratios	0.8	2.6	2.4	1.6	2.6
95% Confidence Intervals	0.2-3.6	1.3-5.1	1.1-5.2	0.7-3.5	0.6-10.8

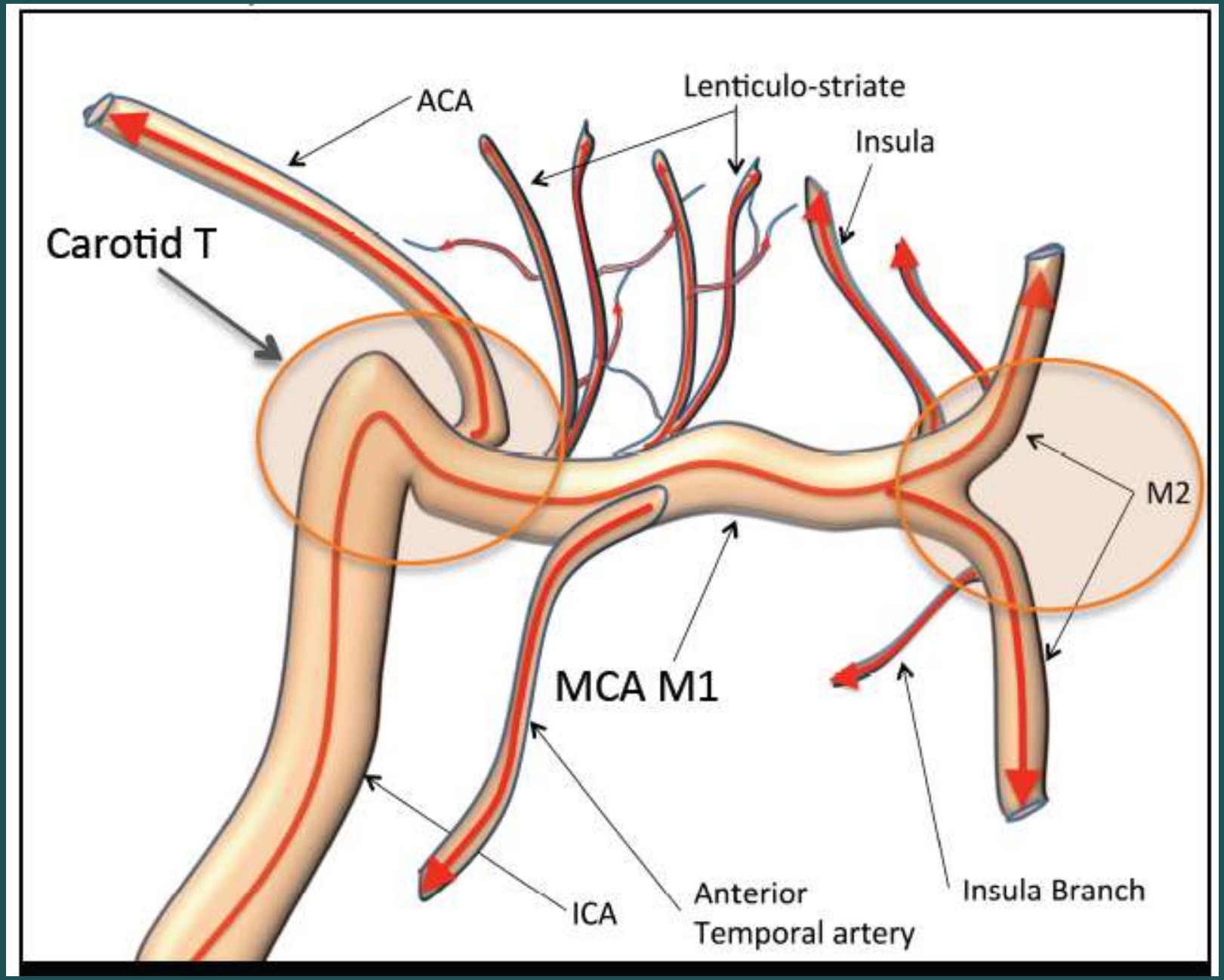
- 2004, meta-analysis of IV rTPA trials inclusive of 2775 patients
- NIHSS > 12 ((Fisher et al Stroke 2005, 36: 2121-25)
- Anatomic location (Gonzalez et al Stroke 2013, 44(11):3109-3113
- Thrombus > 7 mm

IV is the first line recomended therapy for acute ischemic stroke

but if

IV controindication and proximal artery occlusions (resistant)

POSSIBILITY OF MECHANIC DESOBSTRUCTION


ACA
Lenticulo-striate
Insula
Carotid T
M2
MCA M1
ICA
Anterior
Temporal artery
Insula Branch

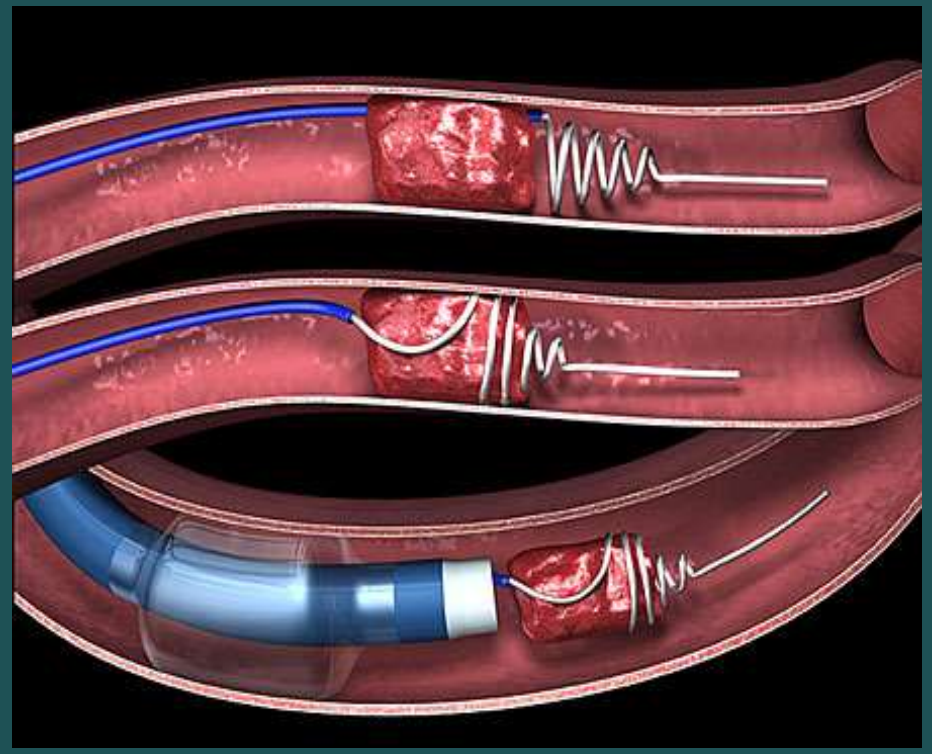
2015

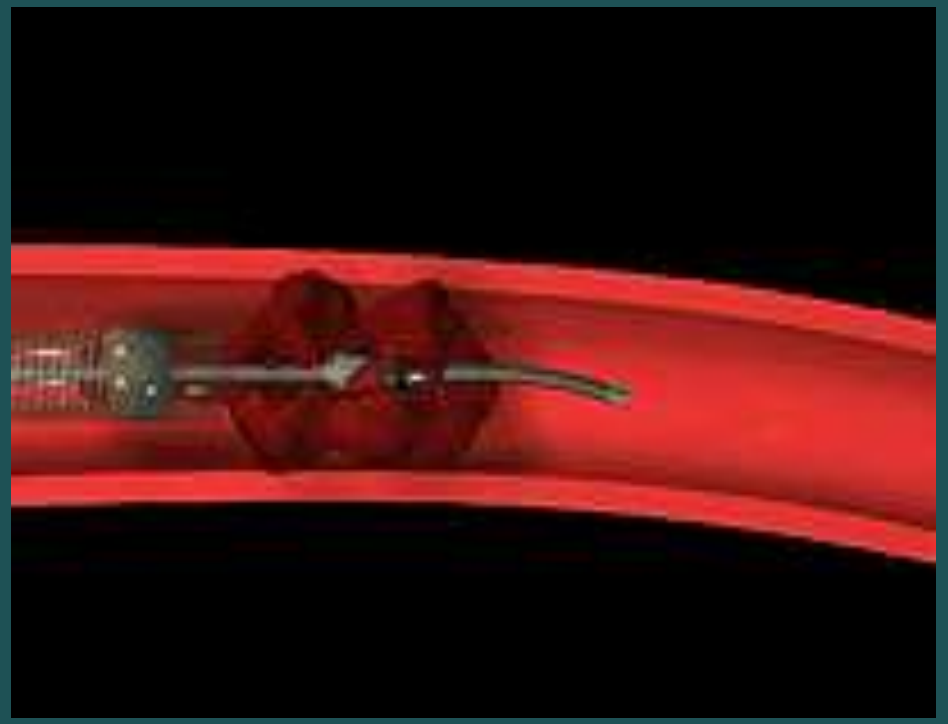
The NEW ENGLAND JOURNAL of MEDICINE

- MR. CLEAN : A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke
- ESCAPE: Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke
- EXTEND-IA: Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection
- SWIFT PRIME: Stent- Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke
- REVASCAT: Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke

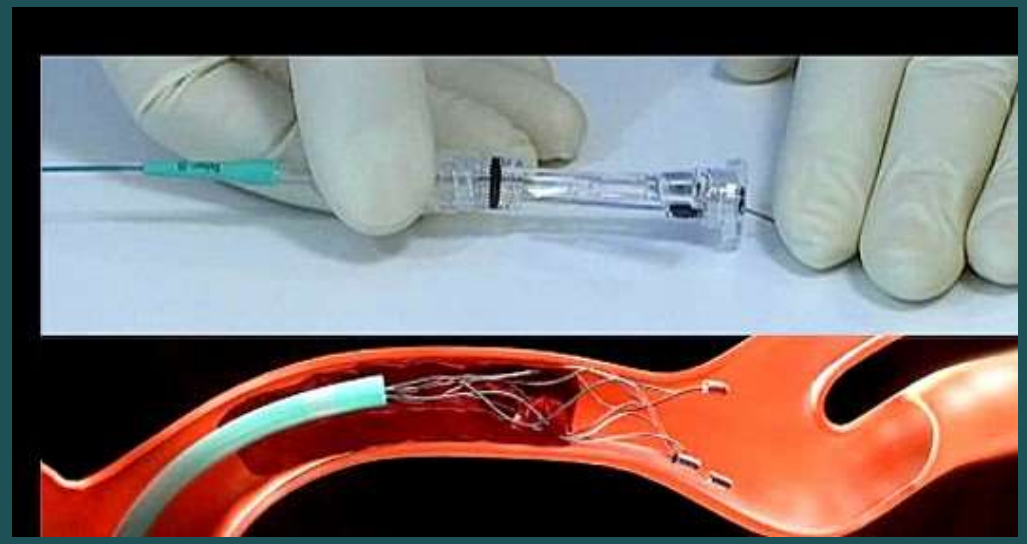
Devices

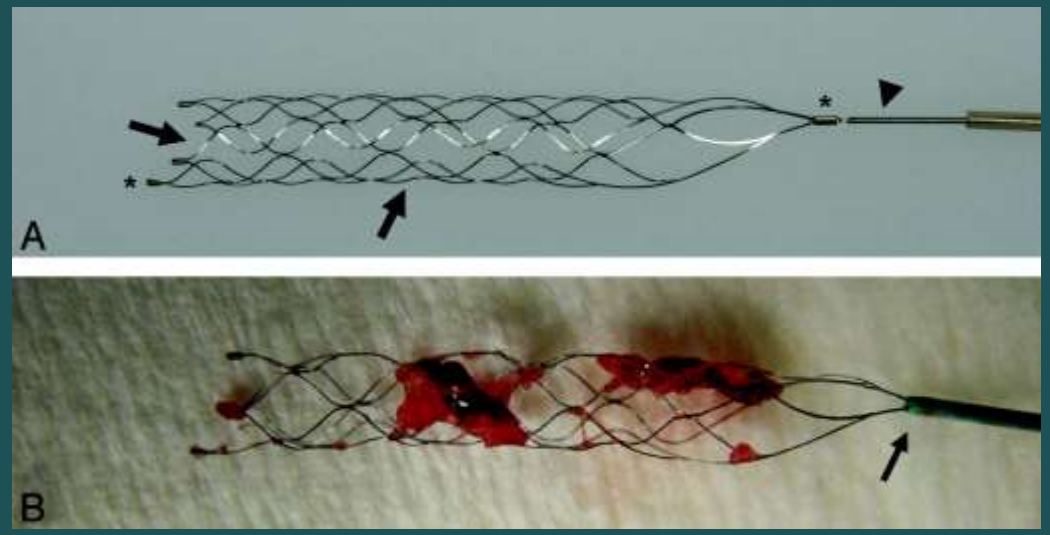
First generation:
•Coil retriever: engages and wraps aroud the clot that is pulled back to the catheter to remove the thrombus
•Aspiration device: uses proximal suction to remove thrombus





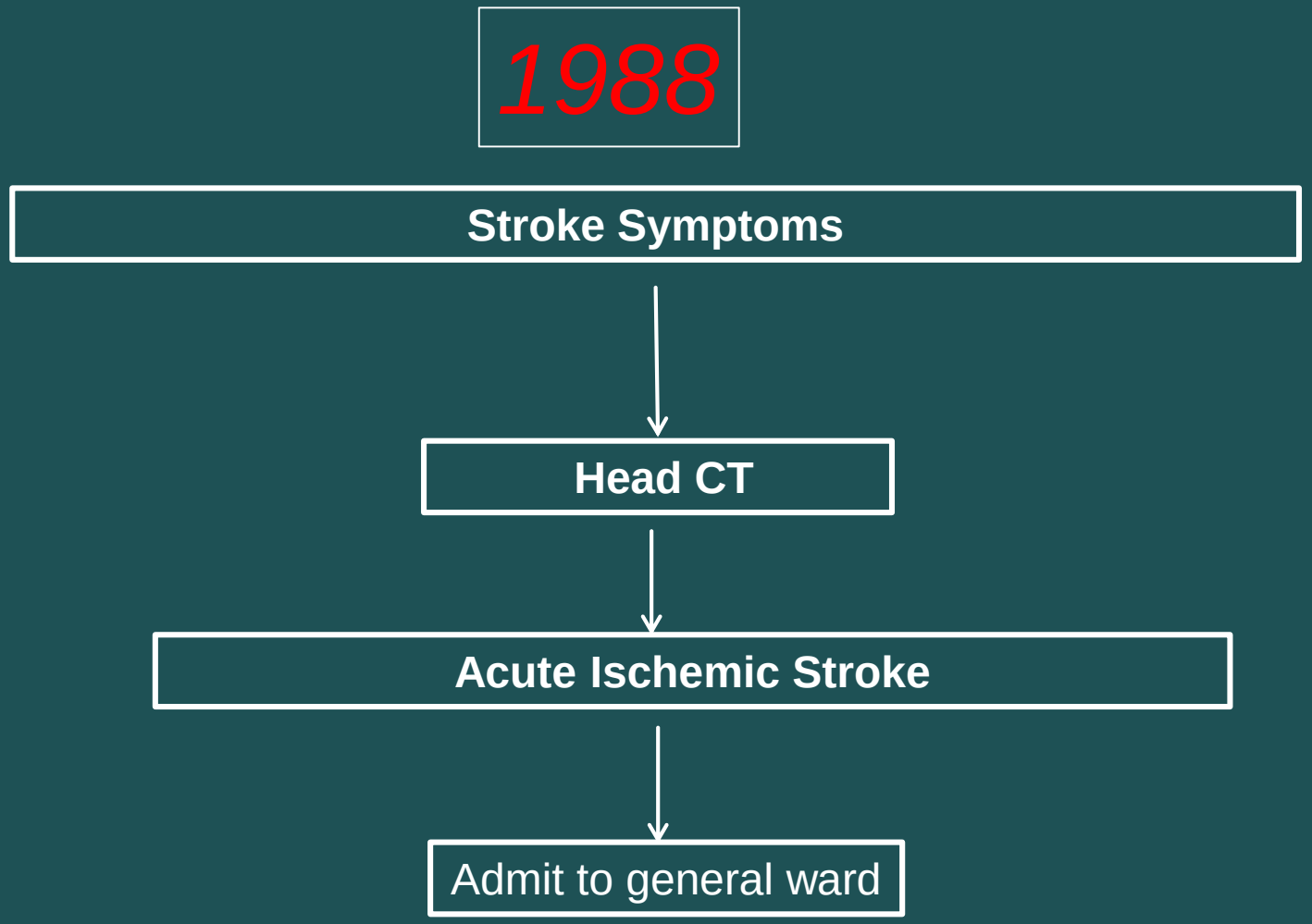
Devices



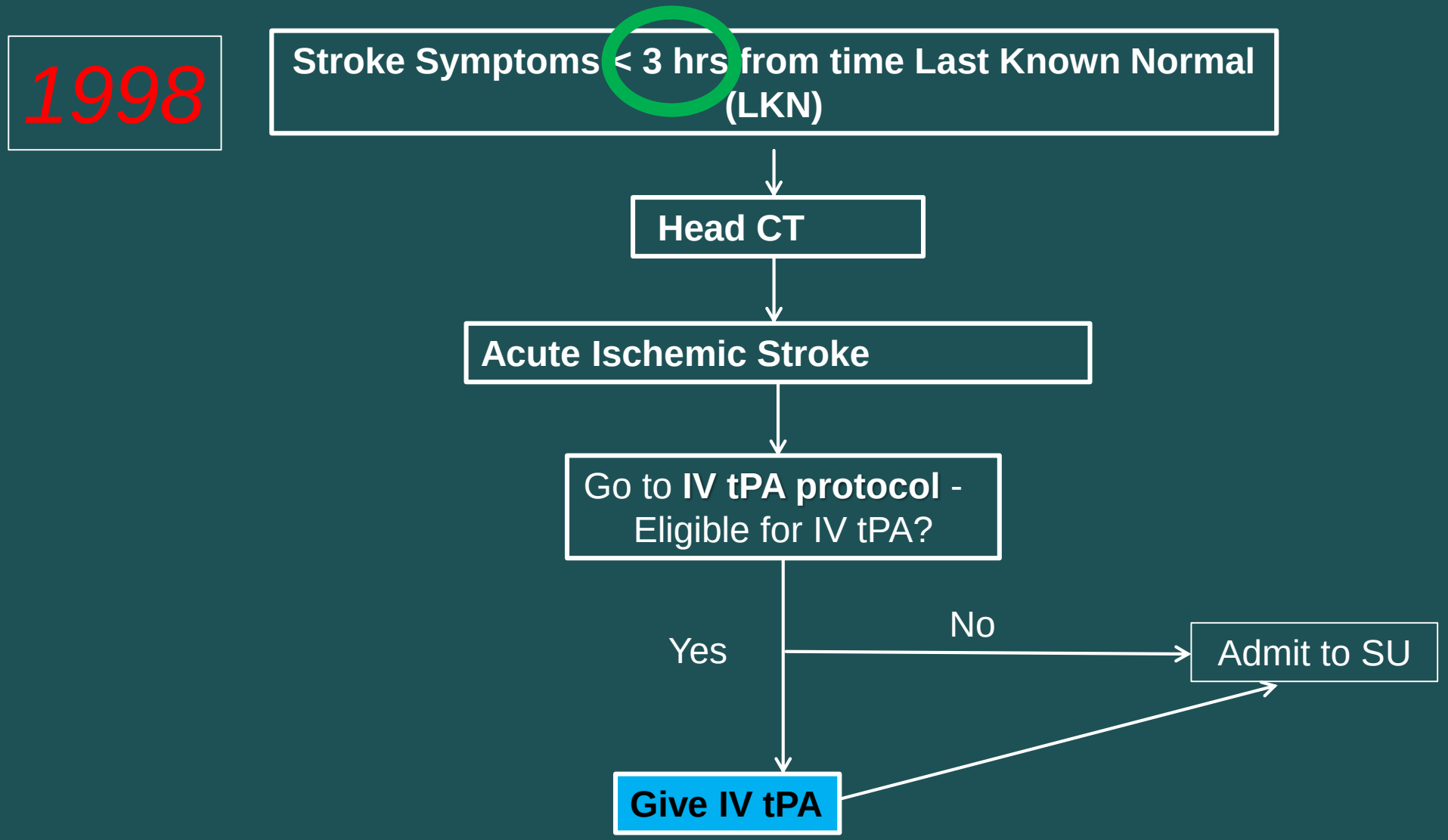


Second generation:
• Stent retrieviers: allow for immediate restoration of blood flow by stent expansion at the site of occlusion followed by:
➢entrapment of the thrombus between the stent and the vessel wall
➢Extraction when the stent is removed

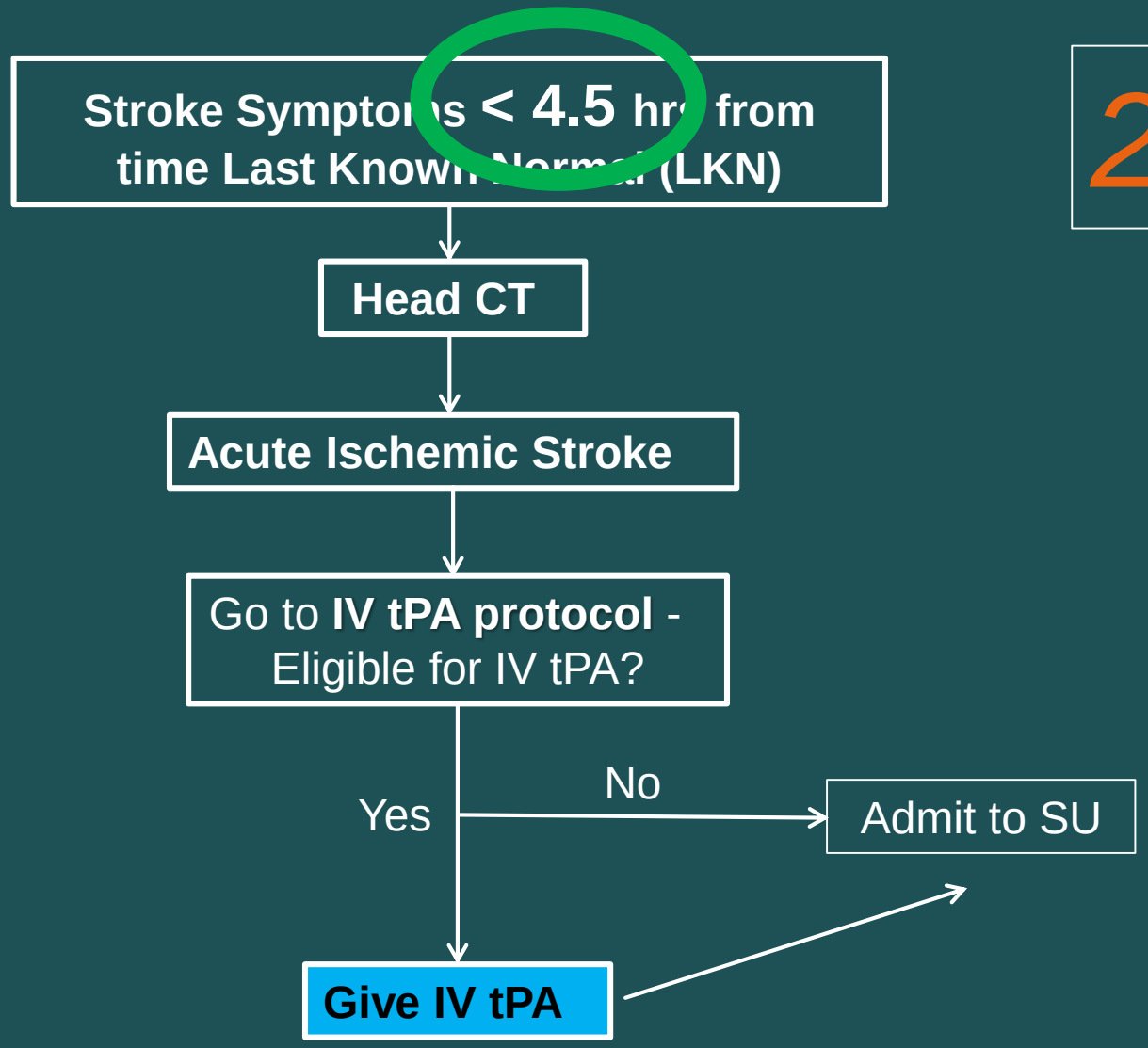
Acute ischemic stroke decision-making



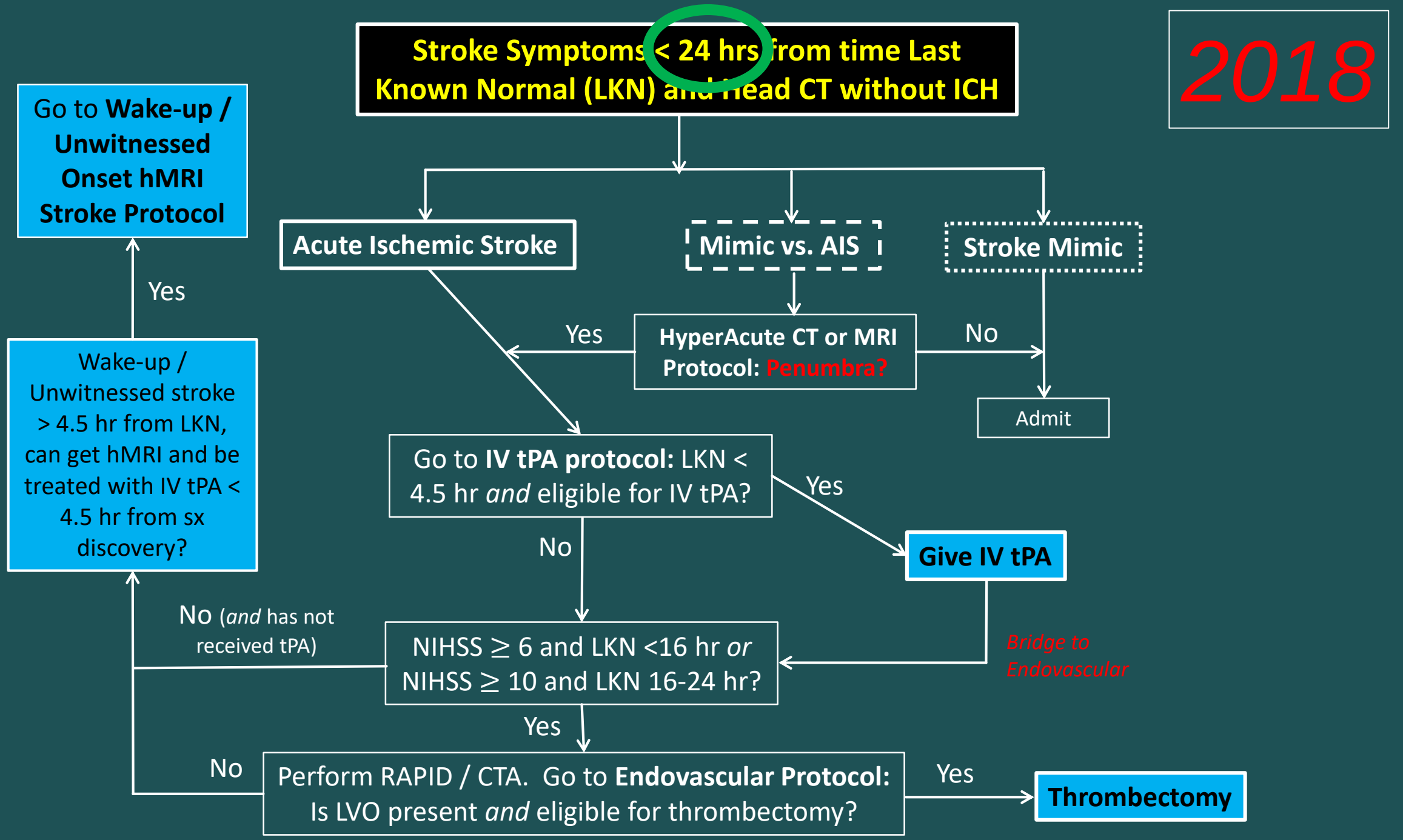
Acute ischemic stroke decision-making



Acute ischemic stroke decision-making



2008


2018
Stroke Symptoms < 24 hrs from time Last Known Normal (LKN) and Head CT without ICH
Acute Ischemic Stroke
Mimic vs. AIS
Stroke Mimic
HyperAcute CT or MRI Protocol: Penumbra?
Yes
No
Admit
Go to IV tPA protocol: LKN < 4.5 hr and eligible for IV tPA?
Yes
Give IV tPA
No
Bridge to Endovascular
NIHSS ≥ 6 and LKN <16 hr or NIHSS ≥ 10 and LKN 16-24 hr?
No (and has not received tPA)
Yes
Perform RAPID / CTA. Go to Endovascular Protocol: Is LVO present and eligible for thrombectomy?
No
Yes
Thrombectomy
Wake-up / Unwitnessed stroke > 4.5 hr from LKN, can get hMRI and be treated with IV tPA < 4.5 hr from sx discovery?
Yes
Go to Wake-up / Unwitnessed Onset hMRI Stroke Protocol

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

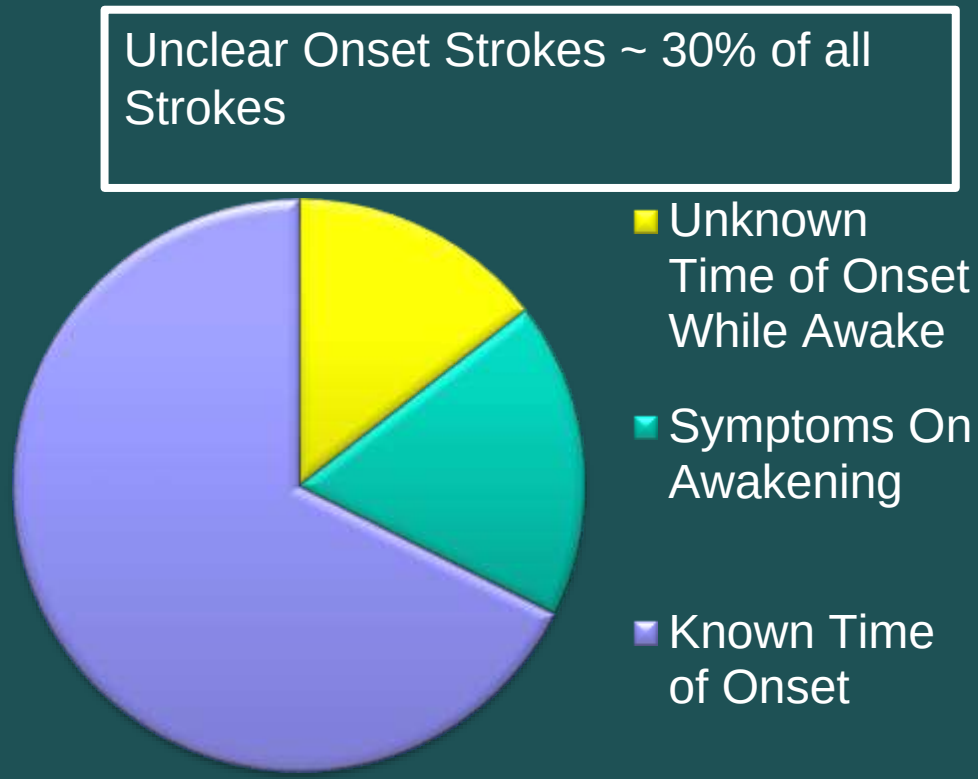
- Finally, imaging selection criteria defined who would benefit for extended time windows out to 24 hours from stroke onset

  → **CTA-CTP for endovascular therapy**

  → **MRI FLAIR-DWI mismatch for thrombolysis**

Expanding the Therapeutic Window for Acute Ischemic Stroke: *Wake-up or Unwitnessed Stroke Onset*

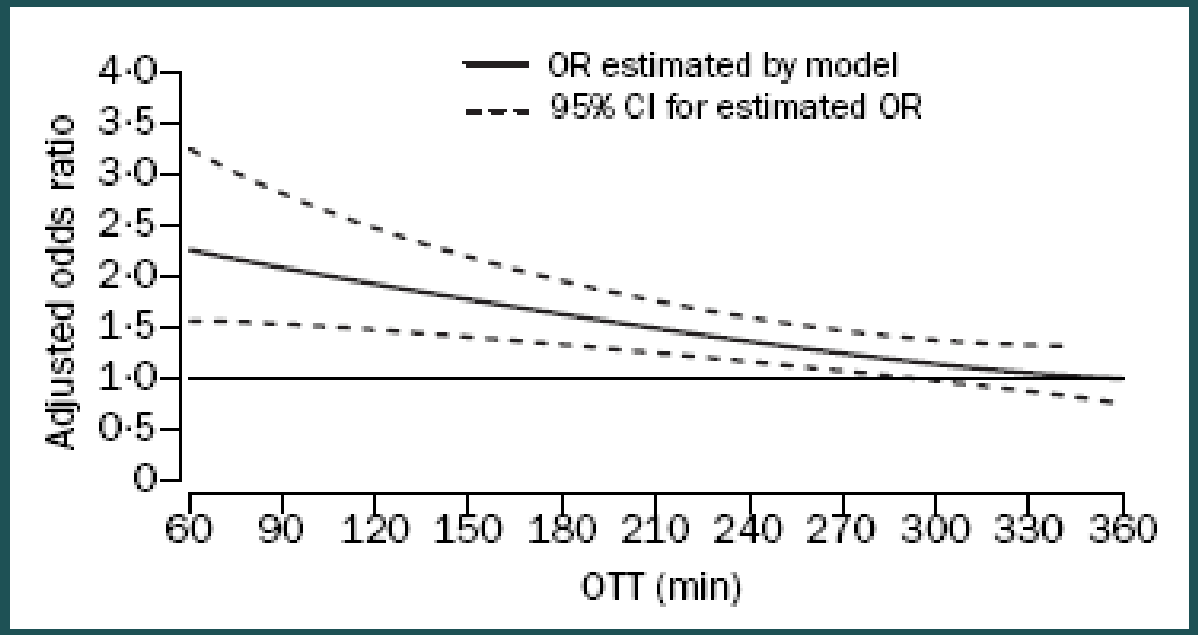
- ~10% of stroke patients arrive within 4.5 hours of symptom onset and can be treated with IV tPA
- Up to 1/3 of stroke patients wake-up with stroke symptoms or have unwitnessed onset
- Historically, they are disqualified from acute treatments



J Stroke Cerebrovasc. Dis. 2011.

Expanding the Therapeutic Window for Acute Ischemic Stroke: *Is Time Still Brain?*

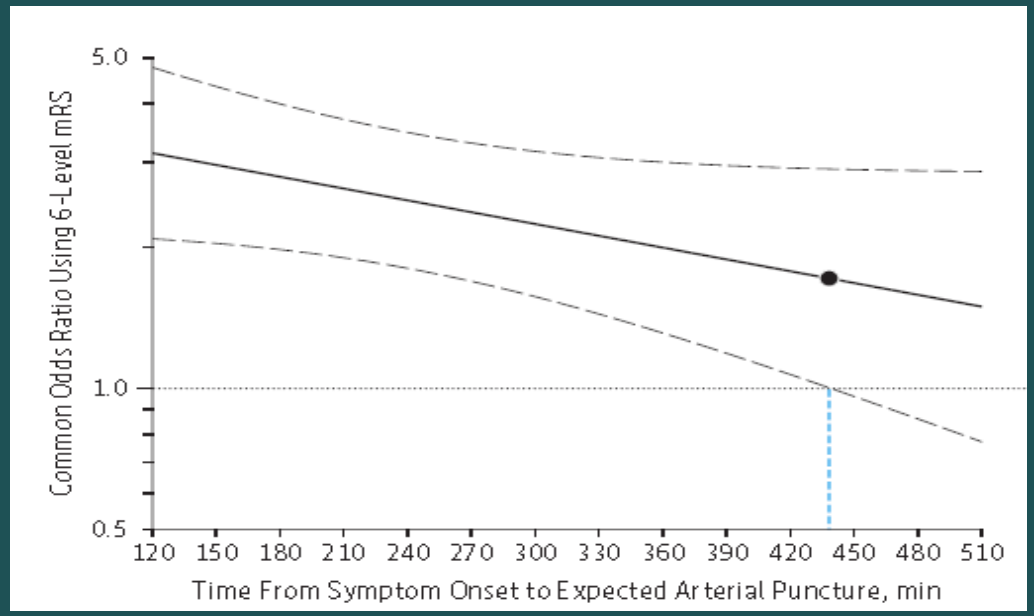
Time to Alteplase and Favorable Clinical Outcome in 3000 Patients



Combined data from ECASS I-III, NINDS, ATLANTIS; Lees et al, Lancet 375:1695-703, 2010.

JAMA | Original Investigation

Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis



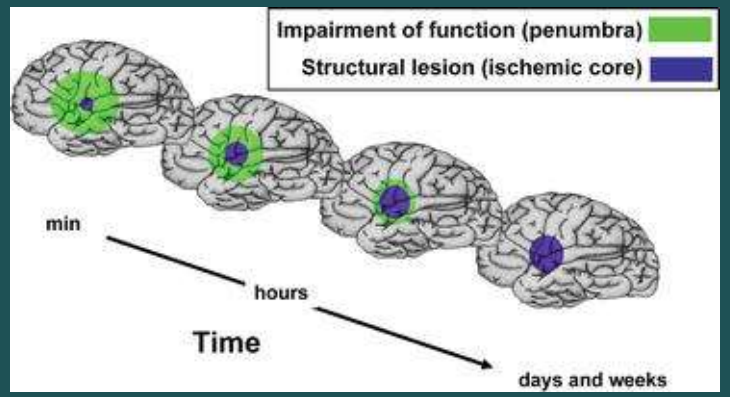
Saver et al, JAMA 2016.

Expanding the Therapeutic Window for Acute Ischemic Stroke: *Is Time still Brain?*

Each minute destroys:

- 1.9 million neurons
- 14 billion synapses
- 7.5 miles of myelinated fibers

Saver. Stroke. 2006. 37(1):263-6.



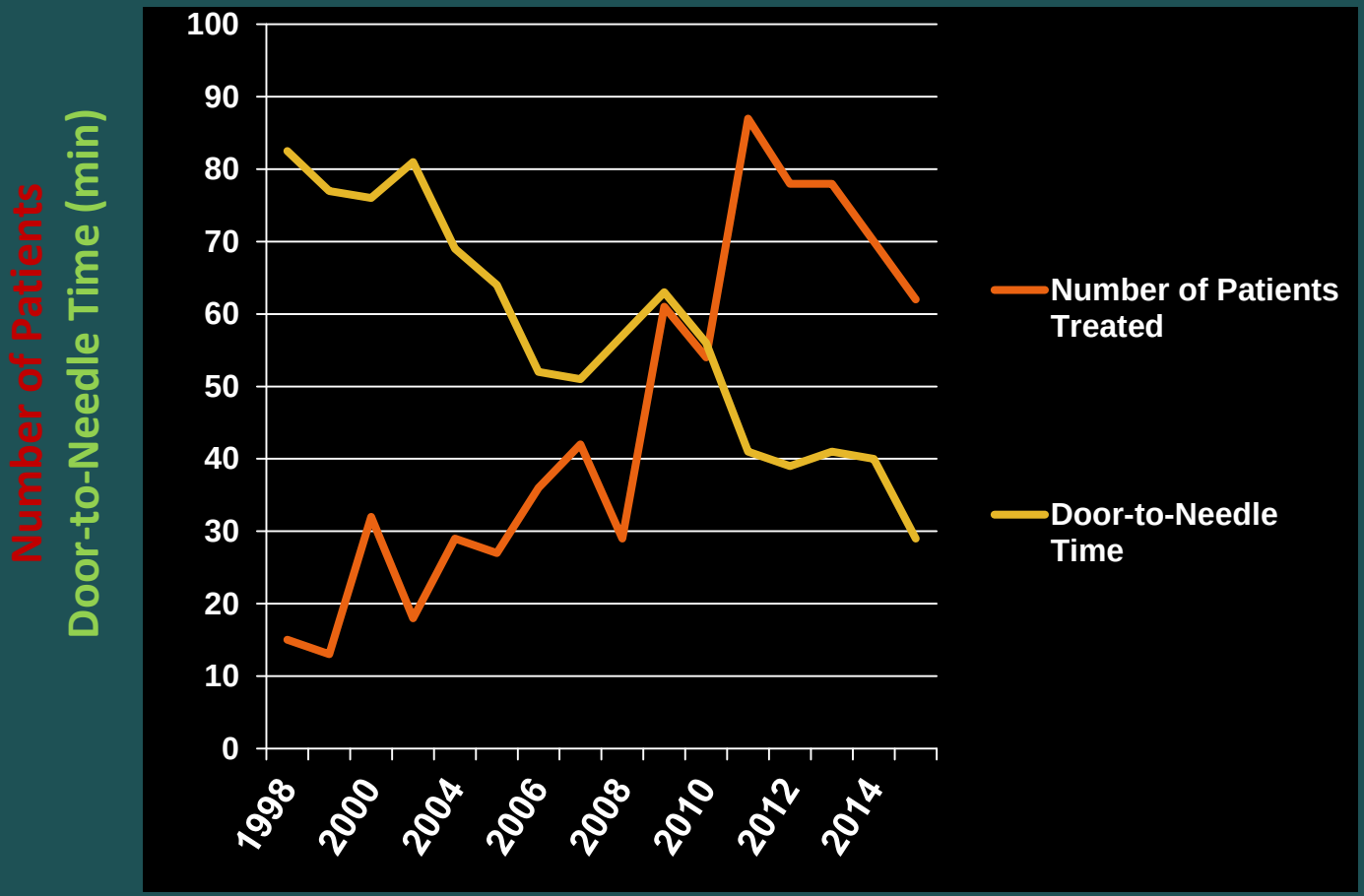
→**Yes, Time is Brain! However, Recent trials suggest the equation is more complex, non-linear, with greater inter-individual variability, now aided by Imaging selection.**

Metrics for Acute Stroke Treatment:

- Onset-to-door time
- Door-to-needle/puncture time
- Onset-to-needle/puncture time

Expanding the Therapeutic Window for Acute Ischemic Stroke: *Institutional Challenges*

- Work across departments
- Frequent, repeated education of physicians and staff
- Protocol development with input across disciplines
- Consistent quality improvement methods to streamline care



Ford et al, Stroke. 2009; Ford et al, Stroke 2012.
Curfman et al, Stroke 2014; Goyal et al. Stroke 2016.

Admit the Patient to Stroke Unit

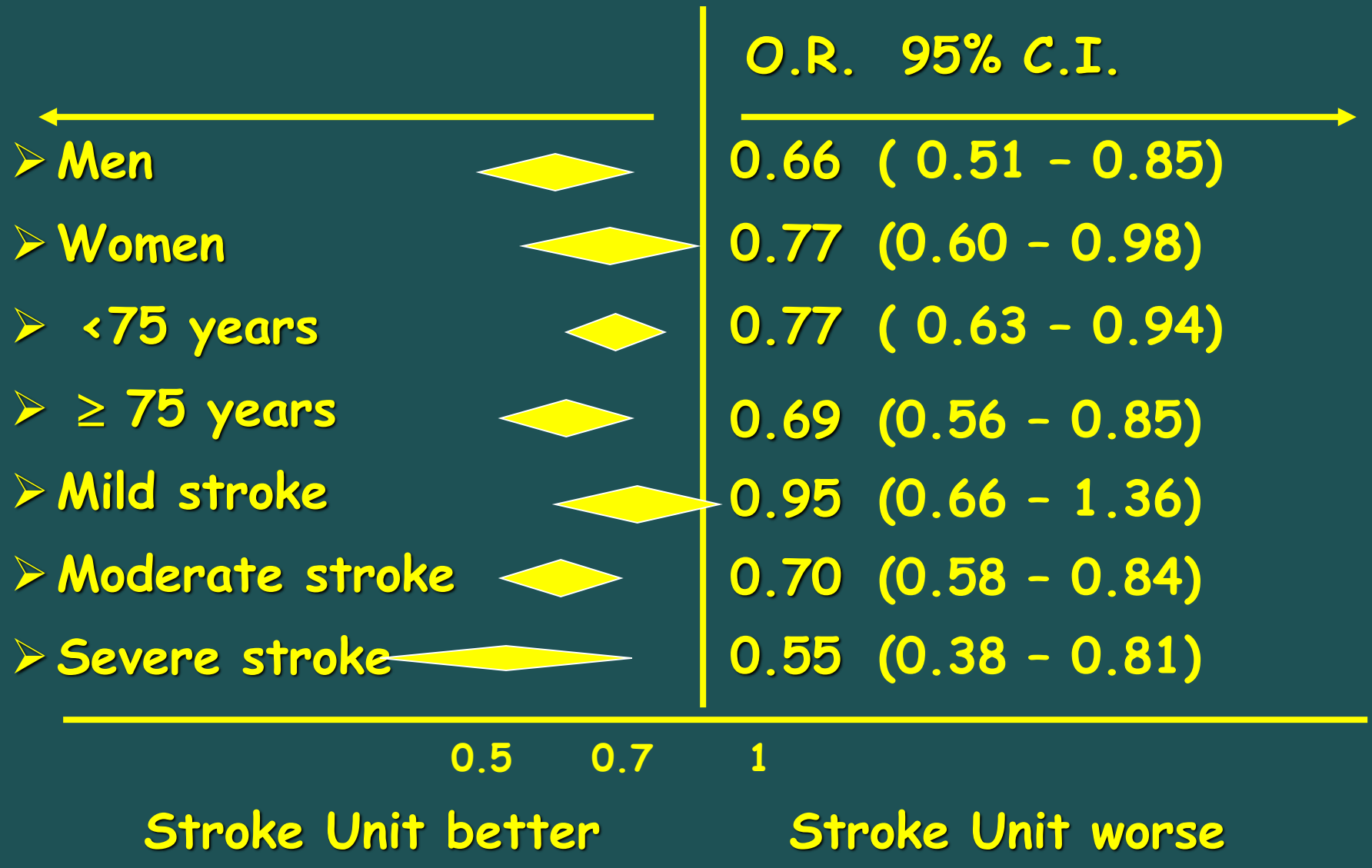
All stroke patients should be admitted to the hospital for observation, diagnostic evaluation, and determination of treatment for secondary stroke prevention.

All patients should be admitted to a **stroke unit** or when not available to a cardiac monitored bed with staffing to perform frequent neurological checks.

As already discussed, thrombolysis patients need ICU care.

The Stroke Unit Trialists' Collaboration

(Cochrane Database Syst Rev 2002;(1):CD000197)



Evaluation During Admission

1. Labs: fasting lipid profile and glucose, Hypercoagulable workup, ESR, ANA, CRP, homocysteine
2. Imaging: All patients should have CT or MRI imaging of brain and vascular imaging of head and neck. Consider TCD, PET, SPECT or other study based on clinical findings
3. Echocardiogram: all patient should have echo – TTE abnormal EKG or lacunar event. All others TEE (more sensitive and cost effective in evaluation of stroke. Ann Intern Med. 1997 Nov 1;127(9):775-87.)
4. Rehabilitation evaluation
5. Bedside or formal swallow evaluation
6. Medications: Home medications except BP meds. Restart or add after patient stable for >48hrs. Again, in general do not treat BP unless >220/120 in the acute phase
7. DVT prophylaxis if indicated

General management of stroke

- Cardiac/respiratory monitoring
- Blood pressure
- Fluid and electrolyte balance
- Glucose metabolism
- Body temperature
- Dysphagia and nutrition
- Brain edema
- Early rehabilitation

Brain edema – Concepts

- Brain edema plays a role in both early (Toni D, Arch Neurol 1995;52:670) and late (Davalos A, Stroke 1999;30:2631) stroke progression

- It is the main responsible of clinical course in malignant MCA infarction (Steiner T, neurology 2001;57(5 suppl2):S61

- It is responsible not only for impairment of level of consciousness and brain herniation, but also for impairment of other neurological functions (as motor strenght, speech etc.) (Toni D, Arch Neurol 1995;52:670)

- It may be aggravated by fever, high blood pressure, hyperglycemia

- When impairment of consciousness: hosmotic agents or skull removal

In the acute period, all ischemic stroke patients should receive 300 mg of ASA within 48hours of onset

Anticoagulants (heparin) only if:

cerebral venous thrombosis

extracranial artery dissection

high risk of cardiac thromboembolism

Hospital Initiation of Secondary Prevention

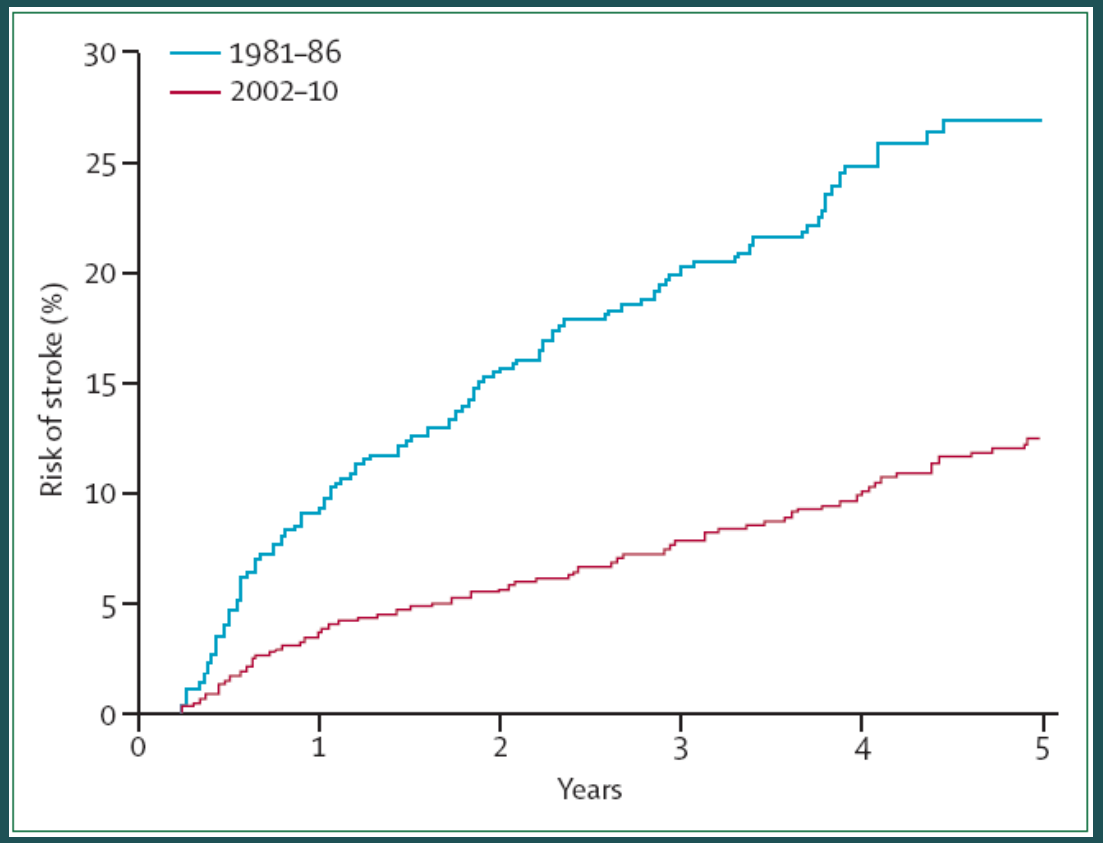
Cumulative Risk of Stroke

	Post-TIA (%)	Post-Stroke (%)
30 days	4 – 8	3 – 10
1 year	12 – 13	5 – 14
5 years	24 – 29	25 – 40

Sacco. *Neurology*. 1997;49(suppl 4):S39.
Feinberg et al. *Stroke*. 1994;25:1320.

Secondary stroke prevention

Decreasing risk of recurrent stroke after TIA or non disabling stroke: effectiveness of secondary prevention strategies



Rothwell et al, Lancet Neurol 2011

Antithrombotic / Anticoagulant Therapy

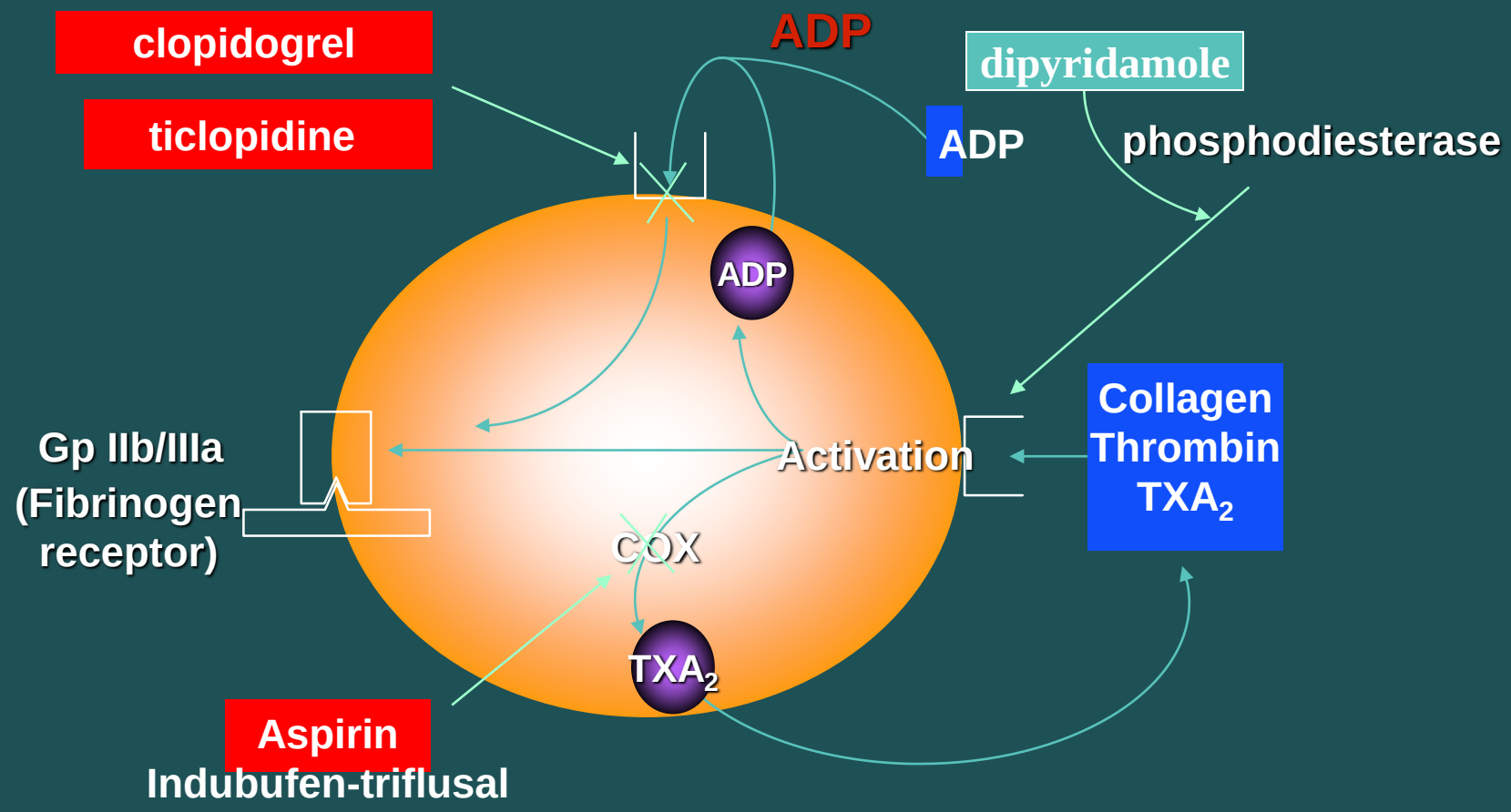
- In patients who have experienced a noncardioembolic stroke or TIA, recommend treatment with an anti-platelet agent. Aspirin at a dose of 100 mg qd; the combination of aspirin, 25mg and extended-release dipyridamole, 200mg bid; or clopidogrel, 75mg qd, are all acceptable options for initial therapy

- Change or add antiplatelet if patient already on therapy

- For cardioembolic stroke: oral anticoagulants (VKI for valvular problems and NOA for AF)

Oral Antiplatelet Agents

Different Mechanisms of Action



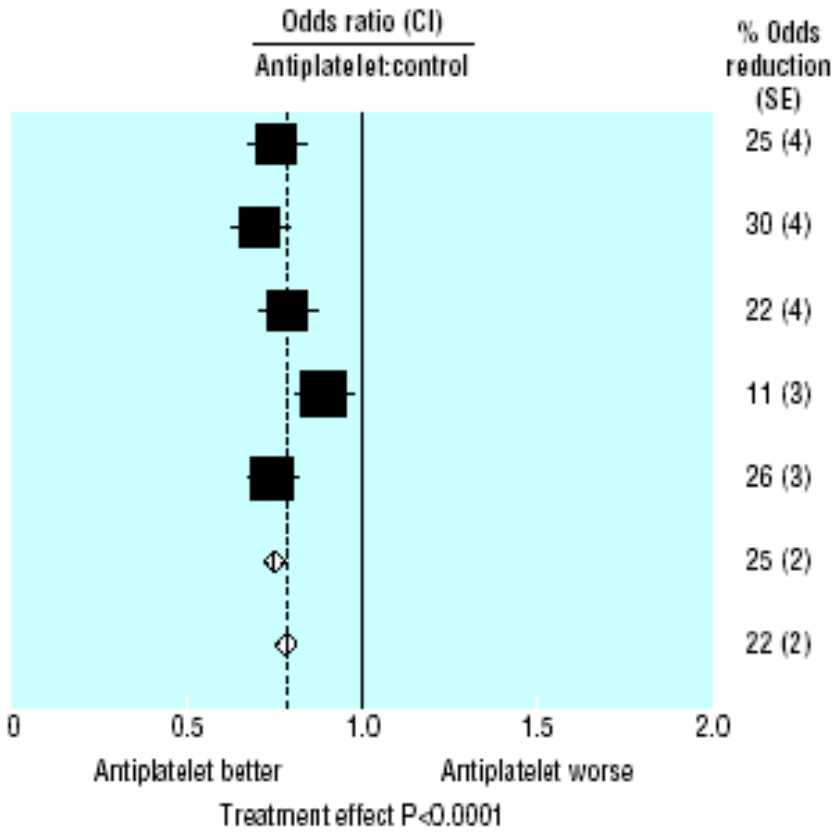
ADP = adenosine diphosphate, TXA_2 = thromboxane A_2, COX = cyclooxygenase.
Schafer AI. *Am J Med*. 1996;101:199-209.

Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients

BMJ 2002;324:71–86

Antithrombotic Trialists' Collaboration

Category of trial	No of trials with data	No (%) of vascular events: Allocated antiplatelet	No (%) of vascular events: Adjusted control	Observed-expected	Variance	% Odds reduction (SE)
Previous myocardial infarction	12	1345/9984 (13.5)	1708/10 022 (17.0)	-159.8	567.6	25 (4)
Acute myocardial infarction	15	1007/9658 (10.4)	1370/9644 (14.2)	-181.5	519.2	30 (4)
Previous stroke/transient ischaemic attack	21	2045/11 493 (17.8)	2464/11 527 (21.4)	-152.1	625.8	22 (4)
Acute stroke	7	1670/20 418 (8.2)	1858/20 403 (9.1)	-94.6	795.3	11 (3)
Other high risk	140	1638/20 359 (8.0)	2102/20 543 (10.2)	-222.3	737.0	26 (3)
Subtotal: all except acute stroke	188	6035/51 494 (11.7)	7644/51 736 (14.8)	-715.7	2449.6	25 (2)
All trials	195	7705/71 912 (10.7)	9502/72 139 (13.2)	-810.3	3244.9	22 (2)



Heterogeneity of odds reductions between:

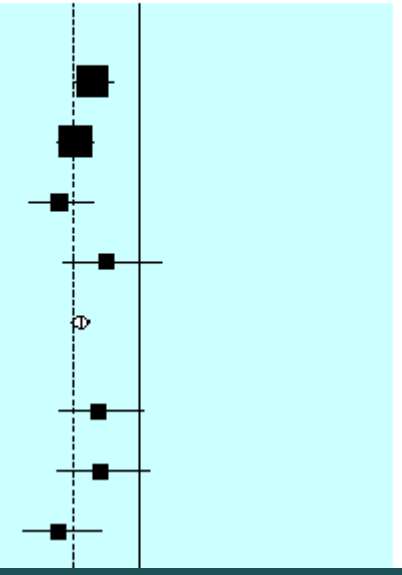
5 categories of trial: χ^2=21.4, df=4; P=0.0003

Acute stroke *v* other: χ^2=18.0, df=1; P=0.00002

Fig 1 Proportional effects of antiplatelet therapy on vascular events (myocardial infarction, stroke, or vascular death) in five main high risk categories. Stratified ratio of odds of an event in treatment groups to that in control groups is plotted for each group of trials (black square) along with its 99% confidence interval (horizontal line). Meta-analysis of results for all trials (and 95% confidence interval) is represented by an open diamond. Adjusted control totals have been calculated after converting any unevenly randomised trials to even ones by counting control groups more than once, but other statistical calculations are based on actual numbers from individual trials

ASA dose and other antiplatelets

Category of trial	No of trials with data	No (%) of vascular events: Allocated antiplatelet	No (%) of vascular events: Adjusted control	Observed-expected	Variance	Odds ratio (CI) Antiplatelet : control	% Odds reduction (SE)
Aspirin alone (mg daily):							
500-1500	34	1621/11 215 (14.5)	1930/11 236 (17.2)	-147.1	707.8		19 (3)
160-325	19	1526/13 240 (11.5)	1963/13 273 (14.8)	-219.9	742.6		26 (3)
75-150	12	366/3370 (10.9)	517/3406 (15.2)	-72.0	183.8		32 (6)
<75	3	316/1827 (17.3)	354/1828 (19.4)	-18.9	136.5		13 (8)
Any aspirin*	65	3829/29 652 (12.9)	4764/29 743 (16.0)	-452.3	1717.0		23 (2)
Other antiplatelet drugs:							
Dipyridamole	15	392/2696 (14.5)	458/2734 (16.8)	-30.9	173.0		16 (7)
Sulfinpyrazone	19	315/2411 (13.1)	361/2416 (14.9)	-23.8	140.7		16 (8)
Ticlopidine	42	278/3435 (8.1)	385/3475 (11.1)	-50.5	132.3		32 (7)



Established and new anticoagulants for stroke prevention in atrial fibrillation

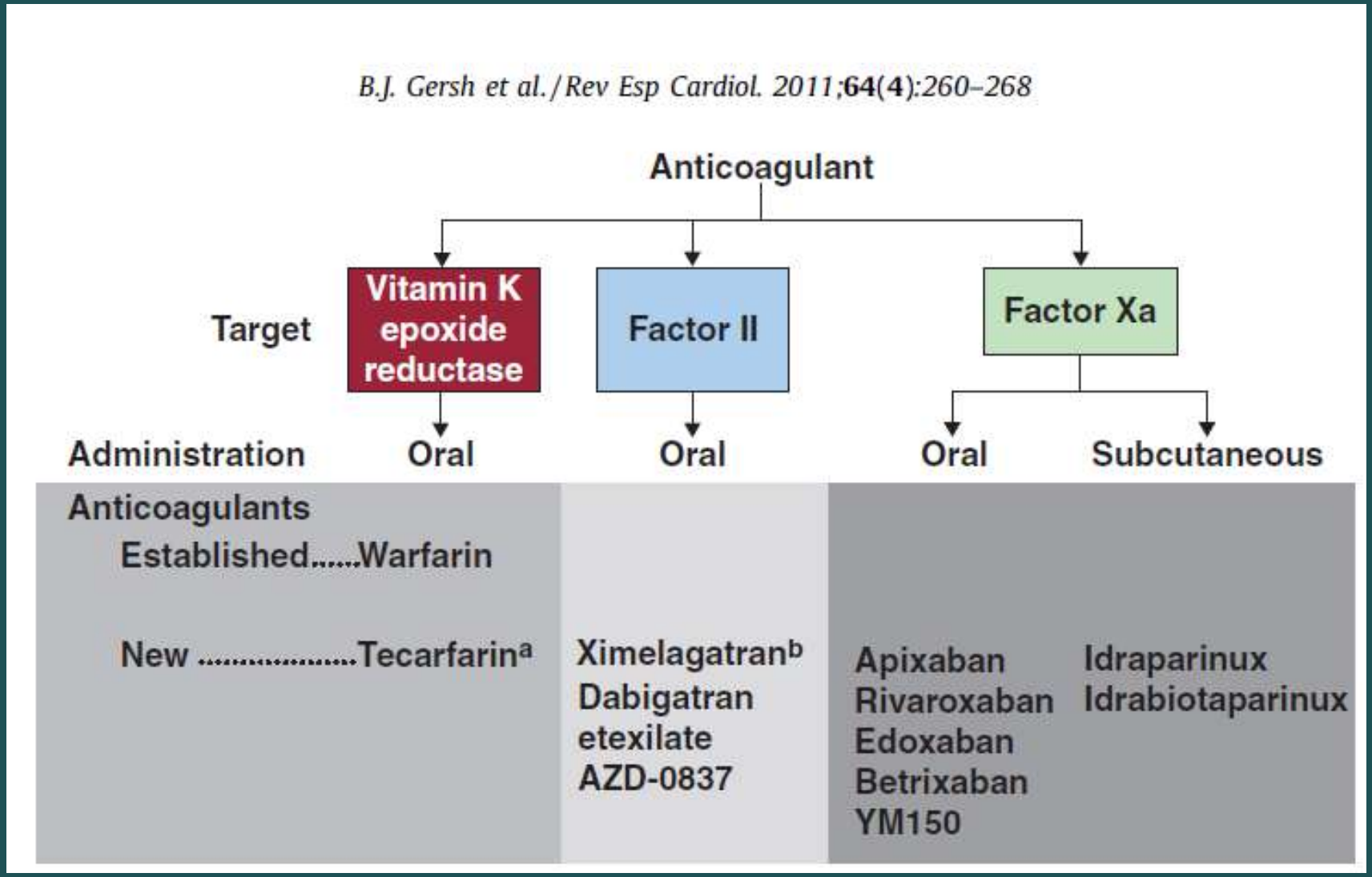


Table II. Comparison of direct thrombin inhibitors and factor Xa inhibitors for anticoagulation in patients with atrial fibrillation.[2,7,8,10]

Drug	Dabigatran	Rivaroxaban	Apixaban
Mechanism of action	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Approved indication	Prevention of stroke and embolism in nonvalvular AF	Prevention of stroke and embolism in nonvalvular AF; thromboprophylaxis following hip or knee replacement surgery	Not yet FDA approved
Dosing and frequency	AF: 150 mg BID	AF: 20 mg/d; VTE prophylaxis: 10 mg/d	AF: 5 mg BID
Renal dosage adjustment	Yes; 75 mg BID	Yes; 15 mg once daily	Yes; 2.5 mg BID
Bioavailability, %	3–7	80–100	66
T_{max}, h	1	2–4	3–4
$t_{½}$, h	12–17	5–9	12
Protein binding, %	35	92–95	87
Common adverse events*	Dyspepsia	Elevated hepatic GGT	Nausea
Reversal agent	None	None	None

AF = atrial fibrillation; FDA = US Food and Drug Administration; GGT = γ-glutamyl transpeptidase; VTE = venous thromboembolism.
*Other than bleeding.

Risk of stroke in patients with AF

CHADSVASC risk score calculator

Please select CHADSVASC and HASBLED risk factors, EHRA score and click copy to clipboard to copy and paste in your electronic files

Chadsvasc risk factors

RISK FACTORS	SCORE
Congestive heart failure	1
Hypertension	1
Age ≥ 75	2
Age 65-74	1
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease	1
Sex Female	1
Your score	0

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CHADSVASC clinical risk estimation. Adapted from Lips et al.

CHA_2DS_2VASc SCORE	PATIENTS (n=7329)	ADJUSTED STROKE RATE (% year)
0	1	0%
1	422	1,3%
2	1230	2,2%
3	1730	3,2%
4	1718	4,0%
5	1159	6,7%
6	679	9,8%
7	294	9,6%
8	82	6,7%
9	14	15,2%

- All patients receive statin with goal LDL<100. Established evidence in patients with CAD and atherosclerotic ischemic stroke. All patients given BP meds with goal <140/90 or <130/80 with DM or renal disease.

- Smoking Cessation

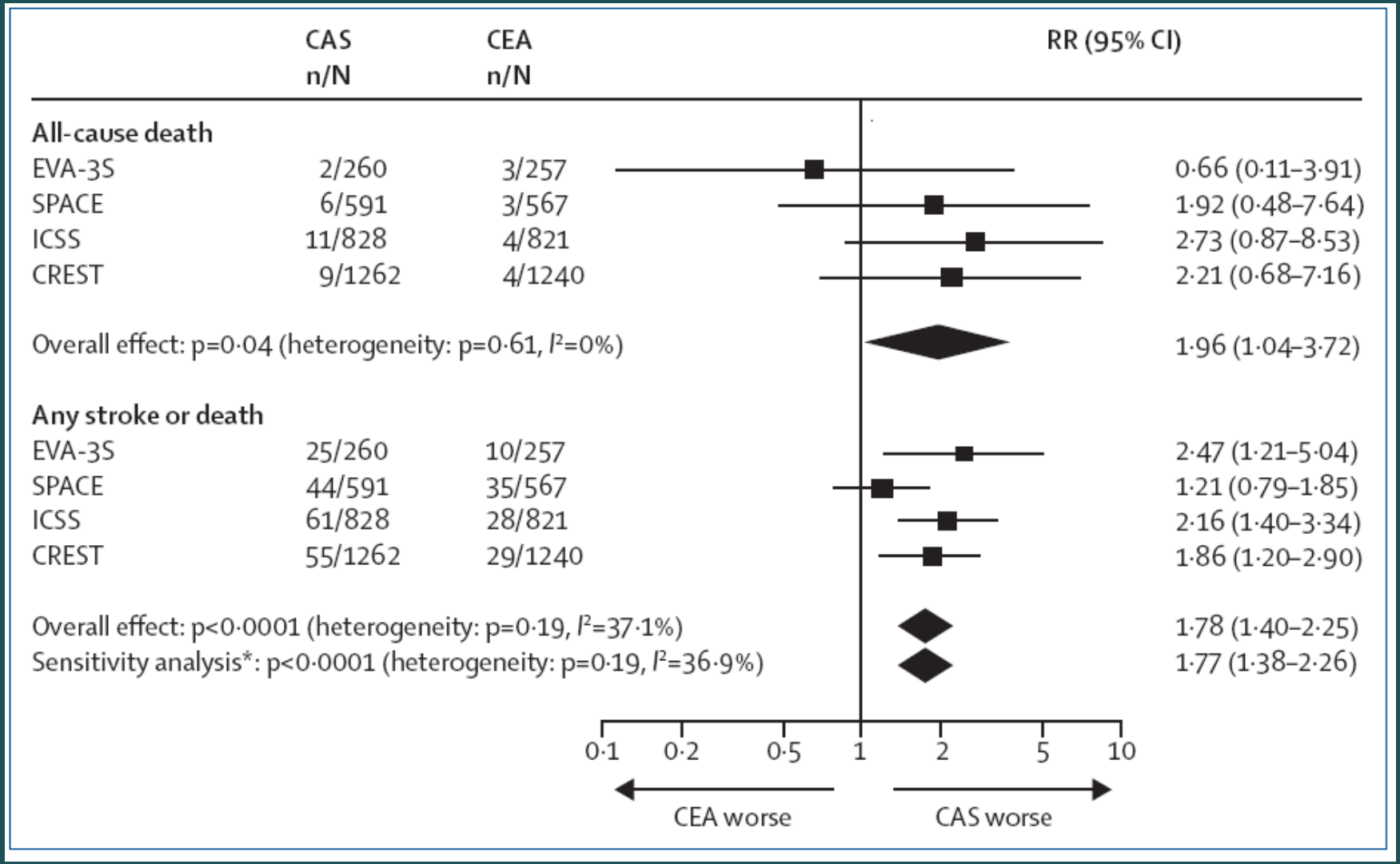
- Diet and Exercise Regimen

- Stroke Education

Mechanisms of Action

- Lipid lowering is not the entire answer
  - Benefits seen in patients with relatively normal levels
- Plaque stabilization
- Anticoagulant effects (fibrinogen, PAI-1)
- Reduces C-reactive protein
- Improves cerebral vasomotor reactivity
- Modulates brain nitric oxide system
- Possible neuro-protective effect in acute strokes

Individual and pooled relative risks of death and of combined stroke and death within 30 days of randomisation in EVA 3S, SPACE, ICSS and CREST trials



Amarenco et al, Lancet 2010

Indications to Carotid Stenting

1. Anatomical conditions:
    a. Restenosis
    b. Previous neck irradiation or neck surgery
    c. High bifurcation
    d. Contralateral carotid occlusion and abnormalities of the circle of Willis (high risk of cerebral ischemia during carotid clamping)
    e. Contralateral laryngeal palsy

Indications to Carotid Stenting

2. High risk patients due to medical comorbidities:
   a. Cardiac
   b. Renal
   c. Pulmonary

CEA or CS?

Individual decision, based on:

Patient history – risk factors – anatomical conditions – plaque characteristics