Practical Considerations in the Early Treatment of Acute Stroke

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Disclosures

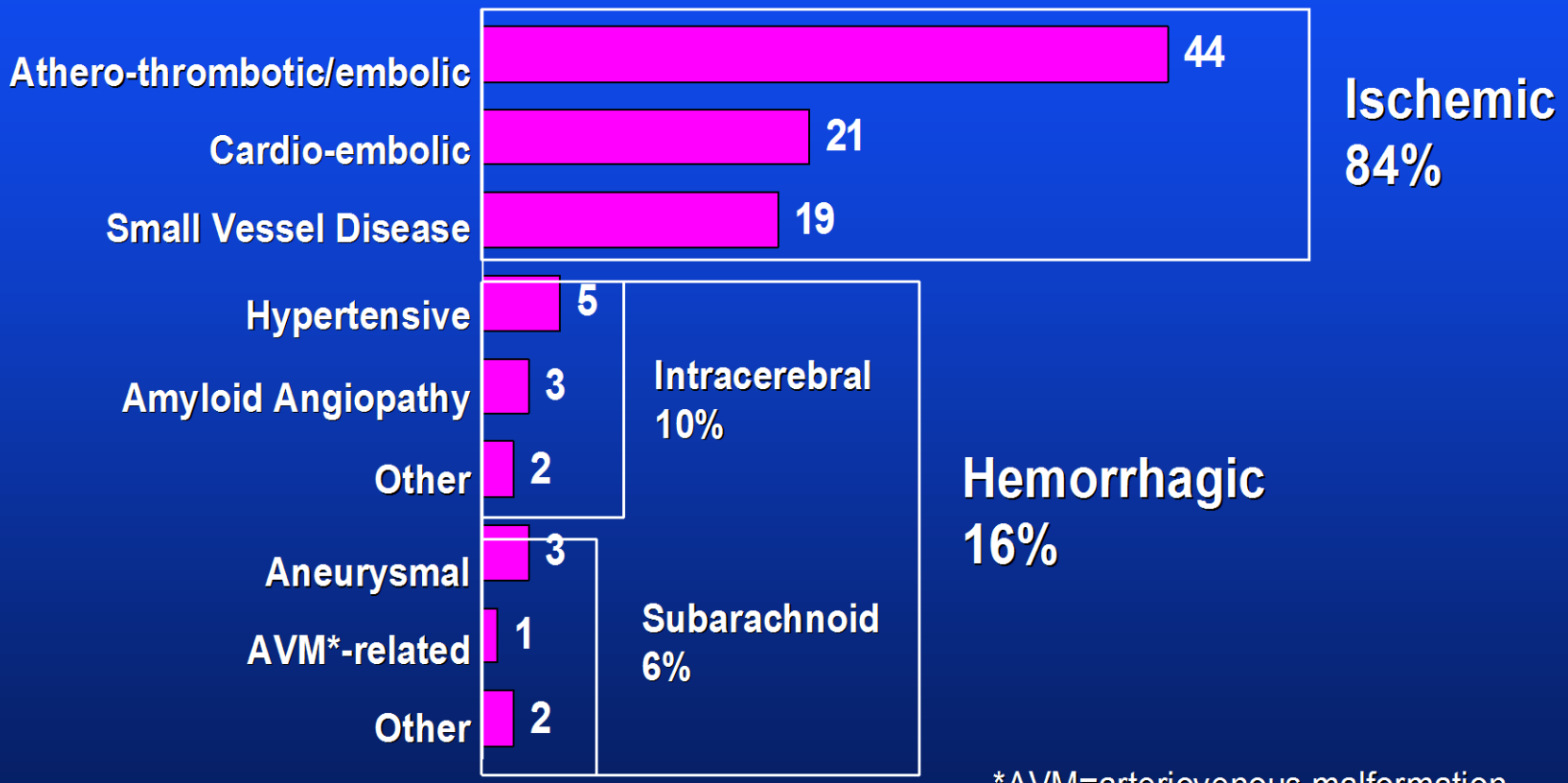
Consultant –	Novartis
	Procter & Gamble
Advisory Board –	Maquet/Datascope
Editor -	Neurology ALERT

Stroke Facts – AHA 2012

- 800,000 new strokes per year in US
- 30% will die within one year
- 2nd leading cause of death world-wide
- #1 cause of permanent disability
- 5,000,000 stroke survivors
- 50% decline in incidence over 30 yrs.
- 4th leading cause of death in US

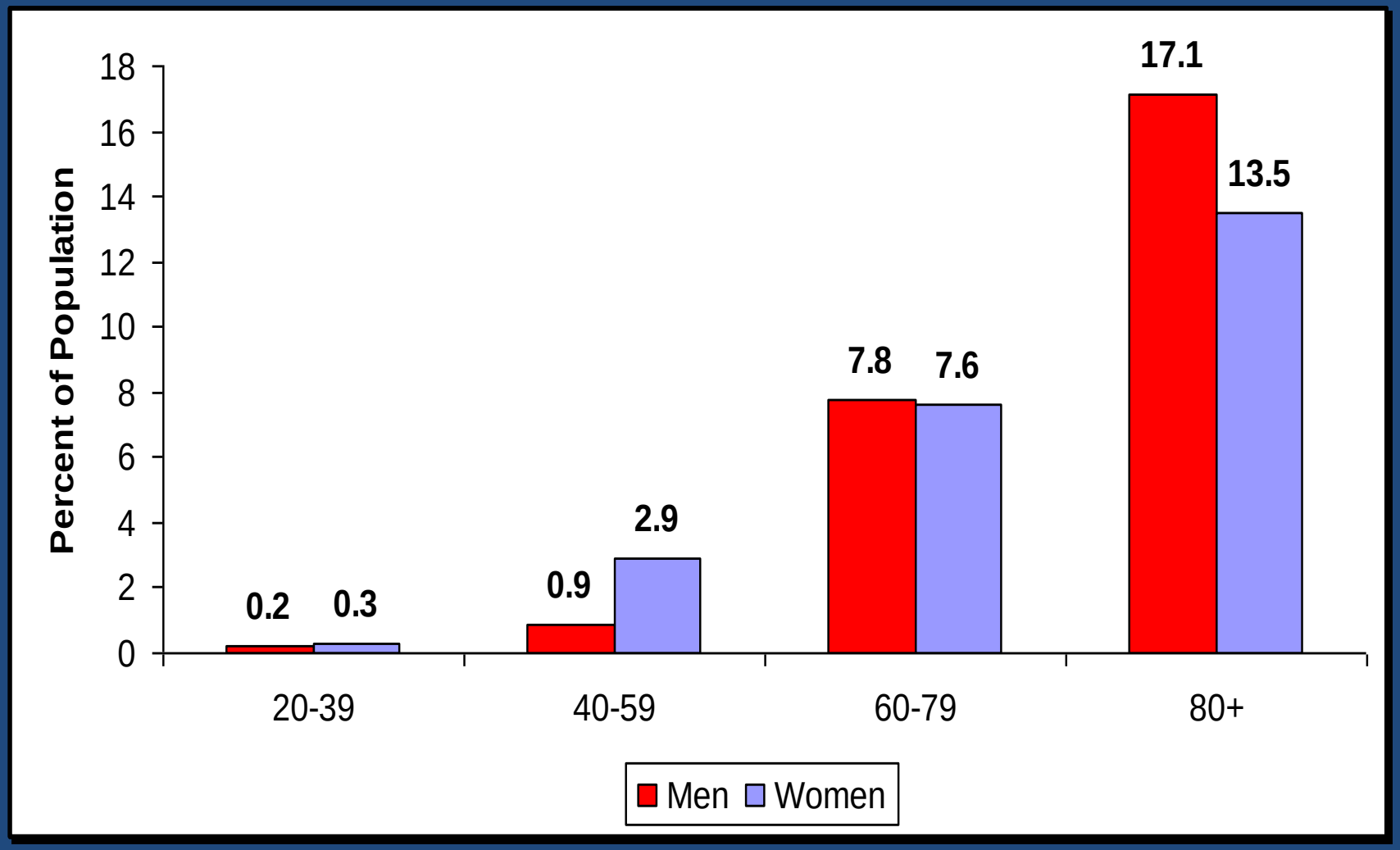
Stroke Classification

Mechanisms of Stroke



*AVM=arteriovenous malformation

Stroke: Clinical Updates 1991;I(5):17 National Stroke Association as adapted from the Harvard Stroke Registry, *Neurology* 1978;28:754-762



Prevalence of stroke by age and sex (NHANES: 2005-2006).

Source: NCHS and NHLBI.


They Started a Joke : Amy Poehler, Seth Meyers, Ed Helms... on fifteen years of the Upright Citizens Brigade. p.30
The Murder Capital of N.Y. / Jonathan Chait on Fed-Bashing
+ Against Bipartisanship, by Frank Rich p.28 / The Myth of the Independent Voter p.32
NEW YORK
REBECCA BLACK
OCTOBER 3, 2011
Is She Just Too Old For This?
New parents over 50 – child-rearing's final frontier.
By Lisa Miller

Trends in Pregnancy Hospitalizations 1994-2004 in the U.S.

Kuklina et.al. CDC. Stroke 2011

Queried National Inpatient Sample for all hospitalizations – pregnancy and stroke

From 1994-95 compared to 2006-07

47% increase for antepartum period

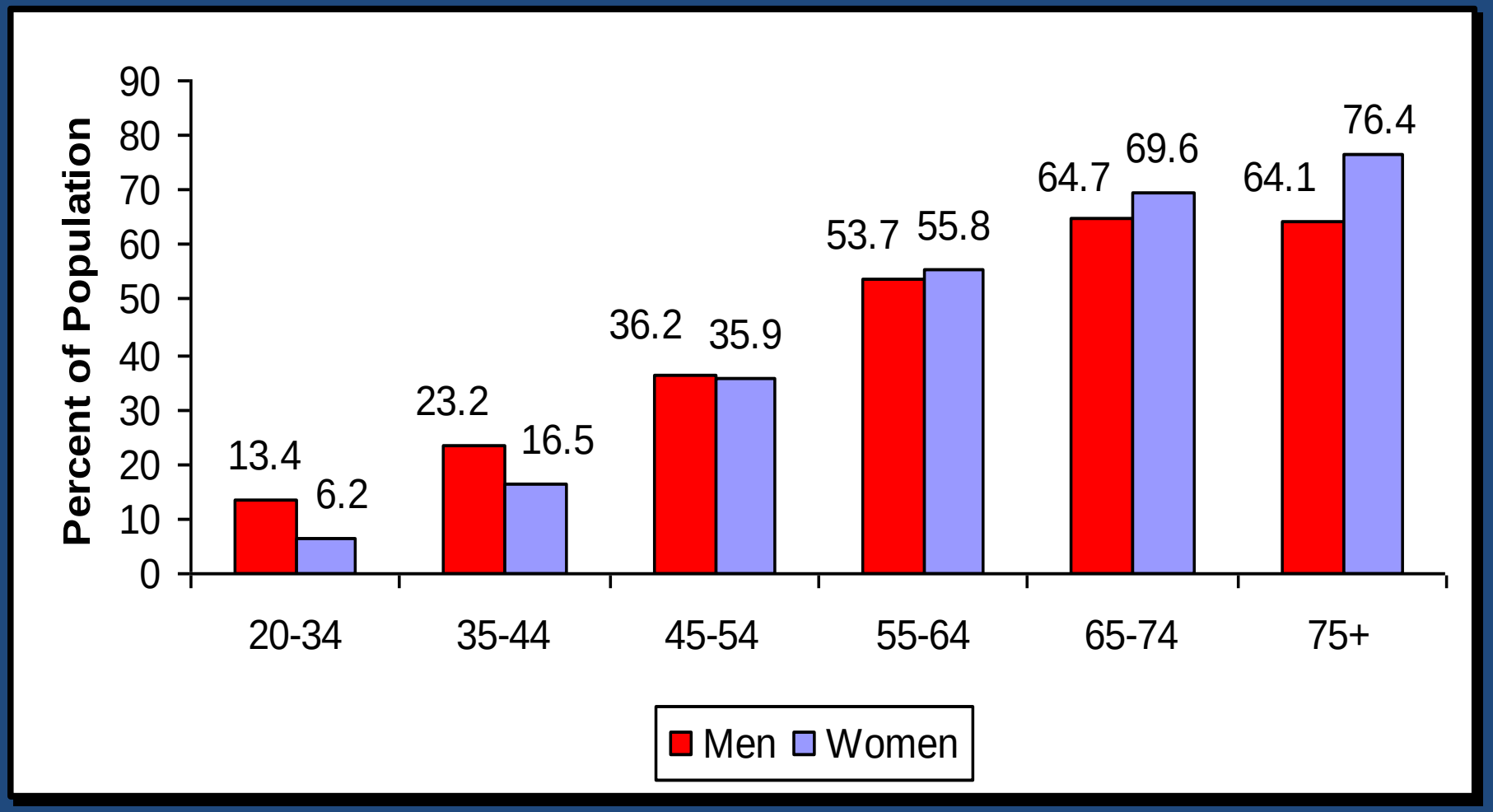
83% increase for postpartum period

Why the increase in pregnancy-associated stroke?

- Age - older women becoming pregnant.

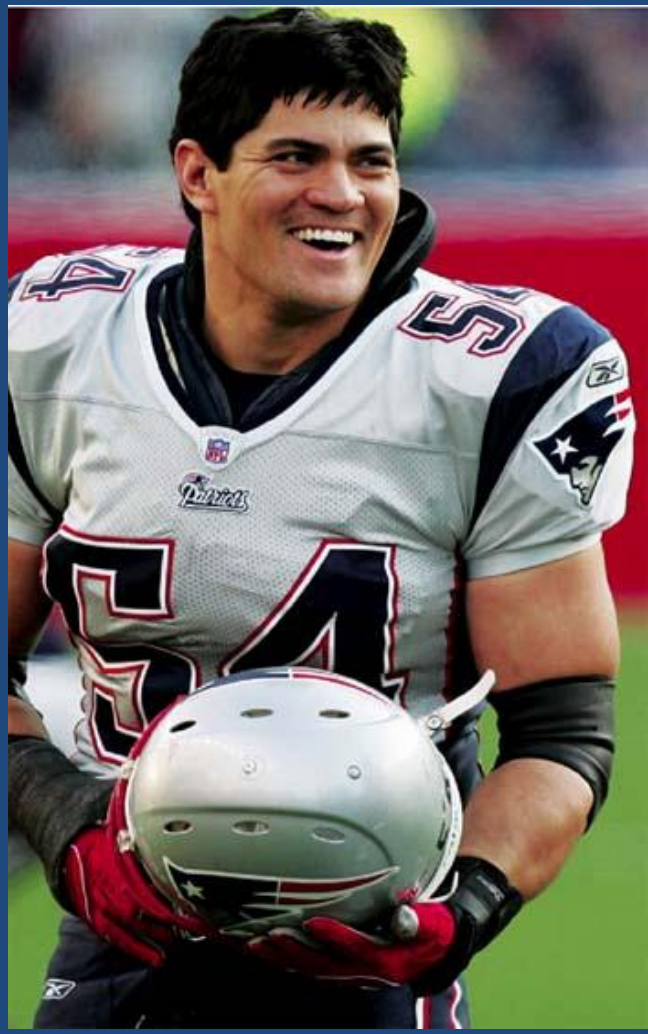
  > age 35 increased from 19% to 25%
- Hypertension in postpartum group increased from 28% to 41%
- Heart disease
- Obesity
- Diabetes
- Multiple births

Carotid atherosclerosis



Prevalence of high blood pressure in Adults by age and sex (NHANES: 2005-2006). Source: NCHS and NHLBI.

At Risk for Stroke?



Cardiac Risk Factors for Stroke
(40% of strokes < age 60)

- Atrial Fibrillation
- Valvular Heart Disease

  MVP, endocarditis, prosthetic valves
- Intracardiac Congenital Defects

  PFO, ASD, AS aneurysm
- Acute Myocardial Infarction

  (AHA/ASA Guidelines, 2006)

	Test or procedure
Antiphospholipid syndrome	Lupus anticoagulant, anticardiolipin, and anti-β-2 glycoprotein antibodies*
Systemic lupus erythematosus, other connective tissue diseases, Wegener's granulomatosis, Churg-Strauss syndrome	ANA, anti-ds-DNA, ENAs, complement, ANCA
Specific infections	Serum titres for syphilis, borrelia, zoster virus, hepatitis B and C virus, and HIV infection†
Hepatitis C virus, other cryoglobulinemias	Cryoglobulins
Illicit drugs	Serum and urine toxicological screening
Primary CNS and other vasculitis, CNS and systemic infections	CSF examination
Hyperhomocysteinaemia	Homocysteine concentrations
Specific deficiencies	Antithrombin III, protein S or C concentrations‡
Specific mutations	Factor V Leiden, prothrombin G20210A mutations
Sickle-cell disease	Haemoglobin electrophoresis§
Several inflammatory, infectious and genetic diseases, retinocerebral arteriopathies	Ophthalmological examination
Primary CNS and other medium and large-vessel vasculitis, non-atherosclerotic arteriopathies	Intra-arterial cerebral angiography¶
Periarteritis nodosa	Abdominal and renal angiography
Takayasu's disease	Aortic PET
Primary CNS vasculitis	Cerebromeningeal biopsy
Fabry's disease	GLA activity
CADASIL	Skin biopsy
MELAS	Muscle biopsy
Specific genetic diseases (Fabry's, CADASIL, HANAC syndrome, MELAS, etc)	Genetic tests

Ferro, Lancet Neurol, 2010

MODIFIABLE RISK FACTORS for STROKE

- Previous Stroke or TIA
- Hypertension
- Cardiac Disease *
- Diabetes+ and Glucose Metabolism
- Hypercholesterolemia
- Carotid Artery Disease
- Cigarette Smoking
- Lifestyle Factors
  (obesity, physical inactivity, diet, illicit drug use, emotional stress)
- Oral contraceptives

* Including: atrial fibrillation, sinoatrial disorder, recent acute myocardial infarction, marantic or subacute bacterial endocarditis, cardiac tumors, left atrial enlargement and valvular disorders, both native and artificial

+ Glucose status

Prevention Conference IV: Executive Summary. *Circulation* 1997;96:701-707.

Goals of Emergency Treatment

- Rapid recognition & treatment of focal ischemia
- Medication for neuronal protection
- Restoration of blood flow to ischemic regions

Signs of Acute Stroke

The Cincinnati Prehospital Stroke Scale

American Stroke Association
A Division of American Heart Association

(Kothari R, et al. *Acad Emerg Med.* 1997;4:986-990.)

Facial Droop (have patient show teeth or smile):

- **Normal** — both sides of face move equally
- **Abnormal** — one side of face does not move as well as the other side

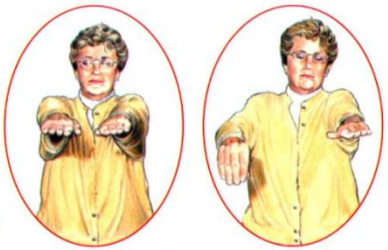
Arm Drift (patient closes eyes and holds both arms straight out for 10 seconds):

- **Normal** — both arms move the same *or* both arms do not move at all (other findings, such as pronator drift, may be helpful)
- **Abnormal** — one arm does not move *or* one arm drifts down compared with the other

Left: normal. Right: stroke patient with facial droop (right side of face).

Abnormal Speech (have the patient say "you can't teach an old dog new tricks"):

- **Normal** — patient uses correct words with no slurring
- **Abnormal** — patient slurs words, uses the wrong words, or is unable to speak



Left: normal. Right: one-sided motor weakness (right arm).

Interpretation: If any *1* of these 3 signs is abnormal, the probability of a stroke is 72%.

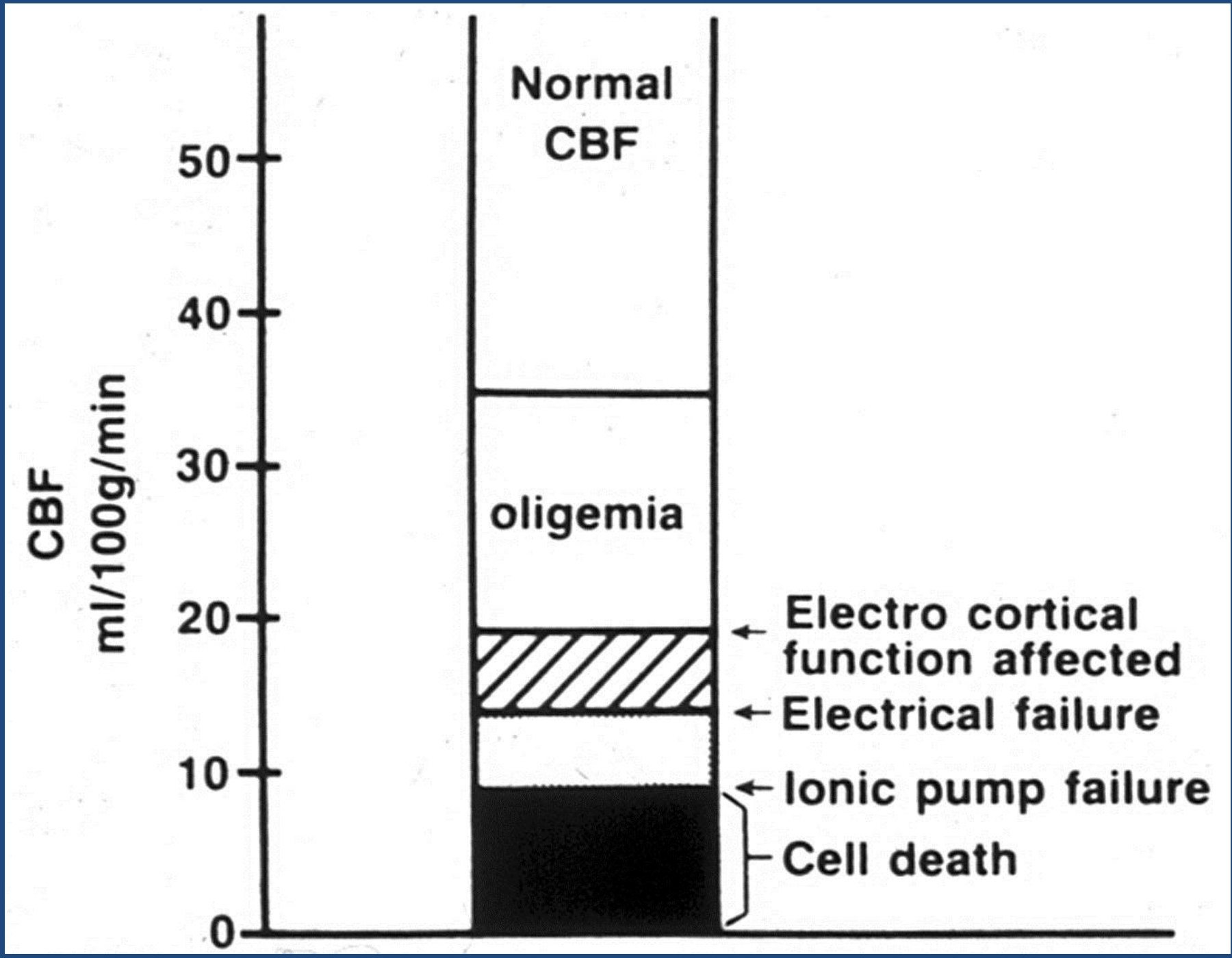
Neuroprotection

- Thousands of compounds have been tested in the laboratory
- Hundreds of compounds have been tested in clinical trials –billions of $$ spent
- So far, none have demonstrated any significant clinical benefits
- The latest failure – SAINT I, II

Reperfusion of the ischemic brain is the most effective therapy for acute ischemic stroke ever known and ever likely to be discovered.

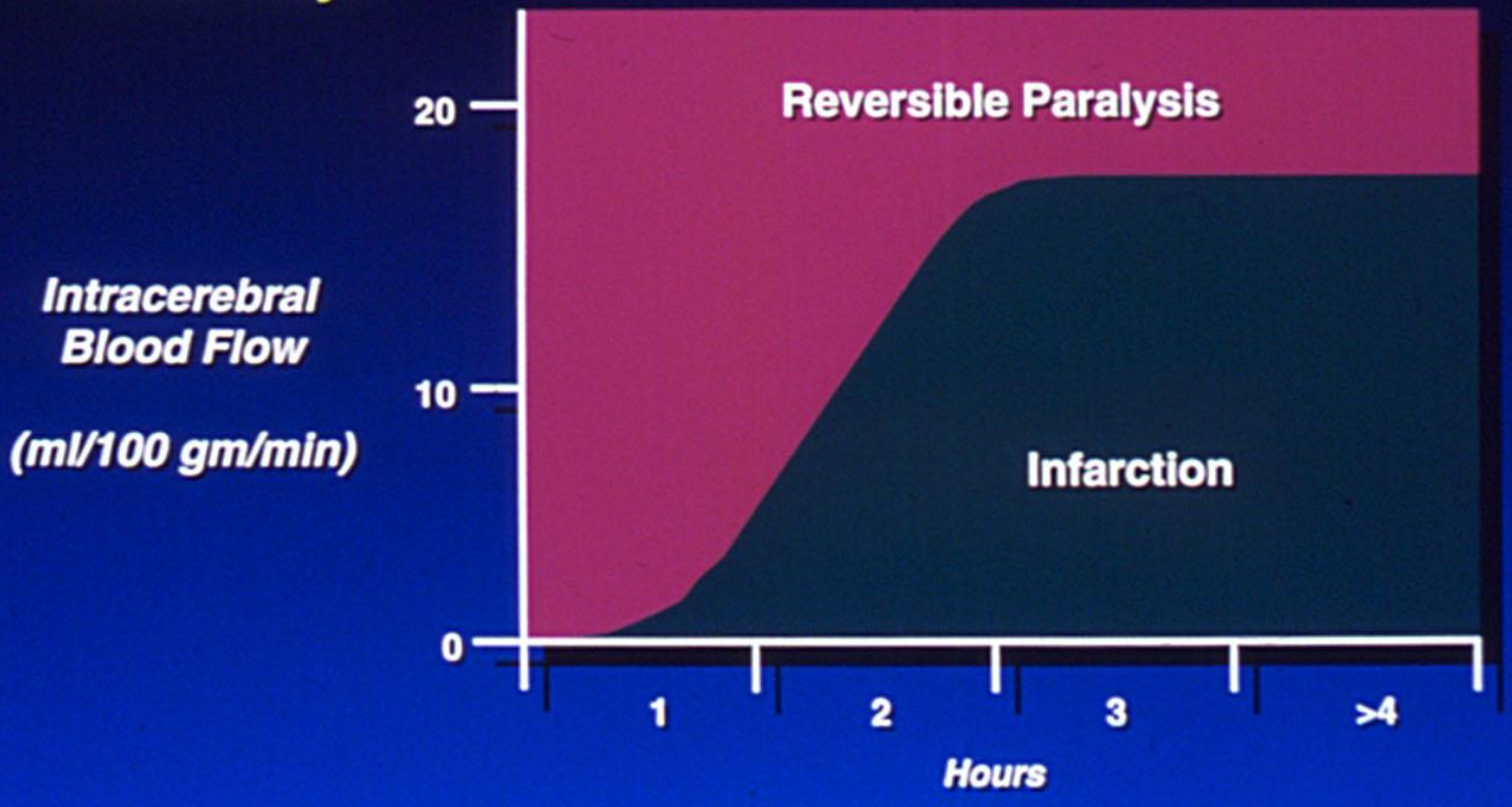
Molina & Saver

Stroke 2005;36:2311


Normal
CBF
oligemia
CBF
ml/100g/min
50
40
30
20
10
0
Electro cortical
function affected
Electrical failure
Ionic pump failure
Cell death

REVERSIBLE AND IRREVERSIBLE ISCHEMIC THRESHOLDS

In Monkeys



Adapted from: Jones TH, et al. J Neurosurg. 1981; 54:773.

Factors That Influence Outcome After Focal Brain Ischemia

1. Duration of Ischemia
2. Degree of Collaterals
3. Animal Species
4. Arterial Blood Pressure
5. p O2
6. Hematocrit
7. Glucose
8. Core Temperature

Algorithm for Suspected Stroke

American Stroke Association℠

A Division of American Heart Association

Suspected Stroke

EMS assessments and actions

Immediate assessments performed by EMS personnel include

- *Cincinnati Prehospital Stroke Scale* (includes difficulty speaking, arm weakness, facial droop)
- *Los Angeles Prehospital Stroke Screen*
- Alert hospital to possible stroke patient
- Rapid transport to hospital

✔ **Detection**
✔ **Dispatch**
✔ **Delivery**

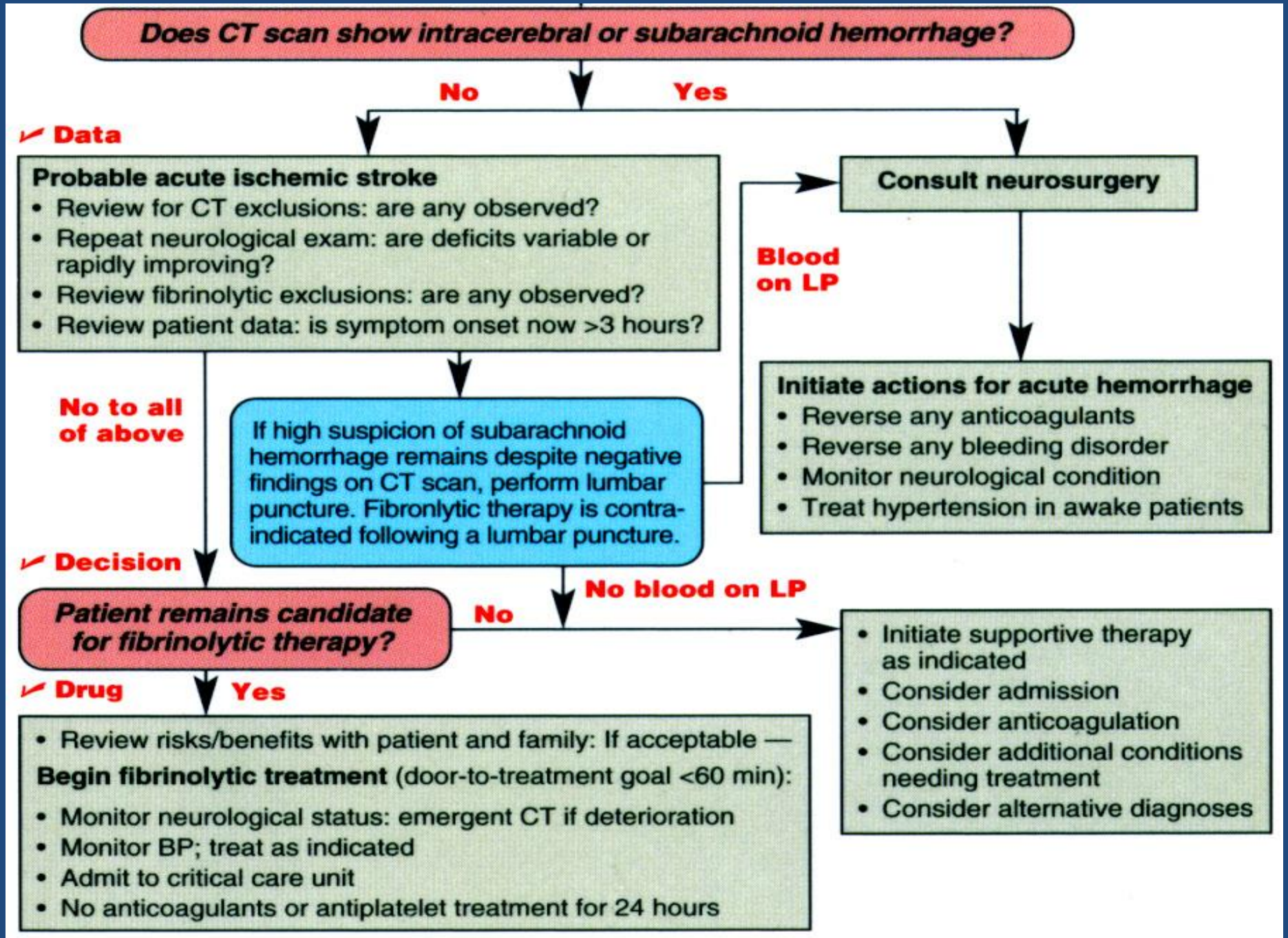
✔ **Door**

Immediate general assessment: <10 minutes from arrival

- Assess ABCs, vital signs
- Provide ***oxygen*** by nasal cannula
- Obtain IV access; obtain blood samples (CBC, electrolytes, coagulation studies)
- Check blood sugar; treat if indicated
- Obtain 12-lead ECG; check for arrhythmias
- Perform general neurological screening assessment
- Alert Stroke Team: neurologist, radiologist, CT technician

Immediate neurological assessment: <25 minutes from arrival

- Review patient history
- Establish onset (<3 hours required for fibrinolytics)
- Perform physical examination
- Perform neurological examination:
  - ✔ Determine level of consciousness *(Glasgow Coma Scale)*
  - ✔ Determine level of stroke severity *(NIH Stroke Scale* or *Hunt and Hess Scale)*
- Order urgent noncontrast CT scan (door-to–CT scan performed: goal <25 minutes from arrival)
- Read CT scan (door-to–CT read: goal <45 minutes from arrival)
- Perform lateral cervical spine x-ray (if patient comatose/history of trauma)


Does CT scan show intracerebral or subarachnoid hemorrhage?
No
Yes
Data
Probable acute ischemic stroke
• Review for CT exclusions: are any observed?
• Repeat neurological exam: are deficits variable or rapidly improving?
• Review fibrinolytic exclusions: are any observed?
• Review patient data: is symptom onset now >3 hours?
Consult neurosurgery
Blood on LP
Initiate actions for acute hemorrhage
• Reverse any anticoagulants
• Reverse any bleeding disorder
• Monitor neurological condition
• Treat hypertension in awake patients
No to all of above
If high suspicion of subarachnoid hemorrhage remains despite negative findings on CT scan, perform lumbar puncture. Fibronlytic therapy is contra-indicated following a lumbar puncture.
Decision
Patient remains candidate for fibrinolytic therapy?
No blood on LP
No
• Initiate supportive therapy as indicated
• Consider admission
• Consider anticoagulation
• Consider additional conditions needing treatment
• Consider alternative diagnoses
Drug
Yes
• Review risks/benefits with patient and family: If acceptable —
Begin fibrinolytic treatment (door-to-treatment goal <60 min):
• Monitor neurological status: emergent CT if deterioration
• Monitor BP; treat as indicated
• Admit to critical care unit
• No anticoagulants or antiplatelet treatment for 24 hours

Transient Ischemic Attacks

What is the risk of stroke?

- One in nine patients will have a stroke within 90 days of TIA (ER diagnosis)
- Half of all strokes occur in the first two days
- Risk with atrial fibrillation is 11%
- Risk with >70% ICA stenosis is 25%

(JAMA 2000;284:290/Arch Neurol 1995;52:246)

Early Questions?

Too much emphasis on the NIHSS !!

- What is the vascular anatomy?
- What is the true age of the acute infarct?
- Is there large vessel, proximal stenosis?
- Is there a cardiac source of embolism?

  (40% < age 60 have cardiogenic embolism)
- Is the deficit disabling?

CT or MR ?

How fast is your hospital?

How responsive are your radiologists ?

Acute Therapy for Ischemic Stroke

- Antiplatelet therapy
- Anticoagulant therapy
- Hemodynamic manipulations
- Thrombolysis – IV and IA
- Angioplasty/Stenting
- Mechanical Clot Removal
- Surgical Interventions

General Care & Treatment

- ABCs
- Temperature
- Cardiac Monitoring & Treatment
- Arterial Hypertension
- Arterial Hypotension
- Hyperglycemia
- Hypoglycemia
- Intracranial Hypertension

NINDS rt-PA Stroke Study

N Engl J Med **1995**;333:1581-7

- 624 patients treated with 0.9 mg/kg/hour
- Treated in less than three hours; ½ less than 90 minutes
- t-PA group: 31-50% complete recovery
- Control: 20-38% complete recovery
- ICH: 6.4% v. 0.6%
- Mortality: 17% v. 20%

ECASS – III

NEJM 2008;359:1317-1329)

Time window can be extended to

4 ½ hours for intravenous rTPA, but is that the best therapy we have to offer ?

(ASA/AHA *Stroke* 2009;40;2945-2948)

ECASS – III

NEJM 2008;359:1317-1329)

0-90 minutes O.R.=2.8

90-180 minutes O.R.=1.6

180-270 minutes O.R.=1.4

ECASS -III

Exclusion Criteria

Age > 80 years

Warfarin use regardless of INR

NIHSS > 25

History of prior stroke and diabetes

(ASA/AHA *Stroke* 2009;40;2945-2948)

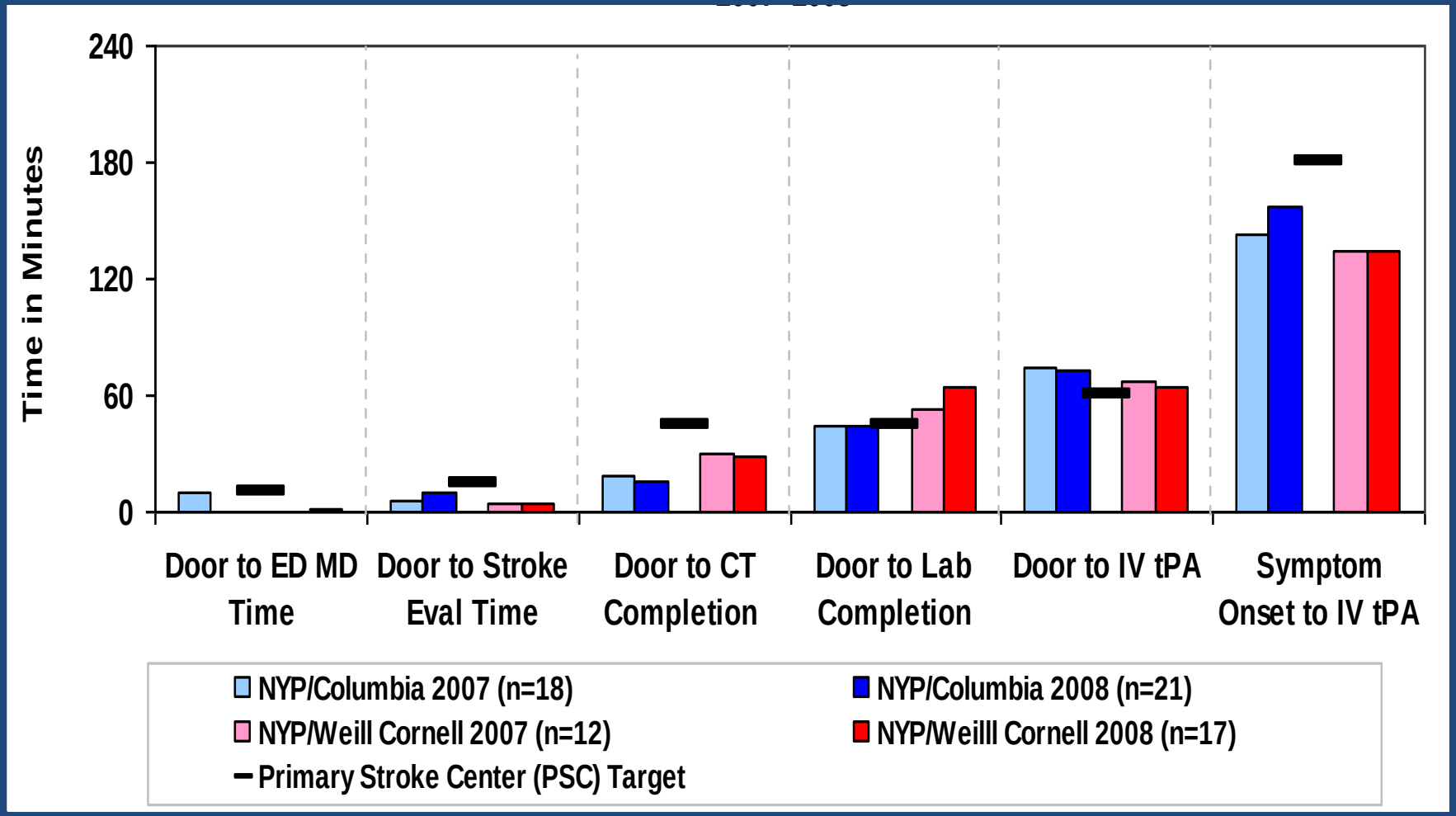
Intravenous Thrombolysis

Disadvantages –

- Short time window
- Poor recanalization of carotid-T, MCA stem, basilar, vertebral
- Systemic exposure to TPA causes bleeding problems

Brain Attack Benchmarks – NYP Results

Acute Stroke Process Measure: IV tPA in the ED



Sources: SPEED QA logs and Get with the Guideline Stroke Registry.
Note: [1.] Time in Minutes are based on median calculations.
[2.] Target times are based on Brain Attack Coalition's recommendations & National Institute of Neurological Disorders and Stroke (NINDS) for Primary Stroke Centers.

Intraarterial Thrombolysis

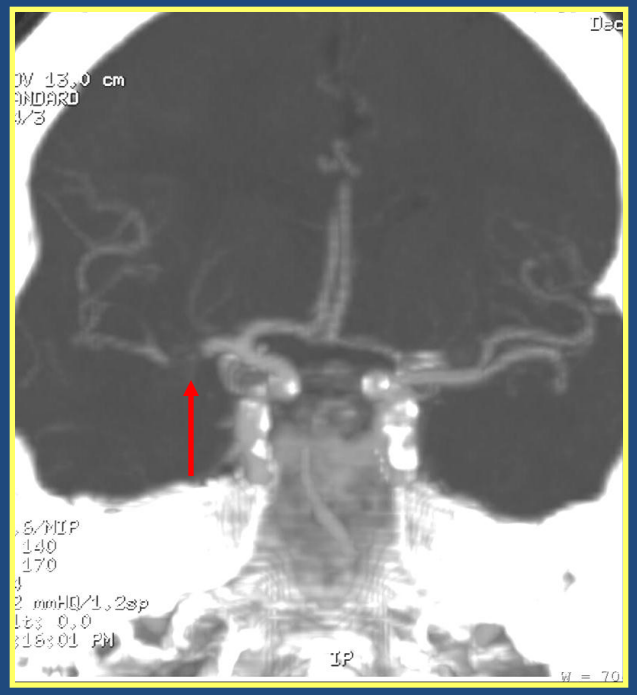
- t-PA , urokinase, or prourokinase
- 75% partial or complete thrombolysis
- PROACT II trial randomized to heparin (1996)
    * treated 3-6 hours after onset
    * MCA occlusion
    * 67% re-opened
    * ICH: 10% v. 2%

Bridging protocol – IV to intraarterial

Acute Ischemic Stroke-CTA

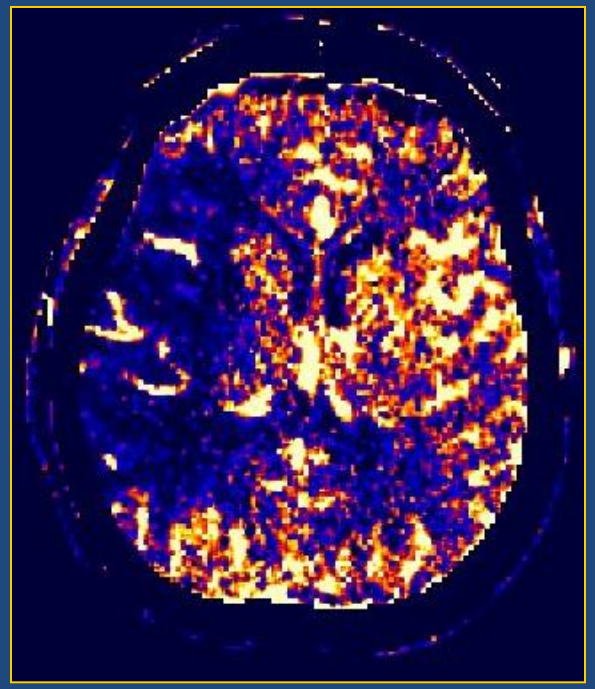
85 yo with left hemiplegia at 3 hours

Non-contrast CT

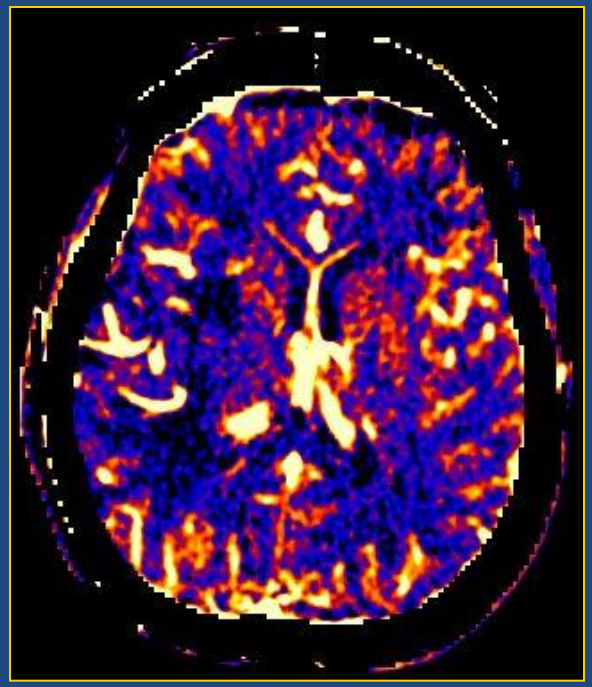


CTangiogram

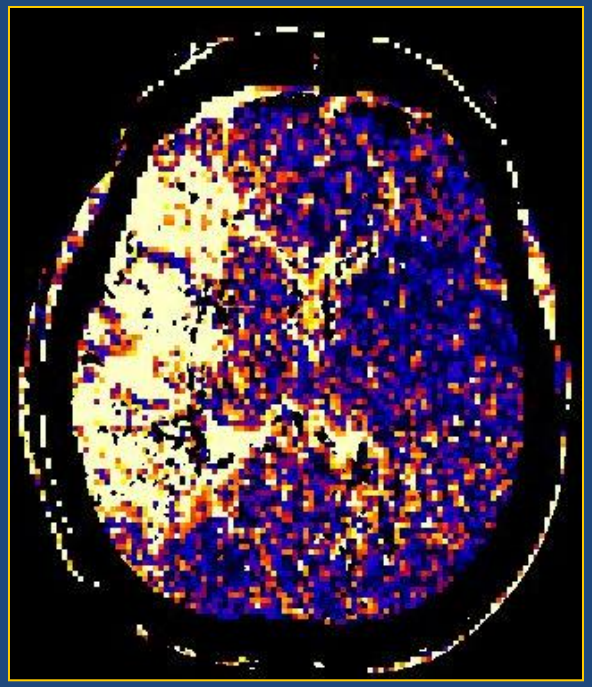
CT Perfusion Studies



CBF

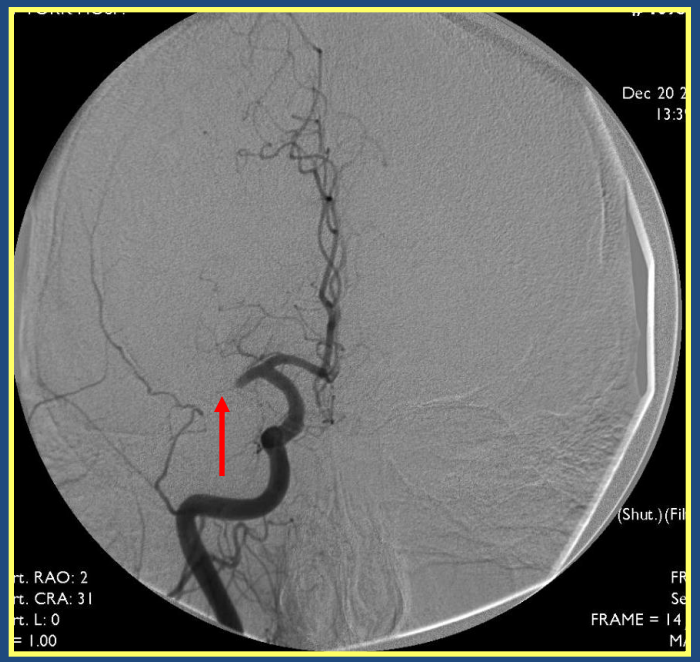


CBV

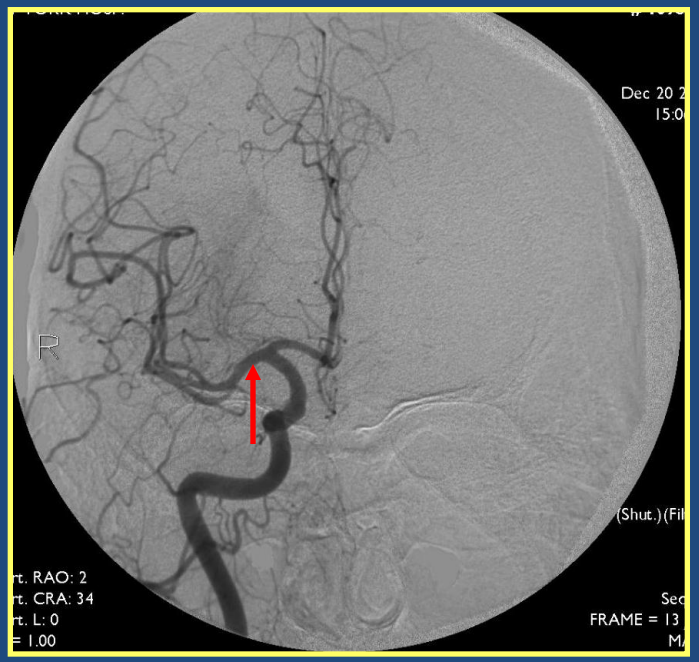


MTT

Intra-arterial TPA

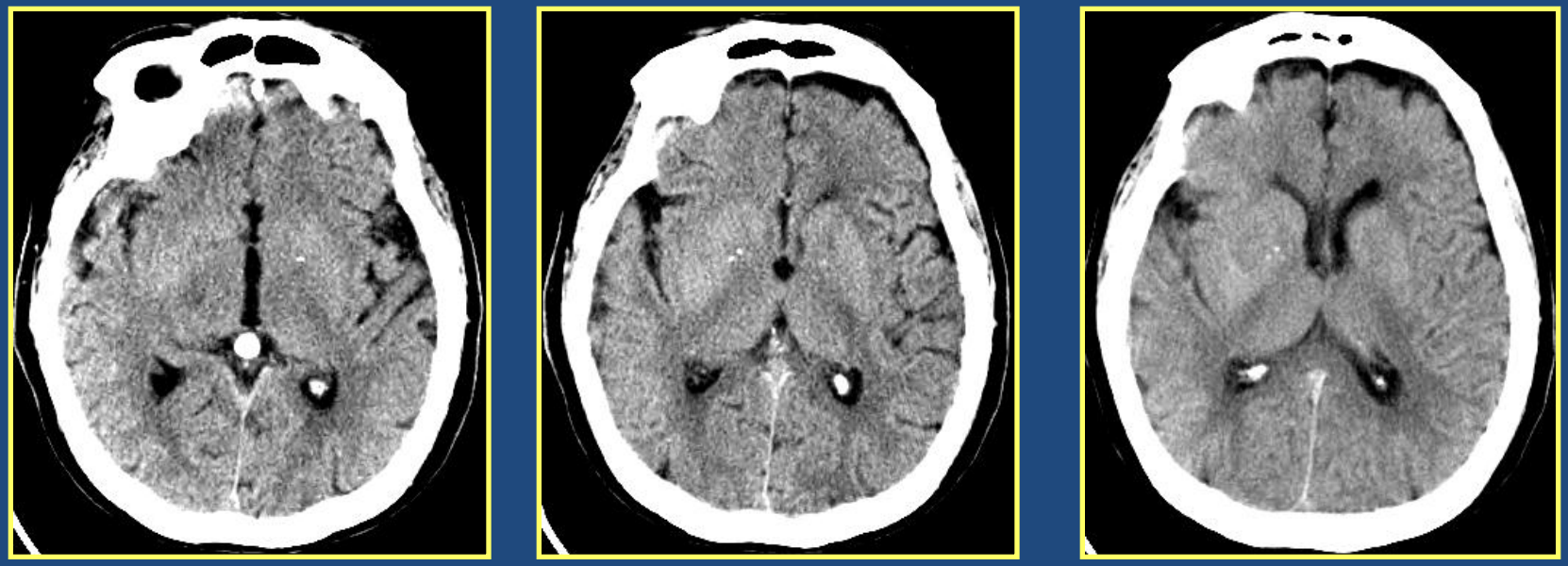


Angio



Post TPA

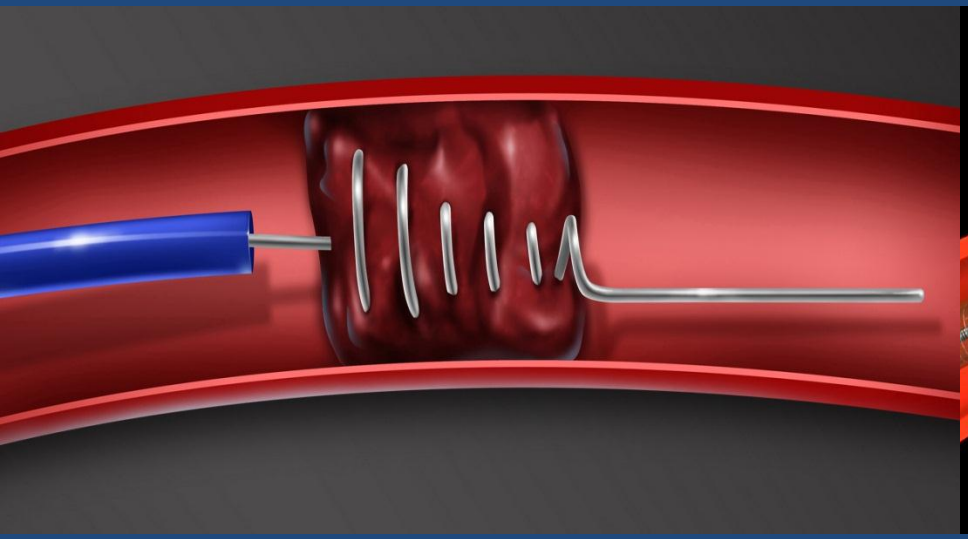
24 hours after IA-TPA



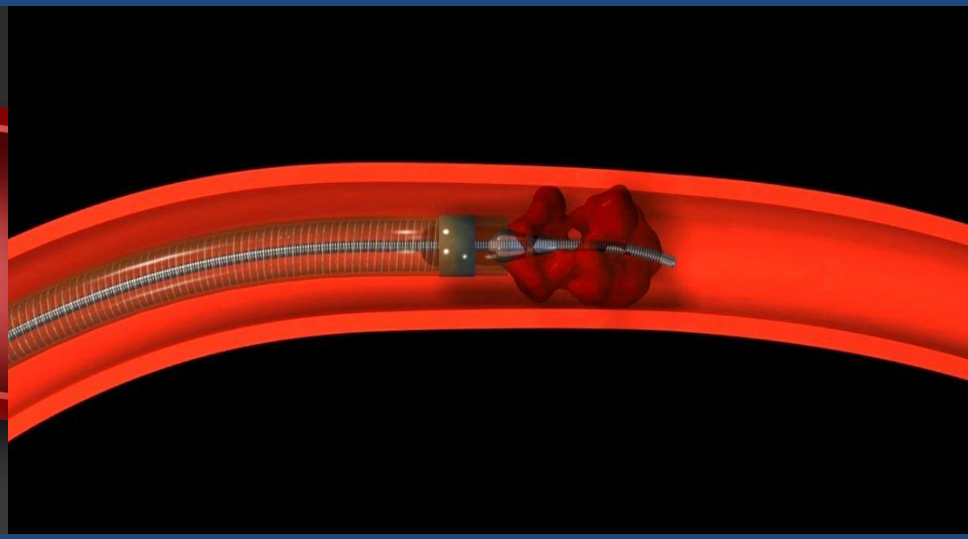
Follow-up CT

Mechanical Thrombectomy

MERCI retriever
FDA Approved in 2004
Concentric Medical, Inc, Mountain View, California



Penumbra system
FDA Approved in 2008
Penumbra, Inc. Alameda, California



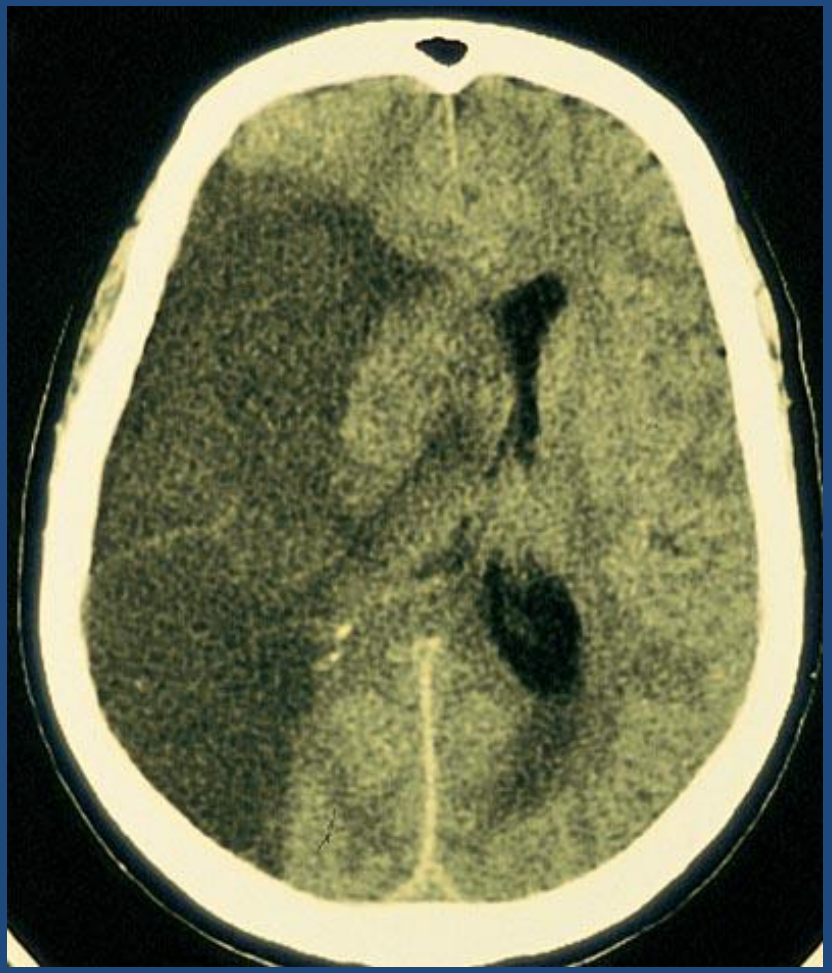
Advantages over chemical thrombolysis:

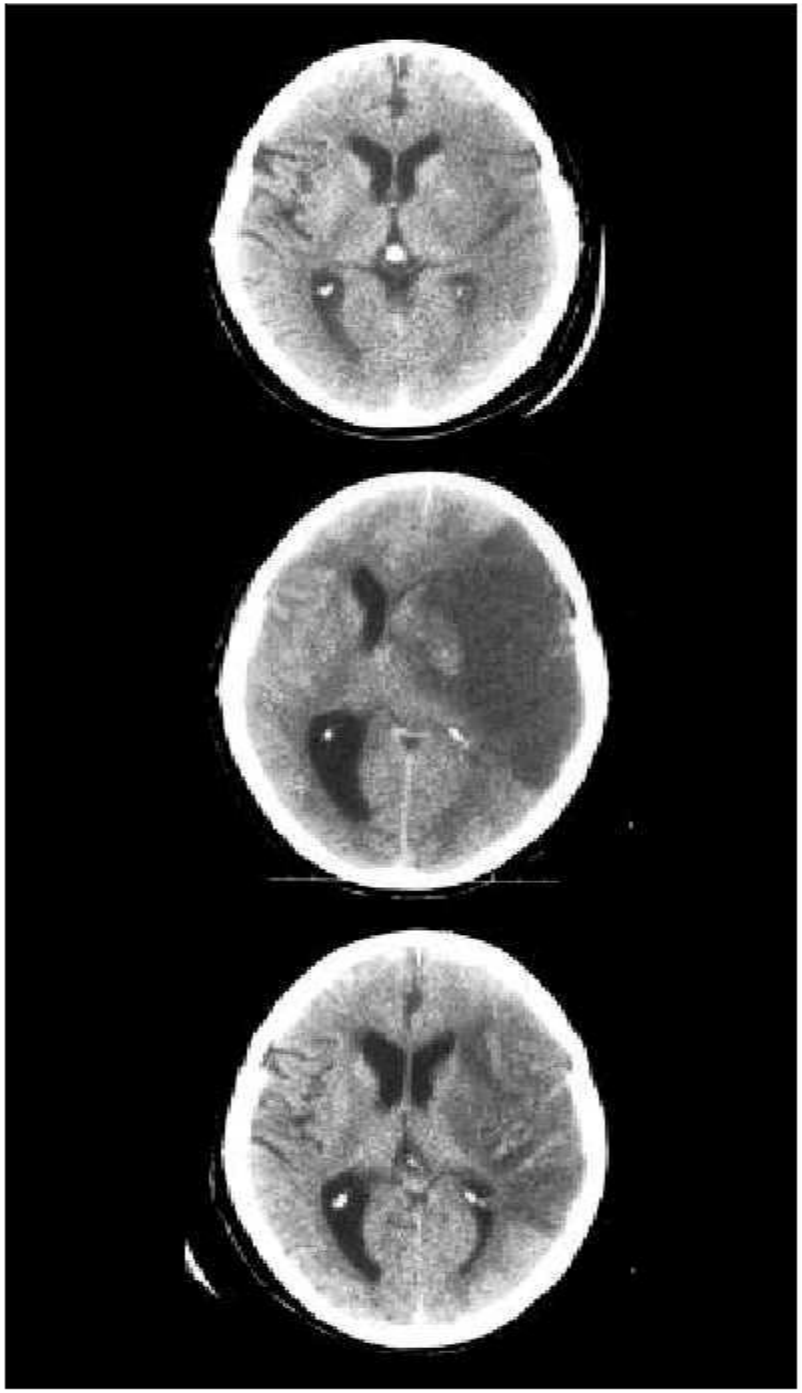
1. Lessens or avoids use of chemical thrombolysis, reducing risk of ICH
2. Extends treatment window beyond 6 hours
3. Faster recanalization (Courtesy of Dr. Daniel Berlin)

Controversial Therapies for Ischemic Stroke

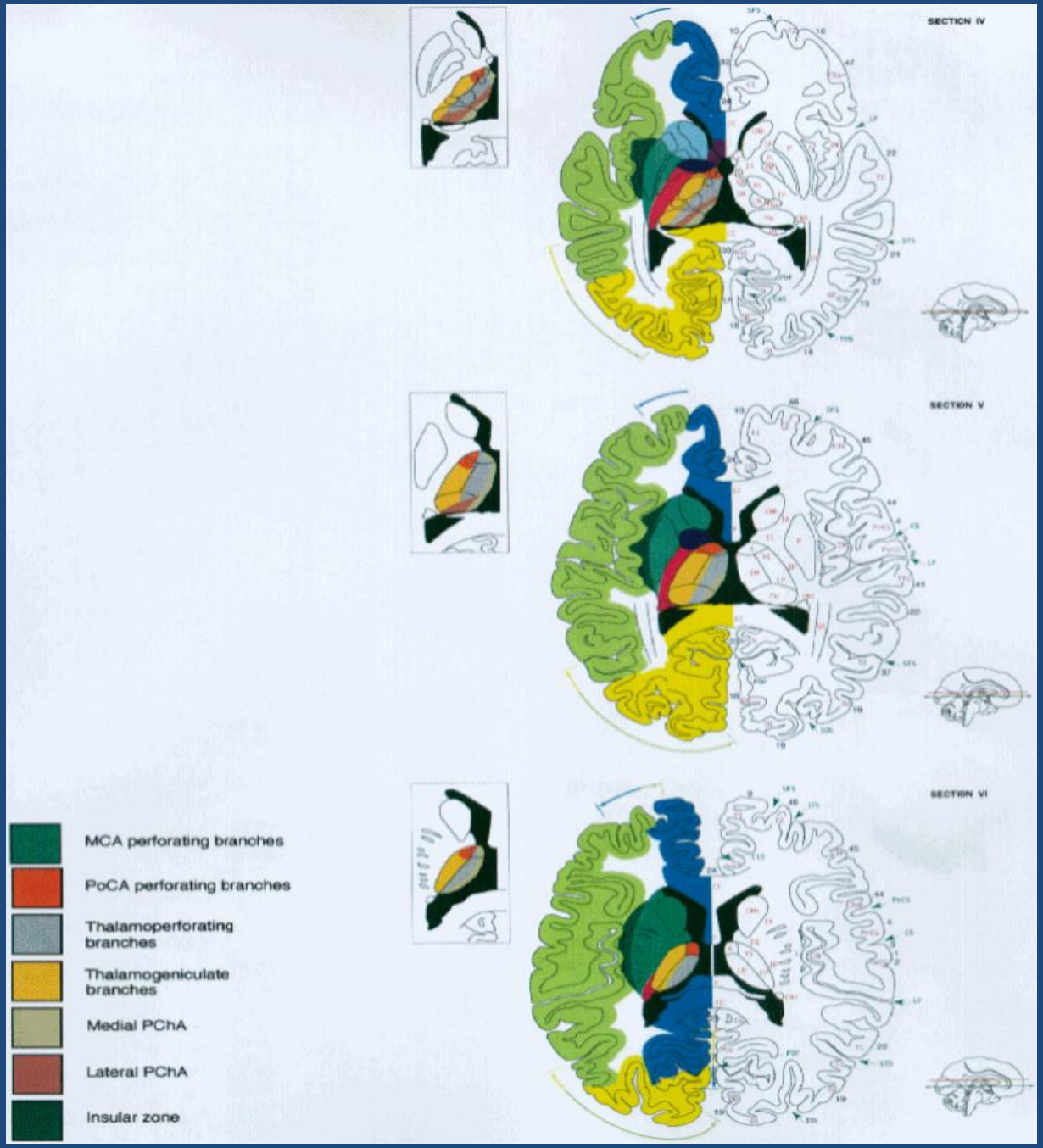
1. Hemicraniectomy for Large Hemispheral Infarcts
2. Induced Hypertension for Ischemic Stroke
3. Therapeutic Hypothermia for Ischemic Stroke

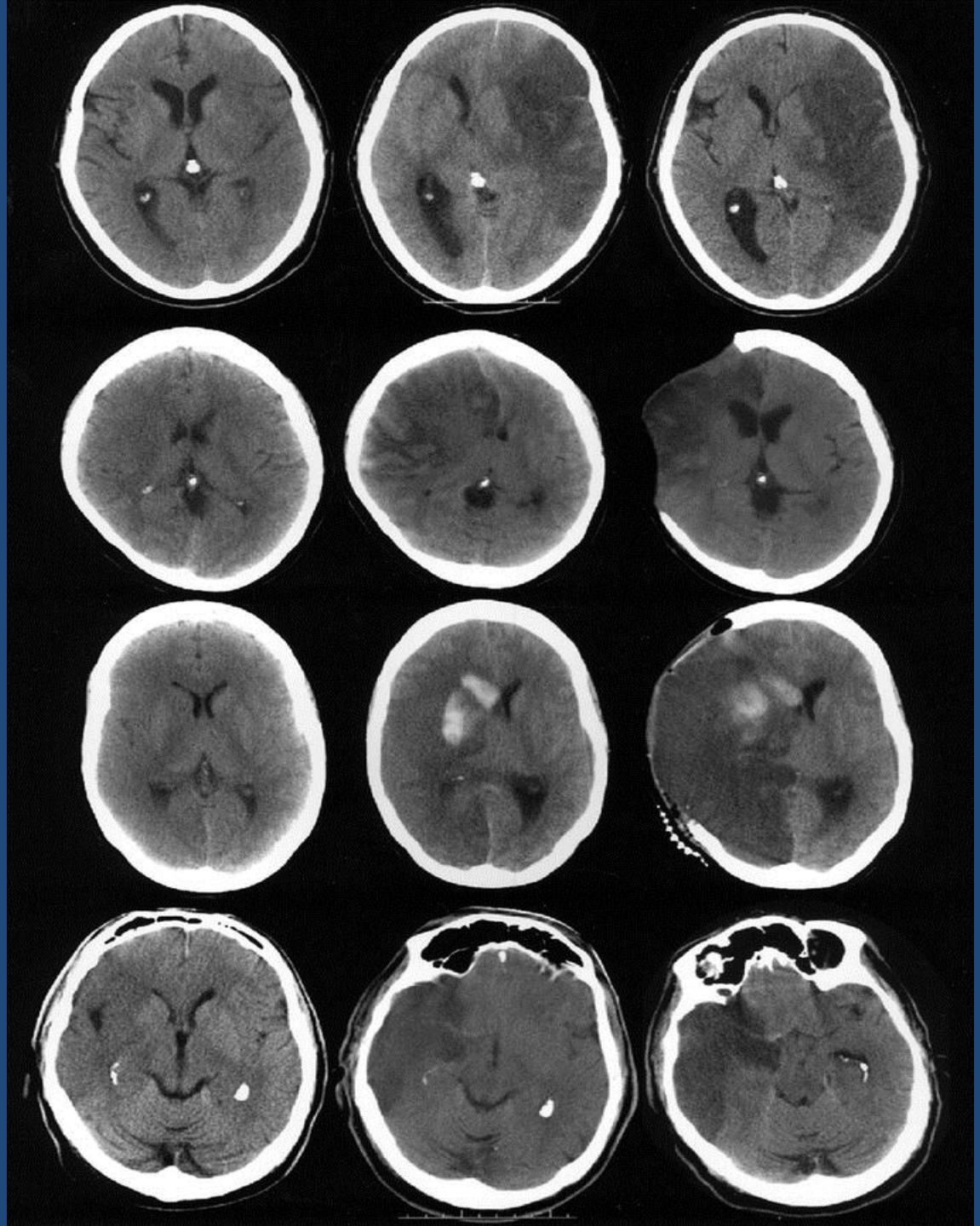
Middle cerebral artery infarction

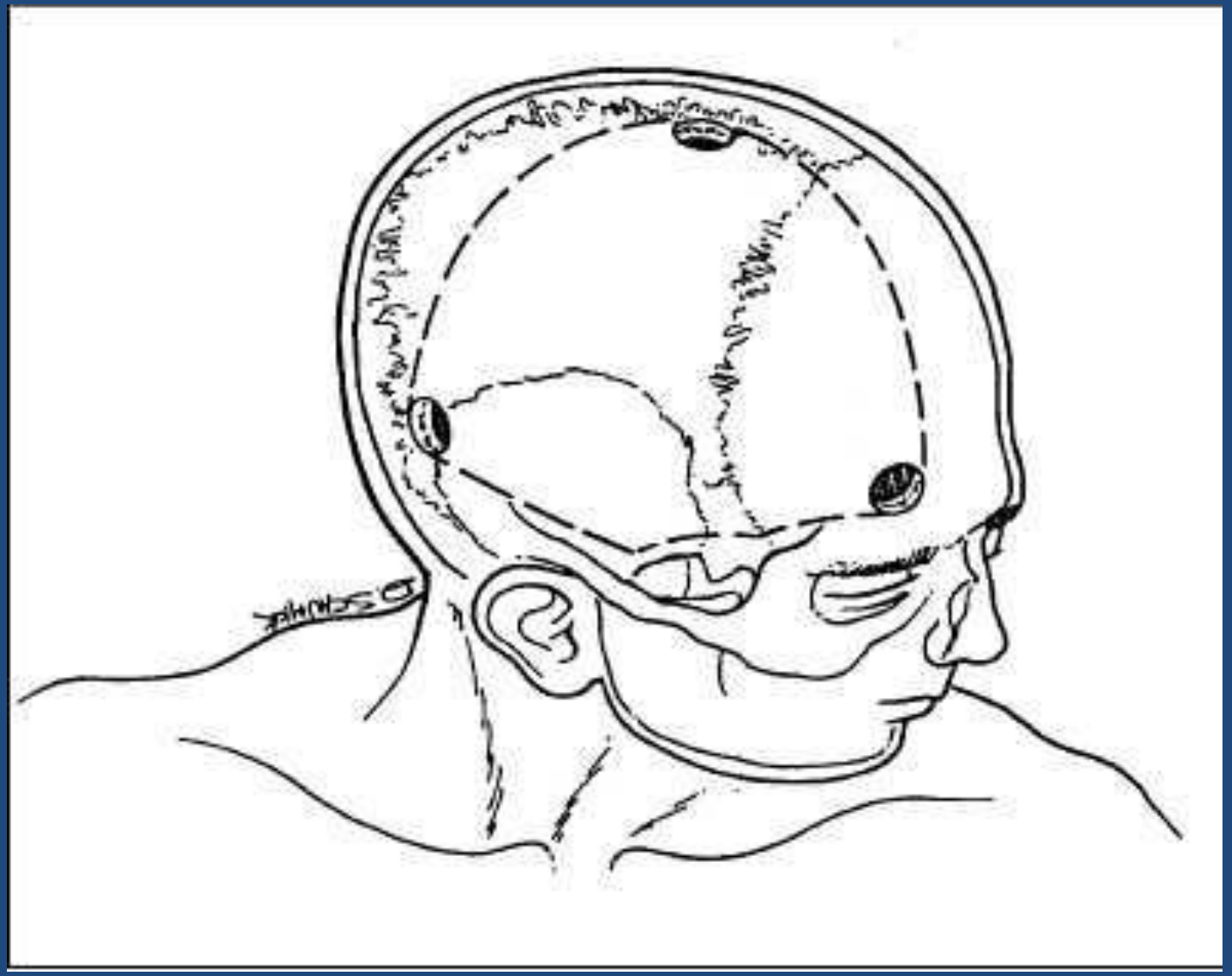




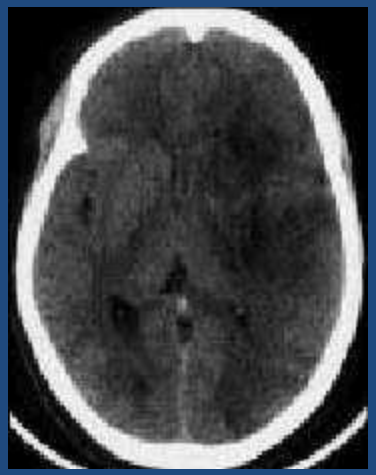
Tatu, 1998

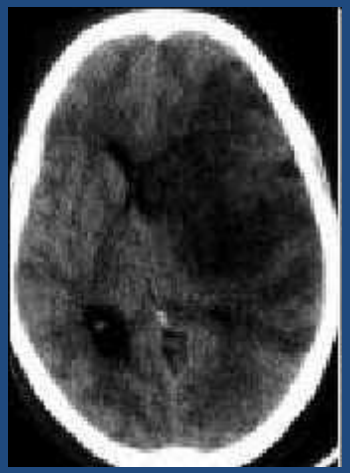

SECTION IV
SECTION V
SECTION VI
MCA perforating branches
PoCA perforating branches
Thalamoperforating branches
Thalamogeniculate branches
Medial PChA
Lateral PChA
Insular zone

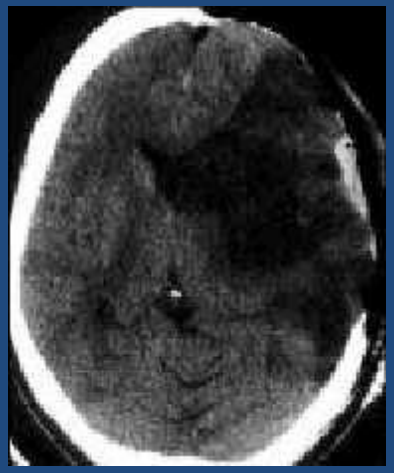




Hemicraniectomy







High Risk for Herniation

- Gaze deviation, hemiplegia and neglect with NIHSS > 15
- Hemiplegia and global aphasia with NIHSS > 20

PLUS nausea or vomiting

CT hypotensity > 50% MCA ± ACA or PCA

Angiography shows carotid “T” occlusion

Hemicraniectomy Algorithm

- Repeat CT in 6-12 hours

  If complete MCA plus ACA or PCA, consider hemicraniectomy

- Watch for decreasing LOC and anisocoria; repeat CT; midline shift

  >10 mm, consider hemicraniectomy

Vahedi, et.al.
Hemicraniectomy Trials
Lancet Neurology 2007;6:215-222

At one Year	Surgery	Medical	
Survived	78%	29%	RR=50%
mRS $\leq$ 4	75%	24%	RR=51%
mRS $\leq$ 3	43%	21%	
mRS = 4	31%	2%	

10X increased risk of disability; unable to walk or attend to bodily needs

Time Is Brain !