Cerebrovascular accident: pathophysiology and symptoms – diagnosis and treatment

Thomas Tegos

Definition of Stroke

- Any disease process that disrupts blood flow to a focal region of the brain.
- Ischemia- hemorrhage

Definition of Stroke

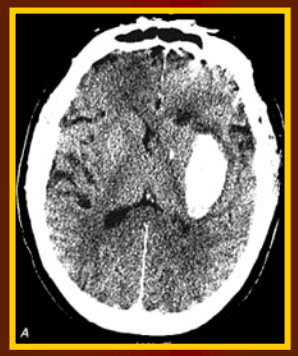
- Focal or generalized neurological symptoms
- Rapid development of symptoms
- Completion of symtoms within 24 hrs
- End point – disability or death
- No other obvious causes apart from vascular

Background

- Third leading cause of death
- Leading cause of adult disability
- Mortality: 19/100/mo
- Incidence: 1.35-4/1000/yr
- 1/3 of patients younger than 65

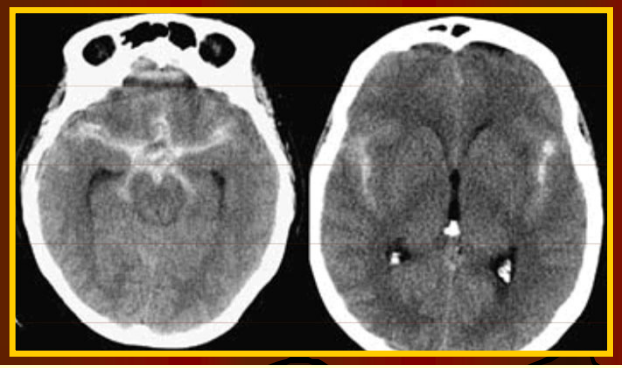
NINCDS (N=1805)

hemorrhage (26%)
parechymatous,
sabarachnoid



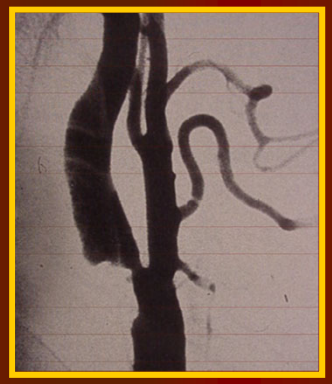
parechymatous
hemorrhage (13%)

subarachnoid
hemorrhage (13%)

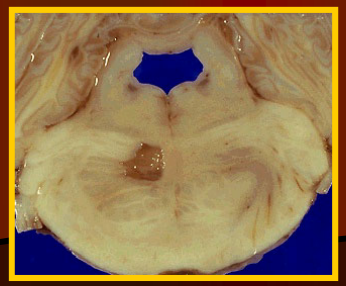


ischemic (71%)
thrombosis,embolism,
haemodynamic

atherothrombosis
(10%)



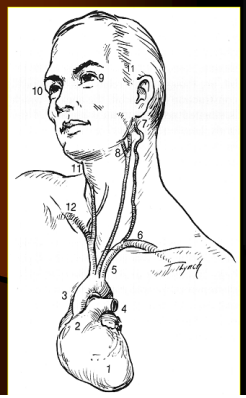
lacunes (19%)
small vessel disease



other
causes
(3%)

cryptogenic
and other causes
(28%)

cardioembolism (14%)



Foulkes MA, Wolf PA, Price TR, Mohr JP, Hier DB.
The Stroke Data Bank: Design, methods and baseline characteristics.
Stroke 1988; 19(5) :547-54

Ischemic Strokes

- *Thrombosis*-most common cause
- Etiology
  - Atherosclerotic disease-most common
  - Vasculitis
  - Dissection
  - Polycythemia-thrombocythemia
  - Hypercoagulable states-primary,secondary
  - Infectious Diseases-HIV, TB, syphilis,HZV

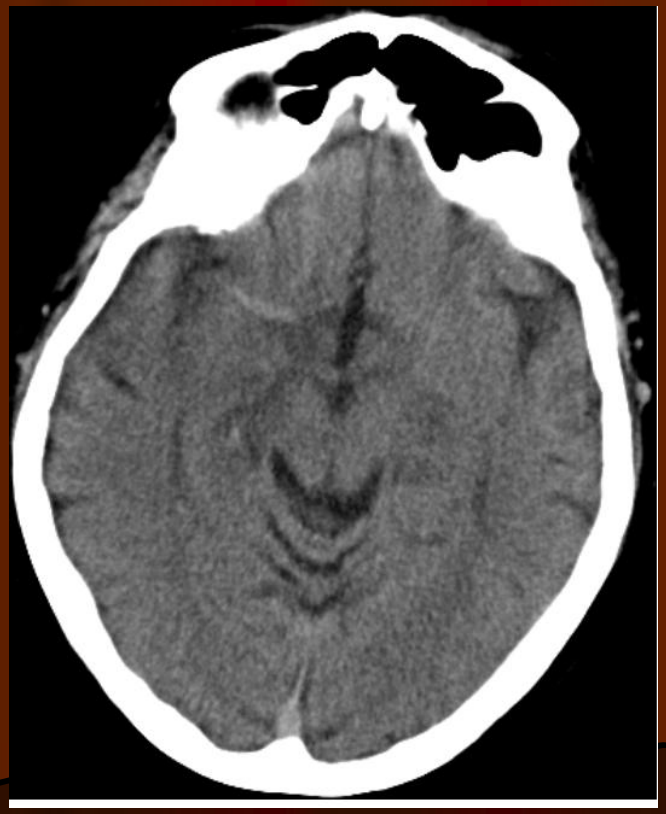
Ischemic Strokes

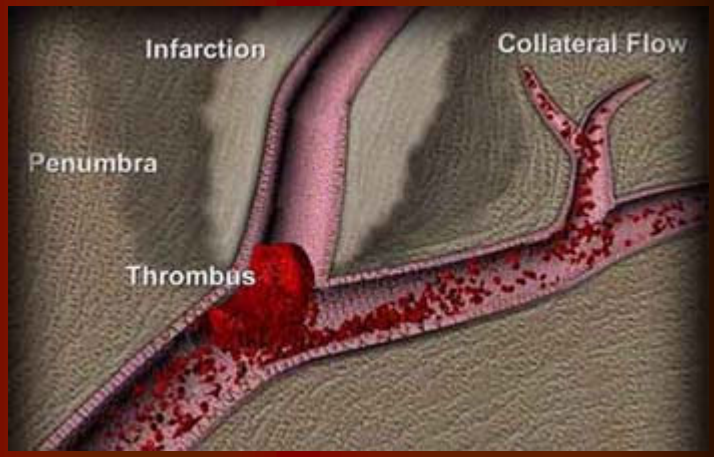
- 25% due to *Embolism*
- Etiology
  - Cardiac
    - Valvular Vegetations
    - Mural thrombi- caused by A-fib, MI, or dysrhythmias
    - Paradoxical emboli-from ASD, VSD
    - Cardiac tumors-myxoma
  - Carotid emboli
  - Fat emboli
  - Particulate emboli – IV drug injections
  - Septic Emboli – heart,aorta

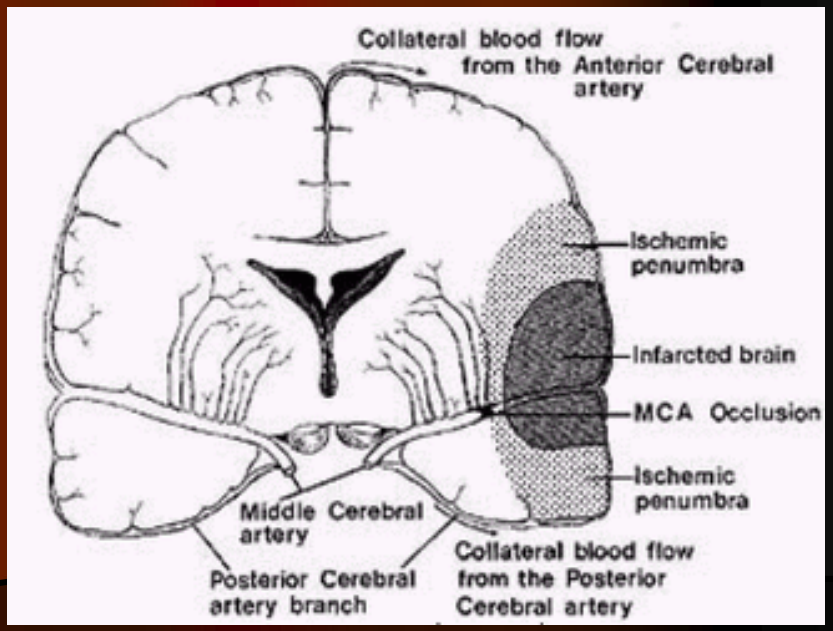
Ischemic Strokes

- *Hypoperfusion* - less common mechanism
- Typically caused by cardiac failure
- More diffuse injury pattern vs thrombosis or embolism
- Usually occur in watershed regions of brain

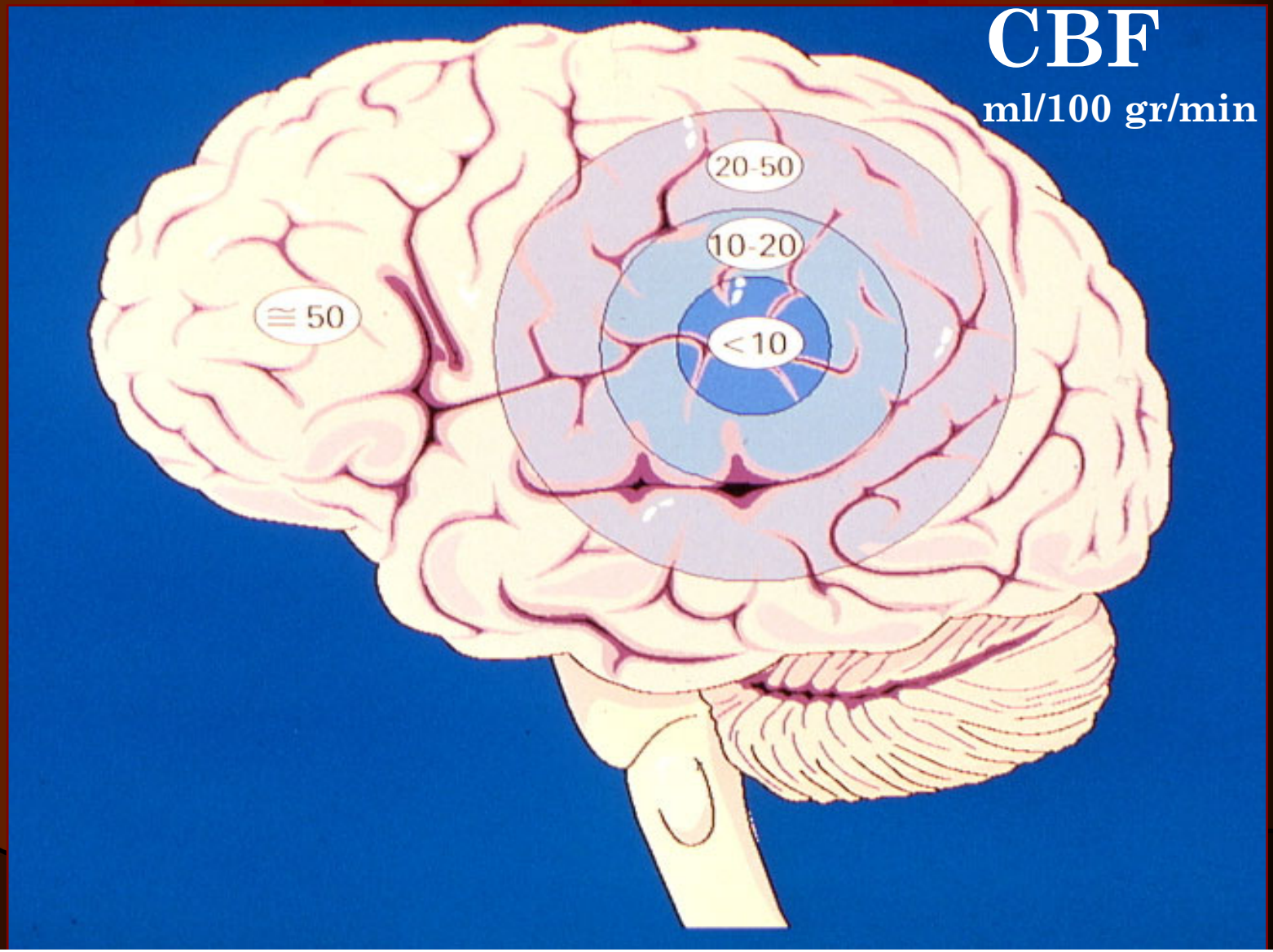
When cerebral artery occlude

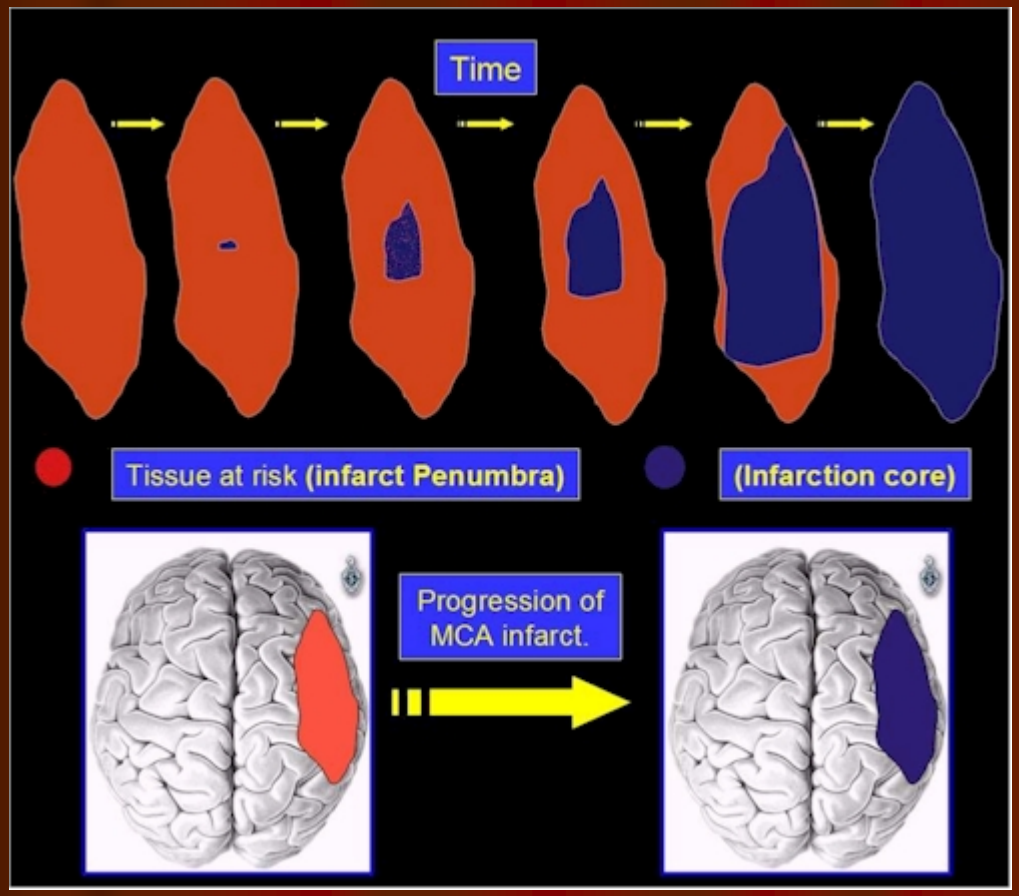






Necrotic core and penumbra

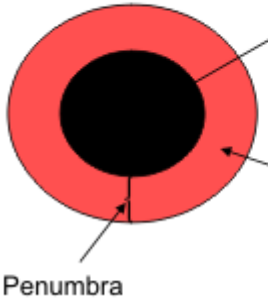




Ischemic Penumbra

DWI / PWI Mismatch

- Diffusion Abnormality
- CBF < 10 ml/100g/min
- Cytotoxic edema
- Irreversible ischemia



- Perfusion Abnormality
- CBF = 10-18 ml/100g/min
- Neuronal paralysis
- Reversible ischemia

Hemorrhagic Strokes

- Intracerebral hemorrhage (ICH)
  - approx. 10% of all strokes
  - Risk Factors
    - HT
    - Increasing Age
    - Race: Asians and Blacks
    - Amyloidosis- esp. in the elderly
    - AVMs or tumors
    - Anticoagulants/Thrombolytic use
    - History of previous stroke
    - Tobacco, ETOH, and cocaine use

Hemorrhagic Stroke

- Subarachnoid hemorrhage (SAH)
- Result from rupture of berry aneurysm or rupture of AVMs, trauma, Moya moya disease, angiitis, dissection, CVT, cerebral tumor, coagulation defect, SCD, HT, malarıa, illicit drugs, labor, idiopathic cases

Clinical Features

- Stroke presentation often subtle and varied
- Key aspects in determining the underlying cause and location of the lesion include:
  - History
  - Physical Exam
  - Neurologic Exam

History

- History of:
  - HT
  - CAD
  - DM
  - Previous TIA in same vascular distribution
  - Symptomatic deficits that wax and wan
  - Gradual onset
- Suggests: atherosclerotic disease and thrombosis-metabolic syndrome

History

- History of
  - AF
  - Valvular replacement
  - Recent MI
  - Multiple TIAs involving different vascular distributions
  - Sudden onset of symptoms
- Suggests: Embolism

History

- History of :
  - Recent neck injury, Sports injury
  - Chiropractic manipulation
- Suggests: Carotid/vertebral dissection

History

- History of:
  - Straining or coughing immediately preceding symptoms of CVA
- Suggests: ruptured aneurysm

History

- History of:
  - Sudden onset of symptoms
  - Headache (minority of patients with ischemic stroke)
- Suggests: Hemorrhagic stroke - SAH

Physical Exam

- Not inclusive, but some pointers:
  - Signs of emboli- Janeway lesions, Osler nodes
  - Bleeding dyscrasia- ecchymosis, petechiae
  - Papilledema- mass lesion, HT crisis, cerebral vein thrombosis
  - Carotid bruit or murmurs- vascular or cardiac etiology.

Neurological exam-NIHSS(0-42)

1. Date performed:
__/__/__
month day year

2. (a) Level of consciousness: Alert ( )0
Drowsy ( )1
Stuporous ( )2
Coma ( )3

(b) Level of consciousness questions:
Answers both correctly ( )0
Answers one correctly ( )1
Incorrect ( )2

(c) Level of consciousness commands:
Obeys both correctly ( )0
Obeys one correctly ( )1
Incorrect ( )2

3. Best gaze: Normal ( )0
Partial gaze palsy ( )1
Forced deviation ( )2

4. Best visual: No visual loss ( )0
Partial hemianopia ( )1
Complete hemianopia ( )2
Bilateral hemianopia ( )3

5. Facial palsy: Normal ( )0
Minor ( )1
Partial ( )2
Complete ( )3

6. Best motor arm right: No drift ( )0
Drift ( )1
Cannot resist gravity ( )2
No effort against gravity ( )3
No movement ( )4

7. Best motor arm left: No drift ( )0
Drift ( )1
Cannot resist gravity ( )2
No effort against gravity ( )3
No movement ( )4

8. Best motor leg right: No drift ( )0
Drift ( )1
Cannot resist gravity ( )2
No effort against gravity ( )3
No movement ( )4

9. Best motor leg left: No drift ( )0
Drift ( )1
Cannot resist gravity ( )2
No effort against gravity ( )3
No movement ( )4

10. Limb ataxia: Absent ( )0
Present in either upper or lower ( )1
Present in both upper and lower ( )2

11. Sensory: Normal ( )0
Partial loss ( )1
Dense loss ( )2

12. Neglect: No neglect ( )0
Partial neglect ( )1
Complete neglect ( )2

13. Dysarthria: Normal articulation ( )0
Mild to moderate dysarthria ( )1
Near unintelligible or worse ( )2

14. Best language: No aphasia ( )0
Mild to moderate aphasia ( )1
Severe aphasia ( )2
Mute ( )3

mild stroke≤6

moderate stroke---7-10

moderately severe stroke---11-15

severe stroke---16-22

very severe stroke≥23

Goldstein LB, 1989

Neurologic Exam

- National Institutes of Health (NIH) Stroke Scale- correlates to infarct volume(0-42)
  - Seven major areas:
    1. LOC
    2. Visual Assessment
    3. Motor Function
    4. Cerebellar Function
    5. Sensation and Neglect
    6. Cranial Nerves
    7. Speech(aphasia, dysarthria)

Ischemic Stroke Syndrome

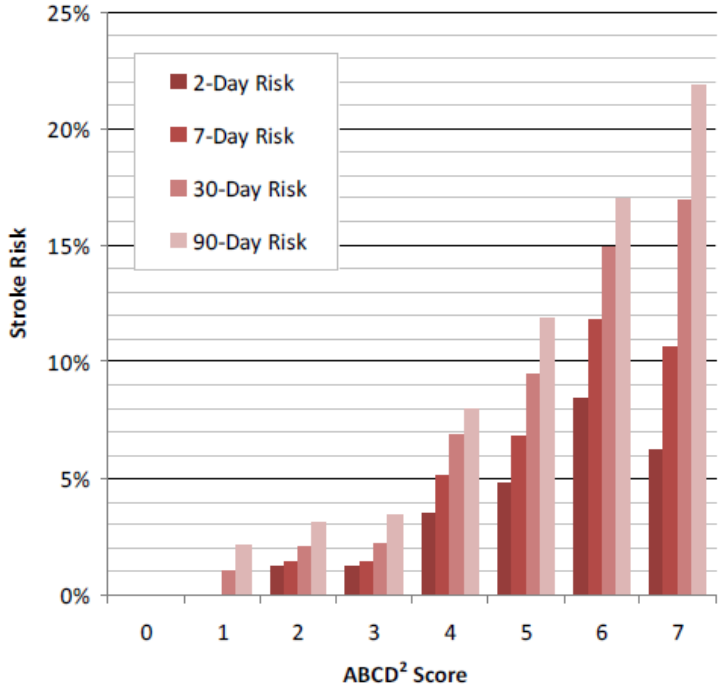
- Transient Ischemic Attack (TIA)
  - Neurologic deficit that resolves within 24 hours
    - Most TIAs resolve < 30 minutes
    - Approx. 10% of TIA patients will have a stroke in 90 days
      - Half of these in just 2 days

Migrating symptoms

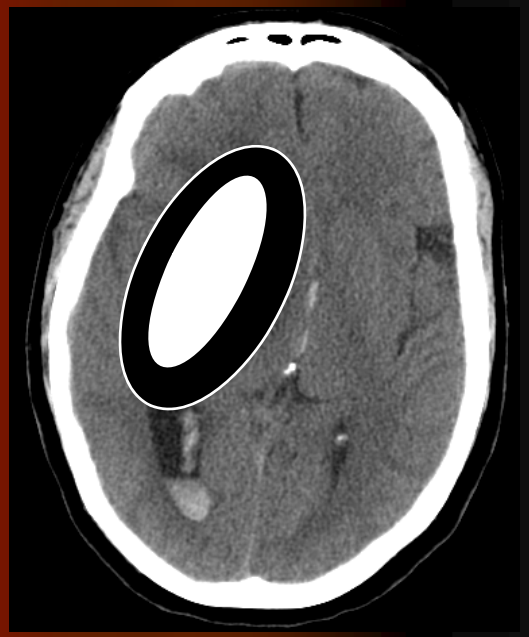
- epilepsy-sec

- migraine-min
- Cerebral amyloid angiopathy-min
- TIA-min

Risk Factor	Points	Score
Age		
≥ 60 years	1	
Blood pressure		
Systolic BP ≥ 140 mm Hg *OR* Diastolic BP ≥ 90 mm Hg	1	
Clinical features of TIA (*choose one*)		
Unilateral weakness with or without speech impairment *OR*	2	
Speech impairment without unilateral weakness	1	
Duration		
TIA duration ≥ 60 minutes	2	
TIA duration 10-59 minutes	1	
Diabetes	1	
***Total ABCD*^{2} score**	0-7	



Mechanisms of Brain Injury in ICH



- Primary
  - Tissue dissection
  - Displacement and brain herniation
- Secondary
  - Perihematoma injury (ischemia-edema)
  - Hematoma expansion
  - Inflammation
  - Apoptotic cell death (Qureshi)

Ischemic Stroke Syndromes

- Anterior Cerebral Artery Infarction
  - Contralateral weakness/numbness greater in leg than arm
  - Dyspraxia – contralateral upper limb
  - Alien hand – contralateral upper limb
  - Abulia

Ischemic Stroke Syndromes

- Middle cerebral artery occlusion
  - Dominant Hemisphere (usually the left)
    - Contralateral weakness/numbness in arm and face greater than leg
    - Contralateral hemianopsia
    - Aphasia (Wernicke's -receptive, Broca's -expressive or may have both)

Ischemic Stroke Syndromes

- Middle cerebral artery occlusion
  - Nondominant hemisphere
    - Contralateral weakness/numbness in arm and face greater than in the leg
    - Dressing apraxia
    - Inattention, neglect, or extinction

Ischemic Stroke Syndromes

- Posterior Cerebral Artery Infarct
  - Contr. Hemianopia (occipital lobe)
  - Visual agnosia (occipital lobe)
  - Reduced level of consciousness(midbrain)
  - Ophthalmoparesis(midbrain)
  - hemiplegia(midbrain)
  - Hemianesthesia(thalamus)
  - Alexia with/without agraphia anomia, memory deficit, thalamic dementia

Ischemic Stroke Syndromes

- Vertebrobasilar Syndrome
  - Posterior circulation supplies brainstem, cerebellum, and visual cortex
    - Dizziness, vertigo, diplopia, dysphagia, ataxia, cranial nerve palsies, and b/l limb weakness, singly or in combination
    - HALLMARK: Crossed neurological deficits: ipsilateral CN deficits with contralateral motor weakness

Ischemic Stroke Syndromes

- Lateral Medullary (Wallenberg) Syndrome
  - Specific post. Circulation infarct involving vertebrobasilar and/or post inferior cerebellar Art. (PICA)
  - Signs:
    - Ipsilateral loss of facial pain and temperature with contralateral loss of these senses over the body
    - Gait and ipsilateral limb ataxia
    - Partial ipsilateral loss of CN V, IX, X, and XI
    - Ipsilateral Horner Syndrome may be present

Ischemic Stroke Syndromes

- Basilar Artery Occlusion
  - Severe quadriplegia
  - Coma
  - *Locked-in syndrome*-complete muscle paralysis except for upward gaze

Ischemic Stroke Syndromes

- Cerebellar Infarction-subset of post. circ. infarcts
  - Symptoms: "drop attack" with sudden inability to walk or stand, vertigo, nausea/vomiting, neck pain
- Diagnosis: MRI, MRA as bone artifact obscures CT
- Cerebral edema develops w/in 6-12 hrs → increased brainstem pressure and decreased LOC
- Treatment: decrease ICP and emergent surgical decompression

Ischemic Stroke Syndrome

- Lacunar Infarction
  - Infarction of small penetrating arteries in pons and basal ganglia
  - Associated with chronic HT present in 80-90% or DM
  - Pure motor deficits, pure sensory deficit, motor-sensory stroke, ataxic hemiparesis, dysarthria-clumsy hand syndrome
  - Fisher CM, 1982

DIAGNOSIS OF VASCULAR DEMENTIA

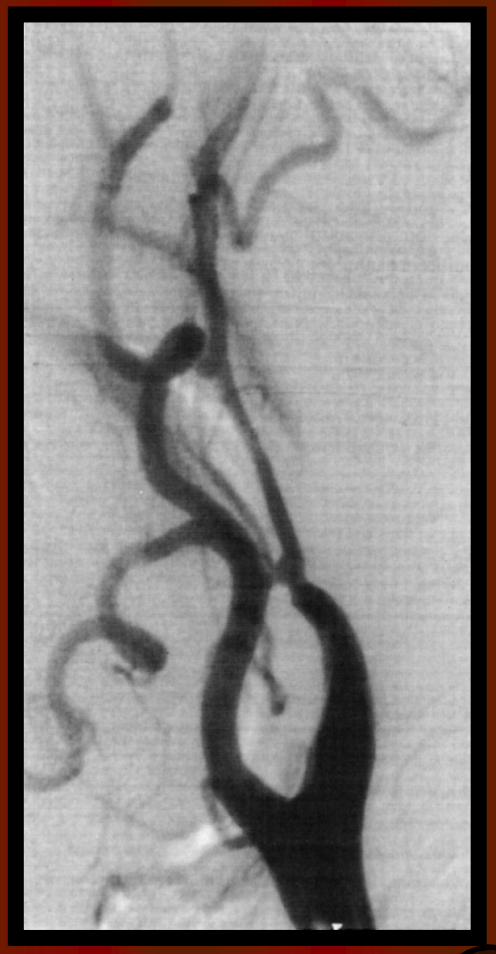
- memory impairment
- aphasia, apraxia, agnosia,disturbance in executive functioning
- impairment in social, occupational functioning – decline from a previous level of functioning
- focal neurological symptoms, signs – positive laboratory neurovascular profile related to the impairment
- relative absence of a delirium

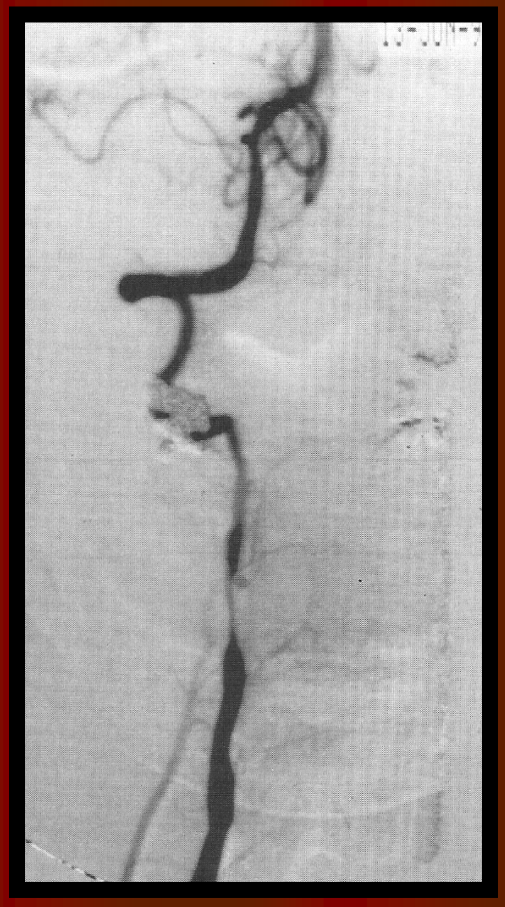
DSM-IV, 1994

Ischemic Stroke Syndrome

- Arterial Dissection
  - Often following severe trauma
  - headache, and neck pain hours to days prior to onset of neuro symptoms – Horner syndrome
    - HT risk factor for spontaneous dissection
    - Marfan syndrome-medial arterial vacuolar necrosis -FMD-migraine
    - idiopathic

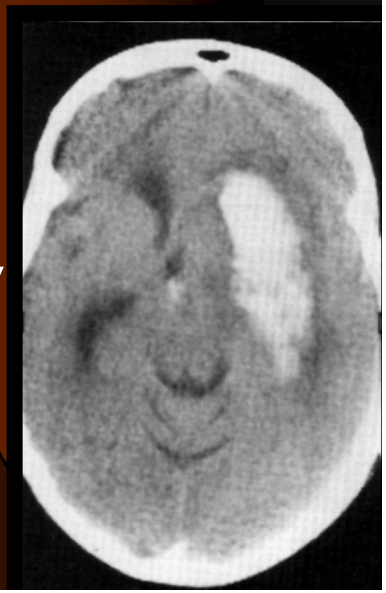
Ischemic Stroke Syndrome





Hemorrhagic Syndromes

- Intracerebral Hemorrhage
  - ICH – sudden onset of symptoms, elevated BP
  - Progressive focal neurologic deficits over minutes
  - Patients may rapidly deteriorate
  - Exertion commonly triggers symptoms
  - Epilepsy, coma, increased ICP, vomiting
  - Bleeding localized to putamen, thalamus, pons-pinpoint pupils, and cerebellum

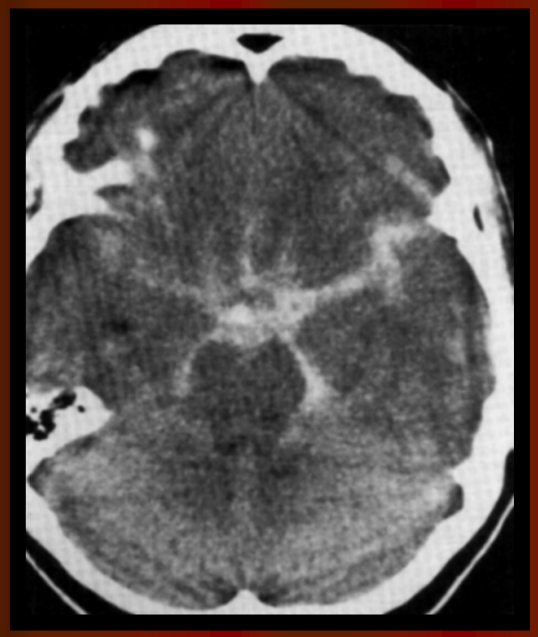


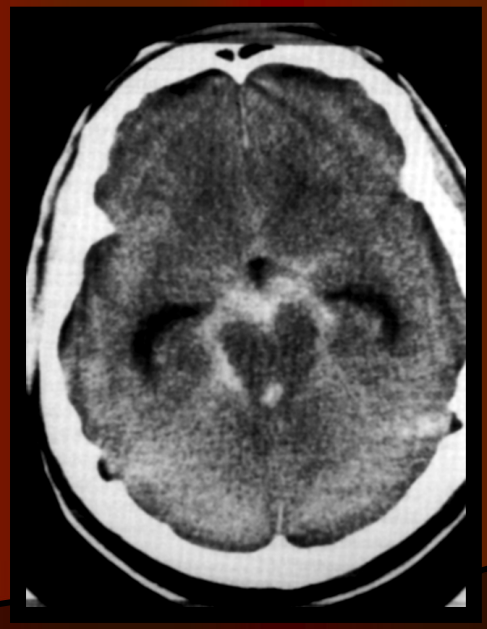
Hemorrhagic Syndromes

- Cerebellar Hemorrhage
  - Sudden onset dizziness, vomiting, truncal ataxia, inability to walk
  - Possible gaze palsies and increasing stupor
  - Treatment: urgent surgical decompression or hematoma evacuation

Hemorrhagic Syndrome

- Subarachnoid hemorrhage
  - Severe headache, vomiting, decreasing level of consciousness
  - headache- often occipital or nuchal in location
  - Sudden onset of symptoms– history may reveal activities increasing BP such as defecation, coughing or intercourse
  - Blood in subarachnoid space, vasospasm between 3-21 days
  - manifestations---headache, photophobia, nuchal rigidity, vomiting, confusion-irritative state, pre-coma or coma, signs of Kerning or Brudzinski





CVT

- ✓ CAUSES —thrombophilia primary or secondary, sinus compression, inflammation and infection, trauma, cancer infiltration, other causes
- ✓ MANIFESTATIONS---increased ICP and cerebral edema- venous infarction – fits/focal signs/ papiledema/ confusion/headache/abulia

Diagnosis-Critical Pathway

- History
  - Last moment patient known to be normal
- Initial orders
  - ECG, Cardiac Enzymes, FBC, PT/a PTT/ INR, biochemistry, LFT, electrolytes, glucose, RFT, +/- drug screen, Noncontrast CT-head
  - Review alteplase inclusion/exclusion criteria

Diagnostic Tests

- Emergent noncontrast CT of head
  - Differentiate hemorrhage vs ischemia
    - MOST ischemic strokes (-) by CT for at least 6 hrs
      - Hypodensity indicating infarct seen 24-48 hrs
    - Can identify hemorrhage greater than 1cm, and 95% of SAH
    - If CT (-) but still considering SAH may do L.P.

Diagnostic Tests

- Depending on circumstances, other helpful tests
  - CTA carotids, vertebral, cerebral vessels
  - Echocardiogram – identifies mural thrombus, tumor, valvular vegetations in suspected cardioembolic stroke
  - Holter monitoring 24 hrs
  - Carotid duplex -for known/suspected high grade stenosis
  - Angiography – "gold standard" identifies occlusion or stenosis of large and small vessels of head/neck, dissections and aneurysms
  - MRI scan – identifies posterior circulation strokes better and ischemic strokes earlier than CT
    - Emergent MRI- considered for suspected brainstem lesion or dural sinus thrombosis
  - MRA scan – identifies large vessel occlusions – may replace angiography in the future
  - CTV, MRV

Diagnostic Tests

- Thrombophilia screen, collagen diseases
- Brain biopsy (cerebral amyloid or congophilic angiopathy)-STA biopsy (TA)
- Brain SPECT – cortical infarcts

Differential Diagnosis

- Ddx of Acute Stroke (not inclusive)
  - Epidural/subdural hematoma
  - Hyponatremia
  - Brain tumor/abscess
  - Postictal paralysis (Todd paralysis)
  - Hypertensive encephalopathy
  - Meningitis/encephalitis
  - Hyperosmotic coma

Differential Diagnosis Cont.

- Wernicke Encephalopathy
- Drug toxicity (lithium, phenytoin, carbamazepine)
- Complicated Migraine
- Bells palsy
- Multiple sclerosis
- Meniere's disease
- Labyrinthitis

Differential Diagnosis Cont.

- Hyperventilation syndrome
- Narcolepsy, cataplexy, sleep paralysis, hypnagogic hallucinations
- TGA(TIA, post-ictal state, migraine equivalent, venous congestion due to jugular vein deficiency, cererbral energy failure, temporal lobe tumors, dissociative hysteria)
- Conversion hysteria

Special Populations In Stroke

- Sickle Cell Disease (SCD)
  - Most common cause of ischemic stroke in children
  - 10% of patients with Sickle Cell Disease have stroke by age 20
  - SCD-↑ frequency of cerebral aneurysm—think SAH
  - Treatment: emergent simple or exchange transfusion to decrease HbS to < 30%, thus improving blood flow and oxygen delivery to infarct zone

Special Populations In Stroke

- Young Adults (age 15 to 50)
  - 20% of ischemic strokes due to arterial dissection
    - Often preceded by minor trauma
  - Cardioembolic etiologies- MVP, rheumatic heart disease, or paradoxical embolism
  - Migrainous stroke- infarction a/w typical attack
  - Air embolism-scuba diving or recent invasive procedure
  - Drugs: heroin, cocaine, amphetamines

Special Populations In Stroke

- Pregnancy
  - ↑risk during peripartum and up to 6 weeks postpartum
    - Contributors to risk-preeclampsia/eclampsia, decrease in blood vol. and hormonal status following birth

TREATMENT-Time is brain!

F  **F**ace is uneven

A  **A**rm is weak

S 

Speech is strange

T 

Time to call **911**

Ischemic Stroke Management

- General Management
  - A, B, Cs
  - IV, oxygen, monitor, elevate head of bed slightly
  - E.D. protocols/Notify stroke team
  - Treat dehydration and hypotension
  - Avoid overhydration – cerebral edema
  - Avoid hyperglycemia and hypoglycemia
  - Fever – worsens neurologic deficits

Ischemic Stroke Management

- Hypertension
  - Treatment indicated for SBP > 220 mm Hg or mean arterial pressure > 130 mm Hg
    - Lowering BP too much reduces perfusion to penumbra converting reversible injury to infarction
    - Use easily titratable Rx (labetalol)
    - SL Ca-channel blockers should be avoided

Management of HTN cont.

- Thrombolytic candidates- use Labetalol to reduce BP < 185/115 to allow tx
- Requirements for more aggressive treatment exclude the use of tissue plasminogen activator.

rtPA Dose and Complications

- rtPA –Total dose 0.9 mg/kg, max. 90mg
  - 10% as bolus, remaining infusion over 60 min.
  - BP and Neuro checks q 15 min x 2 hrs initially
- Treatment must begin within 3 hrs – 4.5 hrs of symptoms and meet inclusion and exclusion criteria
- No ASA or heparin given for 24 hrs after tx

Emergent Management of HT during/following rtPA in Acute Stroke

- Monitor BP closely
  - q 15 min x 2 hrs, then q 30 min x 6 hrs, then q 60 min for 24 hr Total
- If SBP 180-230 or DBP 105-120 mmHg
  - 10 mg labetalol IVP q 10-20 min, max 200 mg
- If SBP > 230 or DBP 121-140 mmHg
  - 10 mg labetalol may repeat q 10-20 min, max 200 mg
  - If BP not controlled by labetalol then consider nitroprusside (0.5-1.0mcg/kg/min), continuous arterial monitoring advised
- If DBP > 140 mmHg
  - Infuse sodium nitroprusside (0.5-1.0mcg/kg/min), continuous arterial monitoring advised

IV Thrombolysis Criteria in Ischemic Stroke

- Inclusion criteria
  - Age 18 years or older
  - Time since onset well established to be < 3 hrs-4.5 hrs
  - Clinical diagnosis of ischemic stroke
  - Cerebral CT- normal or mild CVA(<1/3 of brain)
  - Patient consent

Criteria for IV Thrombolysis cont.

- Exclusion criteria
  - Minor/rapidly improving neurologic signs
  - Evidence of intracranial hemorrhage on pretreatment noncontrast head CT
  - History of intracranial hemorrhage at any previous time
  - High suspicion of SAH despite normal CT
  - GI or GU bleeding within last 21 days

Criteria for IV Thrombolysis cont.

- Exclusion criteria
  - Known bleeding diathesis
    - Platelet count < 100,000 /mm_3
    - Heparin within 48 hours and has an elevated PTT
    - Current use of anticoagulation or PT > 15 seconds or INR > 1.6

Criteria for IV Thrombolysis cont.

- Exclusion criteria
  - Intracranial surgery, serious head trauma or previous stroke within 3 months
  - Major surgery within 14 days
  - Recent arterial puncture at non compressible site
  - Lumbar puncture within 7 days
  - Seizure at onset of stroke

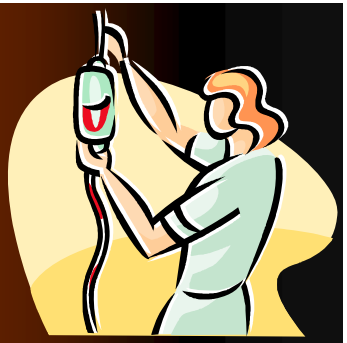
Criteria for IV Thrombolysis cont.

- Exclusion criteria
  - History of ICH, AVM or aneurysm
  - Recent MI – less than 6 wks
  - Sustained pretreatment systolic pressure > 185 mmHg or diastolic pressure > 110 mmHg despite aggressive treatment to reduce BP to within these limits
  - Blood glucose < 50 or > 400 mg/dL

Exclusion criteria

- Cerebral tumor
- INR>1.6 – hemophilia
- Hemorrhagic diseases of the eye
- Bacterial endocarditis
- History of previous CVA and DM
- Pregnancy
- Post MI pericarditis or known AAA

THROMBOLYSIS



- NIHSS (0 - 42 βαθμοί) 3/5-25 – exclusion - speech, hand dexterity, vision
- Stroke Unit (?) monitoring:
- **rt-PA** : Alteplase (Actilyse (R)) iv

  - 0.9 (0.6) mg/kg body weigt, max 90(60) mg, 10 %(15%) bolus, 90(85) % in an hrs time (infuson) NINDSS-ENCHANTED

Stroke Unit Trialists' Collaboration. Cochrane D S R. 2007 17;(4):CD000197, NEJM 2008; 359:1317-29 & 1393-5

Thrombolysis side effects

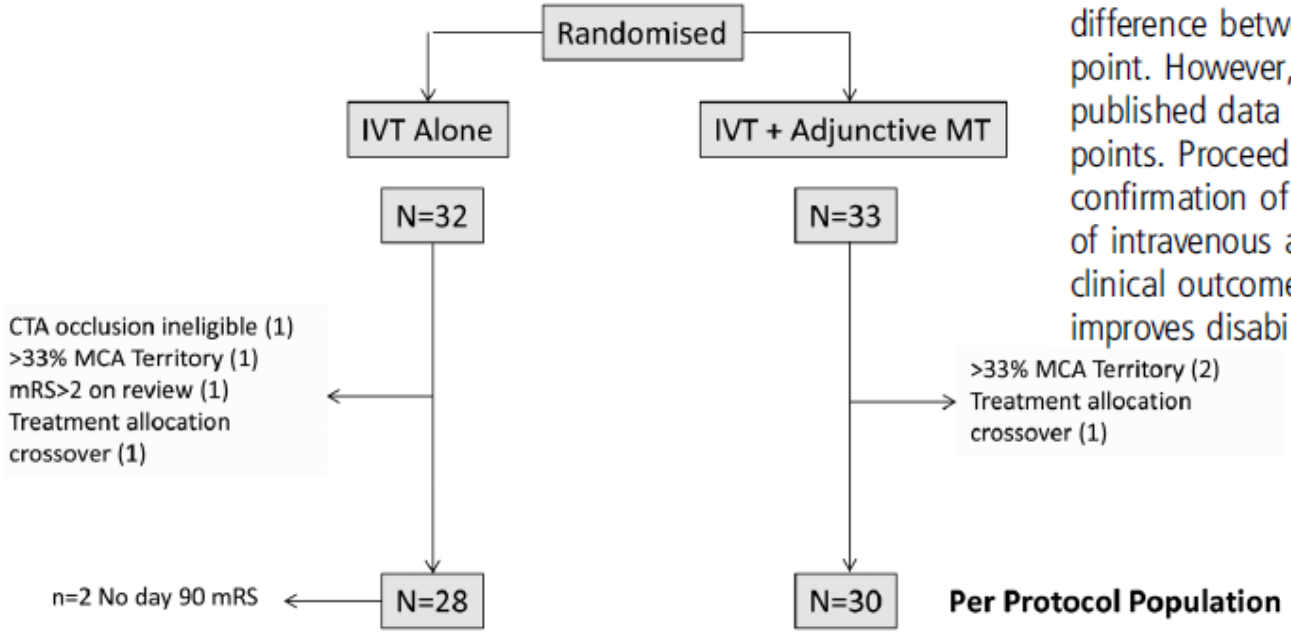
- ICH or hemorrhage(6.4%)-cessaton of thrombolysis, FFP 6 UNITS
- angioedema(5.1%)-adrenaline(0.3 ml SC/IM 0.1% solution), solucortef 125 mg+solumedrol 250 mg IV, fenistil 4 mg/4 ml IV, O2 mask

Thrombolysis and mechanical embolectomy

- In 2014 a positive study was published (MR CLEAN) and in 2015 4 additional positive studies (ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT) and in 2016 another positive study (THRACE) aiming at the management of ischemic CVA with large cerebral vessel occlusion, where the superiority of ME and IV thrombolysis

Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial

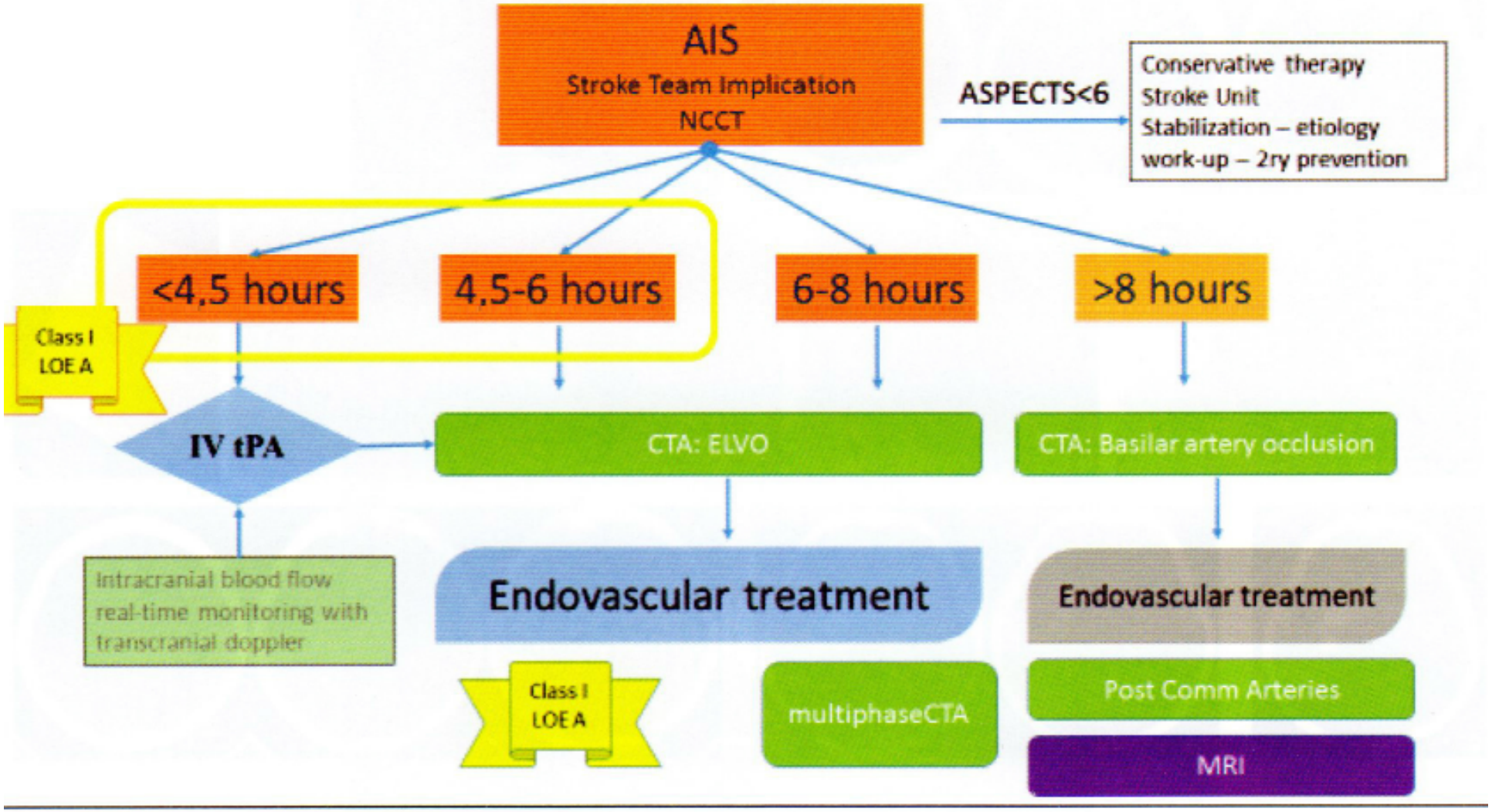
Keith W Muir,[1] Gary A Ford,[2] Claudia-Martina Messow,[3] Ian Ford,[3] Alicia Murray,[1] Andrew Clifton,[4] Martin M Brown,[5] Jeremy Madigan,[4] Rob Lenthall,[6] Fergus Robertson,[5] Anand Dixit,[7] Geoffrey C Cloud,[4] Joanna Wardlaw,[8] Janet Freeman,[9] Philip White,[7] on behalf of the PISTE Investigators



Conclusions The trial did not find a significant difference between treatment groups for the primary end point. However, the effect size was consistent with published data and across primary and secondary end points. Proceeding as fast as possible to MT after CTA confirmation of large artery occlusion on a background of intravenous alteplase is safe, improves excellent clinical outcomes and, in the per-protocol population, improves disability-free survival.

Muir KW, *et al. J Neurol Neurosurg Psychiatry* 2016;**0**:1–7. doi:10.1136/jnnp-2016-314117

- 6-24 HRS



- emergent large vessel occlusion (ELVO)

ORIGINAL ARTICLE

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

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

ABSTRACT

BACKGROUND

The effect of endovascular thrombectomy that is performed more than 6 hours after the onset of ischemic stroke is uncertain. Patients with a clinical deficit that is disproportionately severe relative to the infarct volume may benefit from late thrombectomy.

METHODS

We enrolled patients with occlusion of the intracranial internal carotid artery or proximal middle cerebral artery who had last been known to be well 6 to 24 hours earlier and who had a mismatch between the severity of the clinical deficit and the infarct volume, with mismatch criteria defined according to age (<80 years or ≥80 years). Patients were randomly assigned to thrombectomy plus standard care (the thrombectomy group) or to standard care alone (the control group). The coprimary end points were the mean score for disability on the utility-weighted modified Rankin scale (which ranges from 0 [death] to 10 [no symptoms or disability]) and the rate of functional independence (a score of 0, 1, or 2 on the modified Rankin scale, which ranges from 0 to 6, with higher scores indicating more severe disability) at 90 days.

RESULTS

A total of 206 patients were enrolled; 107 were assigned to the thrombectomy group and 99 to the control group. At 31 months, enrollment in the trial was stopped because of the results of a prespecified interim analysis. The mean score on the utility-weighted modified Rankin scale at 90 days was 5.5 in the thrombectomy group as compared with 3.4 in the control group (adjusted difference [Bayesian analysis], 2.0 points; 95% credible interval, 1.1 to 3.0; posterior probability of superiority, >0.999), and the rate of functional independence at 90 days was 49% in the thrombectomy group as compared with 13% in the control group (adjusted difference, 33 percentage points; 95% credible interval, 24 to 44; posterior probability of superiority, >0.999). The rate of symptomatic intracranial hemorrhage did not differ significantly between the two groups (6% in the thrombectomy group and 3% in the control group, P=0.50), nor did 90-day mortality (19% and 18%, respectively; P=1.00).

CONCLUSIONS

Among patients with acute stroke who had last been known to be well 6 to 24 hours earlier and who had a mismatch between clinical deficit and infarct, outcomes for disability at 90 days were better with thrombectomy plus standard care than with standard care alone. (Funded by Stryker Neurovascular; DAWN ClinicalTrials.gov number, NCT02142283.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Jovin at the University of Pittsburgh Medical Center Stroke Institute, Department of Neurology, Presbyterian University Hospital, 200 Lothrop St., C-400, Pittsburgh, PA 15213, or at jovintg@upmc.edu.

*A complete list of sites and investigators in the DAWN trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Nogueira and Jovin contributed equally to this article.

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ORIGINAL ARTICLE

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

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

ABSTRACT

BACKGROUND

Thrombectomy is currently recommended for eligible patients with stroke who are treated within 6 hours after the onset of symptoms.

METHODS

We conducted a multicenter, randomized, open-label trial, with blinded outcome assessment, of thrombectomy in patients 6 to 16 hours after they were last known to be well and who had remaining ischemic brain tissue that was not yet infarcted. Patients with proximal middle-cerebral-artery or internal-carotid-artery occlusion, an initial infarct size of less than 70 ml, and a ratio of the volume of ischemic tissue on perfusion imaging to infarct volume of 1.8 or more were randomly assigned to endovascular therapy (thrombectomy) plus standard medical therapy (endovascular-therapy group) or standard medical therapy alone (medical-therapy group). The primary outcome was the ordinal score on the modified Rankin scale (range, 0 to 6, with higher scores indicating greater disability) at day 90.

RESULTS

The trial was conducted at 38 U.S. centers and terminated early for efficacy after 182 patients had undergone randomization (92 to the endovascular-therapy group and 90 to the medical-therapy group). Endovascular therapy plus medical therapy, as compared with medical therapy alone, was associated with a favorable shift in the distribution of functional outcomes on the modified Rankin scale at 90 days (odds ratio, 2.77; P<0.001) and a higher percentage of patients who were functionally independent, defined as a score on the modified Rankin scale of 0 to 2 (45% vs. 17%, P<0.001). The 90-day mortality rate was 14% in the endovascular-therapy group and 26% in the medical-therapy group (P=0.05), and there was no significant between-group difference in the frequency of symptomatic intracranial hemorrhage (7% and 4%, respectively; P=0.75) or of serious adverse events (43% and 53%, respectively; P=0.18).

CONCLUSIONS

Endovascular thrombectomy for ischemic stroke 6 to 16 hours after a patient was last known to be well plus standard medical therapy resulted in better functional outcomes than standard medical therapy alone among patients with proximal middle-cerebral-artery or internal-carotid-artery occlusion and a region of tissue that was ischemic but not yet infarcted. (Funded by the National Institute of Neurological Disorders and Stroke; DEFUSE 3 ClinicalTrials.gov number, NCT02586415.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Albers at the Stanford Stroke Center, 780 Welch Rd., Suite 350, Palo Alto, CA 94304-5778, or at albers@stanford.edu.

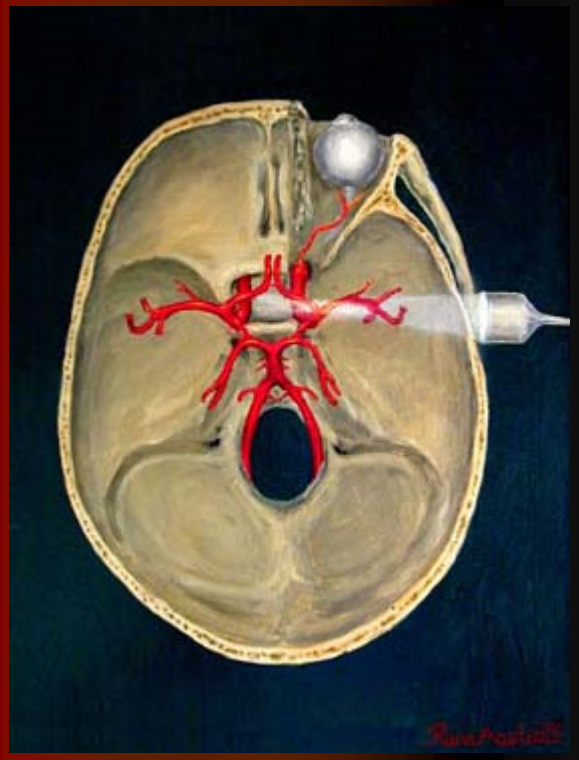
*A complete list of the DEFUSE 3 investigators is provided in the Supplementary Appendix, available at NEJM.org.

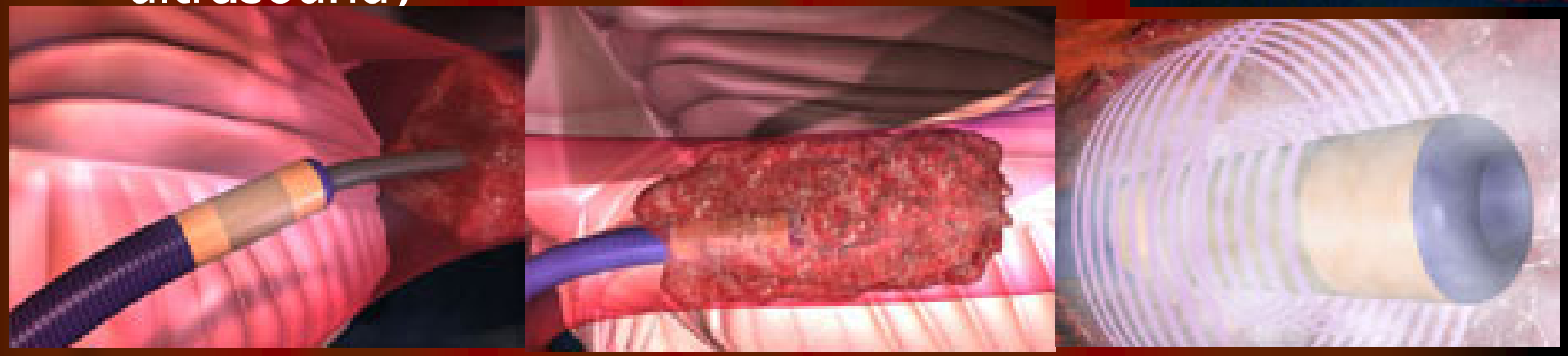
This article was published on January 24, 2018, at NEJM.org.

DOI: 10.1056/NEJMoa1713973

New strategies

- thrombolytic
  - Thrombolysis with TCD(Alexandrov, CLOTBUST trial, non-significant benefit, 2004, NEJM)
- intravascular
  - EKOS (thrombolysis with intravascular ultrasound)



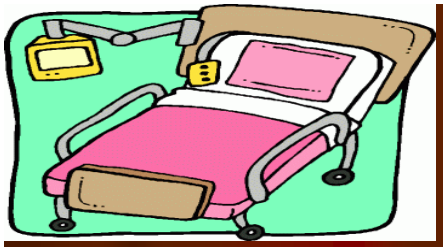


Drug Therapy in Ischemic Stroke

- Majority of pts not thrombolytic candidates
  - Antiplatelet agents-cornerstone for 2° prevention
- Antiplatelet agents
  - ASA: ↓ risk 20-25% vs placebo
    - 70-320 mg dose and will not interfere with tPA therapy
  - Dipyridamole: alone (200mg BID) ↓ risk 15%
  - Clopidogrel: (75 mg qd) 0.5% absolute annual risk reduction when compared to ASA
    - Good Rx for pts who cannot tolerate or fail ASA

Anticoagulants

- Heparin: unproven effect
  - Patiets may expect fewer strokes but benefit is offset by increased ICH
  - Similar results with LMWH
  - Use of UFH, LMWH, or heparinoids to tx a specific stroke subtype or TIA cannot be recommended based on available evidence.
- oral anticoagulants
  - AF, THROMBOPHILIA



ACUTE MANAGEMENT OF ISCHEMIC CVA

- Cardiac/ respiratory function, O2 saturation
- BP
- FBC, aPTT, INR, Na, K, κρεατινίνη, CARDIAC ENZYMES
- Glu levels
- T
- Ro thorax, ECG
- ACID BASE BALANCE
- DYSPHAGIA MANAGEENT AND NUTRITION
- COMPLICATION MANGENENT (infection, pressure ulcers, fits, DVT, PE)

RX

- ASPIRIN 325, CLOPIDRGREL, DIPYRIDAMOLE AND ASPIRIN, TRIFLUSAL
- LMWH – DVT, CVT, CAROTID DISSECTION
- ATORVASTATIN 80 MG FOR 5 DAYS
-

Stroke. 2007;38:1655-711

TIA Management

- Admit-Evaluate for cardiac sources of emboli or high grade stenosis of carotid arteries
- Rx: ASA
  - UFH-for high risk of recurrence – not any more
    - Known high grade stenosis in appropriate distribution of symptoms, cardioembolic source, Crescendo TIAs, TIAs despite antiplatelet therapy
- Urgent CEA for TIAs that resolve in < 6 hrs and > 70% stenosis of carotid artery

ICH Management

- Treat HT >220 mm Hg systolic or > 120 mm Hg diastolic using labetalol
  - Reduce gradually to prehemorrhage levels
- Elevate HOB to 30°
- Hyperventilation-target PaCO2 30-35 mm Hg
- Osmotherapy
  - Mannitol (0.25-1.0 g/kg IV), and lasix (10 mg IV)– target serum osmolality ≤ 310 mOsm/kg
    - Hyperventilation/osmotherapy used for signs of progressive ↑ ICP
    - i.e. mass effect, midline shift or herniation
- Steroids – not recommended

ICH Management cont.

- ICP Monitoring considered if GCS < 9
- Treat seizures with phenytoin
- Surgery – controversial
  - Depends on neuro status of pt, size and location of hemorrhage
  - Best benefit in cerebellar hemorrhage

SAH Management

- Major complications w/in 1st 24 hrs
  - Rebleeding and vasospasm
    - To ↓ rebleed risk: reduce SBP to 160 mm Hg and/or maintain MAP of 110 mm Hg
  - Cerebral ischemia 2° to vasospasm occurs 3-21 days after aneurysm rupture
    - Nimodipine 60 mg PO q 6 hr-↓ incidence and severity of vasospasms
- Prophylactic treatment of pain
- Obtain Neurosurgical consultation

Recommendations for the Management of Cerebral and Cerebellar Infarction With Swelling

Medical Options: Recommendations

1. Osmotic therapy for patients with clinical deterioration from cerebral swelling associated with cerebral infarction is reasonable (*Class IIa; Level of Evidence C*).
2. There are insufficient data on the effect of hypothermia, barbiturates, and corticosteroids in the setting of ischemic cerebral or cerebellar swelling, and they are not recommended (*Class III; Level of Evidence C*).

Eelco F. et al, Stroke, 2014

Recommendations for the Management of Cerebral and Cerebellar Infarction With Swelling

Recognition of Deterioration: Recommendations

1. Clinicians should frequently monitor level of arousal and ipsilateral pupillary dilation in patients with supratentorial ischemic stroke at high risk for deterioration. Gradual development of midposition pupils and worsening of motor response may also indicate deterioration (*Class I; Level of Evidence C*).
2. Clinicians should frequently monitor for level of arousal or new brainstem signs in patients with cerebellar stroke at high risk for deterioration (*Class I; Level of Evidence C*).

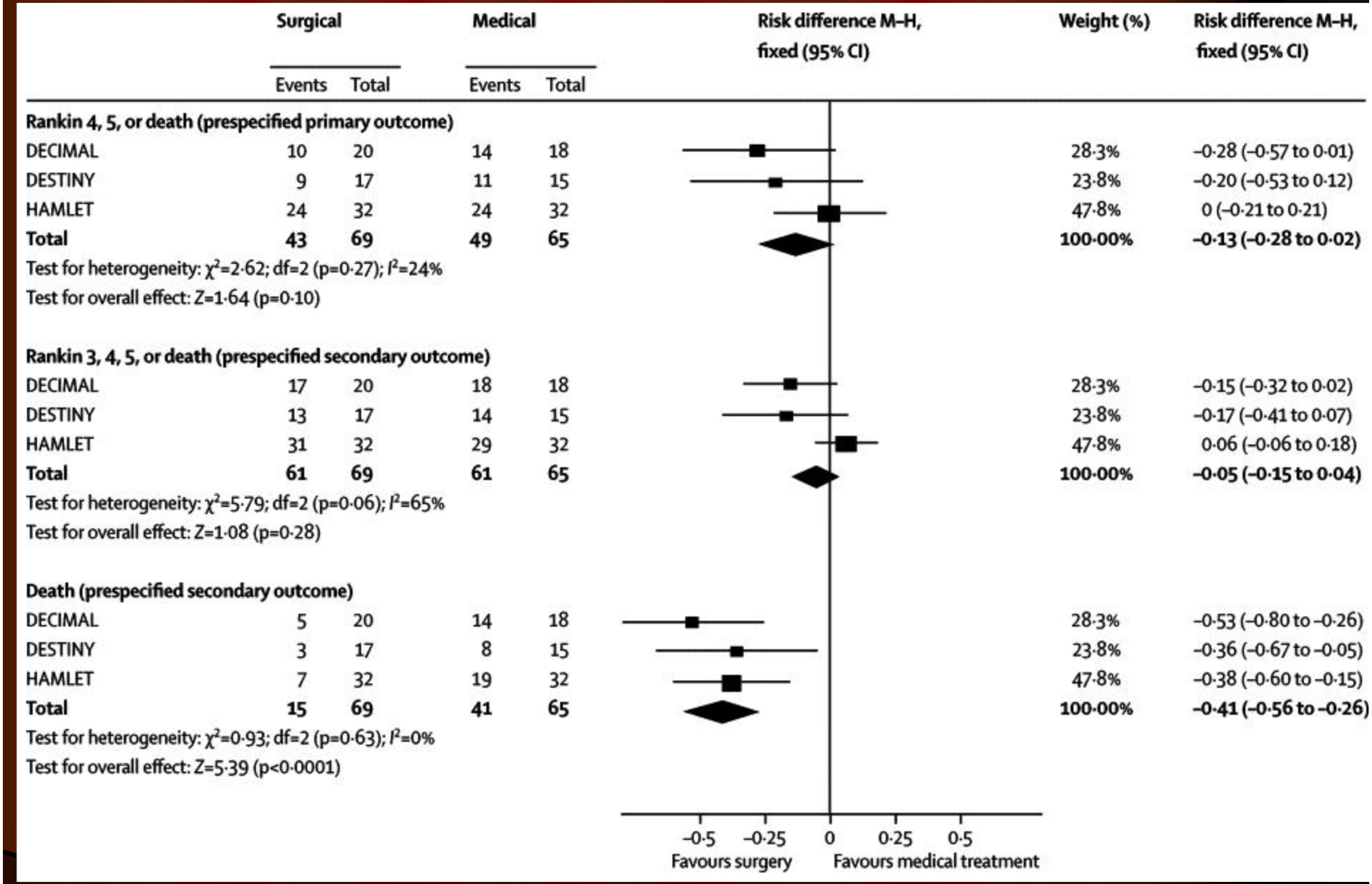
ICP Management: Recommendations

1. Routine ICP monitoring is not indicated in hemispheric ischemic stroke (*Class III; Level of Evidence C*).
2. Ventriculostomy is recommended in obstructive hydrocephalus after a cerebellar infarct but should be followed or accompanied by decompressive craniectomy (*Class I; Level of Evidence C*).

Neurosurgical Options: Recommendations

1. In patients <60 years of age with unilateral MCA infarctions that deteriorate neurologically within 48 hours despite medical therapy, decompressive craniectomy with dural expansion is effective. The effect of later decompression is not known, but it should be strongly considered (*Class I; Level of Evidence B*).
2. Although the optimal trigger for decompressive craniectomy is unknown, it is reasonable to use a decrease in level of consciousness and its attribution to brain swelling as selection criteria (*Class IIa; Level of Evidence A*).
3. The efficacy of decompressive craniectomy in patients >60 years of age and the optimal timing of surgery are uncertain (*Class IIb; Level of Evidence C*).
4. Suboccipital craniectomy with dural expansion should be performed in patients with cerebellar infarctions who deteriorate neurologically despite maximal medical therapy (*Class I; Level of Evidence B*).

Eelco F. et al, Stroke, 2014



The Lancet Neurology Vol 8 July 2009 602-603

REHABILITATION;

- **START SOON WHEN THE CONDITION STABILIZES** (ISCHEMIC CVA FROM 24-48 HRS)
- PHYSIOTHERAPY, HYDROTHERAPY IN REHABILITATION CENTER
- **TREAT:**
  - infections
  - pressure ulcer
  - DVT
  - spasticity
  - neyropathic pain
  - epilepsy
  - depression (33%)
  - sexual problems

- FROM 2-8 MO UP TO 3 YR

Rehabilitation with robotic technology