1. Prevention- The role of Aggressive Medical Management
Medical Management

- Prior trials had used term *Best Medical Treatment* without specifying details or monitoring for effect
- Monitored specified aggressive treatment has now proven as effective or more effective than interventional Rx in
  - SAMMPRIS trial of stenting vs medical management in patients with severe intracranial arterial stenosis
  - Carotid artery stenosis in the neck
SAMMMRPRIS Trial

• WASID trial of warfarin vs aspirin for intracranial stenosis showed that patients with poor BP and lipid control had worse outcomes

• In SAMMMRPRIS aggressive medical therapy alone vs angioplasty/stenting in patients with symptomatic (TIA or stroke) and 70-99% intracranial artery stenosis

• 30 day risk of stroke and death 14.7% in stented group vs 5.8% medical group- p=0.002 and difference persisted for 2 years
SAMMPRIS Trial - medical regime

- Clopidogrel 75 mg + ASA 325 for 90 days then ASA
- Targetted monitored BP (<140 syst; <130 if diabetic)
- Low density lipoprotein cholesterol <70 mg/dl
- Lifestyle modification (using INTERxVENT) with coaches to monitor physical activity, diet, weight, stop smoking
- Risk factor monitoring reports each month to center treating the patient
Aggressive medical treatment

- Spence et al studied asymptomatic 468 patients with >60% ICA stenosis
- There were fewer microemboli (by TCD monitoring) (3.7% vs 12.6%), and a lower rate of stroke, death, MIs, and carotid surgery for symptoms after aggressive medical therapy
- Aggressive medical therapy was posited to be equal or better than surgery/stenting for asymptomatic individuals who did not have persistent microemboli

Arch Neurol 2010;67:180-186
Aggressive medical treatment
Spence et al

• Smoking cessation, exercise, and Mediterranean diet
• Increasing statins to maximum tolerated dose, regardless of LDL levels (eg, 80 mg of atorvastatin or 40 mg of rosuvastatin); when already at maximum tolerated statin dose, add ezetimibe
• In those already taking maximum doses of statins and ezetimibe, adding niacin for non-diabetics and adding fibrates in diabetics
• Prescribing an ACEI or ARB
• Optimizing blood pressure control by individualizing therapy according to the renin/aldosterone profile
• In those with insulin resistance (defined by a high fasting insulin level with normal serum glucose level), metformin or pioglitazone was added before onset of diabetes.
• Antiplatelets
2. Sudden onset focal neurological deficits without major artery occlusions
“Cryptogenic” Stroke

- Occult Atrial fibrillation
- Aortic Plaques
- Occult cardiac lesions
- PFOs
- Arterial non-stenosing plaques (CM Fisher’s ACME)
- Penetrating artery disease (‘lacunar infarcts)
Atrial fibrillation

- Effectiveness of prolonged cardiac rhythm monitoring
- BNP and NT-proBNP for identifying cryptic A fib or other cardiac source
- Newer anticoagulants- dabigatran and apixaban and rivoraxaban
- Poor logic of CHADS$_2$ score as a guide to anticoagulate
CHADS2 scores

• **congestive heart failure**, hypertension, diabetes, age>75, and prior stroke, TIA, or **thromboembolism**

• The A fib trial used stroke as an end-point (not A fib-related embolic stroke)

• All are risk factors for or associated with large and small artery caused strokes, lesions common in older A fib patients

• CHADS2, CHA2DS2-VASc- stroke frequencies are the same with or without A fib (Neurology 2013:80:1009=1017)

• Anticoagulants are posited to be effective only against red-clot embolism related to A-fib

• Anticoagulants are not indicated for these arterial lesions and can be hazardous (hypertension and need for antiplatelets in many)
Red clot vs White clot schema of treatment
Red thrombi
Red Clots
RBCs admixed with Fibrin

- Recent thrombotic occlusions
- Severe arterial narrowing (atherosclerotic, dissection, FMD etc)
- Some cardiac-source embolism
- Venous occlusions
Anti-thrombotic agents
Standard anticoagulants

- Unfractionated heparin
- Low-molecular-weight heparins and heparinoids
- Warfarin
- Factor Xa inhibitors (Apixaban, Rivoraxaban, Fondaparinux)
- Direct thrombin inhibitors
  - Hirudin
  - Argabatran
  - dabigatran
White platelet-fibrin thrombi form in fast moving streams on irregular surfaces
Scanning Electron Micrograph of Microthrombi Formed on SEM under Flow

15KV X396 25.2μM 1101 ZEISS
Agents that alter platelet functions

- Aspirin- Trifusal
- Thienopyridines
  - Clopidogrel
  - Prasugrel
- Phospodiestherase inhibitors
  - Dipyridamole( with or without aspirin) (Aggrenox)
  - Cilostazol (Pletal)
- GpIl/a/IIb inhibitors
- Natural substances- fish oils, black tree fungus etc
Antiplatelet usage

- Decrease platelet function alone - aspirin, clopidogrel, prasugrel
- Effect binding site of platelet with fibrinogen - GPIIb/IIIa inhibitors
- Effect platelets and attachment to the endothelium - dipyridamole, cilostazol
- Vasodilation - dipyridamole, cilostazol
Anti-platelet agents

- Non-stenosing arterial and aortic plaques
- Fibrotic cardiac valve disease-Libman-Sachs endocarditis, APLA valve lesions, NBTE
- Arterial stents
The Aorta
A neglected cause of stroke
Aorta at necropsy
Aortic atherosclerosis
a neglected cause of stroke

• Aortic plaques are common and are a donor source of emboli - calcium, cholesterol crystals, white platelet-fibrin, and red erythrocyte-thrombin emboli

• Large mobile projecting plaques are likely to be red erythrocyte-thrombin clots

• Flat small plaques are likely associated with white fibrin-platelet thromboemboli
CTA of the Aorta

Chatzikonstantinou C et al CTA of the aorta is superior to TEE Cerebrovasc Dis 2012;33:322-328
Chatzikonstantinou C et al. CTA of the aorta is superior to TEE. Cerebrovasc Dis 2012;33:322-328.
Aortic plaques
Emboli from the Aorta during Cardiac Surgery

TEE & TCD monitoring during surgery (Dr Denis Barbut)
Cardiac Surgery–TEE monitoring of aorta
Occult cardiac causes

- Thrombi are too small or abut the walls
- The bird has left the nest. Thromboembolism is a dynamic process
- Evaluation other than echocardiography
Actual size of an atrial clot.
Buckshot within the ICA and MCA - 2 and 3 mm
80 yr old woman- Christian Scientist developed transient left sided weakness in Church
TCD Monitoring
Left ventricular apical mural thrombus (arrow) appears distinctly dark on contrast-enhanced T1-weighted inversion recovery magnetic resonance image.

Axial cardiac images in 61-year-old man with stroke. (a) Early-phase and (b) late-phase cardiac CT angiographic images show oval filling defect (large arrows) in LAA and circulatory stasis (small arrows) just distal to the thrombus.

Hur et al Radiology 2009;251:683-690
Contrast-enhanced Chest CT

(submitted by Drs Litmanovich & Manning)
PFO

Paradoxical embolism
PFO closure trials

• 3 trials- 1 using the STARFlex Septal Closure System (CLOSURE)- N Engl J 2012;366:991-9 and 2 using Amplatzer device (RESPECT) - N Engl J 2013;368:1083-91 and 1092-1100 all had equivocal results

• Key reasons for failure to show effectiveness
  – Patient selection. Patients developed new strokes often unrelated to PFO
  – Effectiveness of medical Rx- antiplatelets or anticoagulants
  – Complications of placement of septal occluder
Caplan criteria for paradoxical embolism
When at least four of these criteria are met, the diagnosis of paradoxical embolism is highly probable.

1) situations that promote leg or pelvic vein thrombosis (e.g., sitting in one position for a long period, recent surgery, and so forth).
2) increased coagulability (use of oral contraceptives, presence of Leiden factor with APC resistence, dehydration)
3) sudden onset of stroke during sexual intercourse, straining at stool, or other activity that includes a Valsalva's maneuver or promotes right-to-left shunting of blood;
4) pulmonary embolism within a short time before or after the neurologic ischemic event
5) the absence of other putative causes of stroke after thorough evaluation.
Non-stenosing arterial plaque
Intrinsic disease within a penetrating branch
Case 1

• At breakfast, a 59 year old business executive suddenly slumped to his left and could not move his left arm or leg. After 1 hour some movement returned in the left leg. He was brought to the hospital 4 hours later by a neighbor

• Past history
  – Angina pectoris and past myocardial infarct
  – Diabetic, on insulin
  – No hypertension
  – No known valvular heart disease
  – No TIAs
  – On aspirin
Case 1

- Examination 4.5 hours after onset;
  - BP 135/80, p 80 regular
  - Awake and alert man
  - Slight left face and moderate arm and hand weakness
  - Diminished position sense left hand
  - No visual field defect or neglect
  - NIHSS- 4
The most likely etiology?

A) Brain embolism from the heart
B) Thrombosis of the right middle cerebral artery
C) Thrombosis of the right internal carotid artery
D) Intracerebral hemorrhage
E) Lacunar infarction
F) Right carotid artery dissection
What is the best acute work-up?

A) Blood tests, CT scan
B) Blood tests, CT, CTA, CT perfusion
C) Blood tests, MRI- T2, T2*, DWI, MRA
D) Blood tests, MRI- Diffusion and perfusion and T2 and T2*
E) B or C
His wife arrives and inquires about tPA. You respond:

A) It is past 3 hours, he improved and so he does not meet published guidelines for IV tPA. We cannot give tPA

B) We do not believe in t-PA in this hospital, we will send him to a stroke center

C) We will give him IV tPA even though he does not meet guidelines

D) We will study him further to see if there is a benefit > risk for either IV tPA or IA thrombolysis or mechanical clot extraction
Professionals who treat Clocks and Watches are called Watchmakers. Professionals who treat Patients and their lesions are called Doctors.
CT and MRI 4.5 hrs after onset
Data needed to logically treat Stroke patients

- The nature, location and severity of the causative vascular-cardiac-hematological conditions
- The mechanism of ischemia- hypoperfusion or embolism
- The cellular and serological components of the blood
- The state of the brain- normal, “stunned”, or infarcted
Perfusion CT

Infarct
Penumbra

IV rtPA

Day 7

M. Wintermark, MD; M. Reichhart, MD
University Hospital, Lausanne, Switzerland
CASE 2

• A 24 yr old woman presented to the emergency room because that morning she had developed temporary numbness of her left hand and foot.

• She delivered her second child 5 weeks before. The pregnancy was without event as was the delivery. Her blood pressure was normal postpartum. Three weeks ago she felt depressed and her physician prescribed sertraline to treat her depression.

• Six days ago she suddenly developed a very severe headache that quickly spread throughout her head. The headache abated after one hour but similar less intense headaches had been occurring daily since. She seldom was without some head discomfort. On one occasion she found it difficult to speak for several hours.
Case 2

• She was quite healthy in the past except for occasional migraine headaches. This was her first pregnancy and there were no recognized complications of the pregnancy.

• On examination, BP 115/80, pulse 85 and regular. No fever.

• No cardiac murmurs or neck or cranial bruits.

• Her neurological examination was normal except that she could not localize touch accurately in her left hand.
Case 2

- CT scan showed a small area of superficial subarachnoid bleeding over the left parieto-occipital convexity. An MRI confirmed the region of subarachnoid blood and also showed several small areas of hyperintensity on FLAIR images that were scattered throughout the cerebral hemispheres.
FLAIR MRI
The most likely diagnosis

A. Ecclampsia
B. Ruptured berry cerebral aneurysm
C. Cerebral vasculitis
D. Reversible cerebral vasoconstriction syndrome (Call-Fleming syndrome)
E. Dural sinus thrombosis
The most important diagnostic testing:

A. MRA and MRV
B. CTA
C. ESR, CRP, Fibrinogen, ANA
D. TCD - Transcranial Doppler ultrasound
E. Catheter cerebral angiography
F. A, B, D or E
The preferred Treatment is

A. Triple H therapy- hypervolemia, hypertension and hemodilution
B. Aspirin
C. Corticosteroids
D. Verapamil or nimodipine
E. Heparin followed by Warfarin
Reversible Cerebral Vasoconstriction Syndrome (RCVS)

- Call, Fleming, Miller Fisher and colleagues reported a series of patients with “reversible cerebral segmental vasoconstriction”
- The French had described a similar condition as postpartum angiopathy
- The condition is most common in the puerperium but occurs in young women, at the menopause and in other situations in which CBF is altered rapidly (e.g. after carotid surgery)
- Similar vasoconstriction can occur in patients with hypercalcemia, pheochromocytoma, and eclampsia
RCVS - Clinical Findings

- Headache, persistent but often intermittent. May begin with a severe “thunderclap” headache
- Multifocal neurological symptoms
- May have scattered small brain imaging abnormalities
- TCD shows diffusely increased blood flow velocities
- Responds to Verapamil
Agents known to promote cerebral vasoconstriction

- Phenylpropanolamine
- Serotonin-uptake inhibitors
- Cocaine
- Amphetamines (epinephrine, norepinephrine, methamphetamine, dextro-amphetamine)
- Tryptans
- Cannabis (especially in binges)