Disclosures

• Medicolegal consulting
• Authorship for American Academy of Family Practice, Ebix, Medscape, Medlink
• Adjudicator for WHI and SOCRATES studies
• Reviewer for Joint Commission
Objectives

• Describe acute management of stroke
• Describe secondary prevention in hypertensive hemorrhagic stroke
• Describe secondary prevention in cerebral amyloid related hemorrhagic stroke
• Describe secondary prevention in non-atrial fibrillation ischemic stroke
Objectives

• Describe secondary prevention in atrial fibrillation ischemic stroke
• Describe secondary prevention in cervical arterial dissection
• Describe secondary prevention in cerebral venous infarction
• Describe secondary prevention in PFO-related ischemic stroke
Non-atrial fibrillation ischemic stroke

Non-atrial fibrillation ischemic stroke

Non-atrial fibrillation ischemic stroke
Acute Management

• Evaluation (High yield)
  – Brain imaging (to distinguish ischemic from hemorrhagic stroke)
  – Blood pressure
  – Neurovascular imaging (especially carotid arteries)
  – Lipid profile
  – Glucose, A1C
  – Cardiac rhythm monitoring (30 days)
  – Urine toxicology
Acute Management

• Evaluation (Low yield)
  – Echocardiogram (TTE and TEE)
  – MR cardiography
  – Hypercoagulable screening (more useful in venous infarction)
  – Angiogram is useful to evaluate for vasculitides
  – Brain biopsy in rare circumstance
Acute management

- Level I data
  - Stroke units
    - 1 less dead or disabled person up to 10 years/20 treated
  - Aspirin 162 mg within 48 hours
    - 1 less dead or disabled person at 6 months/100 treated
  - tPA with 4.5 hours
    - ~12 more patients “cured” of their stroke/100 treated
    - Time to treatment is critical (2 million neurons lost per minute)
Acute management

• Level I data
  – Mechanical thrombectomy
    • 1 less disabled person per 4 treated with large vessel occlusion on CTA
    • There is non-uniform reduction in mortality
  – Blood pressure modification
    • No benefit of early lowering with candesartan in acute ischemic stroke (SCAST)
      – If anything, may have been harmful (higher risk of a poorer functional outcome)
  – SCDs for VTE prophylaxis in stroke (CLOTS III)
Acute management

- Current available data argues against net benefit
  - Heparin/heparinoids
    - For every 9 ischemic strokes prevented, 9 hemorrhagic strokes created
    - Not shown to be of benefit in atrial fibrillation associated stroke (HAEST trial)
    - Appears to be beneficial in venous sinus thrombosis based on small RCTs
  - TEDS stockings for VTE prophylaxis (CLOTS I & II)
Acute management

• No data to support net benefit
  – Oxygen
    • One study found net harm of 100% O2 for 24 hours
    • One small study was stopped early due to increased mortality with normobaric oxygen.
    • Stroke Oxygen Study (8000 patients) found no benefit of either continuous or intermittent oxygen by nasal cannula in stroke patients without hypoxia
  – Intravenous fluids
Acute management

• No level I data to support net benefit
  – Head positioning (flat versus upright versus intermediate) (improve cerebral blood flow versus increasing aspiration pneumonia)
  – Dysphagia screening

• Early versus delayed rehabilitation
  – AVERT III (2100 patients) found net harm to high dose physical therapy early after stroke
  – More studies needed about lower dose physical therapy early after stroke
Acute Management

• Uncertainty
  • There was benefit of lowering systolic BP < 140 mmHg within 6 hours of acute ICH compared to current guidelines of < 180 mmHg (INTERACT2), which was not observed in a similarly designed trial (ATACH-2)
Hemorrhagic infarction (hypertension)
Hemorrhagic infarction (hypertension)

http://dc159.4shared.com/doc/GYosdCR0/preview_html_m54b71766.png
Hemorrhagic infarction (hypertension)

Ping-pong ball
38.0 mm
28.0 mL

ICH (N=188)
0-29 cm³
Mortality 44%
Mortality 19%

Golf ball
1.68 in
40.8 mL

30-60 cm³
Mortality 20%-55%

≥60 cm³
Mortality 91%

Only 1 of 71 patients with ICH volume ≥30 cm³ functioned independently at 30 days

http://dc159.4shared.com/doc/GYosdCR0/preview_html_4b251ecd.png
Hemorrhagic infarction (hypertension)

• **Secondary prevention**
  • Blood pressure < 140 mmHg
  • Blood pressure < 140 mmHg
  • Blood pressure < 140 mmHg
  • Blood pressure < 140 mmHg
  • Moderate alcohol consumption, exercise, stop smoking, healthy eating, health weight
Hemorrhagic infarction (cerebral amyloid angiopathy)

http://radiographics.rsna.org/content/26/5/1517.figures-only
Hemorrhagic infarction (cerebral amyloid angiopathy)

http://radiographics.rsna.org/content/26/5/1517.figures-only
Hemorrhagic infarction (cerebral amyloid angiopathy)

http://radiographics.rsna.org/content/26/5/1517.figures-only
Hemorrhagic infarction (cerebral amyloid angiopathy)

• **Secondary prevention**
• No aspirin or anticoagulants
• Blood pressure < 140 mmHg
• Controversial whether statins should be avoided
• ? Immunosuppression (e.g. Cellcept)
Non-atrial fibrillation ischemic stroke

CT scan
Bright oval skull
Dark CSF
Dark area is infarction (left MCA)

Non-atrial fibrillation ischemic stroke

Non-atrial fibrillation ischemic stroke

Non-atrial fibrillation ischemic stroke

FLAIR sequence
Oval scalp (hydrogen)
Dark CSF
Bright pathology
Shows chronic infarctions

Non-atrial fibrillation ischemic stroke

- This refers ONLY to chronic management, NOT acute
- Antiplatelet monotherapy (aspirin, aspirin/dipryridamole, clopidogrel)
  - Dual antiplatelet therapy for more than 18 months is associated with net harm (increased bleeding some RCTs e.g. MATCH, CHARISMA and increased death in others e.g. SPS3)
  - Cilostazol has been tested in a large Japanese population with advantage over placebo and aspirin but is not FDA approved (CSPS-1, CSPS-2)
Non-atrial fibrillation ischemic stroke

- Alcohol consumption
  - Maximum 2 beverages daily
Non-atrial fibrillation ischemic stroke

• Blood pressure reduction
  – Calcium channel blockers, diuretics, and ACE inhibitors appear to provide the best prevention against stroke recurrence (PROGRESS, MOSES) with similar blood pressure reductions
  – Whether chlorthalidone or HCTZ is superior is unclear
  – ARBs and beta blockers are second line agents
  – The average patient with hypertension requires 3 antihypertensives
Non-atrial fibrillation ischemic stroke

• Cholesterol reduction
  – Statins have proven benefit in secondary stroke prevention (simvastatin in MRC study, atorvastatin in SPARCL)
  – Target LDL is less than 100
  – The SAMMPRIS study (which compared aggressive medical therapy versus stenting) targeted an LDL less than 70 however there was no comparator arm of less than 100
Non-atrial fibrillation ischemic stroke

- Cessation of smoking
  - The average number of quit attempts is 7
  - Varenicline (Chantix®) is may increase risk of stroke and worsen depression which is common after stroke
  - Encourage patients to stop at each visit
  - Many are motivated after stroke
  - Patients with strokes in the insular cortex much more likely to stop smoking than those with strokes in other locations
Non-atrial fibrillation ischemic stroke

• Diabetes management
  – Target A1C < 7.0
Non-atrial fibrillation ischemic stroke

• Diet
  – Mediterranean diet
    • Not specifically tested in stroke patients but has shown benefit in post-MI population and general population
  – DASH diet
    • Lower blood pressure
    • Not tested in terms of reducing stroke risk
Non-atrial fibrillation ischemic stroke

• Drugs
  – Positive cocaine toxicology in 10% in one urban study
  – Crystal meth, heroin also associated
  – ? Marijuana
  – Counseling intervention
Non-atrial fibrillation ischemic stroke

- **Exercise**
  - Population based studies show reduced risk of stroke and death in patients who exercise regularly
  - No randomized trials of regular exercise regimen counseling versus regular counseling in post-stroke patients
  - Physical activity often poses a challenge in patients with disability
Atrial fibrillation ischemic stroke

• This refers ONLY to chronic management, NOT acute
• Anticoagulation
  – Warfarin (Coumadin®)
  – Apixaban (Eliquis®)
  – Rivaroxaban (Xarelto®)
  – Dabigatran (Pradaxa®)
  – Edoxaban (Savaysa®)
  – New oral anticoagulants have not been compared against each other, only against warfarin
Atrial fibrillation ischemic stroke

- Aspirin provides a very small amount of protection.
- If the average annual risk of recurrent stroke is 10%, aspirin reduces the risk to 8%, warfarin to 4%.
Atrial fibrillation ischemic stroke

• Alcohol consumption moderation
• Blood pressure reduction
• Cholesterol reduction
• Cessation of smoking
• Diabetes management
• Diet
• Drug counseling
• Exercise
Arterial dissection: History

• Prior to the late 1970’s, spontaneous dissections of cervical arteries was long thought to be a rare event.
• Fisher et al and Mokri et al described dissections pre-mortem using modern diagnostic procedures which led to an increased detection of these events.

Epidemiology

• Among patients 16-45 years, cervical arterial dissection accounts for up to 25% of strokes
  – In most series, it is about 10%
• Distribution among genders is equal
• Women are about 5 years younger than men at the time of dissection

Pathology

Axial T1-weighted MR image showing crescent of hemosiderin deposition (arrow) in the wall of a carotid dissection with a narrowing of the carotid lumen.

http://imaging.consult.com/image/topic/dx/Interventional?title=Carotid%20Dissection&image=fig3&locator=gr3&pii=S1933-0332(07)71118-7
Ultrasonography

Recurrence risk

- Multicenter European Survey on Natural History of Cervical Artery Dissection
  - 24 centers
  - 459 patients
  - Mean age 44.0 ± 9.7 years
  - 2 deaths, 25 lost to move
  - Mean follow-up of 31 months: 4 (0.9%) presented with recurrent ischemic stroke, 8 (1.8%) had TIA, 2 (0.5%) had recurrent CAD without stroke

Recurrence risk

• Mexico Study
  – 130 patients
  – Mean age 35.4 years
  – 4 (3%) died
  – 126 were followed for approximately 6 months
  – Recurrent ischemic stroke in 6 patients (4.8%) within the first 2 weeks.
  – No difference between aspirin and anticoagulation

Recurrence risk

• Mayo Clinic study
  – Population-based study
  – 48 patients with CAD from 1987-2003 in Olmstead County
  – Average annual incidence of 2.6 per 100,000 population
  – No recurrences during a mean follow-up of 7.8 years

Recurrence risk

• Swiss study
• 298 consecutive patients
• 202 treated with anticoagulants alone, 96 treated with aspirin alone
• At follow-up:
  – Ischemic stroke 0.3%
  – TIA 3.4%
  – Retinal ischemia 1%
• Frequency of the cumulative events did not differ significantly between anticoagulation (5.9%) and aspirin (2.1%)
• Frequency of hemorrhagic events was similar between anticoagulation (2%) and aspirin (1%)

Recanalization rates

- Single center study in Italy
- 76 consecutive patients with 105 dissections
- Mean follow-up of 58 months (range 28-96)
- Complete recanalization occurred in 53/103 (51.4%)
- An additional 21/103 (20.4%) improved to <50% stenosis

Recurrence risk

• Cervical Artery Dissection in Stroke Study – CADISS
• Ongoing RCT comparing aspirin versus warfarin for 3 months
• Outcomes at 6 and 12 months
• 250 patients recruited
PFO-associated ischemic stroke

- 40% of all strokes are cryptogenic
- Presumed etiology is paradoxical embolism
- However, the actual demonstration of a clot traversing the PFO is very rare
PFO and stroke

Figure 1. Transesophageal Echocardiograms of a Patent Foramen Ovale.

In Panel A, a transesophageal echocardiogram in the longitudinal plane shows a separation (arrow) between the primum septum (arrowhead) and the secundum septum — a finding consistent with the presence of patent foramen ovale. Panel B shows a transesophageal echocardiogram, also in the longitudinal plane, obtained during the injection of agitated-saline contrast material through an antecubital vein with use of the Valsalva maneuver. There is complete opacification of the right atrium, and passage of a cloud of bubbles (arrow) between the primum and secundum septa into the left atrium is visible.
Prevalence of PFO

• Autopsy studies: 27%
• Cryptogenic strokes (age < 55): 21%
• Cryptogenic stroke (age > 55): 21%
• “Normal” adults on TTE: up to 18%
• “Normal” adults on TEE: 26%

Webster et al. Lancet 1988
PFO and stroke

- French Patent Foramen Ovale and Atrial Septal Aneurysm Study Group
- 581 patients with cryptogenic stroke (age 15-55)
- All studied with echo (47.7% with atrial abnormality)
- 4-year event rates (All received ASA 300 mg/d):
  - No PFO v. isolated PFO v. PFO + atrial septal aneurysm v. isolated atrial septal aneurysm: 4.2% v. 2.3% v. 15.2% (p<0.05) v. 0%
- Size of PFO did not affect stroke rate

PFO and stroke

- **Mayo Clinic study**
  - 585 randomly sampled, Olmsted County (Minnesota) subjects age 45 years or older participating in the Stroke Prevention: Assessment of Risk in a Community (SPARC) study
  - PFO identified in 140 (24.3%) and ASA in 11 (1.9%)
  - Of 140 with PFO, 6 (4.3%) had an ASA; of 437 without PFO, 5 had an ASA (1.1%, two-sided Fisher exact test, p = 0.028)
  - After adjustment for age and comorbidity, PFO was not a significant independent predictor of stroke (HR 1.46, 95% CI 0.74 to 2.88, p = 0.28).
  - The risk of a cerebrovascular event among subjects with ASA was nearly 4 X higher than that in those without ASA (HR 3.72, 95% CI 0.88 to 15.71, p = 0.074)

Long term follow-up

- Mean follow-up 8.7 years of patients with PFO and stroke (previous publication at 2.3 years in JACC)
- Not randomized
- 158 treated medications, 150 with closure
- Medications were aspirin (48%), clopidogrel (2%), anticoagulants (50%)
- 13 strokes in medical group (8.2%) and 8 in closure group (5.3%)
- Concurrent etiologies for subsequent stroke were identified in 38% of medically treated patients and 44% of closure patients

Mono M-L et al. Stroke 2011
3 RCTs thus far

- CLOSURE-I (909 patients, NMT device)
- PC (414 patients, Amplatzer device)
- RESPECT (980 patients, Amplatzer device)

- ~2300 patients in these 3 trials
- Pooled together, these results fail to show a benefit for secondary prevention of stroke in patients with PFO
- Potential procedural risks include atrial fibrillation, pulmonary embolism, retroperitoneal hemorrhage
CLOSURE-I

- CLOSURE-I
  - Age 18-60 (US and Canada)
  - Stoke or TIA within previous 6 months
  - PFO on TEE
  - Unmasked randomization to medical therapy (aspirin or warfarin) versus percutaneous closure of PFO
  - Primary end point: Stroke, TIA, or death during 2 years of follow-up

Furlan AJ et al. NEJM 2012;366:991-999.
CLOSURE-I

- 909 patients
- 5.5% in the closure group and 6.8% in the medical-therapy group (P=0.37)
- Stroke rate was 3% at 2 years in both groups; TIA was 3% on closure and 4% in medical group
- Atrial fibrillation: more frequent in closure group than medical-therapy group (23 patients [5.7%] vs. 3 patients [0.7%], P<0.001).
- 3 patients had retroperitoneal hemorrhage and 1 had perforated left atrium in closure group

Furlan AJ et al. NEJM 2012;366:991-999.
PC

• PC trial
  – Age ≤ 60 (Europe, Canada, Brazil, and Australia)
  – Stoke (including TIA with + DWI) or peripheral embolism
  – PFO on TEE
  – Patients followed for up to 5 years
  – Primary end point: composite of death, nonfatal stroke, TIA, or peripheral embolism.

Meier B et al. NEJM 2013;368:1083-1091
• 414 patients
• Mean duration of follow-up was 4.1 years
• Primary outcome: 7 patients (3.4%) in the closure group and 11 patients (5.2%) in the medical-therapy group (P=0.34)
• Results of the per-protocol analysis of the primary composite end point were similar to the intention-to-treat analysis, with a hazard ratio of 0.70 (P=0.48)
RESPECT

- **RESPECT trial**
  - Age 18-60 (US, Canada)
  - Cryptogenic stroke (including TIA with positive DWI) within 270 days
  - PFO on TEE
  - Unmasked randomization to medical therapy (aspirin, clopidogrel, aspirin/dipyridamole or warfarin) versus percutaneous closure of PFO
  - Patients followed frequently first 2 years then annually
  - Primary endpoint: Stroke or death

Carroll JD et al. NEJM 2013;368:1092-1100.
RESPECT

• 980 patients with mean duration of follow-up was 2.6 years

• Primary outcome:
  – ITT: **0.66 events/100 patient-years** in closure group vs. **1.38 events/100 patient-years** in medical-therapy group (P=0.08)
  – Per protocol: 0.46 / 100 patient-years in closure group vs. 1.30 / 100 patient-years in medical-therapy group (P=0.03)

• Pericardial tamponade occurred in 2 closure patients.

• Atrial fibrillation occurred in 3% of closure and 1.5% of medical therapy patients (P=0.13).

• Pulmonary embolism in 6 patients (1.2%) in closure group and 1 patient (0.2%) in the medical-therapy group (P=0.12)

Carroll JD et al. NEJM 2013;368:1092-1100.
Venous infarction

• 2 RCTS
  – 20 and 59 = 79 patients
• For patients with CVT, initial anticoagulation with adjusted-dose UFH or weight-based LMWH in full anticoagulant doses is reasonable, followed by vitamin K antagonists, regardless of the presence of ICH (Class IIa; Level of Evidence B)

Saposnik G et al. Stroke 2011; 42:1158-1192
Venous infarction

Saposnik G et al. Stroke 2011; 42:1158-1192
Venous infarction

Saposnik G et al. Stroke 2011; 42:1158-1192
Conclusion

• Acute and chronic management of stroke are different
• The type of stroke does matter with respect to acute and chronic management (i.e. ischemic versus hemorrhagic)
• The mechanism of stroke also influences treatment (atrial fibrillation versus non-atrial fibrillation)
Conclusion

• Some principles are universal:
  – Control blood pressure, control blood sugar, stop smoking, exercise, eat a healthy diet, maintain a healthy weight, treat atrial fibrillation, control cholesterol levels, drink moderately, manage stress
  • 90% of all strokes are attributable to these 10 factors (INTERSTROKE study)