Secondary Stroke Prevention Guidelines & Evolving Practices

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Disclosures

• NIH funding
  – StrokeNet, POINT, SHINE, iDEF, TeleRehab, CREST 2, DEFUSE 3

• WA DOH/CDC funding
  – Coverdell Stroke Program

• Industry funding
  – RESPECT (PFO closure study)
  – NAVIGATE ESUS
Outline

• TIA
• TOAST ischemic subtyping
  – Small vessel disease (lacunar stroke)
    • General ischemic stroke secondary prevention
  – Large artery atherosclerotic stroke
    • Extracranial vs. intracranial
  – Cardioembolic stroke
    • Atrial fibrillation case – NOACs, LAA closure
    • Other cardiac
  – Other determined etiology
    • Dissection, Special situations
  – Undetermined etiology
**Table 1. TOAST Classification of Subtypes of Acute Ischemic Stroke**

CT/MRI, vessels, EKG/telemetry, ECHO

<table>
<thead>
<tr>
<th>Large-artery atherosclerosis (embolus/thrombosis)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardioembolism (high-risk/medium-risk)*</td>
</tr>
<tr>
<td>Small-vessel occlusion (lacune)*</td>
</tr>
<tr>
<td>Stroke of other determined etiology*</td>
</tr>
<tr>
<td>Stroke of undetermined etiology</td>
</tr>
<tr>
<td>a. Two or more causes identified</td>
</tr>
<tr>
<td>b. Negative evaluation ESUS (Embolic Stroke Undetermined Source)</td>
</tr>
<tr>
<td>c. Incomplete evaluation</td>
</tr>
</tbody>
</table>

TOAST, Trial of Org 10172 in Acute Stroke Treatment.

*Possible or probable depending on results of ancillary studies.
Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association


on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease

*Stroke*. 2014;45:2160-2236; originally published online May 1, 2014;
Case

70 y/o patient with hypertension and diabetes presents to you for evaluation in the ER after a 30 minute episode of right sided weakness and aphasia. BP on initial evaluation was 158/94.

What is their risk of stroke in the next 2, 7, 30, 90 days?
# ABCD² or TIA Risk Stratification

<table>
<thead>
<tr>
<th>5 Factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age &gt; 60</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>BP &gt; 140/90 on first assessment after TIA</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td>2</td>
</tr>
<tr>
<td>unilateral weakness</td>
<td></td>
</tr>
<tr>
<td>speech impairment without weakness</td>
<td>1</td>
</tr>
<tr>
<td><strong>Duration of TIA</strong></td>
<td>2</td>
</tr>
<tr>
<td>≥60 minutes</td>
<td></td>
</tr>
<tr>
<td>10–59 minutes</td>
<td>1</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>1</td>
</tr>
</tbody>
</table>

*Lancet* 2007; 369: 283–92
ABCD² or TIA Risk Stratification

Figure: Short-term risk of stroke by ABCD² score in six groups combined (n=4799)

Lancet 2007; 369: 283–92
TIA - Short Term Risk Implications

• Need for prompt workup
  – At time of presentation
    • Especially if recent TIA or high ABCD$^2$ score?
  – In UW system, offer admission to most

• Testing/Interventions
  – Brain imaging (CT or MRI)
  – Carotid imaging
  – Cardiac imaging
  – Rx: antithrombotics, CEA, risk factors (BP, LDL, DM)
77 yo F with hx of HTN, HLD, IDDM II, who presents with 4 days of R sided weakness and slurred speech; her mouth feels "twisted" and she has been having gait difficulty. She has numbness in L face, RUE & RLE and has noted food "getting stuck" in her throat as well as choking on water. Normal carotids, NSR.
General Ischemic Stroke Secondary Prevention

• Lifestyle issues
  – Stop smoking
  – Diet: reduce sodium, Mediterranean > low-fat
  – Exercise: 3-4 x/wk moderate or vigorous intensity

• Antithrombotics
• Hypertension
• High cholesterol
• Diabetes

Stroke. 2014;45:2160-2236
Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

- 5170 pts, China
- 24 hr window
- Dual x 21 days, then clopidogrel vs. aspirin
- US patients different?
  - Etiology
  - RF control
- POINT trial

Survival Free of Stroke

Hazard ratio, 0.68 (95% CI, 0.57–0.81)
P<0.001
Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack

- 13,199 pts
- 33 countries
- 24 hr window
- 90 d follow up
- NS primary endpoint (though close)
- Major hemorrhage no different
- More dyspnea and minor bleeding

![Graph showing cumulative probability of ischemic stroke over time for Ticagrelor and Aspirin.]

Aspirin + Clopidogrel

• Mostly negative results for long term secondary prevention (MATCH, SPS3)

• Stronger case for short term therapy
  – POINT is ongoing NIH funded trial

• HMC approach
  – randomize if TIA/minor stroke, clinical equipoise exists, otherwise
  – consider dual antiplatelet Rx if ASA failure, TIA, minor stroke
  – Perhaps avoid if thought cardioembolic, large stroke
ASA Antiplatelet Guidelines
(atherothrombotic, lacunar, cryptogenic ischemic stroke/TIA)

• Antiplatelets over anticoagulation
• Aspirin, aspirin/ER-DP, clopidogrel acceptable
• Aspirin+clopidogrel reasonable for initiation within 24 hours of minor ischemic stroke or TIA and for continuation for 90 days (Class IIb; Level of Evidence B).
• Aspirin+clopidogrel ↑ hemorrhage over long term, so not recommended for routine long term use
• For aspirin failures...
  – Increasing dose not of proven benefit
  – Changing antithrombotic not proven better

Stroke. 2014;45:2160-2236
HTN post stroke issues

• When?
  – α pathophysiology (CTA, TCDs)
    • large artery stenosis, dependence on collaterals
    • small subcortical stroke

• With what?
  – Mean BP
  – Decrease BP variability
    • Non-loop diuretics, calcium channel blockers
      – Chlorthalidone
      – Amlodipine

SPS3 Blood Pressure Trial

• RCT, 3020 lacunar stroke patients
• Target SBP < 130 mmHg vs. 131-150
• P value 0.08 for ↓19% in all stroke
• ICH significantly reduced (but rare)

“The intervention was safe and well tolerated. Interpreted in the context of previous randomized, controlled trials of blood-pressure lowering after stroke, our results suggest that management of systolic to levels lower than 130 mm Hg is likely to reduce the risk of recurrent stroke in patients with recent lacunar stroke.”
ASA Hypertension Guidelines

• BP Rx recommended after first “several” days, even if no clear hx of HTN
  – Lacunar stroke, perhaps < 130/80
• Target BP uncertain, individualize, at least target to < 140/90
• Lifestyle - ↓salt, weight; ↑fruit, veg, low fat, exercise; moderate EtOH
• Agents – diuretics (+ACEI), amlodipine
  – Otherwise individualize based on co-morbidities

Stroke. 2014;45:2160-2236
SPARCL
(Stroke Prevention by Aggressive Reduction in Cholesterol Levels)

- 4731 patients
- recent TIA, stroke
- LDL 100-190
- Atorvastatin 80 mg vs. placebo
- ↓ First stroke
- ↓ Any CV event
- Hemorrhagic stroke significantly increased
  - HR 1.7
  - Did not cancel overall benefit

ASA Lipid Guidelines

• For ischemic stroke/TIA thought atherosclerotic and with LDL > 100 mg/dL, intensive statins recommended
• For ischemic stroke/TIA thought atherosclerotic and with LDL < 100 mg/dL, intensive statins recommended *(not as strongly)*
• Otherwise manage according to 2013 ACC/AHA cholesterol guidelines, which include lifestyle, dietary and medication recommendations

Stroke. 2014;45:2160-2236
ASA Diabetes Guidelines

• All patients should probably be screened for DM
  – HbA1c may be more accurate than other screening tests in the immediate post event period

• Use of existing guidelines from the ADA for glycemic control and cardiovascular risk factor management is recommended for patients who have DM or pre-DM

Stroke. 2014;45:2160-2236
IRIS – Design
Insulin Resistance Intervention after Stroke

• RCT, 3876 patients, NIH funded
• Recent Stroke or TIA
• Insulin resistance by homeostasis model assessment of insulin resistance
  – > 14 days post stroke, fasting glucose, insulin
  – Cutoff > 3 = highest quartile in non-diabetics
• 1° outcome = any stroke/MI
• Placebo vs. pioglitazone (goal dose 45mg/d)

NEJM 2016 Apr 7;374(14):1321-31
IRIS – Results
Insulin Resistance Intervention after Stroke

• 1° outcome after mean 4.8 yrs 9% vs. 11.8%
  – HR 0.76 (.63-.93), NNT = 36 x 5 yrs
    • Ref: NNT atorvastatin = 32 x 5 yrs (~major CV event)

• 2° outcomes
  – Less new diabetes Dx
  – More weight gain, edema and bone fractures

• Muted response at ISC
  – Pioglitazone fallen from grace
  – Would other agents also work?

NEJM 2016 Apr 7;374(14):1321-31
51 yo M, smoker, polysubstance abuse, presented with 3 days of slurred speech and L sided weakness, then fell.

Diffusion weighted

GAD MRA

CTA

CTA Axial Source images
ASA Symptomatic* Carotid Recs

<table>
<thead>
<tr>
<th></th>
<th>50% to 69% Stenosis</th>
<th>70% to 99% Stenosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endarterectomy</td>
<td>Class I, LOE: B</td>
<td>Class I, LOE: A</td>
</tr>
<tr>
<td>Stenting</td>
<td>Class I, LOE: B</td>
<td></td>
</tr>
</tbody>
</table>

* within last 6 months

Prior CEA, neck radiation, anatomic considerations, high risk for anesthesia, younger?

Early if small, TIA CEA over stenting

Stroke. 2011;42:e464-e540
61 yo male with HTN, HLD, DM, PVD, CAD, carotid atherosclerosis who presented to an OSH with right arm weakness, and aphasia. He was started on ASA and Aggrenox and dc'd to rehab, however 2 days prior to presentation to HMC, the pt started to have worsening right arm weakness and aphasia.
Carotid Artery Occlusion

• Asymptomatic ➔ benign prognosis
• Symptomatic
  – 1/30 of ischemic strokes
  – Recurrence of ipsilateral stroke
    • Overall 2.1% /yr
    • 9.5% /yr if impaired hemodynamics
    • 31% /yr if severely impaired hemodynamics

Neurology 2000;54:878–882
Stroke. 2004;35:e349-e352,
Stroke. 1997;28:2084-2093
JAMA. 1998;280(12):1055-60

• Management
  – Antiplatelet agents, statins
  – If recurrent symptoms assess collaterals/reserve
    • Perfusion scan (MR, CT)
    • TCDs with CO2
    • SPECT w/Diamox
  – Consider ↑ collateral flow
    • Less aggressive BP Rx
    • Contralateral internal carotid intervention
    • Ipsilateral external carotid intervention
    • EC-IC Bypass?
42 yo M, hx HTN, HL, hospitalized for L weakness and numbness and found to have a R MCA ischemic stroke, discharged on ASA, statin. Months later, TIA in the R MCA distribution, CT/MRI negative for stroke, clopidogrel added. Day of admit to HMC had transient L facial droop, L arm/leg weakness and numbness, expressive aphasia, staggering gait, and diplopia. OSH CT perfusion study showed scattered hypoperfusion in the R MCA territory, treated with Heparin gtts and tx to HMC for ? of M1 stenting or EC-IC bypass (not performed).
Intracranial Stenosis Treatment

• WASID observational study suggested decreased risk of recurrent stroke on warfarin vs. aspirin

• WASID RCT showed that 1300 mg/d aspirin better (less death, bleeding) or equal (Ischemic stroke, brain hemorrhage, or death from vascular causes) to warfarin

• SAMMPRIS RCT showed worse outcomes with stenting over aggressive medical therapies

Neurology 45(8), 1995; 1488-1493
NEJM 2005 Mar 31;352(13):1305-16
NEJM 2011 Sep 15;365(11):993-1003
ASA Intracranial Athero Guidelines

• Antiplatelets over warfarin
  – Addition of clopidogrel for 90 days reasonable
• SBP < 140
• High intensity statins
• NO routine stenting, EC/IC bypass
  – Experimental if fail all else
• Cilostazol another antiplatelet agent with possible effectiveness; evidence not clear

Stroke. 2014;45:2160-2236
65 y/o man found down in his apartment in **AFib** with RVR. CT and MRI show large acute L parieto-occipital ischemic stroke with hemorrhagic conversion; established R porencephalic cyst. PMH AFib not anticoagulated, DM, HTN, hyperlipidemia, CAD, smoker.
When to anticoagulate?

HAEST - LMWH vs. ASA

Acute Ischemic Stroke and Afib - Events at 14 Days

Lancet 2000; 355: 1205–10

<table>
<thead>
<tr>
<th>Event</th>
<th>Dalteparin (n=224)</th>
<th>Aspirin (n=225)</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent ischaemic stroke</td>
<td>19 (8.5%)</td>
<td>17 (7.5%)</td>
<td>1.13 (0.57–2.24)</td>
<td>0.73</td>
</tr>
<tr>
<td>Symptomatic cerebral haemorrhage</td>
<td>6 (2.7%)</td>
<td>4 (1.8%)</td>
<td>1.52 (0.42–5.46)</td>
<td>0.54</td>
</tr>
<tr>
<td>Asymptomatic and symptomatic cerebral haemorrhages</td>
<td>26 (11.6%)</td>
<td>32 (14.2%)</td>
<td>0.79 (0.44–1.43)</td>
<td>0.41</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>24 (10.7%)</td>
<td>17 (7.6%)</td>
<td>1.47 (0.77–2.82)</td>
<td>0.26</td>
</tr>
<tr>
<td>Death, any cause</td>
<td>21 (9.4%)</td>
<td>16 (7.1%)</td>
<td>1.35 (0.69–2.66)</td>
<td>0.40</td>
</tr>
<tr>
<td>Recurrence, progression or death</td>
<td>51 (22.8%)</td>
<td>36 (16.0%)</td>
<td>1.55 (0.96–2.49)</td>
<td>0.074</td>
</tr>
<tr>
<td>Recurrence, progression, death or symptomatic cerebral haemorrhage</td>
<td>55 (24.6%)</td>
<td>38 (16.9%)</td>
<td>1.60 (1.01–2.54)</td>
<td>0.048</td>
</tr>
<tr>
<td>Extracerebral haemorrhage</td>
<td>13 (6.8%)</td>
<td>4 (1.8%)</td>
<td>3.40 (1.09–10.61)</td>
<td>0.028</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>1 (0.4%)</td>
<td>5 (2.2%)</td>
<td>0.20 (0.02–1.70)</td>
<td>0.22</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1 (0.4%)</td>
<td>3 (1.3%)</td>
<td>0.33 (0.3–3.22)</td>
<td>0.62</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15 (6.7%)</td>
<td>16 (7.1%)</td>
<td>0.94 (0.45–1.95)</td>
<td>1.0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>8 (3.6%)</td>
<td>5 (2.2%)</td>
<td>1.63 (0.53–5.06)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

- No difference in 3 month outcomes
- High risk groups? Earlier or later?
Advantages

- Rapid onset of anticoagulation
- Less intracranial hemorrhage
- No blood tests
- Less interactions
Table 3. Disadvantages of New Oral Anticoagulants

<table>
<thead>
<tr>
<th>Disadvantage</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short half-life</td>
<td>Potential for increased risk of stroke or systemic embolism with poor drug adherence</td>
</tr>
<tr>
<td>No routine coagulation monitoring required</td>
<td>Potential for increased risk of stroke or systemic embolism with poor drug adherence</td>
</tr>
<tr>
<td>No coagulation assay easily available to precisely measure anticoagulation effect</td>
<td>Cannot titrate dose</td>
</tr>
<tr>
<td></td>
<td>Cannot assess cause for failure of therapy (poor adherence vs failure)</td>
</tr>
<tr>
<td></td>
<td>Cannot easily assess degree of coagulation inhibition in emergent situations such as need for urgent surgery or in the setting of life-threatening bleeding</td>
</tr>
<tr>
<td></td>
<td>No antidote or well-established procedure for reversing anticoagulation in emergent situations</td>
</tr>
<tr>
<td></td>
<td>Cost</td>
</tr>
</tbody>
</table>
PROTECT-AF Trial – WATCHMAN

- left atrial appendage occluder

- RCT, N = 707
- AFib and CHADS2 ≥ 1
- 2:1 WATCHMAN vs. warfarin
- ↓ risk primary outcome
- ↑ ischemic, ↓ ICH
- ↓ risk mortality
- Similar overall safety – 5% complications

The primary efficacy outcome was stroke, systemic embolization, or cardiovascular death.
ASA AFib Guidelines

• If high risk for hemorrhagic conversion (ie, large, hemorrhagic transformation, uncontrolled HTN, or hemorrhage tendency), reasonable to delay anticoagulation beyond 14 days

• Anticoagulation for (almost) all post ischemic stroke
  – Warfarin, NOACs (no expression of clear preference)
  – Possibly add aspirin for significant CAD

• If unable to tolerate anticoagulation, then aspirin
  – Might be reasonable to add clopidogrel

• Usefulness of WATCHMAN device unclear
  – Best for poor anticoagulation candidates? But need 45d warfarin?
  – FDA approved March 2015

Stroke. 2014;45:2160-2236
<table>
<thead>
<tr>
<th>Major source</th>
<th>Minor source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation → Warfarin vs NOACs</td>
<td>Patent foramen ovale → asa/warf/closure?</td>
</tr>
<tr>
<td>Mitral stenosis → antiplatelet?</td>
<td>Atrial septal aneurysm → antiplatelet</td>
</tr>
<tr>
<td>Prosthetic valves → Warfarin (+)</td>
<td>Atrial or ventricular septal defects → closure?</td>
</tr>
<tr>
<td>Infective endocarditis → No aspirin</td>
<td>Calcific aortic stenosis → antiplatelet</td>
</tr>
<tr>
<td>Marantic endocarditis → LMWH</td>
<td>Mitral annular calcification → antiplatelet</td>
</tr>
<tr>
<td>Atrial myxoma → surgery</td>
<td>Fibroelastoma (? major source)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>Surgery after initial vs. recurrent</td>
</tr>
<tr>
<td>Left ventricular thrombus</td>
<td></td>
</tr>
<tr>
<td>Left ventricular akinesis/aneurysm</td>
<td></td>
</tr>
<tr>
<td>Left ventricular failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>? warfarin</td>
</tr>
</tbody>
</table>
• Closure with STARFlex possibly does not provide a benefit
• Closure with the AMPLATZER PFO Occluder:
  – ↓ risk of recurrent stroke (RD -1.7%, 95% CI -3.2% to -0.2%)
  – ↑ the risk of new Afib (RD 1.6%, 95% CI 0.07%–3.2%)
  – likely procedural complications of 3.4% (95% CI 2%–5%)
• Insufficient evidence anticoagulation vs. antiplatelet
• Should not routinely offer PFO closure
• Rarely (e.g. recurrent strokes with no other mechanism), may offer AMPLATZER PFO Occluder (Level C)
  – FDA reviewing AMPLATZER device
Emerging Cardiac Risk Issues

• Extended Cardiac Monitoring in Cryptogenic Ischemic Stroke
  – By 12 months, 12.4% Afib > 30 sec vs. 2% w/o monitoring
  – 30d vs. 24h additional monitoring, Afib > 30 sec in 16.1% vs. 3.2%
    • Significant increase in warfarin use, ASA guidelines endorse in cryptogenic

• Atrial Cardiopathy
  – StrokeNet RCT?

**References**

- Stroke. 2013;44:714-719
- NEJM. 2014;370(26):2467-77
- NEJM. 2014;370(26):2478-86
Other Determined Etiology

• Dissection  
  Lancet Neurol 2015; 14: 361–67
  – Antiplatelets preferred, CADISS RCT

• Hypercoaguable states  
  – Anticoagulation in many cases (esp. APL syndrome)

• Vasculitis  
  J Neurol. 2001;248:451–468
  – Antiplatelets plus immunosuppression

• Sickle Cell Disease  
  Lancet Neurol. 2006;5(6):501-12
  – Exchange transfusion, risk stratify by TCDs

• OSA...others  
  Stroke. 2014;45:2160-2236
# Undetermined Etiology

**TOAST cryptogenic vs. ESUS**

## Diagnostic criteria

**Cryptogenic ischaemic stroke**
- No arterial stenosis (>50%) or occlusion coupled with non-lacunar infarct on imaging
- No clinical lacunar syndrome if imaging shows no infarct or small (<1.5 cm) subcortical infarct
- No major-risk or medium-risk cardioembolic sources

**Embolic stroke of undetermined source (ESUS)**
- Non-lacunar brain infarct on imaging
- Open arteries (<50% stenosis) proximal to the infarct
- No major-risk cardioembolic source

## Necessary diagnostic assessment

**Cryptogenic ischaemic stroke**
- Not specified†

**Embolic stroke of undetermined source (ESUS)**
- Brain CT or MRI showing non-lacunar infarct
- Precordial echocardiography
- ECG and cardiac monitoring for ≥24 h
- Imaging of the extracranial and intracranial arteries supplying the area of the brain infarct

---

ESUS trials ongoing...

*Lancet Neurol 2014; 13: 429–38*
Summary

• TIA – urgent assessment, Rx risk factors

• TOAST ischemic subtyping
  – Small vessel disease (lacunar stroke)
    • General ischemic stroke secondary prevention
      – Lifestyle, Antithrombotics, HTN, statins, DM screen/control
  – Large artery atherosclerotic stroke
    • Extracranial – interventions for high grade stenosis
    • Intracranial – max medical Rx

• Cardioembolic stroke
  • Atrial fibrillation: extended screening, warfarin vs. NOACs, LAA closure
  • Atrial cardiopathy, PFO

• Other determined etiology
  • Dissection, others

• Undetermined etiology
  • Cryptogenic vs. ESUS
Thank you for your attention