Guiding Secondary Stroke Prevention through Evaluation of Ischemic Stroke Etiology

Ann M. Leonhardt Caprio, MS, RN, ANP-BC
Program Coordinator
Comprehensive Stroke Center, Strong Memorial Hospital
Clinical Associate Faculty, School of Nursing
University of Rochester
What is a Stroke?

• 87% of strokes are ischemic

• Brain Ischemia
  – Thrombosis
    • Local blockage of artery
  – Embolism
    • Debris originates proximally

Loss or alteration of bodily functions as a result of insufficient supply of blood to the brain.
Incidence and Prevalence

• An estimated 6.8 million Americans 20 and older have had a stroke
• Annually in the U.S.
  – 795,000 people have a stroke
    • 610,000 new
    • 185,000 recurrent
• Every 40 seconds someone in the U.S. has a stroke
Recurrence

- **Percentage within 5 years of first stroke**
  
<table>
<thead>
<tr>
<th>Age 40-49</th>
<th>Age ≥ 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>13% men</td>
<td>23% men</td>
</tr>
<tr>
<td>22% women</td>
<td>28% women</td>
</tr>
</tbody>
</table>

- **After TIA**
  
  - 10% have a stroke within 90 days
  - 5% within 2 days
  - Highest risk in first 30 days
  - 10 year stroke risk of 18.8%
Impact

• Leading cause of serious, long term disability
• 15-30% of survivors are permanently disabled
• 20% require institutional care at 3 months
• Estimated direct and indirect costs
  • 2009: $68.9 billion
  • 2010: $73.7 billion
Stroke Etiology

**TOAST Criteria**

- Large vessel
  - Intracranial
  - Extracranial
- Cardioembolism
- Small vessel disease
- Other etiology
- Cryptogenic
Determination of Etiology
Diagnostic Testing

• Brain imaging
  – CT
  – MRI

• Vessel imaging
  – CTA
  – MRA
  – CUS

• Cardiac testing
  – ECG
  – Echocardiogram
  – Cardiac rhythm monitoring

• Labs
  – Hemoglobin A1C
  – Lipid profile
  – Additional for cryptogenic stroke
Risk Factor Modification For All

- Hypertension
- Dyslipidemia
- Diabetes
- Obesity
- Physical Inactivity
- Nutrition
- Sleep Apnea
- Smoking
Hypertension

- Prevalence among patients with ischemic stroke: 70%
- Previously untreated
  - Initiate if ≥ 140/90 several days after stroke
- Previously treated
  - Resume several days after stroke
- Goal BP
  - Individualize to patient
  - For most SBP <140, DBP <90

- Medication choice
  - Optimal regimen unclear
  - Individualize to patient factors
  - Diuretic or diuretic in combination with ACE-I reasonable
  - Beta blockers, calcium channel blockers, ARBs all studied
  - Efficacy: lowering of BP regardless of medication used
Sleep Apnea

- 50-75% of patients with stroke or TIA have sleep apnea
- Treatment of sleep apnea improves outcomes in the general population
- In stroke patients associate with
  - Higher mortality
  - Delirium
  - Depression
  - Worse functional status
- Consider sleep study
- CPAP improves outcomes
Additional Risk Factors

**Dyslipidemia**
- High intensity statin use, regardless of LDL and ASCVD
- What qualifies?
  - atorvastatin 40-80 mg daily
  - rosuvastatin 20-40 mg daily

**Diabetes**
- Screen all patients for diabetes after stroke or TIA
  - HbA1C may be more accurate immediately post stroke
- Follow ADA guidelines

**Smoking**
- Don’t smoke!
- Smoking cessation
  - Nicotine replacement
  - Medications

**Obesity, Nutrition, Physical Activity**
- Usefulness of weight loss immediately post stroke/TIA unclear
- If undernourished need nutritionist
- Mediterranean diet (not low fat)
- Vitamin supplements not advised
- 40 minutes moderate exercise 3-4 times weekly
Antiplatelet Therapy

• Preferred for noncardioembolic etiology
• Combination aspirin and clopidogrel is generally not advised
• Adding antiplatelet therapy to warfarin
  – Not for stroke prevention alone
  – Special circumstances: unstable angina, stenting
• For patients taking aspirin at the time of a stroke or TIA
  – No evidence for increasing dose
  – Alternative agents can be considered, but none have been adequately studied
Antiplatelet Therapy

- aspirin 50-325 mg daily
- Combination aspirin and extended-release dipyridalmoole (Aggrenox) 25/200 mg twice daily
- clopidogrel (Plavix) 75 mg daily
- Others
  - ticlopidine (Ticlid): rarely used due to side effects and newer medications
  - prasugrel (Effient): contraindicated, increased risk of serious or fatal bleeding in patients with stroke or TIA
  - ticagrelor (Brilinta): non-superior to aspirin, similar safety
- What about resistance?
Large Artery Extracranial Carotid Disease

- Diagnostic testing results
  - Brain imaging
    - Anterior circulation, hemispheric stroke
    - Watershed infarct of the ACA-MCA or MCA-PCA territories
  - Vessel imaging
    - Stenosis
      - <50% = “not significant”
      - 50-69% = moderate stenosis
      - 70-99% = severe stenosis
      - Occlusion
      - Plaque, thrombus
Large Artery Extracranial Carotid Disease

• Stroke prevention
  – Early revascularization
  – CEA for severe symptomatic stenosis (70-99%)
  – CEA for moderate symptomatic stenosis (50-69%)
    • Consider patient specific factors
    • Perioperative morbidity and mortality estimated <6%
  – CAS as alternative
    • Younger patients
    • Anatomical risk of surgery: radiation induced stenosis, restenosis of prior CEA
  – Medical management for <50% stenosis
  – Routine, long term follow-up imaging with CUS is not recommended
Large Artery Extracranial Vertebrobasilar Disease

• “Vertebrobasilar insufficiency”

• Diagnostic testing results
  – Brain imaging
    • Posterior circulation stroke
  – Vessel imaging
    • Occlusive disease (stenosis) of cervical and proximal vertebral artery
Large Artery Extracranial Vertebrobasilar Disease

- Stroke Prevention
  - Routine preventive therapy
    - Antiplatelet
    - Statin
    - Blood pressure management
  - Stenting is rarely indicated
    - Recurrent symptoms despite maximal medical therapy
Large Artery Intracranial Atherosclerosis

• Diagnostic testing results
  – Vessel imaging
    • >50% narrowing of large intracranial vessels
    • MCA, ACA, PCA, Basilar (not small vessel disease)
  – Brain imaging
    • Stroke in the territory of the stenosis
Large Artery Intracranial Atherosclerosis

• Stroke Prevention
  – aspirin 325 mg daily preferred over warfarin
  – 70-99% stenosis of major intracranial artery (in territory of stroke)
    • aspirin 325 mg AND clopidogrel 75 mg for 90 days
    • aspirin OR clopidogrel long term (after 90 days)
  – High intensity statin
  – Management of SBP below 140
  – Angioplasty and stenting is not recommended
Cardioembolism
Atrial Fibrillation

- Diagnostic testing results
  - Brain imaging
    - "wedge shaped" infarct
    - "multifocal embolic infarcts"
    - Bilateral strokes
  - ECG/Telemetry/Holter/Loop recorder
    - Atrial fibrillation
    - Atrial flutter
  - Echocardiogram
    - Afib/aflutter
    - Left atrial enlargement
    - Left atrial appendage clot
Atrial Fibrillation
Anticoagulation

- **Vitamin K antagonist (VKA)**
  - warfarin (Coumadin)
  - Goal INR 2-3
  - RRR 68%

- **Direct thrombin inhibitor**
  - dabigatran (Pradaxa)

- **Factor Xa inhibitors**
  - apixaban (Eliquis)
  - rivaroxaban (Xarelto)
## Atrial Fibrillation Anticoagulation

<table>
<thead>
<tr>
<th>Trial</th>
<th>RE-LY (dabigatran)</th>
<th>ROCKET-AF (rivaroxaban)</th>
<th>ARISTOTLE (apixaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Dose</td>
<td>150 or 110 mg bid Lower dose with CRI was not evaluated in the trial</td>
<td>20 mg QD (15 mg if cc 30-49 ml/min)</td>
<td>5 mg bid</td>
</tr>
<tr>
<td>Patient Number</td>
<td>18,113 (PROBE)</td>
<td>14,000 (DB)</td>
<td>18,201 (DB)</td>
</tr>
<tr>
<td>Prior Stroke/TIA</td>
<td>20%</td>
<td>55%</td>
<td>19.5%</td>
</tr>
<tr>
<td>Mean CHADS2</td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Warfarin INR 2-3</td>
<td>67% of time</td>
<td>57.8% of time</td>
<td>66% of time</td>
</tr>
<tr>
<td>Primary End Point</td>
<td>1.7% Warfarin 1.54% (Dab. 110mg) (NS) 1.11% (Dab. 150mg) (p&lt;.05)</td>
<td>2.42% Warfarin 2.12% Rivaroxaban (NS by ITT)</td>
<td>1.6% Warfarin 1.27% Apixaban (p&lt;.01 by ITT)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>Less in Dabigatran (110 mg not 150 mg bid)</td>
<td>Same</td>
<td>Less in Apixaban</td>
</tr>
</tbody>
</table>
| ICH            | 0.38% Warfarin 0.12% (p<.001) 0.10% (p<.001)                                      | 0.44% Warfarin 0.26% (p<.019)                                                 | 0.47% Warfarin 0.24% (p<.01)
    | * ICH risk similar to ASA                                                        |                                                                                 |                                                                             |
Advantages and Disadvantages of Novel Agents

ADVANTAGES:
- Rapid onset of action
- Low likelihood of food–drug interactions
- Limited drug–drug interactions
- Predictable anticoagulant effect
- No need for routine coagulation monitoring
- Reduced risk of intracranial bleeding

DISADVANTAGES:
- Increased front cost compared with warfarin
- Antidote
- No specific laboratory marker for monitoring of anticoagulation effect when considered necessary

When choosing consider:
- Time spent in therapeutic range for warfarin
  - Renal function
  - Liver function
  - Lifestyle
- Insurance coverage
Atrial Fibrillation
Anticoagulation

• **Timing of Initiation**
  – Usually within 2 weeks
  – Consider delay
    • Large infarct
    • Hemorrhagic transformation on initial imaging
    • Uncontrolled HTN

• **Bridging**
  – Recommend if high perioperative risk
  – Abrupt discontinuation of new agents associated with increased stroke risk

• **Competing causes of stroke**
  – 25% have afib and another possible cause
  – Focus on presumed cause
  – Usually anticoagulation appropriate
Atrial Fibrillation
Other treatments

• Antiplatelets
  – If unable to tolerate anticoagulation, aspirin alone
  – Combination aspirin and clopidogrel reasonable, but high risk

• Combination therapy (anticoagulation and antiplatelet)
  – Not routine
  – CAD, stent, or other compelling indication

• Atrial appendage occlusion
  – Watchman device
Cardioembolism
Other sources

• Acute MI and LV thrombus
  – warfarin with goal INR 2-3 for 3 months
  – Antiplatelet in addition to warfarin if indicated

• Cardiomyopathy
  – LVEF ≤ 35% individualize antithrombotic choice

• Valvular heart disease
  – With afib: warfarin

• Prosthetic heart valves
  – Mechanical: warfarin with goal INR 2.5-3.5, add aspirin if low bleeding risk
  – Bioprosthetic: aspirin
Small Vessel

- Diagnostic testing results
  - Brain Imaging
    - “Small subcortical”
    - “Lacunar” stroke
  - Vessel Imaging
    - No focal stenosis
    - Lenticulostriates not seen on imaging
Small Vessel

• Stroke Prevention
  – Aggressive blood pressure management
    • SBP goal <130
  – Antiplatelet
  – Intensive statin
  – Diabetes management
  – Smoking cessation
Other Source

- Aortic arch atheroma
  - Antiplatelet, statin
- Arterial dissection
  - Antiplatelet OR warfarin 3-6 months
- PFO
  - If venous source of embolism: anticoagulation
  - Closure?
- Cerebral venous sinus thrombosis
  - Anticoagulation for at least 3 months then antiplatelet
Cryptogenic

- No specific attributable cause
- 23-40% of ischemic strokes
- More frequent in the young
- Advanced diagnostic testing guided by MRI findings
- Detecting occult atrial fibrillation
- Other considerations
Cryptogenic

Application of advanced techniques in cryptogenic stroke.

Oh Young Bang et al. Stroke. 2014;45:1186-1194

Copyright © American Heart Association, Inc. All rights reserved.
Other Considerations

• Anticoagulation after Intracranial Hemorrhage
  – Individualize to patient
  – Consider etiology of ICH
  – Low risk bleeding + high risk ischemic stroke
    • Consider resuming anticoagulation
  – High risk bleeding + low risk ischemic stroke
    • Consider antiplatelet
  – Hemorrhagic ischemic infarct

– Timing
  • Optimal timing unclear
  • ≥ 1 week from bleeding


