Management of Stroke: Some Questions and Some Answers

Harold P. Adams, Jr. M.D.
Division of Cerebrovascular Diseases
Department of Neurology
UIHC Comprehensive Stroke Center
University of Iowa
Conflicts of Interest

- I adjudicate events in clinical trials sponsored by Merck and I serve on the DSMB for a clinical study funded by Medtronic. I am a consultant to Pierre Fabre (France)

- I receive grant support from NINDS and St Jude Medical

- I will discuss therapies for treatment of stroke that are not approved by the FDA
Introduction

- Advances in the diagnosis, prevention and treatment of stroke continue to occur
- Resulting in changes in patient
- These changes are reflected in national guidelines
- These changes also are generating questions by clinicians
- Time to address some of these questions
- Try to answer 7 of these questions
Question # 1

- What should our blood pressure targets be now in the management of patients with acute ischemic or hemorrhagic stroke?
Arterial hypertension is commonly detected in the setting of an acute ischemic or hemorrhagic stroke.

Arterial hypertension is a premier risk factor for premature atherosclerosis and both ischemic and hemorrhagic stroke.

An elevated blood pressure may be a consequence of the stroke:
- Stress of the acute event (headache, agitation, nausea, vomiting, white coats, etc.)
- Compensatory measure to maintain cerebral blood flow in setting of ischemia or increased intracranial pressure.
Impact of Arterial Hypertension – Acute Stroke

- Adverse impact of hypertension
  - Potentiate bleeding or recurrent rupture of aneurysm
  - Hemorrhagic transformation of infarction
- Potential adverse effects of rapid lowering of blood pressure
  - Loss of autoregulation leads to pressure-dependent blood flow
  - Lowering blood pressure may worsen ischemia distal to an arterial occlusion
  - Lowering blood pressure may worsen ischemia in a patient with increased intracranial pressure
Spontaneous decline in blood pressure during first 24 hours
Erratic responses to medications
Uncertainties in medical management
  Level of blood pressure that mandates treatment
  Desired decline in blood pressure
  Selection of acutely administered medications
  Transitioning to longer term care with restarting or adjusting antihypertensive medications
Clinical trials have given inconclusive results
Chinese Antihypertensive Trial in Acute Ischemic Stroke

- Randomized trial – 4071 patients
  - No thrombolysis and treated < 48 hours
  - Goal of reducing blood pressure 10% - 25% in 24 hours and goal of < 140/90 mm Hg
- Outcomes at 14 days/discharge and 3 months
  - Death/disability (mRS > 3)
- Did lower blood pressures – 24 hours
  - Treatment: mean systolic pressure reduced 12.7%
  - Control: mean systolic pressure reduced 7.2%
- Outcomes
  - No significant differences between groups

He et al, JAMA; 2013 (online)
If systolic BP > 200 mm Hg or MAP > 150 mm Hg
  - Aggressive lowering with continuous IV infusion and measurements of blood pressure every 5 minutes
If systolic BP > 180 mm Hg or MAP > 130 mm Hg and there is concern about increased ICP
  - Monitor ICP and reducing BP carefully with intermittent or continuous IV infusion – maintain CPP > 60 mm Hg
If systolic BP > 180 mm Hg or MAP > 130 mm Hg and there is no evidence of increased ICP
  - Modest reduction of blood pressure to MAP 110 Hg or target value of 160/90 – intermittent/continuous meds

Morgenstern et al, Stroke; 2010; 41: 2108
Intravenous administration of

- **Labetalol**
  - Bolus: 5-20 mg every 15 minutes
  - Infusion: 2mg/min (maximum 300 mg/day)

- **Hydralazine**
  - Bolus: 5 – 20 mg every 30 minutes
  - Infusion: 1.5 – 5 µg/kg/minute

- **Nicardipine**
  - Infusion: 5 – 15 mg/hour

**Indications**

- Mean arterial pressure > 120 mm Hg
- Systolic blood pressure > 160 mm Hg
- Diastolic blood pressure > 100 mm Hg
- Maintain cerebral perfusion pressure > 60 mm Hg
Management of Arterial Hypertension – Acute Ischemic Stroke

- Blood pressure < 185 mm Hg systolic AND 110 mm Hg diastolic to administer rtPA
  - Aggressive treatment to achieve blood pressure
  - Keep below these levels after treatment
- In other circumstances, goal is to lower blood pressure by approximately 15% in first 24 hours
  - No solid data, general consensus
  - Treat if blood pressure > 220 mm Hg systolic or 120 mm Hg diastolic

Jauch et al, Stroke, 2013
Medications – Emergency Treatment of Ischemic Stroke

- Short acting medications given intravenously
  - Can be stopped if blood pressure drops too much or if the patient worsens neurologically
- Choices
  - Labetalol 10 – 20 mg over 1 – 2 min, repeat x 1
  - Nicardipine 5 mg/hr infusion, may increase by 2.5 mg/hr q 5 – 15 min, maximum 15 mg/hr
    - Requires continuous blood pressure monitoring
  - Can try hydralazine, enalaprilat, sodium nitroprusside
    - If sodium nitroprusside is required, patient generally cannot receive tPA

Jauch et al, Stroke, 2013
Questions # 2 and # 3

- What is the upper time limit for treatment with rtPA to be effective?
- What is the upper age limit for thrombolytic therapy
### Meta-Analysis

**Trials of Intravenous Thrombolysis**

<table>
<thead>
<tr>
<th>Favorable outcomes</th>
<th>rt-PA</th>
<th>Control</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated &lt; 6 hr</td>
<td>1609/3482</td>
<td>1434/3403</td>
<td>1.18 (1.07-1.30)</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>Treated &lt; 3 hr</td>
<td>365/896</td>
<td>280/883</td>
<td>1.56 (1.28-1.90)</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Treated 3 – 6 hr</td>
<td>1180/2490</td>
<td>1133/2481</td>
<td>1.07 (0.96-1.21)</td>
<td>p = 0.23</td>
</tr>
</tbody>
</table>

Wardlaw et al, Lancet, 2012
Pooled analyses of clinical trials

<table>
<thead>
<tr>
<th>Time</th>
<th>Odds of Favorable Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 90 minutes</td>
<td>2.55 (1.44 – 4.52)</td>
</tr>
<tr>
<td>91 – 180 minutes</td>
<td>1.64 (1.12 – 2.40)</td>
</tr>
<tr>
<td>180 – 270 minutes</td>
<td>1.34 (1.06 – 1.68)</td>
</tr>
<tr>
<td>270 – 360 minutes</td>
<td>1.22 (0.92 – 1.61)</td>
</tr>
</tbody>
</table>

Lees et al, Lancet, 2010; 375: 1695
Expanding the Time Window
Intravenous Thrombolysis

- European trial demonstrated efficacy out to 4.5 hours – time period included in current guidelines
  - Not as effective as earlier treatment
  - Not likely to expand time window much more
- Are some differences in selection criteria from treatment < 3 hours
- Exclusions for 3 – 4.5 hours
  - Age > 80
  - History of diabetes and prior (clinical) stroke
  - NIH Stroke Scale score > 25
  - Use of oral anticoagulants regardless of INR
Age Restrictions
Intravenous Thrombolysis

- No age restriction for treatment of persons < 3 hours
  - Children
  - Elderly
- Age restriction for treatment of persons 3 – 4.5 hours
  - Do not treat persons older than 80
Do carotid Dopplers add anything if we have the results of a MRA of the head/neck?
Choices for Vascular Imaging Patients with Stroke

- **CTA**
  - Extracranial/intracranial vessels – at time of CT
  - Involves IV contrast – contrast nephrotoxicity
  - Availability of 3-D reconstruction of images

- **MRA**
  - Extracranial/intracranial vessels – at time of MRI
  - Involves IV contrast – contraindicated in renal failure
  - Pacemaker, claustrophobia, metal
  - May over-estimate degree of arterial narrowing

- **Carotid duplex (Doppler)**
  - Visualizes carotid bifurcation only
  - Provides information about the arterial wall
  - Subject to performance variability
Non-invasive Vascular Imaging Patients with Stroke

- MRA and CTA are more expensive than carotid duplex
  - Advantage of imaging both intracranial and extracranial vasculature
  - Do not image smaller intracranial vessels
  - Detect aneurysms, vascular malformations
- Some surgeons want confirmation about the nature of the arterial lesion before deciding about carotid endarterectomy
- Generally, a carotid duplex is not needed if carotid endarterectomy is not planned
Question # 5

- Is transthoracic echocardiography sufficient to look for clot?
Cardioembolism

- Accounts for approximately 20% - 25% of ischemic strokes
- Occurs in persons of all ages regardless of sex or ethnicity
- Causes vary by age
  - Congenital heart disease in children
  - Atherosclerotic heart disease in older persons
- Some patients may not have overt cardiac symptoms or signs
Non-invasive

Limited sensitivity
  - Large chest or obese

Images left ventricle – wall, chamber
  - Ventricular aneurysm
  - Ventricular akinesia
  - Intraventricular thrombus or mass

Also may detect atrial myxoma, PFO, valvular lesions
Transesophageal Echocardiography

- Minimally invasive
  - Esophageal disease
  - Risk of bleeding or aspiration
  - Requires sedation and analgesia
- Images
  - Left atrium and appendage
  - Valves
  - Aorta
- More sensitive than TTE
- Detects lesions of uncertain significance
Enlargement of left atrium or appendage
- Thrombus in left atrium or appendage
- Inter-atrial septal lesions
- Atrial turbulence (“smoke”)
- Valvular lesions
  - Vegetation
  - Lambl excrescence
  - Calcification
  - Valvular strands
- Atherosclerotic disease of the aorta
Intravenously administer agitated saline

- Assess movement of bubbles
  - Right and left sides of the heart
  - Early appearance on the left side
    - Right-to-left shunt

- Found with
  - Atrial or ventricular septal defect
  - Patent foramen ovale
  - Pulmonary arteriovenous malformation
Cardiac imaging remains important in evaluation of patients with ischemic stroke.

- Can be avoided if other cause established
- Cardiogenic embolism usually arises from lesions in the left atrium, left atrial appendage, mitral valve

**Indications for TTE**
- Presumed left ventricular origin
- Anterior wall MI, ventricular aneurysm

**Indications for TEE**
- To search most other possible cardiac causes of stroke
What is the role of statins in management of acute stroke?
Increasing evidence that hyperlipidemia is a risk factor for ischemic stroke

- Promotes large artery atherosclerosis and small vessel brain disease
- Also indirectly leads to stroke via cardioembolism in patients with coronary artery disease

Measuring levels of cholesterol in a patient with stroke is a quality measure

- Now done in virtually all patients with ischemic stroke
HMG-CoA Reductase Inhibitors (Statins)

- Inhibit HMG-CoA reductase, the rate-limiting enzyme of the mevalonate pathway for cholesterol synthesis
  - Also increased clearance of LDL lipoprotein from the blood
  - Modest increase in HDL cholesterol levels
  - Reduce triglycerides by 20% - 40%
- Majority of cholesterol synthesis is at night – rationale for giving medication in the evening
  - Improve endothelial function and maintain plaque stability
  - Modulate inflammatory responses
  - Prevent formation of thrombi
Randomized Trial of High-Dose Atorvastatin – Patients with TIA or Stroke

<table>
<thead>
<tr>
<th>Event</th>
<th>Atorvastatin (80 mg/d) N = 2365</th>
<th>Placebo N = 2366</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal or non-fatal stroke</td>
<td>265 11.2%</td>
<td>311 13.1%</td>
<td>0.05</td>
</tr>
<tr>
<td>TIA</td>
<td>153 6.5%</td>
<td>206 8.8%</td>
<td>0.004</td>
</tr>
<tr>
<td>Coronary event</td>
<td>81 3.4%</td>
<td>121 5.1%</td>
<td>0.006</td>
</tr>
<tr>
<td>Death</td>
<td>216 9.1%</td>
<td>211 8.9%</td>
<td>0.77</td>
</tr>
<tr>
<td>ICH</td>
<td>55</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>

SPARCL, N Engl J Med, 2006; 355: 549
Statins and Ischemic Stroke

- Most powerful medications to lower LDL cholesterol
- First choice for treatment of most patients with ischemic stroke
- Choice of medication
  - Rosuvastatin, atorvastatin, and simvastatin have the greatest impact on lowering LDL cholesterol
  - Atorvastatin and fluvastatin do not require dose adjustment in patients with renal disease
  - Lower doses of pravastatin or rosuvastatin in patients with liver disease
  - Pravastatin and fluvastatin are the least likely to cause muscle toxicity
Statins, Hemorrhagic Stroke and Muscle Disease

- May be some increase in risk of hemorrhagic stroke with aggressive lowering of LDL cholesterol
  - May wish to avoid medications in this situation
- Muscle disease
  - Relatively uncommon with treatment with statin alone
    - Myalgias: 2% - 11%, myositis: 0.5%, myoglobinuria: 0.1%
    - Usually begins within the first weeks of treatment
    - Monitored by CK levels
  - Variation of SLCO1B1 gene, which is involved in the absorption of statins, increases risk
  - Increased risk if renal dysfunction
  - Increased risk with medications that block CYP3A4
Is there a role for SSRIs in acute stroke?
Approximately 75% persons with stroke survive and need some rehabilitation (400,000 annually)

- Measures to maximize recovery could be prescribed to large numbers of patients
- No medical treatment has been established as effective – given as an adjunct to current rehabilitation
- Potential for a much larger impact on the public’s health than time-limited acute treatments
Recovery After Stroke

- Changes in metabolic activity in both the ipsilateral and contralateral cerebral hemispheres
- First hours and days
  - Changes in CBF and CMRO2
  - Edema, diaschisis, inflammation
- First days and weeks
  - Cellular growth and excitability
  - Structural and physiological changes
- First weeks and months
  - Treatment and experience effects

Cramer, Stroke, 2004; 36: 2695
Depression After Stroke

- Common consequence of stroke
- Associated with impaired recovery
  - Motor performance
  - Cognitive recovery
  - Activities of daily living
- Associated with increased mortality
- Effects persist even when adjusting for age, severity of impairments, and comorbid illnesses
SSRIs increase expression of VEGF in the dentate gyrus of the hippocampus in experimental models. The effects of SSRIs may be augmented because of increases in VEGF. SSRIs may improve both motor and sensory deficits after stroke. Thus, SSRIs may be superior to other classes of antidepressants to improve outcomes after stroke.

o Randomized trial in 8 French centers testing fluoxetine 20 mg/day for 3 months in addition to rehabilitation
  o Fluoxetine – 57 subjects, placebo – 56 subjects
  o Outcomes assessed at 3 months by Fugl-Myer and mRS scores

<table>
<thead>
<tr>
<th></th>
<th>Fluoxetine</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fugl-Myer</td>
<td>53.7 +/- 27.8</td>
<td>35.1 +/- 22</td>
<td>0.0006</td>
</tr>
<tr>
<td>FM Improve</td>
<td>36.4 +/- 21.3</td>
<td>21.9 +/- 16.7</td>
<td>0.003</td>
</tr>
<tr>
<td>mRS 0 – 2</td>
<td>15 (26%)</td>
<td>5 (9%)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Chollet et al, Lancet Neurology, 2011; 10: 123
Have tried to answer some of the more common questions about stroke care

The management of hypertension in the setting of acute stroke remains unsettled

Still, recommendations about situations to lower BP

Caution should be exercised in lowering the BP

The time window for treatment with intravenous thrombolysis has expanded to 4.5 hours

Generally the same criteria as for treatment < 3 hours

Do not treat persons older than 80 in period of 3 – 4.5 hours
Examination of the vasculature and heart remain important components of the assessment for the cause of ischemic stroke.

Carotid duplex ultrasonography is an option but its limitations should be recognized.

In general, TEE provides more information about the cause of stroke than does TTE.

TTE does have some role in evaluation.

Treatment of hyperlipidemia is an important part of long-term care of persons with ischemic stroke.

The use of SSRI may help augment recovery after stroke.