The Latest in Stroke Science and Research: 
*Clinical Application*

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Classification and Recommendations and Levels of Evidence
One of Ten Great Public Health Achievements---United States in the 20th Century

- Vaccine-Preventable Diseases
- Prevention and Control of Infectious Diseases
- Tobacco Control
- Maternal and Infant Health
- Motor Vehicle Safety
- Cardiovascular Disease and Prevention
- Occupational Safety
- Cancer Prevention
- Childhood Lead Poisoning Prevention
- Public Health Preparedness and Response

*Stroke.* 2014;45:315-353.
The Decline in Stroke Mortality

• 2011 Stroke fell from the 3rd to 4th leading cause of death
  – (2012, 36.9 deaths per 100,000)

• 2013 Stroke again fell, now 5th leading cause of death
  – (2013, 36.2 deaths per 100,000)

• Globally, over the past four decades stroke incidence rates have fallen by 42% in high-income countries and increased by more than 100% in low- and middle-income countries.

Center for Disease Control and Prevention, 2013.
Factors Influencing the Decline in Stroke Mortality

- Recurrent Stroke
- Hypertension
- Diabetes
- Atrial Fibrillation (AF)
- Hyperlipidemia
- Aspirin and other Antiplatelets
- Neurological and Technical Advances
- Air Pollution and Environmental Factors
- Exercise
- Obesity and Body Mass
- Research and Program Funding

Neurological and Technical Advances in Stroke

- FDA approved tPA
  - Demonstrated time-dependent improvement in functional independence at 3 months and 1 year
  - NOT convincingly shown a reduction in stroke mortality
- 3 trials determined endovascular therapy has not been found to reduce mortality from stroke
- MRI has improved the accuracy of stroke diagnosis, insufficient evidence to the relationship of stroke mortality
- Advances in diagnosis, management, and prevention strategies have the potential for significant impact on stroke mortality

Neutral Trials

• To test the ability of IA therapy to rescue pts. with severe strokes despite treatment with IV tPA

• 2013, disappointment in the field when IMS III showed no benefit of IA therapy in addition to the benefit of IV tPA
Neutral Trials

• IMS III (IMS, IMS I/II and IMS III)
  – Interventional Management of Stroke Trial

• MR RESCUE
  – Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy

• SYNTHESIS Expansion
  – Intra-arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke

ISC, Honolulu, HI 2013.
Fast forward to *ISC Nashville, TN 2015*

- The field moved from injecting thrombolytic agents that dissolved clots over time to

- Deploying stents that could capture the clot and remove it from the artery when the device is removed from the vessel

- Stent retrievers being more effective in removing clots

- Are easier and faster to deploy than previous devices

- Latest trials utilized the Solitaire stent retrieval device
Fast Forward to ISC 2015 Nashville, TN

Major finding

• Results of four randomized endovascular therapy trials
  MR CLEAN
  ESCAPE
  EXTEND IA
  SWIFT PRIME

• Each showed that in patients with acute IS caused by a proximal vessel occlusion, endovascular treatment improved functional outcomes.
Where’s the Clot?
Figure 1. ASPECTS study form adapted from Barber et al.4 Score allows deductions based on occupancy of lesion in each of 10 ASPECTS regions.

A = anterior circulation
P = posterior circulation
C = caudate
L = lentiform
IC = internal capsule
I = insular ribbon
MCA = middle cerebral artery
M1-M6 = Territories of MCA cortex

Subcortical Structures
MCA cortex

Robert K. Kosior et al. Stroke. 2010;41:455-460
Alberta Stroke Program Early CT Score (ASPECTS)
10-point quantitative CT scan score in pts. with MCA stroke

- Caudate
- Putamen
- Internal capsule
- Insular cortex
- M1: “anterior MCA cortex,” corresponding to frontal operculum
- M2: “MCA cortex lateral to insular ribbon” corresponding to anterior temporal lobe
- M3: “posterior MCA cortex” corresponding to posterior temporal lobe
- M4: “anterior MCA territory immediately superior to M1”
- M5: “lateral MCA territory immediately superior to M2”
- M6: “posterior MCA territory immediately superior to M3”

(M1 to M3 are at the level of the basal ganglia and M4 to M6 at the level of the ventricles immediately above the basal ganglia)

An ASPECTS score less than or equal to 7 predicts worse functional outcome at 3 months as well as symptomatic hemorrhage.
ASPECTS score <8 treated with thrombolysis did not have a good clinical outcome
<table>
<thead>
<tr>
<th>SCORE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>

MRS scores of 0-1 are generally considered good outcomes, while 2 or higher are poor outcomes. 1995 NINDS tPA trial, MRS of 0-1 was a measurement of good outcome. This endpoint is consistently utilized.
Retrievable stents used

• Trevo
• Solitaire
• Revive
• Catch
• Capture
• 3D separator
Intra-arterial Intervention

• Intra-arterial treatment for acute ischemic stroke is safe and effective
  – after IV tPA if indicated
  – in patients with contra-indications for IV tPA

• General anesthesia is associated with worse outcomes than local anesthesia

• Speed matters

• Pts who are not perfused within 6 hours of symptom onset are unlikely to benefit from the procedure

• Use of stent retrievers

• Need to report results

• Pool data
New trials needed

- Stroke severity (NIHSS) and treatment effect
- Age and Gender treatment effect
- More precise estimates of time to treatment effect
- More precise estimates of treatment effect in very elderly patients
- More precise estimates of neuroimaging and vessel imaging interactions with treatment
- What co-medication is needed during and immediately after intervention?
  - Heparin
  - Thrombolytics
  - Antiplatelet agents (endothelial damage and plt aggregation)
- Is immediate IAT better than IAT after IVT?
- Quality of life, recurrent events, cost
Stroke Systems of Care

- EMS
- Telestroke
- Drip and Ship
- Clinical Trials
Guideline for the Primary Prevention of Stroke
A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of these guidelines as an educational tool for neurologists.

Endorsed by the American Academy of Neurological Surgeons, the Congress of Neurological Surgeons, and the Preventive Cardiovascular Nurses Association

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Migraine and Stroke

• Migraine is a chronic intermittent primary headache disorder that involves the neuronal and vascular systems

• Characterized by pulsating pain of moderate to severe intensity often accompanied by other autonomic and gastrointestinal symptoms
  – nausea, photophobia, phonophobia

• Prevalence for migraine 11.7% (17.1% in women, 5.6% in men)

• Most consistently associated with stroke in young women especially those with migraine with aura compared with those without aura.

• Prevalence peaks mid life and lower in adolescents and those >60 years

• Thought to double the risk of stroke

Migraine and Stroke

- Mechanism for increased risk of stroke with migraine has not been uncovered

- Migraine (MA) directly causes the infarct
  - Cortical Spreading Depression (CSD) with CBF reductions
  - Hyper or hypoperfusion of neural tissue
  - Vasospasm
  - Endothelial dysfunction

- Increased risk d/t genetic, prothrombotic and other vascular RFs.

- Treatments (ergots, triptans) increase stroke risk from vasoconstriction, overuse, or concomitant thrombogenic conditions

- Migraine associated with paradoxical embolism via PFO (more common in young pts), presumed lack of filtration of microemboli or toxic substances

Aneesh Singhal, MD (MGH Stroke Neurologist, 2014)
Migraine: Recommendations

• Due to the increased risk of stroke seen in women with migraine headaches with aura and smoking, smoking cessation should be strongly recommended in women with migraine headaches with aura (Class I, Level of Evidence B).

• Due to the increased risk of stroke seen in women with migraine headaches with aura and oral contraceptives, especially those containing estrogen, alternatives to oral contraceptives might be considered in women with active migraine headaches with aura (Class IIb, Level of Evidence B).

• Because there is an association between higher frequency of migraine and risk of stroke, treatments to reduce migraine frequency might be reasonable, though evidence is lacking that this treatment reduces the risk of stroke (Class IIb, Level of Evidence C).

• Closure of patent foramen ovale is not indicated for preventing stroke in patients with migraine (Class III, Level of Evidence B).

Hypertension

• Hypertension (HTN) remains the most important well-documented, modifiable stroke risk factor.

• 32.6% of US adults ≥20 years of age have HTN, ~80 million

• Treatment of hypertension is among the most effective strategies for preventing both ischemic and hemorrhagic stroke.

• Reduction in BP is generally more important than the specific agents used to achieve this goal.

• Hypertension remains undertreated in the community.
Hypertension: Recommendations

- Regular blood pressure screening and appropriate treatment of patients with hypertension, including lifestyle modification and pharmacological therapy, are recommended (Class I, Level of Evidence A).

- Regular (annual) blood pressure screening and health-promoting lifestyle modification are recommended for patients with pre-hypertension (systolic blood pressure of 120 to 139 mm Hg or diastolic blood pressure of 80 to 89 mmHg) (Class I, Level of Evidence A).

- Patients who have hypertension should be treated with antihypertensive drugs to a target blood pressure of <140/90 mm Hg (Class I, Level of Evidence A).

- Successful reduction of blood pressure is more important in reducing stroke risk than the choice of a specific agent, and treatment should be individualized based on other patient characteristics and medication tolerance (Class I, Level of Evidence A).

- Self-measured blood pressure monitoring is recommended to improve blood pressure control (Class I, Level of Evidence A).
Diabetes

• 9.3% of US population has diabetes, 29.1 million Americans

• 86 million age >20 has pre-diabetes

• People with diabetes mellitus have an increased susceptibility to atherosclerosis and to increased prevalence of atherogenic risk factors (hypertension and abnormal lipids)

• Diabetes is an independent risk factor for stroke

• Diabetes more than doubles the risk for stroke and about 20% of patients will die of stroke

• A comprehensive program that includes tight control of hypertension with ACEI or ARB treatment reduces the risk of stroke in people with diabetes

• Glycemic control reduces microvascular complications
Diabetes: Recommendations

- Control of blood pressure in accordance with AHA/ACC guidelines to a target of <140/90 mmHg is recommended in patients with type I or type II diabetes (Class I, Level of Evidence A).

- Treatment of adults with diabetes with a statin, especially those with additional risk factors, is recommended to lower the risk of first stroke (Class I, Level of Evidence A).

- Adding a fibrate to a statin in people with diabetes is not useful for decreasing stroke risk (Class III, Level of Evidence B).

- The usefulness of aspirin for primary stroke prevention for patients with diabetes but low 10-year risk of cardiovascular disease is unclear (Class IIb, Level of Evidence B).
Atrial Fibrillation

- Atrial fibrillation (AF) is a prevalent, potent, and treatable risk factor for prevention of embolic stroke

- About 2.3 million Americans have either sustained or paroxysmal AF

- Non-valvular AF is associated with a 4-5 fold increased risk of ischemic stroke

- The mechanism for stroke is embolism of stasis-induced thrombi forming in the left atrial appendage (LAA)

- Knowing which treatment offers the optimal balance of benefits and risks for a particular patient remains challenging

- Despite improving public awareness, anticoagulation for suitable AF patients remains underutilized, particularly among the very elderly.
Risk Stratification Schemes for Patients with AF

**CHADS²**
(Risk Score range = 0-6 points)
- Congestive heart failure (1 point)
- Hypertension (1 point)
- Age ≥ 75 years (1 point)
- Diabetes mellitus (1 point)
- Stroke/TIA (2 points)

**CHA₂DS₂-VASc**
(Risk Score range = 0-9 points)
- Congestive heart failure (1 point)
- Hypertension (1 point)
- Age 65-74 years (1 point), ≥ 75 years (2 points)
- Diabetes mellitus (1 point)
- Stroke/TIA (2 points)
- Vascular disease (eg, PAD, MI, aortic plaque) (1 point)
- Female sex (1 point)

**ACCP treatment guidelines based on estimated risk for thromboembolic stroke**
- Low risk: no therapy
- Moderate risk: OAC
- High risk: OAC

**HAS-BLED (bleeding risk schema)**
(Risk score range = 0-9 points)
- Hypertension (1 point)
- Abnormal renal function (1 point)
- Abnormal liver function (1 point)
- Prior stroke (1 point)
- Prior major bleeding or bleeding predisposition (1 point)
- INR in therapeutic range < 60% of time (1 point)
- Age > 65 years (1 point)
- Use of antiplatelet or non-steroidal drugs (1 point)
- Excessive alcohol use (1 point)

Scores > 2 associated with clinically relevant and major bleeding.

• **Levels of risk for thrombotic stroke**
  - Low = 0 points
  - Moderate = 1 point
  - High risk ≥ 2 points
Atrial Fibrillation: Recommendations

• For patients with valvular AF at high risk for stroke, defined as a CHA$_2$DS$_2$-VASc score of $\geq 2$ and acceptably low risk for hemorrhagic complications, long-term oral anticoagulant therapy with warfarin at a target INR of 2.0 to 3.0 is recommended. (Class I, level of evidence A).

• For patients with non-valvular AF, a CHA$_2$DS$_2$-VASc score of $\geq 2$, and acceptably low risk for hemorrhagic complications, oral anticoagulants are recommended (Class I). Options include warfarin (INR, 2.0 to 3.0) (Level of Evidence A), dabigatran (Level of Evidence B), apixaban (Level of Evidence B), and rivaroxaban (Level of Evidence B).

• The selection of antithrombotic agent should be individualized on the basis of patient risk factors (particularly risk for intracranial hemorrhage), cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including the time that the INR is in therapeutic range for patients taking warfarin.
Atrial Fibrillation: Recommendations

• Active screening for AF in the primary care setting in patients ≥ 65 years of age by pulse assessment followed by ECG as indicated can be useful (Class IIa, Level of Evidence B).

• For patients with non-valvular AF and CHA2DS2-VASc score of 0, it is reasonable to omit antithrombotic therapy (Class IIa, Level of Evidence B).
Sleep Disordered Breathing: Recommendations

- Because of its association with stroke risk, screening for sleep apnea through a detailed history, including structured questionnaires like the Epworth Sleepiness Scale and Berlin Questionnaire; physical examination; and, if indicated, polysomnography may be considered (Class IIb, Level of Evidence C).

- Treatment of sleep apnea to reduce the risk of stroke may be reasonable, although its effectiveness for primary prevention of stroke is unknown (Class IIb, Level of Evidence C).
Physical Inactivity

• A sedentary lifestyle is associated with several adverse health effects, including an increased risk of stroke.

• Clinical trials documenting a reduction in risk of a first or recurrent stroke with regular physical activity have not been conducted.

• Evidence from observational studies is sufficiently strong to make recommendations for routine physical activity to prevent stroke.
Physical Inactivity: Recommendations

- Physical activity is recommended because it is associated with a reduction in the risk of stroke (Class I, Level of Evidence B).

- The 2008 Physical Activity Guidelines for Americans are endorsed and recommend that adults should do at least 150 minutes a week of moderate-intensity, or 75 minutes a week of vigorous-intensity aerobic physical activity (Class I, Level of Evidence B).
Diet and Nutrition: *Recommendations*

- Reduced intake of sodium and increased intake of potassium as indicated in the US Dietary Guidelines for Americans are recommended to lower blood pressure *(Class I, Level of Evidence A)*.

- A DASH-style diet, which emphasizes fruits, vegetables, and low-fat dairy products and is reduced in saturated fat, also lowers blood pressure and is recommended *(Class I, Level of Evidence A)*.

- A diet that is rich in fruits and vegetables, and thereby high in potassium, is beneficial and may lower the risk of stroke *(Class I, Level of Evidence B)*.

- A Mediterranean diet supplemented with nuts may be considered in lowering the risk of stroke *(Class IIa, Level of Evidence B)*.
Cerebral Microbleeds

• Primarily affects elderly
  – typically age >70
  – demented patients
• Cerebral Amyloid Angiopathy (CAA)
  – may exceed HTN as the cause of ICH
• Hypertensive Vasculopathy (HV)
• CT - white matter hyperintensities (WMH)
• Radiation, chemotherapy
• # of microbleeds
Palliative and End-of-Life Care in Stroke
A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons, The American Academy of Hospice and Palliative Medicine, American Geriatrics Society, Neurocritical Care Society, American Academy of Physical Medicine and Rehabilitation, and American Association of Neuroscience Nurses

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AHA/ASA Scientific Statement
Palliative and End-of-Life Care in Stroke

• Stroke care is dominated by clinically challenging, emotionally intense, and ethically complex medical choices.

• Palliative care should be integrated into all stroke systems of care and managed by the primary stroke team.

• This should be viewed not as an alternative to offering life-sustaining therapies, but as an important supplement that can enhance care delivery for patients, families, and providers alike.