Update on stroke prevention, 2013

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Stroke Statistics

- 795,000 strokes a year in the United States
- 1 stroke every 40 seconds, fatal stroke every 3 minutes
- 11 million “silent strokes”: vascular dementia
- 4th leading cause of death (160,000/y)
- A leading cause of disability, 5.8 million stroke survivors
- Risk in males, older people, AA, Latinos
- Most strokes are preventable


The Stroke Belt


Stroke: Time is Brain:
Every minute, 1.9 million neurons are lost

Transient ischemic attacks:
The “warning signs” of stroke

- Sudden loss of vision, one eye
- Sudden difficulty speaking or understanding
- Weakness or numbness on one side
- Dizziness, with loss of balance, difficulty walking
- Sudden, severe headache

Prognosis After TIA

1707 patients with TIA identified by ED physicians among 16 hospitals in northern California; follow-up to 90 days

Stroke Risk and ABCD² Score
Oxfordshire TIA Study

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
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<tbody>
<tr>
<td>Age ≥ 60 years</td>
<td>1 point</td>
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<tr>
<td>Blood pressure ≥ 140/90 mm Hg</td>
<td>1 point</td>
</tr>
<tr>
<td>Clinical features [of TIA]</td>
<td>2 points for unilateral weakness; 1 point for speech impairment without weakness</td>
</tr>
<tr>
<td>Duration [of TIA]</td>
<td>2 points for ≥ 60 minutes; 1 point for 10-59 minutes</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 point</td>
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</table>

Maximum score is 7. Score 6 or 7 = high risk.

7-day stroke risk was 8.5-10.5%.

EXPRESS Results
Phase I-Usual care: rate of stroke 10.3%
Phase II-Urgent care: rate of stroke 2.1% (p<.0001)

What do we do for TIA patients?
- Admit for observation
- ECG monitoring, carotid/VB imaging, echocardiogram, fasting lipids, A1C
- Initiate medical therapy (usually aspirin, but note CHANCE study and ongoing POINT study, early ASA+clopidogrel load)

Risk Factors for Stroke

Modifiable
- Hypertension
- Diabetes
- Cardiac disease
- Atrial fibrillation
- TIA/prior stroke
- Dyslipidemia
- Cigarette smoking
- Alcohol abuse
- Obesity
- Physical inactivity
- Carotid stenosis
- Sleep apnea

Nonmodifiable
- Age
- Gender
- Race/ethnicity
- Heredity
- Stress

Menu for Stroke Prevention
(Primary and Secondary)
- Hypertension
- Hyperlipidemia (diet/statins)
- Diabetes
- Smoking
- Exercise
- Sleep apnea management
- Carotid endarterectomy/stenting
- Atrial fibrillation and other emboli, anticoagulation
- Antiplatelet therapy: aspirin, clopidogrel, ASA/ER-dipyridamole
Antihypertensives and Stroke Prevention

- Hypertension in 1/3 of U.S. population, the largest risk factor for stroke
- Risk of stroke is 6 times higher in people with hypertension than those with normal BP
- Multiple studies support 1% stroke reduction with antihypertensive Rx, upwards of 40%

Hypertension and Stroke

- ACE inhibitors (HOPE, 1st prevention, PROGRESS, 2nd prevention): 28-32% reductions in stroke
- ACE Receptor Blockers (ARB’s): multiple studies (LIFE, SCOPE, ACCESS, VALUE, MOSES) also effective; OnTarget: ARB telmisartan equal to ramipril, both had increased toxicity
- ALLHAT: thiazide as effective as ACE, ACE alone ineffective in African American patients
- ACE or ARB + diuretic, Ca channel blockers effective and well tolerated, Beta blockers not as effective in stroke prevention

ALLHAT Stroke by Treatment Group

- No significant differences

BP and stroke

- All patients with chronic kidney disease or diabetes in BP goal of <130/80 mm Hg
- May consider ACEI, ARB, CCB, or combination

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**PROGRESS Trial: secondary stroke prevention**

- 28% RR
- 95% CI 17 - 38%
- \( P < 0.0001 \)

**Blood Pressure and stroke**

**What to conclude?**

- All studies support detection and aggressive treatment of hypertension
- Stroke prevention of 40-50% possible primary, 28% secondary
- Control of BP is more important than exact choice of agent
- ACE-I or ARB + diuretic may be advantageous, Ca channel blockers

**Cholesterol and Stroke**

- Little direct correlation between serum cholesterol and stroke (Framingham)
- Statin drugs: new data, "pleotropic effects": plaque stability, antiatherogenic, antiinflammatory (CRP), etc.
- Post MI: 4S, CARE, LIPID trials all show that statins prevent stroke as well as recurrent MI
- Simvastatin and pravastatin FDA indicated for post-MI stroke prevention
- ATPIII: stroke indication only carotid disease
- Recent studies (HPS, SPARCL) suggest statin therapy is indicated after stroke

**NCEP ATP III: National Cholesterol Education Program**

**Adult Treatment Panel III (ATP III) Guidelines**

**Stroke Prevention with Aggressive Reduction in Cholesterol Levels (SPARCL)**

- 4731 patients with stroke or TIA, LDL 100-190
- Randomized to atorvastatin 80 mg v placebo
- Mean on treatment LDL
  - Atorvastatin 73 mg/dL
  - Placebo 129 mg/dL
- 16% RRR for stroke (\( p < 0.03 \))
- 23% reduction in stroke or TIA (\( p < 0.001 \))
- Slight increase in cerebral hemorrhage
- Conclusion: most stroke pts should receive statin

**SPARCL**

**Effects of High-dose Atorvastatin After Stroke or TIA**

- HR, 0.77 (95% CI, 0.67–0.88); \( P < 0.001 \)

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*Welch KM. 15th European Stroke Conference (ESC); May 18, 2006; Brussels, Belgium*
**Diabetes and Stroke**
- Patients with diabetes require more rigorous control of blood pressure (<130/80 mm Hg) and blood lipids (LDL < 100)
- Tight glycemic control can reduce microvascular disease, including neuropathy
- Trends towards reduction in macrovascular disease (MI, stroke), but excessive glycemic control can increase mortality
- Aim for HbA1C < 7

**SMOKING CESSATION**
- Smoking increases stroke risk 2-3 fold
- Risk decreases to baseline ~4 years after stopping
- Importance of providing help in hospital
- Behavioral therapy
- Rx: bupropion, patches, varenicline (Chantix™)

**Stroke Subtypes**
- **Hemorrhagic Stroke (17%)**
  - Intracerebral Hemorrhage (59%)
  - Subarachnoid Hemorrhage (41%)
- **Ischemic Stroke (83%)**
  - Atherothrombotic Cerebrovascular Disease (20%)
  - Lacunar (SV) (25%)
  - Embolism (20%)

**Carotid endarterectomy and stenting**

**Absolute Benefits of Carotid Endarterectomy (CEA)**

<table>
<thead>
<tr>
<th>No Sx</th>
<th>Sx 50-69%</th>
<th>Sx 70-99%</th>
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<tbody>
<tr>
<td>1.2</td>
<td>1.3</td>
<td>8.5</td>
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CEA showed only marginal benefits on annual rates of ipsilateral stroke for patients with asymptomatic or moderate lesions. Dramatic benefit was seen for high-grade symptomatic stenoses.
CREST final results (CEA v CAS) (Brott T et al. N Engl J Med 2010;363:11-23)

- 2502 pts, 53% asymptomatic
- 1st endpoint: stroke, MI, death
- CAS 7.2%, CEA 6.8% (p=0.51)
- Stroke or death 6.4% CAS, 4.7% CEA (p=0.03)
- Perioperative Stroke 4.1% vs 2.3% (p=0.01) but severe strokes ~1% in each group
- Perioperative MI 1.1% vs 2.3% (p=0.03)
- After the periprocedural period, ipsilateral stroke rates were CAS 2.0%, CEA 2.4%

When to use warfarin in stroke? (Red Clot vs White Clot)

- Atrial fibrillation and related cardiac sources
- PFO/Atrial septal aneurysm (?)
- Venous sinus thrombus Hypercoagulable states (APL antibody (??))
- Carotid, vertebral dissections (?)
- Intracranial stenosis (X)
- "Treatment failures" (X)

Warfarin Aspirin Recurrent Stroke Study (WARSS)

- 2200 ischemic, non A Fib stroke patients
- > 50% small vessel
- Warfarin INR 1.4-2.8 v. ASA 325 mg
- No difference in stroke (trend favored ASA)
- Slight trend favoring warfarin in “cryptogenic”
- No difference: anticardiolipin Ab, PFO
- Warfarin: limited indications in stroke

CHADS2 Stroke Risk Stratification Scheme for Patients with Nonvalvular AF


O: low risk, ASA only
1,2: intermediate risk, ASA or warfarin (most do warfarin for 2)
>3: high risk, warfarin

New Anticoagulants

- Direct thrombin inhibitor, dabigatran
- Two Factor Xa inhibitors: rivaroxaban and apixaban
- All have shorter half life, predictable effect on coagulation, do not require INR monitoring or dietary changes, few drug interactions
- More expensive, no reversal agents, renal


ROCKET AF: Primary Efficacy and Safety Outcomes Non-Inferiority Analysis

P<0.001 for noninf
ICH = 0.5 vs 0.7

Event rates are per 100 patient-years. Based on safety on treatment or ITT.
Mahaffey KW. Presented at American Heart Association 2010 Scientific Sessions; November 15, 2010; Chicago IL

ROCKET AF: Primary Efficacy and Safety Outcomes

ROCKET AF: Primary Efficacy and Safety Outcomes

WASID: Warfarin-Aspirin Symptomatic Intracranial Disease Study: Results at Termination

*Defined as any intracranial hemorrhage or systemic hemorrhage requiring hospitalization, blood transfusion, or surgery.
**SAMMPRIS: Stenting vs Aggressive Medical Therapy for Intracranial Arterial Stenosis**


- Enrollment was stopped after 451 randomized pts, because the 30-day rate of stroke or death was 14.7% in the PTAS group vs 5.8% in the medical group (P=0.002).
- > 30 days, stroke in the same territory occurred in 13 pts in each group.
- The probability of a primary end-point event at 1 year was 20.0% in the PTAS group, 12.2% in the medical group (P=0.009).
- **Conclusion:** “In pts with intracranial stenosis, aggressive medical Rx was superior to PTAS with the Wingspan stent, both because the risk of early stroke after PTAS was high and because the risk of stroke with aggressive medical therapy alone was lower than expected.”

**Oral Antiplatelet Agents: Mechanisms of Action**

- ADP
- Dipyridamole, cilostazol
- phosphodiesterase
- Collagen
- TXA₂
- ADP = adenosine diphosphate, TXA₂ = thromboxane A₂, COX = cyclooxygenase.

**Efficacy of Antiplatelets in Prevention of Ischemic Events (mostly ASA)**

- ADP = adenine diphosphate, TXA₂ = thromboxane A₂, COX = cyclooxygenase.

**CAPRIE: Efficacy of Clopidogrel vs. Aspirin in MI, Stroke, or Vascular Death (n= 19,185)**

- Aspirin 8.7%* Overall
- Clopidogrel 5.32%

*ITT analysis.
**What about ASA + clopidogrel?**

- Effective in acute coronary syndrome (CURE)
- 3 secondary stroke prevention studies all negative: MATCH, CHARISMA, SPS3; all showed increased bleeding
- Hence, should not be used routinely
- ? Effective in very acute Rx of stroke/TIA (CHANCE study, ongoing POINT study)
- ? Effective in TIA/stroke and IC stenosis (SAMPRIIS)


**What about ASA+ER-dipyridamole?**

- ESPS 2: Effects on Stroke–RRR (Pairwise Comparisons)

<table>
<thead>
<tr>
<th> </th>
<th>ESPRIT trial: Nonrandomized, ASA v ASA + ER-dipyridamole, also showed 1r events in 13% (A+D), 16% (ASA)</th>
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<tbody>
<tr>
<td></td>
<td><strong>PRoFESS</strong> Prevention Regimen for Effectively avoiding Second Strokes 2x2 factorial design involving 20,000 stroke patients</td>
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<tr>
<td></td>
<td><strong>PRoFESS:</strong> Primary Efficacy Outcome</td>
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<td>Table</td>
</tr>
<tr>
<td><strong>ER-DP + ASA</strong></td>
<td><strong>Clopidogrel</strong></td>
</tr>
<tr>
<td>Telmisartan</td>
<td>(200 mg/24 mg) + (80mg)</td>
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<tr>
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<td>(5,000 pts)</td>
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<tr>
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<td></td>
<td>7.7%</td>
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</table>
Primary Outcome: Stroke Recurrence

![Graph showing stroke recurrence rates for different treatments.](image)

* Covariates in Cox model are age, baseline ASA-chloride use, Modified Rankin, and baseline diabetes status. (PRoFESS NEJM manuscript)

**Cilostazol**

(Dr. Y. Shinohara, ISC, 2/10)

- Cilostazol Stroke Prevention Study in Japan, more effective than placebo in secondary stroke prevention
- CSPS-2, 2757 noncardioembolic stroke pts, cilostazol 100 mg bid vs ASA 81 mg
- Stroke: 82/1337 C vs 119/1335 A, fatal 2 v 3
- ICH or major hemorrhage 23 C vs 57 A
- Other side effects: HA, palpitations, diarrhea, dizziness
- Cilostazol (Pletal®) may offer an alternative in stroke prevention

**What’s new with antiplatelet Rx**

- Reanalysis of Triton TIMI 38 prasugrel study found no influence of PPI use on outcomes
- Genetic variants CYP2C19 system (poor metabolizers): increased events in some trials, 2% Caucasians, 4% AA, 14% Chinese, ? Genetic testing
- Platelet resistance testing: VerifyNow, P300, platelet aggregometry: no consensus of which test is most accurate; need for "personalized medicine"
- New agents, prasugrel, ticagrelor (trial pending)

**ASA/AHA Guidelines for Secondary Stroke Prevention 2011**

Noncardioembolic Stroke or TIA

- Antiplatelet agents rather than oral anticoagulation are recommended to reduce the risk of recurrent stroke and other cardiovascular events (Class I, Level of Evidence A)
- Aspirin (50 to 325 mg/d), the combination of aspirin and extended-release dipyridamole, and clopidogrel are all acceptable options for initial therapy (Class IIa, Level of Evidence A)
- ASA-ER dipyridamole recommended over aspirin (2/A)
- Clopidogrel may be considered over aspirin (2/B)
- Clopidogrel in ASA-allergic patients (1/A)

**Stroke Centers**

JCAHO/AHA credentialing begun 2004

2013: 8 measures

- IFA considered in all candidates (requires stroke team 24 hrs/7days, CT within 30 minutes, labs <45 min)
- Anticoagulation for atrial fibrillation
- Antiplatelet Rx on discharge
- DVT prophylaxis in nonambulatory pts
- Antiplatelet therapy initiated by 48 hrs
- Fasting lipid profile, statin if LDL >100
- Stroke education
- Rehab plan documented
- Smoking cessation management (not in 2013 list)
- (Swallowing assessment): not in 2013 list

**Get With The Guidelines—Stroke**

Performance on Selected Treatment and Quality of Care Indicators for Acute Stroke and Secondary Prevention (cont)

<table>
<thead>
<tr>
<th>Performance Indicator</th>
<th>Baseline</th>
<th>GWTG</th>
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<tbody>
<tr>
<td>Antithrombotics at discharge*</td>
<td>91.5%</td>
<td>97.6%</td>
</tr>
<tr>
<td>Anticoagulation for atrial fibrillation at discharge*</td>
<td>81.4%</td>
<td>97.6%</td>
</tr>
<tr>
<td>Therapy at discharge if LDL &gt;100 mg/dL or on therapy at admit*</td>
<td>58.7%</td>
<td>81.6%</td>
</tr>
<tr>
<td>Counseling for smoking cessation*</td>
<td>38.8%</td>
<td>83.8%</td>
</tr>
<tr>
<td>Lifestyle changes recommended for BMI &gt;25 kg/m²</td>
<td>43.2%</td>
<td>42.1%</td>
</tr>
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*Indicates 1 of the 7 key performance measures targeted in GWTG-Stroke.

Data collected from 14,149,149-identified patients admitted to 778 hospitals participating in the GWTG-Stroke program from January 1, 2006, through December 31, 2006.

Conclusions

- Ischemic stroke is a major cause of mortality and disability in the United States
- Most strokes could be prevented by risk factor Rx
- Diet, exercise, smoking cessation, antihypertensive, lipid lowering Rx important
- Anticoagulation for atrial fibrillation, related disorders
- Carotid endarterectomy, stenting
- Antiplatelet therapy for all but warfarin-indicated patients; no evidence for ASA + clopidogrel
- New guidelines for primary and secondary stroke prevention published in 2011, acute stroke management just released