Ischemic Stroke Prevention
A Primary Care Problem

Burden of Disease - Stroke
- 5+ million Americans have had a stroke
- 800,000/year (600K first stroke)
- 20% mortality per event
  - 18% unable to return to work
  - 4% total custodial care
$80 Billion U.S. annually
AHA, Jan 27, 2015 Heart and Stroke Statistical Update

Stroke Definitions
1. Stroke – Abrupt onset of a non-convulsive/non-metabolic focal neurological deficit lasting more than 24 hours
2. Transient Ischemic Attacks (TIA) – Focal non-convulsive/non-metabolic neurological changes lasting less than 24 hours
Harrison’s Textbook of Medicine

Stroke and Women
- 2x more than breast Ca
- 3rd leading cause of death (vs 5th in men)
- Worse outcomes
  - More long-term care
  - National Stroke Association (2015 guideline)
Stroke and Women- Unique risk factors

Meta-analysis 78 studies >10 million subjects

- **Any Stroke:**
  - Preterm delivery (1.62 RRI), Stillbirth (1.86 RRI), oophorectomy (1.42 RRI), Gestational HTN (1.52 RRI)

- **Ischemic Stroke:**
  - Gestational HTN- 1.80 RRI

- **Hemorrhagic Stroke:**
  - Menopause >55yo (2.24 RRI), Gestational HTN (5.10 RRI)
  - Migraine with aura, OCPs/HRT
  - Smoking increase in women


Etiologies of Strokes

Table 36-1: Pathophysiological Classification of Cerebrovascular Diseases

<table>
<thead>
<tr>
<th>Stroke Subtype</th>
<th>Frequency, %</th>
<th>CT Findings</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>25</td>
<td>Hypodensity usually &lt;1 cm²</td>
<td>Lipohypertrophy of small arteries, Atherosclerosis</td>
</tr>
<tr>
<td>Vascular</td>
<td>20</td>
<td>Occlusive arterial disease</td>
<td>Occlusive arterial disease</td>
</tr>
<tr>
<td>Cardiosgenic</td>
<td>15</td>
<td>Hypodensity of basilar artery</td>
<td>Hypertensive arterial disease</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>30</td>
<td>Hypodensity of cerebral vessels</td>
<td>Hypertensive arterial disease</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>Necrosis or embolism</td>
<td>Necrosis</td>
</tr>
</tbody>
</table>

Note: AVM, arteriovenous malformation; CT, computerized tomography.

Take Home Message: Up to 66% of all strokes are potentially preventable

Case #1- What is the most important reason for the 60% reduction in strokes since the early 1970’s?

A- Reduced smoking rates in adults
B- Anticoagulation for atrial fibrillation
C- Better lipid management
D- Lying statistics
E- Hypertension control

Percent Decline in Age-Adjusted Mortality Rates for Stroke by Sex and Race: United States, 1972-94

The decline in age-adjusted mortality for stroke in the total population is 59.0%.
Case #1 - What is the most important reason for the 60% reduction in strokes since the early 1970’s?
A- Reduced smoking rates in adults
B- Anticoagulation for atrial fibrillation
C- Better lipid management
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E- Hypertension control

Hypertension is the biggest stroke risk factor

Hypertension is the biggest stroke risk factor. According to the American Heart Association, 2002, and personal studies, hypertension is a leading risk factor for stroke. Galarza et al. (1997); Gorelick (1995); Gorelick (1997); He, J Hypertens, 1999.

SHEP Study – and HTN Control

4700 patients >65 randomized to either diuretic or placebo
- mean SBP 170
- Total mortality over 4.5 years of study decreased 13%

Systolic BP is directly correlated to risk of stroke

Hypertension - 44+% prevalence
- Only 30% controlled

Hypertension bottom line:
- Aggressive control to JNC (and Bobby Baron) guidelines
A 72 year old woman with controlled hypertension presents with 3 hours of mild dysarthria and left hand weakness that has resolved completely while in the ER. She already takes 81mg of aspirin daily. Her EKG in normal sinus and vascular imaging is negative. How do you treat her?

A- Increase dose of aspirin to 325mg daily
B- Change her to aspirin/dipyridamole 25/200 bid
C- Add clopidogrel 75 mg daily
D- Change to warfarin adjusted INR from 2-3

European Stroke Prevention Trial 2

- Factorial design (n=6202 for two years)
- Secondary prevention- stroke specific outcomes
  - Placebo vs. ASA vs. DPA vs. DPA+ASA
- Strokes ORs NNT/year
  
<table>
<thead>
<tr>
<th>ORs</th>
<th>NNT/year</th>
</tr>
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<tbody>
<tr>
<td>Asa 0.79</td>
<td>76</td>
</tr>
<tr>
<td>DP 0.81</td>
<td>84</td>
</tr>
<tr>
<td>DP-ASA 0.59</td>
<td>36</td>
</tr>
</tbody>
</table>

- NO change in mortality rates


Match Trial

Secondary Prevention: Plavix + Aspirin or Plavix + Placebo

- N=7599 followed for 18 months
- Outcomes: CVA, MI, hospitalization or death
  - Dual Rx. 596/3793 (15.7%)
  - Clopidogrel 636/3802 (16.7%)- no asa alone arm….
  - RRR 6.4% (-4.6-16.3)
  - Significant increase in bleeding on dual therapy
- Conclusions: Dual Rx no better than clopidogrel alone
  - And probably no better than aspirin
  - VA Neuro- change antiplatelet agent

Lancet Vol. 364 July, 2004
Severity of Subsequent Stroke

- ESPS II data shows:
  - Antiplatelet agents reduce rate, lengthen time
    - But NOT severity of subsequent stroke

ASA/DP vs. Clopidogrel

RCT, 20K patients, 2.5 years

Clopidogrel 75 vs. ASA/DP 25/200

HR= 1.01 for recurrent stroke
9% ASA/DP vs. 8.8% Clopidogrel


Bottom Line: Antiplatelet Agents

- Aspirin first line therapy
- Stroke/TIA on asa then:
  - Change to DP+ASA or Clopidogrel for ASA breakthrough (no dual therapy)
  - No advantage to coumadin  

Your previous patient’s 51 year old neighbor is very afraid of having a stroke after watching a friend recently become debilitated by one. She heard that aspirin prevents strokes in women. Her 10 year CV Framingham risk score is 8%. How do you advise her?

A- Start aspirin 325 mg daily
B- Start aspirin 81mg daily
C- Start aspirin 81mg every other day
D- Risk outweighs benefits
E- Shared decision making

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A- Start aspirin 325 mg daily
B- Start aspirin 81 mg daily
C- Start aspirin 81 mg every other day
D- Risk outweighs benefits (can be argued)
E- Shared decision making

Aspirin and Primary Prevention

Non-fatal MI
RR, 0.78
Begun at 5 years
No dosing diff.

Non-fatal CVA
- RR, 0.95
  [CI, 0.85 to 1.06]

Aspirin vs no aspirin

<table>
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<tr>
<th>Outcomes at 4 to 10 y</th>
<th>Number of trials (n)</th>
<th>Weighted event rates</th>
<th>RRI (95% CI)</th>
<th>NNH (CI)</th>
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<td></td>
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<td></td>
<td>No aspirin</td>
</tr>
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<td>Major gastrointestinal bleeding</td>
<td>7 (94 307)</td>
<td>0.59%</td>
<td>0.37%</td>
<td>59% (32 to 90)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>9 (113 266)</td>
<td>0.25%</td>
<td>0.19%</td>
<td>33% (3 to 71)</td>
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Stroke Primary Prevention-ASA

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ASA for Primary CV Prevention-
Bottom Line

- The USPSTF believes the answer is “yes” for adults 50 to 59 years of age who have a ≥10% 10-year CV risk, are not at increased risk for bleeding, have a life expectancy of ≥10 years, and are willing to take low-dose aspirin for ≥10 years

- For other adults (most patients), the USPSTF recommends individual decision-making.
Case 3- Which of the following statements about stroke prevention in atrial fibrillation is false?

A- Strokes due to afib are more common with increasing age.
B- Coumadin reduces mortality in atrial fibrillation
C- Aspirin reduces stroke in atrial fibrillation
D- Cardioversion prevents stroke in atrial fibrillation
E- Hypertension control remains the most important preventable stroke risk factor
**Stroke Prevention in A. Fib-Rx**

Meta-analysis Data – 9874 participants, 16 trials

1. Warfarin vs. Placebo → 62-68% RRR INR 2-3
   - Absolute risk bleeding 0.3%/year
   - **Reduction** of all cause mortality 26% (ARR 1.6%/Year)
2. Aspirin vs. Placebo → 21-22% RRR ANY Dose
   - Absolute risk bleeding 0.2%/Year
   - No **reduction** of mortality

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**Warfarin Versus Aspirin**

5 Trials with 2837 participants and 205 strokes over 2 years

Relative risk reduction 36% favoring **warfarin**

- NNT 167 primary prevention
- NNT 14 secondary prevention
- AR major bleeding 0.2%/year **increase** with warfarin

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**CHADS2 Prediction Rule**

AFI, SPAF - 2 large prediction rule trials
- don’t always agree
- **Framingham** hard to use

- **C** – CHF in last 100 days
- **H** – Hypertension
- **A** – Age >75 Years
- **D** – Diabetes
- **S2** – x2 previous Stroke or TIA

Gage et al. JAMA June 13, 2001

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**CHADS2 Stroke Risk Score and Treatment**

<table>
<thead>
<tr>
<th>CHADS2</th>
<th>Annual Stroke Risk</th>
<th>Usual Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1-2 %</td>
<td>Aspirin 81 mg</td>
</tr>
<tr>
<td>1</td>
<td>3 %</td>
<td>Aspirin 325 mg or Warfarin</td>
</tr>
<tr>
<td>2</td>
<td>4 %</td>
<td>Warfarin (NOAC)</td>
</tr>
<tr>
<td>3</td>
<td>6 %</td>
<td>Warfarin</td>
</tr>
<tr>
<td>4</td>
<td>8 %</td>
<td>Warfarin</td>
</tr>
<tr>
<td>5</td>
<td>12 %</td>
<td>Warfarin</td>
</tr>
<tr>
<td>6</td>
<td>16 %</td>
<td>Warfarin</td>
</tr>
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</table>

Bottom Line Afib: **Anticoagulate!!**
**Case 4-** A 50 year old woman who takes coumadin for atrial fibrillation due to dilated cardiomyopathy has seen TV commercials for medications that could improve her chances of not having a stroke. Which would be considered a relative contraindication for changing her to a novel oral anticoagulant?

A- History of GI bleeding  
B- Stage 3-4 chronic kidney disease  
C- History of a mechanical valve replacement  
D- Lack of prescription coverage in her health insurance  
E- All of the above
Atrial Fibrillation Bottom Line:
1- Rate Control likely more important than Rhythm control
   - stroke risk similar with paroxysmal afib
2- Apply CHADS2
3- Anticoagulate!!
   -3+%/year (higher in elderly)

Use of New Oral Anticoagulants
- Consider new oral anticoagulants in patients with normal renal function that are similar to study participants
  - Previously untreated or poorly controlled
  - Even with good INR control (given lower ICH rates)
- Warfarin may be preferred for
  - Severe renal insufficiency
  - Valvular AF, mechanical valves
  - Cost concerns; Poor adherence
  - Need for quick reversal
  - Higher risk of GI bleed (for dabigatran & rivaroxaban)?

Cryptogenic Stroke
Case 5- A 75 year old woman arrives a week after being sent home from the ER after experiencing 2 hours of mild dysarthria. She was diagnosed by neurology with a TIA. Her CTA showed no carotid or vertebral vascular disease, her tele no afib and she had a normal echo. She is on atorvastatin for hyperlipidemia and chlorthalidone for well controlled hypertension. She is on clopidogrel for a coronary stent. You recommend which of the following:
A- Add aspirin to clopidogrel
B- Change atorvastatin to rosuvastatin
C- Change chlorthalidone to atenolol
D- Ambulatory cardiac monitoring for one month
E- Order carotid ultrasound
Cryptogenic Stroke
Cerebral infarcts without cause after standard workup

A 75 year old woman arrives a week after being sent home from the ER after experiencing 2 hours of mild dysarthria. She was diagnosed by neurology with a TIA. Her CTA showed no carotid or vertebral vascular disease, her tele no afib and she had a normal echo with bubble study. She is on atorvastatin for hyperlipidemia and chlorthalidone for well controlled hypertension. She is on clopidogrel for a coronary stent. You recommend which of the following:
A- Add aspirin to clopidogrel
B- Change atorvastatin to rosuvastatin
C- Change chlorthalidone to atenolol
D- Ambulatory cardiac monitoring for one month (2 weeks)
E- Order carotid ultrasound

Cardiac Monitoring Cryptogenic Stroke

- 2 large RCTs of 30 day monitor vs. 24 hours
  - Outcome: Incident atrial fibrillation
- Embrace Trial
  - 572 patients, age 73, 89% white
  - 30 day event triggered recorder vs. standard
  - New afib >30 seconds
- Crystal-AF Trial
  - 441 patients, age 62, 87% white
  - NEJM 370:26 June 26, 2014

Stroke Evaluation Diagram


Rates of AFIB Detected

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention Group (N=286)</th>
<th>Control Group (N=205)</th>
<th>Absolute Difference (95% CI)</th>
<th>P Value</th>
<th>No. of Patients Needed to Screen (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: detection of atrial fibrillation with duration ≥30 seconds within 9 days</td>
<td>41 (14.2%)</td>
<td>52 (25.6%)</td>
<td>11.4% (6.0-16.8%)</td>
<td>&lt;0.001</td>
<td>5.5 (3.9-7.1)</td>
</tr>
<tr>
<td>Secondary outcome: detection of atrial fibrillation with duration ≥60 seconds</td>
<td>41 (14.2%)</td>
<td>52 (25.6%)</td>
<td>11.4% (6.0-16.8%)</td>
<td>&lt;0.001</td>
<td>5.5 (3.9-7.1)</td>
</tr>
<tr>
<td>Detection of atrial fibrillation with duration ≥120 seconds</td>
<td>38 (13.3%)</td>
<td>41 (20.1%)</td>
<td>6.8% (1.0-12.6%)</td>
<td>&lt;0.001</td>
<td>16.3 (8.8-29.4)</td>
</tr>
<tr>
<td>Detection of atrial fibrillation of any duration</td>
<td>38 (13.3%)</td>
<td>41 (20.1%)</td>
<td>6.8% (1.0-12.6%)</td>
<td>&lt;0.001</td>
<td>16.3 (8.8-29.4)</td>
</tr>
</tbody>
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*The number of patients needed to screen was defined as the number of patients who would need to be screened in order to detect atrial fibrillation in one additional patient with a 24-hour monitoring strategy vs. repeat 24 hour Holter monitoring.

This primary analysis included all patients who underwent randomization for whom outcome data were available (i.e., patients who underwent any amount of random monitoring or 6-day follow-up in the group of patients whose atrial fibrillation detection could be determined). In this primary analysis, atrial fibrillation was detected either clinically or by means of study monitoring.

The primary analysis included all patients who underwent randomization and any amount of cardiac monitoring, the detection of atrial fibrillation in the secondary analysis was by means of the study monitors.

Atrial fibrillation of 277 (3.2%) controls

**Cryptogenic Stroke Conclusions**

- **Limitations:**
  - Primary Outcome: >30 secs afib
  - Not designed to show reduced stroke
- **Implications:**
  - Cryptogenic stroke patients should receive **14-30 days** of cardiac monitoring for atrial fibrillation
  - Anticoagulation decisions based on results

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**Case 5 - How narrow is this carotid artery and what factors make it more difficult to fix?**

A- 90%, Ulcerated plaque
B- 75%, Ulcerated plaque
C- 100%, left sided lesion
D- 80%, left sided lesion
E- Ask the radiologist, Left sided lesion, ulcerated, Female patient
NASCET- (North American Symptomatic Carotid Endarterectomy Trialists)

-70-99% stenosis; major ipsilateral stroke or death at 2 years
-2.5% surgical vs. 13.1% medical (P<0.001)
-Remained constant over 7 years of follow-up

NEJM 1991;325:445

NASCET Subgroup Analysis

- Elderly > 75 years had increased benefit
- Early surgery (< 30 days) no difference in outcomes
- 5 baseline characteristics predicted surgical risk
  1) Hemispheric TIA
  2) Left sided procedure
  3) Contralateral carotid occlusion
  4) Ipsilateral ischemic lesion on CT
  5) Irregular or ulcerated plaque

Symptomatic Carotid Stenosis- Bottom Line

CEA – Number Needed to treat
(NASCET, ECST Data)

<table>
<thead>
<tr>
<th>% Stenosis</th>
<th>NNT/2years</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-99%</td>
<td>8</td>
</tr>
<tr>
<td>50-69%</td>
<td>20</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>67</td>
</tr>
</tbody>
</table>

-Assumes <6% complications

Surgical benefit erased if complications >10%....
KNOW your vascular surgeons!
TIMING????

Timing of Carotid Surgery

You are rounding a day after your 75 year old female patient has an ipsilateral TIA with this MRA. The vascular surgeons ask when you want her to go to the OR for CEA. She is otherwise healthy. You answer:
A- Up to you, you are the experts
B- Immediately or <48 hours
C- Between 3-14 days
D- Re-evaluate in a month
E- Let’s do carotid stenting instead
You are rounding a day after your 75 year old female patient has an ipsilateral TIA with this result. The vascular surgeons ask when you want her to go to the OR for CEA. She is otherwise healthy. You answer:

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C- Between 3-14 days  
D- Re-evaluate in a month  
E- Let’s do carotid stenting instead

Recurrent stroke before CEA/CAS

2.7% (1 day), 5.3% (3 days), 11.5% (14 days), and 18.8% (90 days)

Natural History: recurrent ipsilateral ischemic stroke prior to CEA/CAS

BOTTOM LINE: Perform > 48 hours but < 2 weeks

The radiologist who read the carotid MRA suggests that carotid stenting would be a good alternative for your 75 year old woman who had the TIA. Your response is.

A- Carotid stenting is safer for elderly patients  
B- The safety of carotid stenting is not dependent on patient age.  
C- Carotid outcomes are better than CEA after 120 days  
D- CEA is the procedure of choice for patients ≥ 65 years old
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**Current Indications for Carotid Stents**

1- Lesions not suitable for surgery
   - High cervical lesions
   - Post XRT stenosis
   - Unacceptable surgical risk
2- Center of Excellence!
   - (and in a trial)
3- Consider < 60 years old if #2 fulfilled

![Stent in Carotid Artery](stent-in-carotid-artery.png)