Ischemic Stroke Prevention
A Primary Care Problem

No conflict of interest
Jeff.kohlwes@ucsf.edu

Stroke and Women

- 2x more than breast Ca
- 3rd leading cause of death (vs 5th in men)
- Worse outcomes
  - More longterm care
- Unique Risks:
  - OCPs/HRT
  - Pregnancy (htn/cv)
- Migraine with aura
  - Snaking!!
  - National Stroke Association

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

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
Etiologies of Strokes

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

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

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

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
Hypertension is the biggest stroke risk factor.

**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%

**Hypertension - 44+% prevalence**
- Only 30% controlled

**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 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
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 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

<table>
<thead>
<tr>
<th>Strokes</th>
<th>ORs</th>
<th>NNT/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>0.79</td>
<td>76</td>
</tr>
<tr>
<td>DP</td>
<td>0.81</td>
<td>84</td>
</tr>
<tr>
<td>DP-ASA</td>
<td>0.59</td>
<td>36</td>
</tr>
</tbody>
</table>

-NO change in mortality rates


---

**Severity of Subsequent Stroke**

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

---

**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
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

Case 2- 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
**Atrial Fibrillation**

<table>
<thead>
<tr>
<th>AGE</th>
<th>PREVALENCE</th>
<th>AF%</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59 Years</td>
<td>0.5%</td>
<td>1.5%</td>
<td>4.0</td>
</tr>
<tr>
<td>60-69 Years</td>
<td>1.8%</td>
<td>2.8%</td>
<td>2.6</td>
</tr>
<tr>
<td>70-79 Years</td>
<td>4.8%</td>
<td>9.9%</td>
<td>3.3</td>
</tr>
<tr>
<td>80-89 Years</td>
<td>8.8%</td>
<td>23.5%</td>
<td>4.5</td>
</tr>
</tbody>
</table>

- Common disorder, increases with age
- Stroke risk increases:
  - 17X for valvular afib
  - 5 times for nonvalvular
- How to RX?

**Rate vs Rhythm Control on Stroke**

*Atrial fibrillation follow-up investigation of rhythm management - AFFIRM*

Randomized 4060 patients to cardioversion vs rate control

*All received coumadin*

<table>
<thead>
<tr>
<th>Overall</th>
<th>Rate Group (n=2027)</th>
<th>Rhythm Group (n=2033)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic Stroke 157</td>
<td>77 (5.5%)</td>
<td>80 (7%)</td>
</tr>
<tr>
<td>After D/C of Warfarin 69</td>
<td>25</td>
<td>44</td>
</tr>
</tbody>
</table>

No significant difference noted

*Rate control = rhythm control*

--paroxysmal afib = chronic afib

--high rates of stroke after d/c of coumadin

**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

**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
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

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>
</tbody>
</table>

Bottom Line Afib: Anticoagulate!!

Case 3- 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
Pharmacological Properties of New Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Direct thrombin inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
</tr>
<tr>
<td>Onset of action</td>
<td>0.5-2 h</td>
<td>3.4 h</td>
<td>3.4 h</td>
</tr>
<tr>
<td>1 1/2</td>
<td>12-14 h</td>
<td>12 h</td>
<td>7-11 h</td>
</tr>
<tr>
<td>Renal Clearance</td>
<td>80%</td>
<td>25%</td>
<td>98%</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>P-gp inhibitors</td>
<td>P-gp inhibitors, CYP3A4</td>
<td>P-gp inhibitors, CYP3A4</td>
</tr>
<tr>
<td>Laboratory Monitoring Required?</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Phase III Studies of New Oral Anticoagulants: Major Results

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>RE-LY</td>
<td>ROCKET-AF</td>
<td>ARISTOTLE</td>
</tr>
<tr>
<td>Measure</td>
<td>INR (75% CI)</td>
<td>INR (75% CI)</td>
<td>INR (75% CI)</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Non-inferior</td>
<td>Non-inferior</td>
<td>Superior</td>
</tr>
<tr>
<td>Stroke/systemic embolization</td>
<td>0.70 (0.60-0.80)</td>
<td>0.70 (0.60-0.80)</td>
<td>0.70 (0.60-0.80)</td>
</tr>
<tr>
<td>ICH</td>
<td>0.61 (0.28-0.90)</td>
<td>0.67 (0.47-0.90)</td>
<td>0.67 (0.47-0.90)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>0.53 (0.41-0.67)</td>
<td>0.44 (0.30-0.60)</td>
<td>0.44 (0.30-0.60)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.58 (0.41-0.75)</td>
<td>0.31 (0.20-0.49)</td>
<td>0.31 (0.20-0.49)</td>
</tr>
</tbody>
</table>

Summary of Pivotal Phase III Trials

- Similar (rivaroxaban) or superior efficacy (dabigatran, apixaban) for prevention of stroke/systemic embolization compared to warfarin
- All associated with lower ICH risk compared to warfarin
- Similar (dabigatran, rivaroxaban) or lower (apixaban) major bleeding risk
  - Higher GI bleeding (dabigatran, rivaroxaban)
- Mortality benefit for apixaban
- Edoxaban (ENGAGE AF-TIMI 48, NEJM 2014)
  - FDA application pending

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 patients
  - 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)?
**Atrial Fibrillation Bottom Line:**
1- Rate Control likely more important than Rhythm control
   - stroke risk similar with paroxysmal afib
2- Apply CHADS2
3- Anticoagulate!!
   - 3-5%/year (higher in elderly)

**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. 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

**Stroke Evaluation Diagram**
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

Cryptogenic Stroke Conclusions

- Limitations:
  - Primary Outcome > 30secs 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
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

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

www.neuro.jhmi.edu/ cerebro/images/endart.jpg
Symptomatic Carotid Stenosis - Bottom Line

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

<table>
<thead>
<tr>
<th>% Stenosis</th>
<th>NNT/2 years</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

Outcomes after emergent CEA ≤48 hours after TIA/stroke vs. Medical management

Caused us to wait ONE MONTH prior to CEA
Rerkasem Stroke. 2009; 40: e564-e572
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
**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

---

**Really last case:** You are out for dinner tonight in Hawaii and are trying to decide between Hawaiian Grass-fed beef and fresh caught fish and you wonder if there is any association with stroke prevention in your choice. You decide on?

A- Fish  
B- Beef  
C- Too hard to choose

---

**Fish Oil Meta-Analysis**

- All Cause Mortality RRR=16%
- Fatal MI RRR=24%
- 36% RRI! for non-fatal stroke (not significant)
- NNT for 37 months treating 1000 patients would avoid 15 deaths from all causes and 13 fatal MIs
  - Stroke data still unclear....

---

**Bottom Line #s- Stroke Prevention**

<table>
<thead>
<tr>
<th>Prevention</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>7937</td>
</tr>
<tr>
<td>Statin</td>
<td>13,333</td>
</tr>
<tr>
<td>Endarterectomy</td>
<td>51</td>
</tr>
<tr>
<td>ACAS - &gt;60%, &lt;3%</td>
<td></td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>??</td>
</tr>
<tr>
<td>ACP - &gt;10%, 10 year risk</td>
<td>??</td>
</tr>
<tr>
<td>Fish Oil</td>
<td>??</td>
</tr>
<tr>
<td>Tastes good…</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prevention</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>51</td>
</tr>
<tr>
<td>Statin</td>
<td>57</td>
</tr>
<tr>
<td>Warfarin/afib</td>
<td>13</td>
</tr>
<tr>
<td>INR=2-3, CHADS2 &gt;2</td>
<td></td>
</tr>
<tr>
<td>NOAC</td>
<td>12.8</td>
</tr>
<tr>
<td>Endarterectomy</td>
<td>20 (8)</td>
</tr>
<tr>
<td>NASCET - &gt;50%, &lt;6%</td>
<td></td>
</tr>
<tr>
<td>Smoking Cessation</td>
<td>43</td>
</tr>
<tr>
<td>Aspirin</td>
<td>77</td>
</tr>
<tr>
<td>second agent post TIA</td>
<td></td>
</tr>
</tbody>
</table>

---

Yezbey, Fundamental & Clinical Pharmacology Volume 18 Page 581 - October 2004

Strauss et al JAMA; Vol 288, No. 11, 2002
Non-modifiable Risk Factors

1. Female
2. Non-white race (African Americans- 2-3X increased risk)
3. Family History
4. LVH
5. Coronary Artery Disease
6. Diabetes***

*No compelling data on glycemic control and stroke prevention

Modifiable Risk Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Prevalence, %</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>25-40</td>
<td>3-5</td>
</tr>
<tr>
<td>Elevated total cholesterol</td>
<td>6-40</td>
<td>1.8-2.6</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>150-170 mmHg</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>25</td>
<td>1.5</td>
</tr>
<tr>
<td>Physically active</td>
<td>75</td>
<td>2.7</td>
</tr>
<tr>
<td>Obesity</td>
<td>18</td>
<td>1.8-2.4</td>
</tr>
<tr>
<td>Asymptomatic carotid stenosis</td>
<td>2-8</td>
<td>2</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>2-5</td>
<td>1.8</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
<td>5 (nonanticoagulant, 17 anticoagulant)</td>
</tr>
</tbody>
</table>

*Factors arranged in order of population prevalence. Data are from references 4-8.

PFO Repair?
Intracranial Stenosis

- Recent discovery
  - With CTA/MRA technology
- 8-10% Prevalence in CVA
- Chinese, AA, Hispanics
  - estimates 10-29%
- Re-CVA 10-24%/year

Hartmann, Current Opinion in Neurology 2005; 18: 39-45

Intracranial Stenosis- Rx

- ASA (1800mg) safer than warfarin (INR=1-2)
  - 2 years f/u
  - 4.3% asa, 9.7% warfarin
  - NNT=18
    - Chimowitz et al. NEJM 2005;352:1305
- Intracranial stents
  - Promising, one prospective study
  - SSylvia study- Stroke 2004;35
CEA vs. Protected Stenting
(in high risk patients)

334 High Risk patients
>80% stenosis asymptomatic
>50% stenosis symptomatic
-death, ipsilateral stroke at 1yr
20/167- 12.2 % stent
32/167- 20.1% CEA
NNH=11

Sapphire investigators. NEJM 2004;351

EVA-3S Trial
(Endarterectomy vs. Angioplasty in patients with symptomatic severe carotid stenosis)

French Trial
527 symptomatic, >70% stenosis
3.9% CEA Stent
9.6% Stent

(30-day CVA or death P<0.05)

6 month data- 6.1% vs. 11.7%
RR (6 mos.) = 1.9
NNH=18 over 6 mos.
Trial stopped due to harm

Problems:
-27% used embolic protection devices
-Surgeons>angiographers in experience

Last Case:
45 year old pregnant woman who had a hemiplegic stroke after straining at stool has a + echo with bubble study showing a PFO without aneurysm. You order a hypercoagulable workup and lower extremity ultrasound. How should she be treated?

A- Aspirin is first line without blood clots
C- Warfarin is first line without blood clots
D- Surgical closure is first line
E- Endovascular placement of closure device
Patent Foramen Ovale and Stroke

Cryptogenic stroke
- Autopsy series 27% with PFO
  - PFO 6x increase with CVA pts
  - 25% AR if found
- 581 pts <55 with CVA- 4yrs
  - 2.3% with PFO
  - 15.2% with PFO and Atrial Septal Aneurysm

Wu et al. Arch. IM, Vol. 164, May 10, 2004

• Medical Management 3.8-12%
  - Coumadin=aspirin
  - Coumadin only with DVT or hypercoagulable state!
• Surgical Closure 0-5%
  - Open rarely done currently
  - Catheter assisted


CAPRIE
Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events

19185 patients \rightarrow Clopidogrel 9553, Aspirin 9546
-Ischemic Stroke, MI, Vascular Death – average 2 years f/u

OUTCOMES:

<table>
<thead>
<tr>
<th>Clopidogrel</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>939 events / 17636 pt years</td>
<td>1021 events / 17519 pt years</td>
</tr>
<tr>
<td>5.32% / 2 years</td>
<td>5.83% / 2 years</td>
</tr>
<tr>
<td>P=0.043</td>
<td></td>
</tr>
</tbody>
</table>

RRR 8.7% (19.2% for MI, 5.2% CVA – not significant)
ARR = 0.5%/2yrs NNT = 400 / year prevent triple outcome

CAPRIE Investigators Lancet Vol. 348: November 16, 1996
CURE Trial

*Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
<th>CV Death, MI, Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA + Placebo for 3-12 months</td>
<td>6303</td>
<td>11.4% 20% RRR ARR = 2.1% NNT = 50</td>
</tr>
<tr>
<td>ASA + Clopidogrel for 3-12 months</td>
<td>6259</td>
<td>9.3%</td>
</tr>
</tbody>
</table>

ASA + Clopidogrel = 37% RRR  ARI = 1%  NNH = 100  (remember NNT=50)

CURE Trial Side Effects

- Major Bleeding (intracerebral bleed, >2 unit transfusion)
  - ASA + Clopidogrel = 37%
  - ASA Alone = 2.7%  38% RRI  ARI = 1%
  --NNH = 100  (remember NNT=50)
  --Minor Bleeding NNH = 37

Stroke Prevention – Antiplatelet Agents

1. Aspirin - Blocks thrombocyte pathway
   - 18-25% RRR for secondary prevention
   - ANY dose has same effect (50-1300mg)
   - Albers et al. Stroke 1999:30:2502-2511

2. Thienopyridines - Blocks ADP dependent pathway
   - No trials vs. placebo

3. Aspirin + Extended release dipyridamole
   - blocks PDE/adenosine deaminase
   - vasodilation  plt inhib

Eating fish 1-3x/week lowers risk of ischemic CVA by 44%

Fish Intake: Health Professionals Study

- He et al. JAMA Dec 25, 2002

Figure. Multivariate Relative Risk of Ischemic Stroke as a Function of Fish Consumption