Aspirin for Primary Prevention of Cardiovascular Events

Just another day in clinic...

- 69 yo Filipina woman, non-smoker
  - DM on metformin, hgb A1c 7.1
  - Hyperlipidemia on atorva, TC 190, TG 199, LDL 81, HDL 69
  - HTN on benazepril, BP 145/84
- 80 yo Eritrean man, non-smoker
  - HTN on lisinopril, BP 159/85
  - HLD not on meds, TC 241, TG 102, LDL 165, HDL 56
- 49 yo Latino man, non-smoker
  - DM on metformin and insulin, s/p amputation, A1C 7.9
  - HLD starting meds, TC 366, TG 351, LDL 243, HDL 53
  - HTN on benaz, 138/82

Roadmap

- Epidemiology
- Pathophysiology and Dosing
- Contraindications
- Guidelines and Evidence for:
  - General population
  - Diabetes
  - Very elderly
  - Colon cancer prevention
- Simple approach + resources
- Cases revisited

Epidemiology (a.k.a. Why We Care)

- CV disease leading cause of death in U.S.
- 1 out of 2.8 deaths
- Aspirin known to work for secondary prevention
- LOTS of trials for 1st prevention → mixed results
  - MI
  - Stroke
  - Mortality
  - GI bleeds
  - Hemorrhagic stroke

Mechanism of Action and Dosing

- Low dose: blocks thromboxane A2 → blocks platelet aggregation
  - 75-300mg/day
- Higher dose can block prostacyclin → thrombosis
  - 500mg/day
- Cumulative effect if taken daily
- Reduces C-reactive protein – anti-inflammatory
- U.S. use 81mg/day

Contraindications

- Relative:
  - <21 y/o (Reye)
  - Concurrent anticoagulation
  - Concurrent NSAIDs
  - Poorly controlled HTN (risk of intracranial bleeding)
**USPSTF Guidelines: Aspirin for 1st Prevention**

- Potential benefit: reduction of
  - MI for men
  - Ischemic stroke for women
- Potential harm: GI bleed, hemorrhagic stroke
- Lowest dose (81mg for us)
- Re-assess q5 years or when new CV risk factors

**USPSTF Guidelines Continued**

- Men 45-79 for MI reduction when benefit > harm (A)
- Women 55-79 for ischemic stroke reduction when benefit > harm (A)
- Insufficient evidence for men/women >80 (I)
- Men <45, women <55 → don’t use (D)

*So how do we weigh the benefits and harms?*

**10-year Risk Assessment for Stroke and MI**

**Men: MI**
- Age
- BP
- DM
- Smoking hx
- Cholesterol (total and HDL)

**Women: Stroke**
- Age
- BP
- DM
- Smoking hx
- h/o CVD
- Atrial fibrillation
- LVH

**2006 JAMA Meta-Analysis**

- 6 trials, ~95,000 individuals
- Aspirin dose: 100mg every other day, 75mg-162mg/day, 500mg/day
- Endpoints
  - Nonfatal MI
  - Nonfatal stroke
  - CV mortality
  - Major bleeding events, nonfatal stroke, CV mortality, major bleeding
- Mostly low-risk populations

**GI Bleed Risk Factors/Considerations**

- Men 2x > women
- NSAID use – 4x
- h/o GI ulcer – 2-3x
- Upper abdominal pain
- Uncontrolled HTN
- Anticoagulation
- No difference with enteric-coated/buffered preps
- Shared decision-making
Meta-analysis results

- Effect of aspirin in women:
  - OR 0.88 for CV events (12% reduction)
  - OR 0.85 for stroke (17% reduction)
  - No effect on MI or mortality
  - OR 1.68 for bleeding

- Effect of aspirin in men:
  - OR 0.86 for CV events (14% reduction)
  - OR 0.68 for MI (32% reduction)
  - No effect on CV mortality
  - OR 1.72 for bleeding

JAMA Meta-analysis cont’d: NNT

- Absolute risk reduction:
  - 0.30% for women
  - 0.37% for men

- NNT for 1000 people over 6.4 years
  - 333 women (3 per 1000)
  - 270 men (4 per 1000)

- Number needed to harm from bleeding:
  - 400 women (2.5 per 1000)
  - 303 men (3 per 1000)

JAMA: reasons for sex differences

- Difference in aspirin metabolism
- Ladies have more strokes, Gents have more MIs → statistical artifact
- Ladies more aspirin resistant

Effect of Aspirin by Risk Category: Men and MI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Aspirin Prevented (per 1000)</th>
<th>MI in Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 80+ Years</td>
<td>20.2</td>
<td>17.7</td>
<td>18.7</td>
</tr>
<tr>
<td>Age 60-80 Years</td>
<td>20.7</td>
<td>17.4</td>
<td>18.1</td>
</tr>
<tr>
<td>Age 60-79 Years</td>
<td>20.1</td>
<td>17.6</td>
<td>18.1</td>
</tr>
</tbody>
</table>
| Type of event | 18% | 19% | 18%
| Risk level | 12% | 12% | 12%

Summary: Harms ≈ Benefits

<table>
<thead>
<tr>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>10-Year CHD Risk, %</td>
</tr>
<tr>
<td>45-59</td>
<td>≥4</td>
</tr>
<tr>
<td>60-69</td>
<td>≥3</td>
</tr>
<tr>
<td>70-79</td>
<td>≥2</td>
</tr>
</tbody>
</table>

JAMA: reasons for sex differences

- Difference in aspirin metabolism
- Ladies have more strokes, Gents have more MIs → statistical artifact
- Ladies more aspirin resistant

Effect of Aspirin by Risk Category: Women and Stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimated Risk Prevented (per 1000)</th>
<th>MI in Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 80+ Years</td>
<td>17.7</td>
<td>18.7</td>
</tr>
<tr>
<td>Age 60-80 Years</td>
<td>17.4</td>
<td>18.1</td>
</tr>
<tr>
<td>Age 60-79 Years</td>
<td>17.6</td>
<td>18.1</td>
</tr>
<tr>
<td>Type of event</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Risk level</td>
<td>12%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Summary: Harms ≈ Benefits

<table>
<thead>
<tr>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>10-Year CHD Risk, %</td>
</tr>
<tr>
<td>45-59</td>
<td>≥4</td>
</tr>
<tr>
<td>60-69</td>
<td>≥3</td>
</tr>
<tr>
<td>70-79</td>
<td>≥2</td>
</tr>
</tbody>
</table>

Assume net strokes prevented (ischemic prevented – hemorrhagic incurred)
### Geriatrics – USPSTF

- >80 yo: insufficient evidence
- Stroke/MI and GI bleed risks all go up
- Consider aspirin if:
  - No risk factors for GI bleed
  - Good potential to tolerate GI bleed: normal hgb, good renal function, easy access to emergency care
- Counsel on signs/symptoms GI bleed
- Discuss harms/benefits

### Geriatrics – Beers Criteria

- “Potentially Inappropriate Medications” in older adults
- No aspirin >325mg/day, esp if h/o GI ulcer
- Asa for primary prevention >80yo may do more harm than good → use with caution
  - Low quality evidence, weak recommendation

### What about in Diabetes?

- 2-4x increased risk CV events
- 68% deaths from CAD, 16% from stroke
- Mixed data on efficacy of asa for 1° prevention
- Guidelines:
  - Yes for >10% risk, No for <5% risk, Maybe for 5-10% risk
  - Yes for Men > 50 or Women > 60 with another risk factor
  - No for Men <50 or Women <60 with no risk factors
  - Maybe for everyone else (consider starting at 40yo for men, 50yo for women)
- Risk calculators: UKPDS, ARIC, American Diabetes Association Risk Assessment Tool, Framingham on Med Calc

### Diabetes Continued

- 2010 Meta-analysis 7 RCTs
  - 2 looking at DM
  - 5 with DM as sub-groups
- Non-significant reduction in major CV events, MI, stroke, all-cause mortality
- Non-significant increase in GI bleeding

### What about Colon Cancer?

- Lancet review: 5 RCTs over 20 years
- Aspirin for primary and secondary CV prevention
- 14k patients, 391 CRC cases
- Significantly reduced proximal colon cancer incidence and mortality
  - We have less effective screening for these
- Benefit greatest with aspirin > 5 years
  - Incidence HR 0.75, ARR 1.21%
  - Mortality HR 0.61, ARR 1.36%
- Very low-dose (30mg) not effective
- USPSTF recommends against routine use (Grade D)

### Cases Revisited

- 69 yo Filipina woman, non-smoker
  - DM on metformin, hgb A1c 7.1
  - Hyperlipidemia on atorva, TC 190, TG 199, LDL 81, HDL 69
  - HTN on benazepril, BP 146/84
- 80 yo Eritrean man, non-smoker
  - HTN on lisinopril, BP 159/85
  - HLD not on meds, TC 241, TG 102, LDL 165, HDL 56
- 49 yo Latino man, non-smoker
  - DM on metformin and insulin, s/p amputation, A1c 7.9
  - HLD starting meds, TC 366, TG 351, LDL 243, HDL 53
  - HTN on benaz, 138/82
Summary: Harms ≈ Benefits

<table>
<thead>
<tr>
<th>Age</th>
<th>10-Year CHD Risk, %</th>
<th>Age</th>
<th>10-Year Stroke Risk, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-69</td>
<td>≥4</td>
<td>65-69</td>
<td>≥3</td>
</tr>
<tr>
<td>60-69</td>
<td>≥4</td>
<td>65-69</td>
<td>≥3</td>
</tr>
<tr>
<td>70-79</td>
<td>≥12</td>
<td>70-79</td>
<td>≥11</td>
</tr>
</tbody>
</table>

Take-Home Points 1

- Good evidence for 1° prevention of:
  - MI in men
  - Stroke in women
- 81mg is sufficient
- Calculate 10-year risk to determine whether pt should be on aspirin – lower threshold at younger age

Take-Home Points 2

- Diabetes:
  - Consider at 40yo
  - Yes for >10% risk, no for <5% risk, maybe for 5-10% risk
  - Yes in men >50 or women >60 with additional risk factor
- Geriatrics (>80)
  - Consider GI bleed risk factors, physiologic reserve
  - Shared decision-making
- Colon cancer prevention
  - Some evidence, could tip the balance

References


Thank You!