Who Has an Aspirin Indication?
Making Sense of Aspirin Recommendations for the Prevention of Cardiovascular Disease

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Objectives

• Review the pharmacologic activities of aspirin and their effects on cardiovascular disease

• Identify patients who would benefit from aspirin therapy for primary or secondary prevention of cardiovascular events

• Discuss controversies surrounding the appropriate dose of aspirin for prevention of thromboses
First recorded clinical trial – Willow bark for malarial symptoms 1763
Salicin extracted and purified from Willow bark 1829
Salicin modified to form salicylic acid 1838
Acetylsalicylic acid synthesized 1852
40,000 tons produced each year, 10-20B tablets taken each year by >50M patients in the United States alone 2016

Fuster V, Circulation. 2011

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Aspirin’s History and Uses

• Despite over 3000 years of use, little was known about aspirin’s pharmacologic activities until the 1970s
  • Prostaglandins were discovered in 1935 and were suspected to play a role in nociception, inflammation, and fever
  • In 1971, Vane et al. described the dose-dependent relationship between NSAIDs and inhibition of prostaglandin synthesis
  • Vane also described a substance released during anaphylaxis in rabbits – he called it “rabbit aorta contracting substance.”

NSAID: non-steroidal anti-inflammatory drug

Fuster V, Circulation. 2011
Vane JR, Nature. 1971
Aspirin’s History and Uses

Arachidonic Acid

Cyclooxygenase

Prostaglandins

Aspirin

Vasoconstriction
Platelet aggregation

Pain
Inflammation
Fever
Vasodilation

Thromboxane $A_2$

Fuster V, Circulation. 2011
Clinical Use in Cardiovascular Disease

Randomized Trial of IV Streptokinase, Oral Aspirin, Both, or Neither Among 17,187 Cases of Suspected Acute Myocardial Infarction

Second International Study of Infarct Survival Collaborative Group (ISIS-2)

ISIS-2, J Am Coll Cardiol. 1988
ISIS-2 Study

- 2x2 factorial design allocating individuals to receive either:
  - Streptokinase + Aspirin
  - Streptokinase + Placebo
  - Placebo + Aspirin
  - Placebo + Placebo

- All patients were within the 24 hour window of suspected acute myocardial infarction
- Aspirin dose: 162.5 mg daily for 1 month

ISIS-2, J Am Coll Cardiol. 1988
**ISIS-2 Study**

**Outcomes**

- **Vascular Mortality @ 5 Weeks**
  - Aspirin: 9.4%
  - Placebo: 11.8%
  - Significance: p < 0.00001

- **Nonfatal reinfarction**
  - Aspirin: 1.0%
  - Placebo: 2.0%
  - Significance: p < 0.05

- **Bleeding Requiring Transfusion**
  - Aspirin: 0.4%
  - Placebo: 0.4%
  - Significance: p > 0.05

Poll Question

- DJ is a 62 year old male presenting to clinic for his yearly check-up. During his visit, he asks if he should be taking a daily aspirin tablet to prevent a heart attack.

- **Medical/Surgical History**
  - Depression
  - Anxiety
  - Osteoarthritis
  - Appendectomy (1992)

- **Family History**
  - Father: Deceased (stroke at age 74)
  - Mother: Living (NSTEMI at age 81)

- **Home Meds**
  - Fluoxetine 20 mg PO daily
  - Acetaminophen prn
  - Loratadine 10 mg PO daily

- **Social History**
  - Never smoker
  - Social alcohol use
Poll Question

• Would you recommend that DJ begin taking aspirin on a daily basis?

1. Yes
2. No
The Physician’s Health Study

• The first randomized, double-blind, placebo-controlled study investigating the effect of aspirin on prevention of cardiovascular morbidity and mortality

n = 22,071
Healthy physicians
Age 40-84

n = 11,021
Placebo

n = 11,025
Aspirin 325 mg every other day

The Physician’s Health Study

Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Aspirin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Infarction</td>
<td>2.16</td>
<td>1.26</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.07</td>
<td>0.89</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td>0.73</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Mean Follow-Up: 60.2 Months

p < 0.00001
p = 0.15
p = 0.87

The Physician’s Health Study

The Physician’s Health Study

- 74% of the physicians assigned to placebo switched to aspirin at the conclusion of the study.
- “The decision whether to take aspirin to reduce the risks of cardiovascular disease should be an individual judgment made only with the advice of a physician.”

Aspirin for Primary Prevention of CVD

- In addition to the Physicians’ Health Study, several large, randomized, controlled trials evaluation have been performed:
  - British Doctors Study
  - Thrombosis Prevention Trial
  - Hypertension Optimal Treatment
  - Primary Prevention Project
  - Womens’ Health Study

Fuster V, *Circulation*. 2011
### Aspirin for Primary Prevention of CVD

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>Mean Follow-Up (years)</th>
<th>Aspirin Dose</th>
<th>Efficacy Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDT</td>
<td>1988</td>
<td>5,139</td>
<td>5.6</td>
<td>500 mg/d</td>
<td>No change in rates of MI, stroke, or death</td>
</tr>
<tr>
<td>PHS</td>
<td>1988</td>
<td>22071</td>
<td>5.0</td>
<td>325 mg every other day</td>
<td>44% RRR for MI in aspirin group</td>
</tr>
<tr>
<td>TPT</td>
<td>1998</td>
<td>5,085</td>
<td>6.7</td>
<td>75 mg/d</td>
<td>32% RRR in nonfatal CV events in aspirin group</td>
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<tr>
<td>HOT</td>
<td>1998</td>
<td>18790</td>
<td>3.8</td>
<td>75 mg/d</td>
<td>35% RRR in MI in aspirin group</td>
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<tr>
<td>PPP</td>
<td>2001</td>
<td>4,495</td>
<td>3.7</td>
<td>100 mg/d</td>
<td>41% RRR in cardiovascular events in NON-diabetics</td>
</tr>
<tr>
<td>WHS</td>
<td>2005</td>
<td>39,876</td>
<td>10.1</td>
<td>100 mg every other day</td>
<td>No significant difference in rates of MI or CV death, though w/ lower risk of stroke</td>
</tr>
</tbody>
</table>

# Aspirin for Primary Prevention of CVD

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>Mean Follow-Up (years)</th>
<th>Aspirin Dose</th>
<th>Safety Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDT</td>
<td>1988</td>
<td>5,139</td>
<td>5.6</td>
<td>500 mg/d</td>
<td>30.2% RR increase in bleeding</td>
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<tr>
<td>PHS</td>
<td>1988</td>
<td>11,025</td>
<td>5.0</td>
<td>325 mg every other day</td>
<td>13.4% RR increase in bleeding complications, 50% RR increase in duodenal ulcers</td>
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<tr>
<td>TPT</td>
<td>1998</td>
<td>5,499</td>
<td>6.7</td>
<td>75 mg/d</td>
<td>23% RR increase in minor bleeding</td>
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<tr>
<td>HOT</td>
<td>1998</td>
<td>9,399</td>
<td>3.8</td>
<td>75 mg/d</td>
<td>Not reported</td>
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<tr>
<td>PPP</td>
<td>2001</td>
<td>4,495</td>
<td>3.7</td>
<td>100 mg/d</td>
<td>1.7% AR increase in bleeding complications in aspirin group</td>
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<tr>
<td>WHS</td>
<td>2005</td>
<td>39,876</td>
<td>10.1</td>
<td>100 mg every other day</td>
<td>Significantly increased risk of GI bleeding, requirement for transfusion, peptic ulcer, and epistaxis</td>
</tr>
</tbody>
</table>

References:
- Peto R, BMJ. 1988
- Kjeldsen SE, Hypertension. 1998
- Sacco M, Diabetes Care. 2003
- Meade TW, Lancet. 1998
- Ridker PM, NEJM. 2005
Aspirin for Primary Prevention of CVD

- ADA/AHA/ACCF (2010)
  - Aspirin 75-162 mg daily for adults if 10 year CV risk > 10%, AND:
    - Male > 50 w/ diabetes and ≥ 1 other CV risk factor
    - Female > 60 w/ diabetes and ≥ 1 other CV risk factor

- Canadian Cardiovascular Society (2011)
  - Aspirin 75-162 mg daily if:
    - Multiple CV risk factors
    - Age > 40 w/ diabetes, and ≥ 1 other CV risk factor
    - ESRD w/ low bleeding risk

Pignone M, *Diabetes Care*. 2010
Bell AD. *Canadian Journal of Cardiology*. 2011
Aspirin for Primary Prevention of CVD

• American College of Chest Physicians (2012)
  • Aspirin 75-100 mg daily for adults > 50 (2B)

  • “Low-dose” aspirin in adults w/ ≥ 10% 10-year CVD risk who have a life expectancy > 10 years, are willing to take aspirin for at least 10 years, and place a higher value on preventing an MI than on avoiding a GI bleed
    • Age < 50 (Insufficient evidence)
    • Age 50-59 (Level B recommendation)
    • Age 60-69 (Level C recommendation)
    • Age ≥ 70 (Insufficient evidence)
Aspirin for Primary Prevention of CVD

• FDA (2014)
  • “…does not believe the evidence supports the general use of aspirin for primary prevention of a heart attack or stroke. In fact, there are serious risks associated with aspirin, included increased bleeding in the stomach and brain…”
Poll Question

• DJ is a 62 year old male presenting to clinic for his yearly check-up. During his visit, he asks if he should be taking a daily aspirin tablet to prevent a heart attack.

• Medical/Surgical History
  • Depression
  • Anxiety
  • Osteoarthritis
  • Appendectomy (1992)

• Family History
  • Father: Deceased (stroke at age 74)
  • Mother: Living (NSTEMI at age 81)

• Home Meds
  • Fluoxetine 20 mg PO daily
  • Acetaminophen prn
  • Loratadine 10 mg PO daily

• Social History
  • Never smoker
  • Social alcohol use
Should DJ Receive Daily Aspirin?

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>American Heart Association</td>
<td>😞</td>
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<tr>
<td>Canadian Cardiology Society</td>
<td>😞</td>
</tr>
<tr>
<td>American College of Chest Physicians</td>
<td>😊</td>
</tr>
<tr>
<td>US Preventative Services Task Force</td>
<td>?</td>
</tr>
<tr>
<td>Food and Drug Administration</td>
<td>😞</td>
</tr>
</tbody>
</table>
Case

CP is a 58 year old male with a medical history significant for coronary artery disease. He is admitted to your hospital service for CAP.

Medical/Surgical History
- CAD (NSTEMI in 2014)
- HTN
- Hyperlipidemia
- T2 Diabetes

Home Meds
- Simvastatin 10 mg daily
- Metformin 500 mg BID
- HCTZ 12.5 mg PO daily
- Metoprolol XL 50 mg PO daily

Family History
- Father: Deceased (MI at age 55)
- Mother: Deceased (Alzheimer’s disease)

Social History
- 20 pack-year smoking history (quit in 2014)
Case continued

• Upon questioning, CP states that after his heart attack, he was prescribed aspirin and clopidogrel by his cardiologist “to keep the stent open.”

• He remembers the directions on his clopidogrel bottle: “Take 75 mg orally daily with aspirin for one year”
Case continued

• CP stopped taking aspirin when his prescription for clopidogrel expired. Should he continue to take aspirin?

1. Yes
2. No
## Aspirin for Secondary Prevention of CVD

<table>
<thead>
<tr>
<th>Indication</th>
<th>n</th>
<th># of trials</th>
<th>Aspirin % with CV event</th>
<th>Control % with CV event</th>
<th>% Odds Reduction</th>
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</thead>
<tbody>
<tr>
<td>Previous MI</td>
<td>20,006</td>
<td>12</td>
<td>13.5</td>
<td>17.0</td>
<td>25</td>
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<tr>
<td>Acute MI</td>
<td>19,302</td>
<td>15</td>
<td>10.4</td>
<td>14.2</td>
<td>30</td>
</tr>
<tr>
<td>Previous CVA/TIA</td>
<td>23,020</td>
<td>21</td>
<td>17.8</td>
<td>21.4</td>
<td>22</td>
</tr>
<tr>
<td>Acute CVA/TIA</td>
<td>40,821</td>
<td>7</td>
<td>8.2</td>
<td>9.1</td>
<td>11</td>
</tr>
<tr>
<td>Other High Risk</td>
<td>40,902</td>
<td>140</td>
<td>8.0</td>
<td>10.2</td>
<td>26</td>
</tr>
<tr>
<td>All Trials</td>
<td>144,051</td>
<td>195</td>
<td>10.7</td>
<td>13.2</td>
<td>22</td>
</tr>
</tbody>
</table>

What Dose?

• Evaluating the safety and efficacy of various aspirin doses used in primary and secondary prevention studies is muddied by inter- and intra-study differences in dosing.

• In vitro data suggests that 100 mg is enough for complete inhibition of thromboxane A$_2$ production.

• The most robust evidence for aspirin dosing comes from the CURE study.  
  
  Awtry EH. Circulation. 2000
What Dose?

- Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) evaluated the efficacy of clopidogrel added to aspirin in patients with UA or NSTEMI.

- Patients took aspirin 75 – 325 mg daily

- n = 12,562

What Dose?

• Peters et al. performed a post-hoc analysis of the CURE trial
  • Patients were subdivided into three groups based on the aspirin dose they took over one year
    • ≤ 100 mg/day
    • 101 – 199 mg/day
    • ≥ 200 mg/day

Peters RJG, Circulation. 2003
What Dose?

Incidence of Primary Outcome (CV death, Nonfatal MI, or Stroke)

Aspirin

Aspirin + Clopidogrel

OR 1.3 (1.08 – 1.52)

OR 1.2 (0.95 – 1.40)

What Dose?

Incidence of Major Bleeding

Excess Bleeding With Added Clopidogrel

<table>
<thead>
<tr>
<th>Aspirin Dose</th>
<th>% of Patients</th>
<th>Aspirin</th>
<th>Aspirin + Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 100 mg</td>
<td>1.9%</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>101 - 199 mg</td>
<td>2.8%</td>
<td>3.4</td>
<td>4.9</td>
</tr>
<tr>
<td>≥ 200 mg</td>
<td>3.7%</td>
<td>4.9</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

What Dose?

Incidence of Life-Threatening Bleeding

**Aspirin Dose**

- ≤ 100 mg: 1.26
- 101 - 199 mg: 1.9
- ≥ 200 mg: 2.37

**Aspirin + Clopidogrel**

- ≤ 100 mg: 1.75
- 101 - 199 mg: 1.39
- ≥ 200 mg: 3.29

**OR**

- OR 1.64 (1.04 – 2.59)
- OR 1.82 (1.22 – 2.71)

What Dose?

• This analysis of data from CURE suggests that:
  1. Higher doses of aspirin are not associated with a reduction in the composite rate of cardiovascular death, nonfatal MI, or stroke.
  2. The risk of major and life-threatening bleeding increases with increasing doses of aspirin, regardless of whether or not the patient is concomitantly taking clopidogrel.

Peters RJG, Circulation. 2003
A Special Case: Atrial Fibrillation

- Current guidelines from ACCP and AHA recommend aspirin for patients at low risk of cardioembolic stroke
  - ACCP
    - CHADS2 = 0
      - No therapy (2B)
      - Aspirin 75-325 mg/day (2B)
      - Aspirin + clopidogrel (2B)
    - CHADS2 = 1
      - Anticoagulation over aspirin (2B)
      - Aspirin + clopidogrel (2B)

January CT, J Am Coll Cardiol. 2014
A Special Case: Atrial Fibrillation

- Current guidelines from ACCP and AHA recommend aspirin for patients at low risk of cardioembolic stroke
  - AHA/ACC/HRS
    - CHADS$_2$VASc = 1
      - No therapy (2B)
      - Aspirin 75-325 mg/day (2B)
Japan Atrial Fibrillation Stroke Trial

- 426 Japanese patients with low risk NVAF were randomized to receive either placebo or aspirin (150-200 mg/day)

- **Primary Endpoints**
  - Cardiovascular death
  - Stroke
  - TIA

- **Secondary Endpoints**
  - Noncardiovascular death
  - Intracranial hemorrhage
  - Major bleeding

Japan Atrial Fibrillation Stroke Trial

Outcomes at 2.1 years

- CV Death: Aspirin 0.7, Placebo 0.7 (p = 1.00)
- Stroke: Aspirin 4.0, Placebo 4.0 (p = 0.967)
- Cardiogenic Embolism: Aspirin 3.2, Placebo 2.7 (p = 0.609)
- Major Bleeding: Aspirin 1.6, Placebo 0.4 (p = 0.101)

Sato H, Stroke. 2006
Aspirin for Atrial Fibrillation

Relative Risk Reduction (95% CI)

AFASAK I
SPAF I
EAFT
LASAF
  Daily
  Alternate day
UK-TIA
  300 mg/day
  1200 mg/day
JAST
SAFT
ESPS II
ALL TRIALS

Favors Aspirin
Favors Placebo

100%
50%
0%
-50%
-100%
Red Clot vs White Clot

• Up to 25% of strokes in patients with atrial fibrillation are **NOT** cardioembolic.

• Aspirin lacks apparent efficacy in preventing red clots.

• The risk reduction in stroke seen in patients taking aspirin for atrial fibrillation is likely a decrease in non-cardioembolic strokes.

Hart RG, *Cerebrovasc Dis.* 2000
Lip GYH, *Stroke.* 2006
Summary

• Aspirin is not benign and its role in primary prevention of cardiovascular disease is limited.

• Doses of aspirin > 100 mg/day are rarely (if ever) indicated.

• Aspirin has limited utility for cardioembolic stroke prevention – an examination of other cardiovascular risk factors likely has more utility.
Assessment Question #1

Which of the following patients would likely derive net benefit from daily aspirin?

1. 52 year old female with a family history of cardiovascular disease
2. 58 year old male with total cholesterol of 162 mg/dL
3. 81 year old male with CABG at age 67
4. 38 year old female with type 2 diabetes
Assessment Question #2

- Which of the following statements is false?
  1. For secondary prevention, aspirin doses > 100 mg/day are not associated with increased efficacy compared with doses < 100 mg
  2. In the CURE study, higher aspirin doses were associated with higher efficacy, but at a cost of higher bleeding rates
  3. Aspirin is indicated indefinitely in patients with established cardiovascular disease and low bleeding risk
  4. Aspirin inhibits cyclooxygenase, reducing downstream production of thromboxane A₂
Assessment Question #3

• Which of the following statements is false?
  1. The majority of strokes in patients with atrial fibrillation are caused by fibrin-rich “red clots.”
  2. Aspirin is more efficacious in preventing platelet-rich “white clots” than “red clots.”
  3. Aspirin is a suitable alternative to warfarin in a patient with atrial fibrillation and a CHADS$_2$ score = 3.
  4. Aspirin 325 mg is preferred over 81 mg in the setting of an acute myocardial infarction.
Questions & Discussion