Use of Aspirin and NSAIDS in patients with Heart Disease

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Maryland ACP Chapter Annual Scientific Meeting Jan 2016
Disclosures

None
Warm-up questions: 1

• Husband and wife ask your opinion about starting a daily aspirin.

• 50 yo AAM, 150/90, no meds, -DM, +h/o tob, - Fhx, Chol 220, Hdl 60

• 48 yo AAF, 150/90, Lisin-Hct, +DM, 1/2PPD tob, -Fhx, Chol 180, Hdl 50
Warm-up questions: Patient 2

- 67 yo male h/o Htn, Inf MI, s/p RCA stent 3 yrs ago, recently hospitalized with new Afib.
- He comes to the office after discharge taking Warfarin and ASA 81mg

Would you:
- Change to a NOAC
- Stop the ASA
- Make no changes
Warm-up questions: Patient 3

- 62 yo with NICM, LVEF 30%, NYHA Class II, complains of worsening knee OA sx

Which statement is true:
- An OTC (ie low dose) NSAID can safely supplement Acetaminophen
- High dose Acetaminophen and/or Tramadol are the best options
- Use of NSAIDs would not be an issue if the patient had HFpEF
Outline

• Brief review of prostaglandin synthesis
• Review data/recommendations for Aspirin use in Patients with ACS
• Approach to primary prevention decisions
• Review data / recommendations regarding NSAID use in Pts with CVD
A Tale of two Eicosanoids

**Prostacyclin (PGI$_2$)**
- Produced by endothelium
- Blocks platelet aggregation, anti-thrombotic
- Antagonizes TxA2-mediated vasoconstriction
- Cardioprotective in ischemia-reperfusion

**Thromboxane A2 (TxA2)**
- Released by activated platelets
- Potent stimulator of platelet aggregation
- Promotes vasoconstriction
Prostaglandin Synthesis

Membrane Phospholipids

Phospholipase A₂

Arachidonic Acid

Cyclooxygenase Activity

PGG₂

Peroxidase Activity

PGH₂

Prostaglandin Endoperoxide H₂ Synthase (PGHS)

2O₂

COX-1, COX-2

Thromboxane A₂ Synthase

Prostaglandin E₂, D₂, F₂α Synthase

Prostacyclin Synthase

Thromboxane A₂

Prostaglandin E₂

Prostaglandin D₂

Prostaglandin F₂α

Prostacyclin 6-keto-PGF₁α

Hydrolysis
COX-1 isoform

- Constitutively expressed in most tissues
- Only isoform in mature platelets
- Vascular endothelium
- Gastrointestinal epithelium
- Kidney
Cox-2 isoform

- Inflammatory response to injury
- Induced by endotoxins, cytokines, growth factors
- Expressed in atherosclerotic plaques, during wound healing and angiogenesis
- Key source of PGI$_2$ from endothelium
- Constitutively expressed: macula densa and renal medullary interstitium
  - Inhibition => ↓ natriuresis, increased BP*
Mechanism of ASA Benefit in CVD

• Low dose aspirin irreversibly acetylates and inhibits COX-1 and only weakly inhibits COX-2
• In platelets, COX-1 inhibition leads to ↓ TxA2 production
• Platelets cannot replenish COX-1 (no nucleus) thus inhibition is permanent for the life of the platelet.
• In contrast, endothelial cells can make new COX-1 as well as COX-2.
• Higher doses of aspirin would be required for inhibition of PGI2 production (via Cox-2)
Benefits of Aspirin in ACS

STEMI

- 23% ↓ vascular mortality (at 5wks) if ASA given w/in first 24 hrs. (9.4% vs 11.8%)
- 50% reduction in non-fatal MI (1% vs 2%)
- 50% reduction in stroke (0.3% v 0.6%)
- No increased risk of bleeding in acute setting
- Initial dose: 160 – 325 mg
Benefits of Aspirin in ACS

**NSTEMI-USA**

Antithrombotic Trialists' Collaboration*

meta-analysis ~200,000 pts

Aspirin dose range 75 – 1500mg

- 30% ↓ non-fatal MI/CVA or vascular death in NSTEMI pts
- 46% ↓ non-fatal MI/CVA or vascular death in USA pts

Recommendation: 160-325mg loading dose Aspirin followed by low dose 81 to 162mg daily

*BMJ. 2002;324(7329):71*
Aspirin for Secondary prevention

"Heads, you get a quadruple bypass. Tails, you take a baby aspirin."
Aspirin for Secondary Prevention

Myriad trials => Clinically and statistically significant reductions in all vascular events including death

Antithrombotic Trialists' Collaboration (195 trials)

- Recurrent MI
- CVA
- Vascular death

22% decrease in events
Aspirin dose for 2ndary prevention

Current-Oasis 7 (25,000 Pt, s/p MI- PCI)
Randomized to 75-100mg vs 300-325 mg ASA
30 day MACE (cardiovascular death, MI, CVA)
Results:
- No difference in MACE
- No difference in bleeding events
Aspirin dose for secondary prevention

TRANSLATE-ACS (10,000 Pt s/p MI- PCI registry)
6 month MACE (cdv death, cva, MI)
ASA discharge dose: 325mg vs 81mg

Results:
- Similar rates of MACE
- Higher rate of minor bleeding events with 325mg

SECONDARY PREVENTION:
LOW DOSE ASPIRIN STRONGLY RECOMMENDED

Aspirin for Primary Prevention

“To prevent a heart attack, take one aspirin every day. Take it out for a run, then take it to the gym, then take it for a bike ride...”
Aspirin for Primary Prevention

9 large, randomized, primary prevention trials comparing ASA (75-500mg) vs placebo

• Significant reduction in serious vascular events = MI, CVA, and vascular death (SCD, PE, hemorrhage) Mostly ↓ in 1st non-fatal MI.

• Significant increase in major GI bleeds and extracranial bleeds

• Reductions were similar for men and women
Women’s Health Study

• 100 mg QOD for 10 yrs
• 90% of subjects < 65 yo (too young for MI)
• Findings:
  – Significant decrease in risk of 1st CVA
  – No benefit for MI risk
  – 10% of subjects ≥ 65 had 30% of events
    • MI risk reduced commensurate to prior trials with men
Major primary prevention trials

- Physician’s Health Study – Aspirin 325 mg daily every other day*
- British Doctor’s Trial, ASA 500 mg daily
- Thrombosis Prevention Trial - 75 mg ASA and warfarin therapy
- Hypertension Optimal Treatment Trial –75 mg daily*
- Primary Prevention Project – enteric-coated 100 mg daily
- Women’s Health Study ASA 100 mg on alternate days for a mean of 10.1 years *
- Aspirin for Asymptomatic Atherosclerosis trial –100 mg daily
- Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes trial – ASA 81 to 100 mg daily to patients with diabetes
- Prevention of Progression of Arterial Disease and Diabetes trial – ASA 100 mg daily to patients with diabetes

* 80% of Pts came from these three trials
ASA Prim Prev is **not** for everyone

- Absolute risk reduction in low risk pts may not justify the increased bleeding risk
- United States Preventive Services Task Force recommends individualized assessment-prescription of ASA when “magnitude of the absolute benefit exceeds the magnitude of the absolute harm”

Estimated myocardial infarctions (MIs) prevented and estimated harms of using aspirin for 10 years in a hypothetical cohort of 1000 men

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimated MIs prevented (per 1000 men), n</th>
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<tbody>
<tr>
<td></td>
<td>10-year CHD risk, percent</td>
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<tr>
<td>1</td>
<td>3.2</td>
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<tr>
<td>2</td>
<td>6.4</td>
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<td>28.8</td>
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<table>
<thead>
<tr>
<th>Type of event</th>
<th>Estimated harms, n</th>
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<tbody>
<tr>
<td>GI bleeding</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
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</table>
Heart Risk Calculator

Calculate your 10-year risk of heart disease or stroke using the algorithm published in 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk.

This calculator assumes that you have not had a prior heart attack or stroke.

UPDATE (9/18/15) -- The calculator now also incorporates draft guidelines from the USPSTF for initiating aspirin therapy.

UPDATE (5/26/14) -- The calculator now also incorporates guidelines from JNC-8 for blood pressure management.

An excel spreadsheet is also available for download.

AHA/ACC CVD Risk Calculator  http://www.cvriskcalculator.com/
Heart Risk Calculator

25.1%
10-year risk of heart disease or stroke

On the basis of your age alone, the USPSTF guidelines suggest there is no evidence you will benefit from starting aspirin for heart disease and stroke risk reduction.

On the basis of your age and risk for heart disease or stroke, the ACC/AHA guidelines suggest you should be on a moderate to high intensity statin.

Based on your age and race, your blood pressure is poorly-controlled, and you should initiate lifestyle interventions and consider starting a thiazide diuretic, ACE/ARB, or calcium channel blocker.

<table>
<thead>
<tr>
<th>Demography</th>
<th>Cholesterol</th>
<th>Blood pressure</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: 70</td>
<td>Total: 180</td>
<td>Systolic: 140</td>
<td>Diabetes: no</td>
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<tr>
<td>Gender: male</td>
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<td>Smoking: no</td>
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<tr>
<td>Race: not African-American</td>
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<td>On medication: yes</td>
<td></td>
</tr>
</tbody>
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Note: moderate intensity statin may be atorvastatin 10mg, pravastatin 40mg, or simvastatin 20-40mg. High intensity statin may be atorvastatin 40mg-80mg.

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# Heart Risk Calculator

**38.6%**

10-year risk of heart disease or stroke

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On the basis of your age alone, the USPSTF guidelines suggest there is no evidence you will benefit from starting aspirin for heart disease and stroke risk reduction.

On the basis of your age, risk for heart disease or stroke, and diabetes, the ACC/AHA guidelines suggest you should be on a high intensity statin.

Based on your age, your blood pressure is well-controlled.

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<td>Age: 70</td>
<td>Total: 180</td>
<td>Systolic: 130</td>
<td>Diabetes: yes</td>
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<tr>
<td>Gender: male</td>
<td>HDL: 40</td>
<td>Diastolic: 80</td>
<td>Smoking: no</td>
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Heart Risk Calculator

72.3%
10-year risk of heart disease or stroke

On the basis of your age alone, the USPSTF guidelines suggest there is no evidence you will benefit from starting aspirin for heart disease and stroke risk reduction.

On the basis of your age, risk for heart disease or stroke, and diabetes, the ACC/AHA guidelines suggest you should be on a high intensity statin.

Based on your age and race, your blood pressure is poorly-controlled, and you should initiate lifestyle interventions and consider starting a thiazide diuretic or calcium channel blocker.

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<tbody>
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<td>Systolic: 160</td>
<td>Diabetes: yes</td>
</tr>
<tr>
<td>Gender: male</td>
<td>HDL: 30</td>
<td>Diastolic: 100</td>
<td>Smoking: yes</td>
</tr>
<tr>
<td>Race: African-American</td>
<td></td>
<td>On medication: yes</td>
<td></td>
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Note: moderate intensity statin may be atorvastatin 10mg, pravastatin 40mg, or simvastatin 20-40mg. High intensity statin may be atorvastatin 40mg-80mg.

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### Heart Risk Calculator

#### 10-year risk of heart disease or stroke

**13.5%**

**Based on your age, your blood pressure is well-controlled.**

---

On the basis of your age and risk for heart disease or stroke, the USPSTF guidelines suggest you **start taking aspirin 81mg every day** if you are not at increased risk for bleeding and are willing to take it every day for at least 10 years.

On the basis of your age, risk for heart disease or stroke, and diabetes, the ACC/AHA guidelines suggest you should be on a **high intensity statin.**

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Aspirin associated bleeding

• 2006 review of 22 trials using ASA (75-325mg) and Clopidogrel
  – ASA ↑ risk of any major bleeding 1.7 – 2.1 vs placebo
    [includes major GI and intracranial bleeding]
  – Absolute annual risk = 1.3/1000 pts - major GI
    3/10,000 pts - intracranial
  – No difference in bleeding risk based on ASA dose
    75-162mg vs 162-325mg

McQuaid KR. Am J Med. 2006;119(8):624
Secondary prevention of GI bleeding

70 yo pts with ASA-associated ulcer- GI bleeding, treated for H. Pylori, then re-challenged with anti-platelet rx

Recurrent bleeding rates at 1 yr:
- Low-dose ASA (100 mg/day) – 14.8 %
- Clopidogrel (75 mg/day) for low-dose ASA – 8.6 %
- Low-dose ASA (80 to 100 mg/day) with a PPI – 0.7 to 1.6 %
Pending trials for PP

ASPREE (ASPIrin in Reducing Events in the Elderly)
- 19,000 Pts ≥ 70 yo, Australia and US
- Outcomes: CDV dz, dementia, cancer
- Closed 2014, analysis through 2017

ARRIVE (ASA to Reduce Risk of Initial Vascular Events)
- 12,000 Pts in 7 countries (US and Western Europe)
- Moderate cardiovascular risk, 10-20% 10 yr risk
- 5 yr followup
## Pts with Afib/flutter

<table>
<thead>
<tr>
<th>CHA2DS2-VASc</th>
<th>Points</th>
<th>SCORE</th>
<th>annual stroke risk</th>
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</thead>
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<tr>
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<td></td>
<td>0</td>
<td>0.20%</td>
</tr>
<tr>
<td>Congestive HF</td>
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<td>1</td>
<td>0.60%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>2</td>
<td>2.20%</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>2</td>
<td>3</td>
<td>3.20%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>4</td>
<td>4.80%</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
<td>5</td>
<td>7.20%</td>
</tr>
<tr>
<td>Vascular disease (prior MI, PAD, or aortic plaque)</td>
<td>1</td>
<td>6</td>
<td>9.70%</td>
</tr>
<tr>
<td>Age 65 to 74 years</td>
<td>1</td>
<td>7</td>
<td>11.20%</td>
</tr>
<tr>
<td>Sex category (ie, female sex)</td>
<td>1</td>
<td>8</td>
<td>10.80%</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
<td>9</td>
<td>12.20%</td>
</tr>
</tbody>
</table>

- Aspirin losing favor for stroke prevention in low risk pts, weak supportive data
- In Pts with indication for anticoagulation, ASA should be stopped if > 1yr after ACS/PCI
Summary – ASA rx in CDV dz

• ASA 160-325 mg immediate initial dose for ACS
• 81-162 mg daily maintenance dose for effective secondary risk reduction of all vascular events
• Primary prevention requires assessment of individual 10 yr CVD risk and potential for bleeding risk. (eg. chronic NSAID use, GI hx, etc)
• ASA can be stopped in stable CVD Pts on AC
• Become familiar with AHA/ACC risk calculator
Drug Safety Communication

FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes
Mechanism of NSAID CDV Harm

- Endothelial cells make COX-1 as well as COX-2.
- COX-2 is primary source of PGI$_2$
- PGI$_2$ is anti-thrombotic, promotes endothelial health
- NSAIDs lead to inhibition of PGI$_2$ production
- Selective COX-2 inhibition spares TxA2
- Cox-2 is constitutively expressed in the macula densa and renal medullary interstitium
Relative cyclooxygenase-1 and cyclooxygenase-2 selectivity of nonsteroidal antiinflammatory drugs

Concentrations of various nonsteroidal antiinflammatory drugs required to inhibit the activity of cyclooxygenase-1 and cyclooxygenase-2 by 50 percent (IC50) in assays of whole blood. The diagonal line indicates equivalence. Drugs plotted below the diagonal line are more potent inhibitors of cyclooxygenase-2 than of cyclooxygenase-1. 6-MNA denotes 6-methoxy-2-naphthylacetic acid.

NSAID effects on BP

• Decreased natriuresis
  – only in those with prior CKD, HTN or HF

• Attenuation of prostacyclin-mediated vasodilation

• Decreased glucuronidation of Aldosterone leading to higher concentrations

• Meta-analysis from 90’s => NSAIDs can increase BP 5-6 mmHg in Hypertensive Pts*

PGI₂
vasodilation
NSAIDS in Pts with HF

• NSAIDs or Coxibs are not associated with a 1st occurrence of HF

• NSAID use in Pts with HF is associated with:
  – increased risk for HF exacerbation
  – decreased GFR
  – Attenuated response to ACEi and diuretics
  – Possible increased mortality (observational data)

• Similar response is expected in Pts with HFpEF
Real world data

• Cross-sectional study investigated patterns of NSAIDs use in about 1700 community-dwelling men aged ≥70 years.
• Of the 8.2% of participants who reported regular NSAIDs use, the mean duration was close to 5 years.
• Only 25% of regular NSAIDs users also took PPIs.
• Regular NSAIDs users were more likely than non–regular users to report chronic pain, recent pain, and chronic intrusive pain, and to take opioid analgesics (all P < .001).
NSAIDs summary

• NSAIDs and Coxibs should be avoided in Pts with elevate risk for CVD due to evidence of increased risk of ACS, HF, HTN, arrhythmia.

• Absolute risk is low but increases with:
  – Higher doses, increased frequency of use, presence of CVD

• Recommendations suggest using the lowest possible dose for the shortest period of time

• Naprosyn has the most favorable profile although based on suboptimal data
Pending NSAID trial

**PRECISION**

**Prospective Randomized Evaluation Of Celecoxib Integrated Safety Vs Ibuprofen Or Naproxen**

- Primary hypothesis: celecoxib is non-inferior to naproxen
- Pts with OA or RA with/ or at risk of developing cardiovascular disease
- MACE at 18 months
- Oct 2006 – March 2016
Warm-up questions: 1

• Husband and wife ask your opinion about starting a daily aspirin.

• 50 yo AAM, 150/90, no meds, -DM, +h/o tob, - Fhx Chol 220, Hdl 60
  
  ⇒ 10yr risk 6.8%  ASA not indicated

• 48 yo AAF, 150/90, Lisin-Hct, +DM, 1/2PPD tob, -Fhx, Chol 180, Hdl 50
  
  ⇒ 10yr risk 26.2%, ASA not recommended
  ⇒ Consider Cardiac CT for Calcium score
Warm-up questions: Patient 2

• 67 yo male h/o Htn, Inf MI, s/p RCA stent 3 yrs ago, recently hospitalized with new Afib.
• He comes to the office after discharge taking Warfarin and ASA 81mg

Would you:
• Change to a NOAC
• Stop the ASA
• Make no changes
Warm-up questions: Patient 3

- 62 yo with NICM, LVEF 30%, NYHA Class II, complains of worsening knee OA sx

Which statement is true:

- An OTC (ie low dose) NSAID can safely supplement Acetaminophen
- **High dose Acetaminophen and/or Tramadol are the best options**
- Use of NSAIDs would not be an issue if the patient had HFpEF