Considerations relevant to Aspirin or NSAIDS use in patients with cardiovascular disease

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Disclosures

None
Outline

• Brief review of prostaglandin synthesis
• Review data/recommendations for Aspirin use in Patients with ACS
• Review Aspirin indications for primary prevention of CDV events
• Review data / recommendations regarding NSAID use in Pts with CVD
Arterial trauma - normal healing response

TXA$_2$ activates platelets to promote hemostasis.

Endothelium is not present to block platelet aggregation.
Same pathways active in the normal healing process promote arterial occlusion and acute coronary syndrome when the vessel “trauma” is a ruptured plaque.
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
          - PGI₂
            - Prostacyclin Synthase
              - Hydrolysis
                - 6-keto-PGF₁α
          - Prostaglandin E₃, D₂, F₂α Synthase
            - Hydrolysis
              - PGE₂
                - Prostaglandin E₂ Synthase
                  - Thromboxane A₂ Synthase
                    - TxA₂
                      - Hydrolysis
                        - TXB₂

- NSAID
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
- Expressed in atherosclerotic plaques, during wound healing and angiogenesis
- Key source of PGI$_2$ from endothelium
- Continuously produced in the kidney
  - Inhibition $\Rightarrow$ ↓ natriuresis, increased BP*
Mechanism of ASA CDV Benefit

- Low dose aspirin 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. (~ 7 days)
- Endothelial cells can make both COX-1 and COX-2 but 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 reinfarction (1% vs 2%)
• 50% reduction in stroke (0.3% v 0.6%)
• No increased risk of bleeding in acute setting
• Initial dose: 325 mg (given QOD in the ISIS-2 trial)
Benefits of Aspirin in ACS

NSTEMI-USA
Antithrombotic Trialists' Collaboration*
meta-analysis ~200,000 pts
Aspirin dose range 75 – 1500mg
• 30% ↓ non-fatal CVA or vascular death in NSTEMI pts
• 46% ↓ non-fatal MI/CVA or vascular death in unstable angina

Recommendation: 160-325mg loading dose uncoated Aspirin followed by low dose 75 to 100 mg 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

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 patients, s/p MI- PCI)
Randomized: 75-100mg  vs  300-325 mg ASA
30 day MACE  (cardiovascular death, MI, CVA)

Results:
- No difference in MACE
- No difference in major bleeding events
- Increased GI bleeding events with high dose

Aspirin dose for 2ndary prevention

TRANSLATE-ACS (10,000 patients 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

Aspirin 75-100 mg daily – effective and safest
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...”
Can aspirin use prevent 1st MI?

- 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
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
ASA $1^\circ$ Prevention 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>2</td>
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<td>19</td>
<td>20</td>
</tr>
<tr>
<td>20</td>
<td>Type of event</td>
</tr>
<tr>
<td>G1 bleeding</td>
<td>8</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1</td>
</tr>
</tbody>
</table>

As indicated, the estimated number of MIs prevented varies with 10-year CHD risk. The estimated harms of using aspirin vary with age. Therefore, both 10-year CHD risk and age must be considered when determining whether the potential harms of aspirin use outweigh the potential benefit in terms of MIs prevented. The boldfaced numbers indicate the combinations of 10-year CHD risk and age for which the number of harms (G1 bleeding and hemorrhagic stroke) are greater than or approximately equal to the number of MIs prevented.*

CHD: coronary heart disease; G1: gastrointestinal; MI: myocardial infarction.

* Calculations of estimated benefits and harms rely on assumptions and are by nature somewhat imprecise. Estimates of benefits and harms, especially at the borders of the boldfaced and non-boldfaced areas, should be considered in the full context of clinical decision making and used to stimulate shared decision making. The calculations in the table are based on the following assumptions: that there is a 32 percent risk reduction of MIs with regular aspirin use and that gastrointestinal bleeding includes serious hemorrhage, perforation, or other complications leading to hospitalization or death. The harm of G1 bleeding in the table assumes that the risk for G1 bleeding increases with age and that the men are not taking nonsteroidal anti-inflammatory drugs, do not have upper G1 pain, or do not have a history of G1 ulcer. Estimates are based on age and 10-year CHD risk. Reproduced from: US Preventive Services Task Force. Aspirin for the Prevention of Cardiovascular Disease: Recommendation Statement. AHRQ Publication No. 09-05129-EF-2, March 2009. Agency for Healthcare Research and Quality, Rockville, MD. [http://www.ahrq.gov/clinic/uspstf09/aspirincvd/aspvcdrs.htm](http://www.ahrq.gov/clinic/uspstf09/aspirincvd/aspvcdrs.htm).
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.
Sample patient 1
- Aspirin not recommended

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, your blood pressure is well-controlled.

Demography

<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>
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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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<tr>
<td>Race: not African-American</td>
<td></td>
<td>On medication: yes</td>
<td></td>
</tr>
</tbody>
</table>

Notes and further reading

- **Moderate intensity statin** may be atorvastatin 10mg, pravastatin 40mg, or simvastatin 20-40mg. **High intensity statin** may be atorvastatin 40mg-80mg.
- AHA/ACC guidelines stress the importance of lifestyle modifications to lower cardiovascular disease risk in all patients. This includes eating a heart-healthy diet, regular aerobic exercises, maintenance of desirable body weight and avoidance of tobacco products.
- Before initiating statin therapy, clinicians and patients ought to engage in a discussion which considers addressing risk factors such as smoking and optimal lifestyle, the potential for ASCVD risk reduction benefits, adverse medication effects, drug-drug interactions, and patient preferences for treatment.
- Additional factors may be considered to inform treatment decision making. These factors may include primary LDL-C greater than 160 mg/dL or other evidence of genetic hyperlipidemia, family history of premature ASCVD with onset less than 55 years of age in a first degree male relative or less than 65 years of age in a first degree female relative, high-sensitivity C-reactive protein greater than 2 mg/L, CAC score greater than 300 Agatston units or greater than 75 percentile for age, sex, and ethnicity, ankle-brachial index less than 0.9, or elevated lifetime risk of ASCVD.
Sample patient 2
- Aspirin not recommended

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

38.6%
10-year risk of heart disease or stroke

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>
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<td>Systolic: 130</td>
<td>Diabetes: yes</td>
</tr>
<tr>
<td>Gender: male</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.
Sample patient 3
- Aspirin **not** recommended

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.

52.4%
10-year risk of heart disease or stroke

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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<th>Demography</th>
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<th>Risk factors</th>
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<td>Gender: male</td>
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Sample patient 4
- Aspirin recommend due to acceptable age + risk > 10%

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**.

13.5%
10-year risk of heart disease or stroke

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

<table>
<thead>
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<th>Demography</th>
<th>Cholesterol</th>
<th>Blood pressure</th>
<th>Risk factors</th>
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<td>Diastolic: 80</td>
<td>Smoking: no</td>
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<td>Race: not African-American</td>
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<td>On medication: yes</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.
Recommendations for 60 yr old pts

• The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.
Aspirin associated bleeding

- 2006 review of 22 trials using ASA (75-325mg)
  - ASA ↑ risk of any major bleeding 70% vs placebo
  - RR: major GI (2.0) and intracranial bleeding (1.65)
  - Absolute annual risk = 1.3/1000 pts - major GI
    3/10,000 pts - intracranial
  - 769 pts treated with Asa to cause 1 major bleed/yr

Major bleeding = 1)fatal  2)needing hospitalization or transfusion
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 %
  – PPI => e.g. omeprazole (Prilosec)
Pending primary prevention trials with Aspirin

**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
• 3.1. For patients with AF and stable coronary artery disease (eg, no acute coronary syndrome within the previous year) and who choose oral anticoagulation, we suggest adjusted-dose VKA therapy alone (target international normalized ratio [INR] range, 2.0-3.0) rather than the combination of adjusted-dose VKA therapy and aspirin (Grade 2C).

Aspirin AND oral Anticoagulation together?

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: ACCP Evidence-Based Clinical Practice Guidelines
Summary – ASA rx in CDV dz

• ASA 160-325 mg immediate initial dose for ACS
• 75-100 mg daily maintenance dose for effective secondary risk reduction of all vascular events
• Primary prevention requires assessment of individual 10 yr CDV risk and potential for bleeding risk. (eg. chronic NSAID use, GI hx, etc)
• ASA can be stopped in stable CVD Pts who also require long term anticoagulation
#NSAID

non-steroidal anti-inflammatory drugs

Many cold, allergy, and sinus medications contain NSAIDs

SOME NSAIDS ARE:

- aspirin
- Motrin
- Advil
- ibuprofen
- Aleve

For an extensive list of NSAIDs visit www.clarityallergycenter.com
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 and COX-2.
- COX-2 primary source of PGI₂; COX-1 => TxA2
- PGI₂ => blocks platelet aggregation & thrombus formation, promotes endothelial health
- TxA2 => +vasoconstriction and plt aggregation
- NSAIDs lead block production of PGI₂
- Selective COX-2 inhibition spares TxA2
- Reduced renal Cox-2 levels increases BP 5-6 mmHg
NSAID Targeted effect
NSAIDs increase cardiovascular events

2013 meta-analysis

- 280 trials NSAID vs placebo, 474 trials NSAID vs NSAID
- ~350,000 pts

Outcomes: major vascular event (MI, CVA, death), HF, GI event

Findings:

– Coxibs increased risk of vascular events 37%, Diclofenac 41%
– ACS only: Coxib 76%, Diclofenac 70%, Ibuprofen 22% ↑ risk
– Vascular death: Coxibs 58%, Diclofenac 65% ↑ risk
– No increase risk of vascular events noted with Naproxen use
– All NSAIDs ↑ HF risk x2

Lancet. 2013;382(9894):769
NSAIDS in Pts with HF_{rEF}

• NSAIDs or Coxibs have been associated with a 1\textsuperscript{st} occurrence of HF

• NSAID use in Pts with HF is associated with:
  – increased risk for HF exacerbation/hospitalization
  – worsened renal function
  – diminished response to ACEi and diuretics
  – Possible increased mortality (observational data)

• Similar response is expected in Pts with HF_{pEF}
NSAIDs in all-comers

- 5 population healthcare databases of 4 EU countries
- 2000-2010: Any adult > 18 who started NSAIDs
- 92,163 admissions for CHF vs 8 million nested controls

Results:
- 19% incr risk for HF admission if NSAID use w/in 14 days compared to use > 6 months out
- Risk doubled for diclofenac, indomethacin, piroxicam use at high doses. Medium dose Indomethacin also significant.
- Risk for HF was independent of HF history

NSAIDS and hemorrhagic stroke risk

• Meta-analysis of 10 studies (7 case-control, 3 cohort studies) => ~ 1.5 million pts.
• Collectively, all NSAIDs
  => small, insignificant risk (RR= 1.09)
• For Diclofenac and Meloxicam pts
  => significant increased risk (RR =1.27)
<table>
<thead>
<tr>
<th>NSAID</th>
<th>Case patients</th>
<th>Controls</th>
<th>Odds ratio (95% CI)</th>
<th>Odds ratio (95% CI)</th>
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<tr>
<td>Ketorolac</td>
<td>449/0.49</td>
<td>17 459/0.21</td>
<td>1.83 (1.66 to 2.02)</td>
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<tr>
<td>Etoricoxib</td>
<td>835/0.91</td>
<td>50 039/0.61</td>
<td>1.51 (1.41 to 1.62)</td>
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<tr>
<td>Indomethacin</td>
<td>267/0.29</td>
<td>13 556/0.16</td>
<td>1.51 (1.33 to 1.71)</td>
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<tr>
<td>Rofecoxib</td>
<td>1213/1.32</td>
<td>78 930/0.96</td>
<td>1.36 (1.28 to 1.44)</td>
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<td>Sulindac</td>
<td>16/0.02</td>
<td>639/0.01</td>
<td>1.32 (0.79 to 2.21)</td>
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<tr>
<td>Piromoxicam</td>
<td>974/1.06</td>
<td>74 422/0.90</td>
<td>1.27 (1.19 to 1.35)</td>
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<tr>
<td>Acemetacin</td>
<td>16/0.02</td>
<td>979/0.01</td>
<td>1.21 (0.73 to 2.02)</td>
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<tr>
<td>Diclofenac</td>
<td>3228/3.50</td>
<td>261 792/2.93</td>
<td>1.19 (1.15 to 1.24)</td>
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<tr>
<td>Diclofenac</td>
<td>3228/3.50</td>
<td>261 792/2.93</td>
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<td>Diclofenac, combination</td>
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<td>37 292/0.45</td>
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<td>3647/0.04</td>
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<td>Etorolac</td>
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<td>3578/0.04</td>
<td>0.87 (0.63 to 1.19)</td>
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<tr>
<td>Dexketoprofen</td>
<td>8/0.01</td>
<td>528/0.01</td>
<td>0.86 (0.41 to 1.81)</td>
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<td>Celecoxib</td>
<td>1253/1.36</td>
<td>118 925/1.44</td>
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<td>Current use of any NSAID</td>
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<td>1 193 537/14.44</td>
<td>1.19 (1.17 to 1.22)</td>
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</table>

Fig 1 | Distribution of current use of individual NSAIDs among cases and controls and pooled associations between current use of individual NSAIDs and risk of hospital admission for heart failure, with past use of any NSAID as reference. Estimates obtained by pooling individual data from all available databases. Pooled odds ratios and 95% confidence intervals estimated by fitting a conditional logistic regression model after correcting for available covariates.
PRECISION trial
Prospsective Randomized Evaluation Of Celecoxib Integrated Safety Vs Ibuprofen Or Naproxen

• Hypothesis: celecoxib is non-inferior to naproxen/ibuprofen
• 24,000 Pts with OA/RA with/or at risk of CVD
• Primary outcome: CV death, nonfatal MI, or nonfatal stroke
• Oct 2006 – March 2016, mean tx 20 mo.s, + f/u of 34 mo.s
• Avg daily doses: 209mg / 852mg / 2045mg respectively
• 69% stopped study drug, 27% lost to f/u
• Intention-to-treat analysis and on-treatment analysis
  – Moderate doses of Celecoxib were non-inferior to ibuprofen or naproxen with regard to cardiovascular safety.

Critique: 200mg daily dose of Celebrex relatively low impact on sx's
NSAID use in older patients

- 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).
Low Back Pain Tx Recommendations
American College of Physicians 4/2017

• Nonpharmacologic therapies are recommended as first-line treatment for patients with acute or subacute low back pain (lasting 12 weeks or less).
  – e.g. superficial heat, massage, acupuncture, and spinal manipulation

• Most low back pain is self-limited, with many patients showing considerable improvement within the first 4 weeks.

• Acute or subacute pain:
  – When drug therapy is considered, NSAIDs or skeletal muscle relaxants should be used.
  – Acetaminophen is no longer recommended, given new evidence indicating a lack of benefit.

• Chronic pain (i.e., beyond 12 weeks):
  – Clinicians should start with nonpharmacologic approaches, such as exercise, multidisciplinary rehabilitation, acupuncture, and mindfulness-based stress reduction.
  – If non-drug therapies aren't sufficient, NSAIDs should be tried first, then tramadol or duloxetine (Cymbalta).
  – Opioids may be considered only when prior treatments fail, the potential benefits for the patient outweigh the risks, and the benefits and risks are discussed with the patient.
NSAIDs summary

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

• Absolute risk is likely low but increases with:
  – 1)Higher doses, 2)frequency of use, 3)presence of CVD

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

• Naprosyn has the most favorable profile based on observational data.

• Celecoxib at low doses appears relatively safe (compared to Ibuprofen and naproxen) in pts with CVD