Adverse Cardiovascular Effects of NSAIDS

Victor Sharpe, MD, FACP
Yakima Heart Center

Cardiac Issues 2017

No Disclosures

Objectives

- Review the history of NSAID prescribing
- Review NSAID classes
- Review the biochemical pathways
- Understand risks of NSAID use in patient with/without heart disease
- Review factors to consider when prescribing NSAIDS

Historical Background

- 1899 drug and dye firm, Bayer, began selling Aspirin around the world
- 1963 indomethacin first created (FDA approved 1965)
- Since then over 20 additional NSAIDs developed
- 1998 first selective COX-2 inhibitor (Celebrex) launched
- With development of newer agents and higher dosing, new toxicity profiles began to emerge (surprise since ASA had been shown to be cardioprotective at doses up to 1500 mg/day) [NEJM 2005;353:2373-2383.]

Historical Background – Withdrawals and FDA Black Box Warnings

- September 2004: Merck voluntarily withdraws rofecoxib (Vioxx)
- December 2004:
  - FDA adds a black box contraindication for use of valdecoxib (Bextra) post CABG
  - NIH suspends use of celecoxib (Celebrex) in Adenoma Prevention Trial due to increased cardiac events
  - NIH stops the Alzheimer's Disease Anti-inflammatory Prevention Trial due to increased cardiovascular events in patients receiving naproxen
  - FDA issues a public health advisory for all 4 of these drugs on December 23, 2004
- April 2005:
  - FDA requests suspension valdecoxib (Bextra)
  - FDA requires black box warning on celecoxib and all prescription NSAIDs

- FDA recommends OTC NSAIDs to have more specific warnings about CV and GI effects

Historical Background – July 2015: FDA Drug Safety Communication

"Based on our review and the advisory committees' recommendations, the prescription NSAID labels will be revised to reflect the following information:

- The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID.
- The risk appears greater at higher doses.
- It was previously thought that all NSAIDs may have a similar risk. Newer information makes it less clear that the risk for heart attack or stroke is similar for all NSAIDs; however, this newer information is not sufficient for us to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.

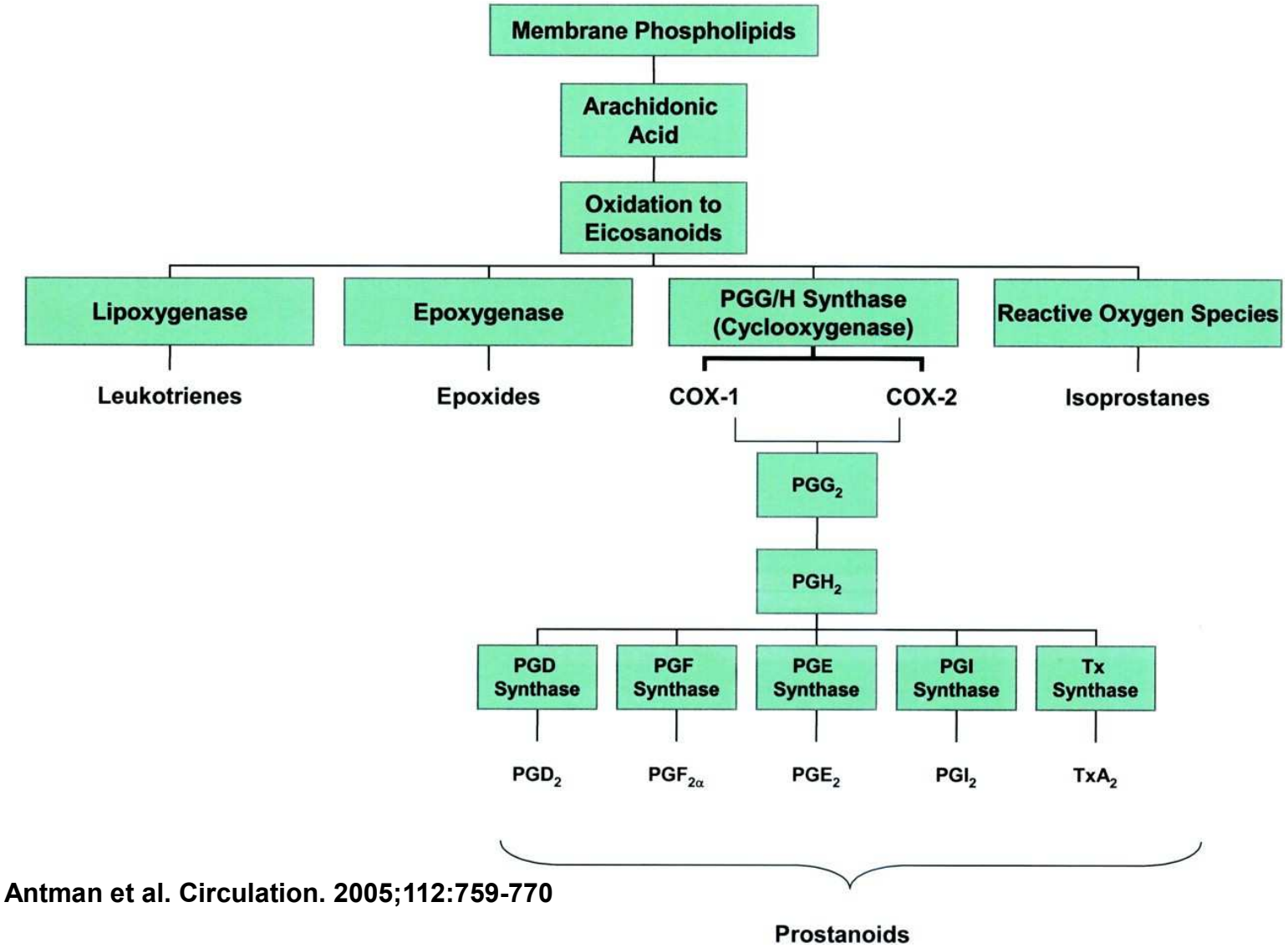
Biochemistry of NSAIDs

- Chemically heterogeneous group of compounds
- Therapeutic effects… Analgesia

  Anti inflammatory

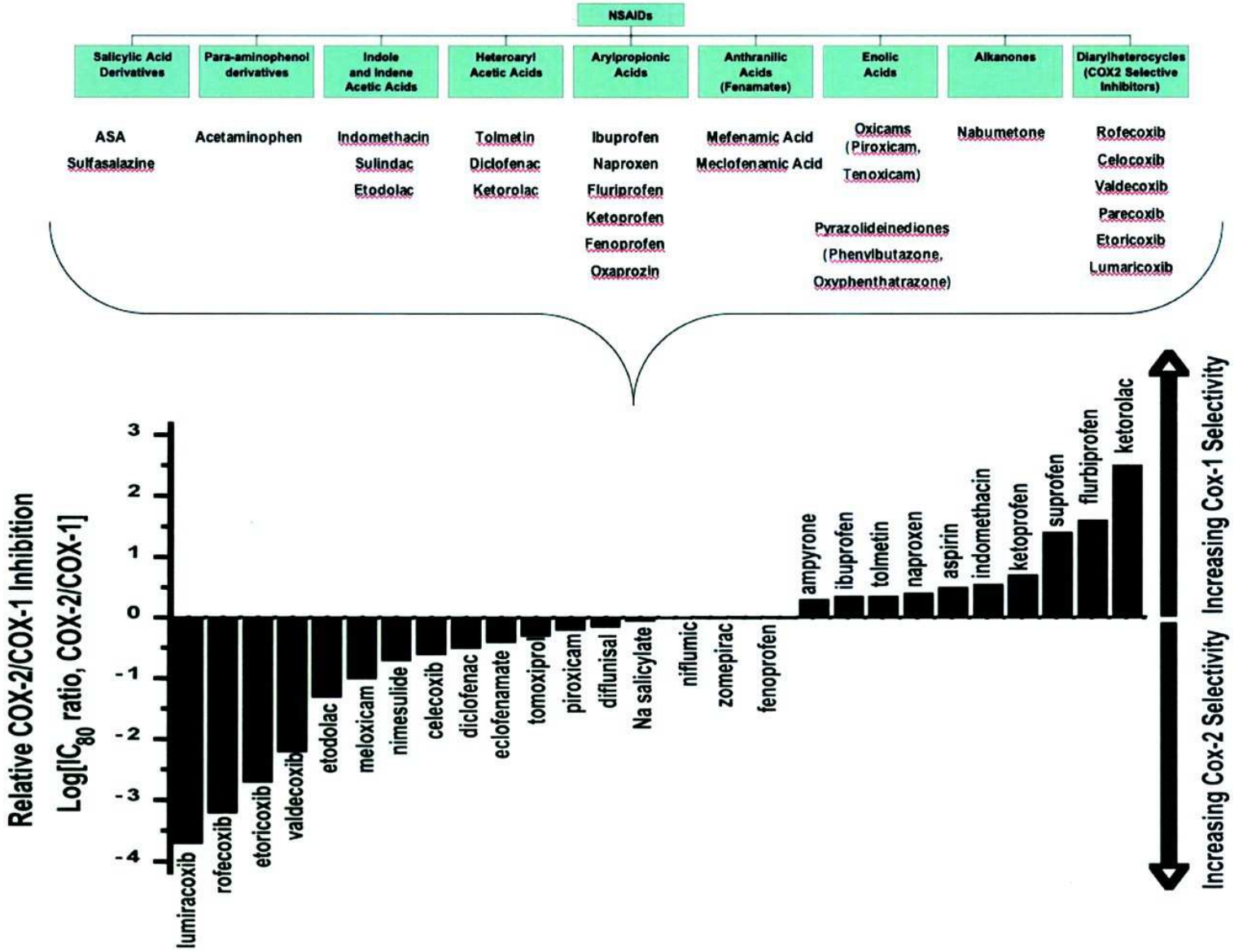
  Anti pyretic
- Inhibit cyclooxygenase (COX); exists in at least 2 isoforms
  - COX-1 is constitutive and is most strongly associates with organ protective effects (maintenance of the gastric mucosal barrier)
    - Only isoenzyme expressed in platelets
  - COX-2 is inducible by inflammatory cytokines in many cells

Figure 1. Molecular pathways for formation of eicosanoids and prostanoids.



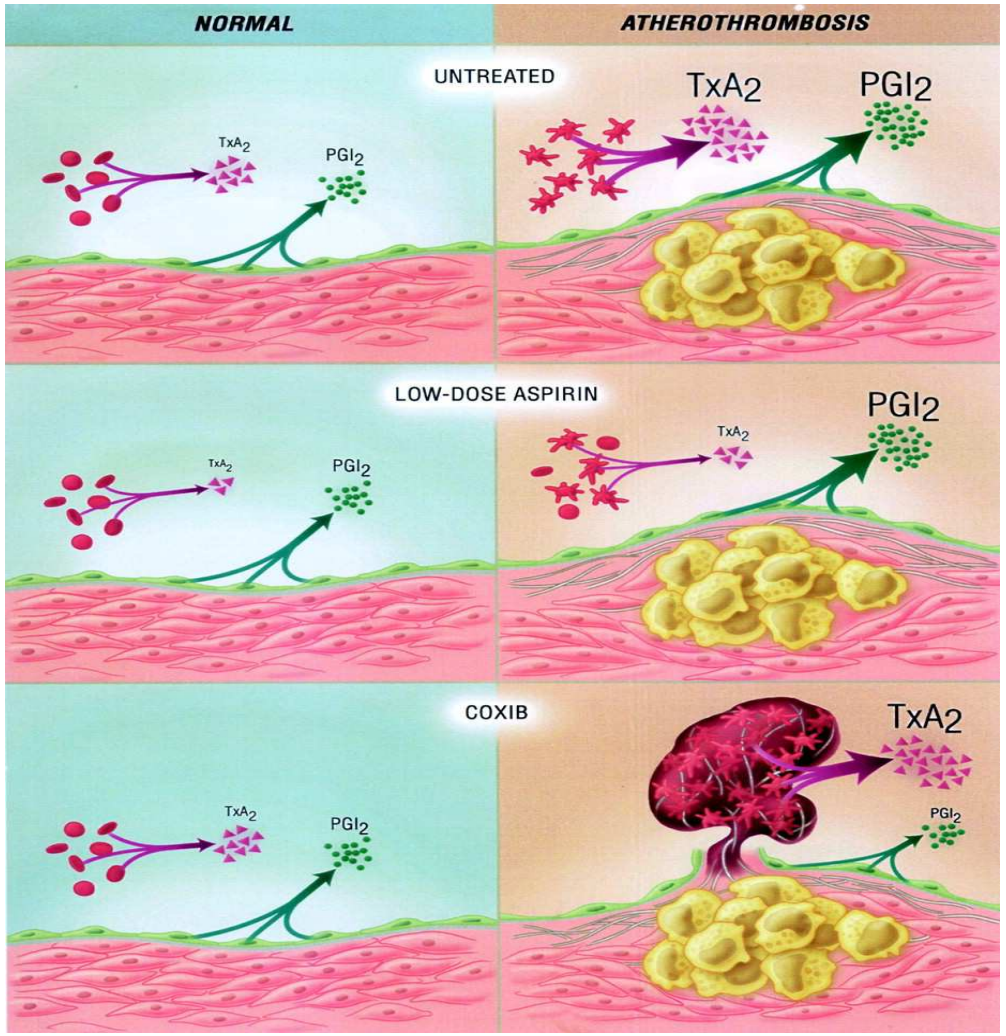
Elliott M. Antman et al. Circulation. 2005;112:759-770

Figure 2. NSAIDs.



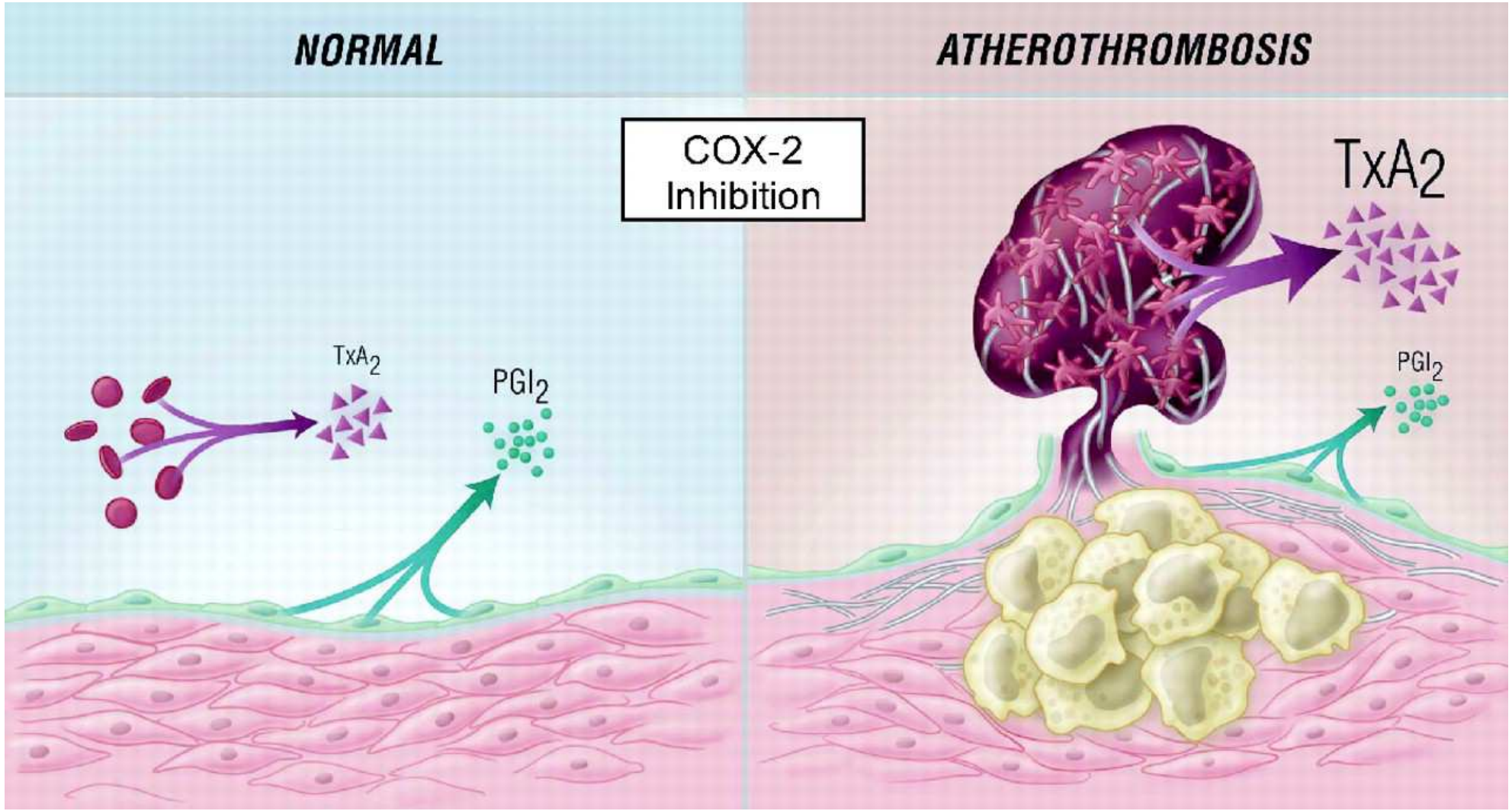
Elliott M. Antman et al. Circulation. 2005;112:759-770

Figure 4. Consequences of COX inhibition for prostacyclin and thromboxane A2 production in normal and atherosclerotic arteries.



Elliott M. Antman et al. Circulation. 2005;112:759-770

Figure 5. Consequences of COX inhibition for prostacyclin and TXA2 production in normal and atherosclerotic arteries.



Elliott M. Antman et al. Circulation. 2007;115:1634-1642

General Considerations

Nonselective NSAIDS

vs

Selective NSAIDS (coxibs)

Patients without known cardiovascular disease

vs

Patients with or at high risk for cardiovascular disease

What We Know about NSAID Risk

- Patients without known cardiovascular disease
- Patients with cardiovascular disease

What we Know About NSAID Use in Patients without Known Cardiovascular Disease

- Even in these patients, there is a small risk (1-2 excess deaths per 1000 person years) of adverse cardiovascular events
- The risks of major cardiovascular events (MI, stroke, and death), appear to be increased to a similar degree by use of most nonselective NSAIDs at high doses.
- For most of these patients, the small increase risk rarely influences the decision whether to use one of these drugs
- Principles for prescribing
  - Nonselective NSAID – naproxen
  - Lowest dose to accomplish the therapeutic goal
  - Shortest duration

Types of Adverse Cardiovascular Effects

- Ischemic Events (MI, stroke, death)
- Hypertension
- Heart Failure
- Atrial Fibrillation
- Venous Thromboembolism

Types of Adverse Cardiovascular Effects

- Ischemic events (MI, stroke, death)
- Hypertension
- Heart Failure
- Atrial Fibrillation
- Venous Thromboembolism

NSAIDS and Coronary/Ischemic Events

- 2013 Meta analysis of > 300,000 patients in over 600 randomized trials (Lancet. 2013;382(9894):769)
- Major cardiovascular events (non fatal MI or stroke, vascular death)
  - High dose diclofenac vs placebo: adjusted rate ratio 1.41
  - High dose ibuprofen vs placebo: adjusted rate ratio 1.44 (ns)
  - High dose naproxen did not result in increase in major CV events (0.93)
  - Limited data on the individual non-selective agents led to wide confidence intervals
- Vascular death was increased by diclofenac (RR 1.65) and coxibs (RR 1.58); the risk with ibuprofen (RR 1.90) did not reach statistical significance. Naproxen did not increase risk of vascular death (RR

Cardiac Issues 2017

Types of Adverse Cardiovascular Effects

- Ischemic events (MI, stroke, death)
- Hypertension
- Heart Failure
- Atrial Fibrillation
- Venous Thromboembolism

NSAIDs and Hypertension

- All NSAIDs can increase BP in hypertensive and normotensive patients
- Average rise is 3/2 mmHg but varies considerably with dose and NSAID
- May reduce effect of antihypertensive drugs except calcium channel blockers
- Mechanism is likely due to reducing renal sodium excretion
- NSAIDS can cause acute deterioration in GFR and no NSAID appears to be safer than any other

Types of Adverse Cardiovascular Effects

- Ischemic events (MI, stroke, death)
- Hypertension
- Heart Failure
- Atrial Fibrillation
- Venous Thromboembolism

NSAIDS and Heart Failure

- Use of most NSAIDs is likely associated with a small increased absolute risk of heart failure but in the absence of significant underlying cardiovascular disease it is uncommon for heart failure to develop.
- 2013 Meta analysis study of > 300,000 patients (Lancet. 2013;382(9894):769)

  Risk of HF doubled; risk was lower with nonselective NSAIDs
- 2016 Case control study of > 90,000 patients (BMJ. 2016 Sep;354:i4857)

  19% increased risk of hospitalization for heart failure.

  Risk is dose dependent and present for most nonselectives

Types of Adverse Cardiovascular Effects

- Ischemic events (MI, stroke, death)
- Hypertension
- Heart Failure
- Atrial Fibrillation
- Venous Thromboembolism

NSAIDS and Atrial Fibrillation

- Some but not all case-control studies have suggested a modest increased risk for the development of atrial fibrillation (AF) in patients taking NSAIDs

Types of Adverse Cardiovascular Effects

- Ischemic events (MI, stroke, death)
- Hypertension
- Heart Failure
- Atrial Fibrillation
- Venous Thromboembolism

NSAIDS and Venous Thromboembolism

- It is uncertain whether NSAIDs increase the risk of DVT and PE
- A 2014 systematic review and meta-analysis

  6 observational studies (one cohort study and five case-control studies)

  21,401 venous thromboembolic (VTE) events, found an increased risk of VTE (DVT or PE) in users of NSAIDs, compared with non-users (risk ratio 1.80, 95% CI 1.28-2.52)

- Study limitations: marked differences between studies in definitions and study design

[Rheumatology (Oxford). 2015;54(4):736.].

What We Know about NSAID Risk

- Patients without known cardiovascular disease
- Patients with cardiovascular disease

Suggested Approaches to Prescribing - Patients with Cardiovascular Disease

- NSAIDs increase the risk of new cardiovascular events in patients with established heart disease
- Increased risk evident within the first weeks of use, but resolves with discontinuation [Circulation. 2011;123(20):2226]
- Regardless of the agent, use the…
    - Lowest dose
    - Shortest duration
- Celebrex preferred over non-selective NSAIDS
- Of the nonselective NSAID – naproxen sodium preferred [little data about other nonselective NSAIDS (besides ibuprofen and diclofenac)]

Adverse Cardiovascular Effects with NSAIDS Coronary Heart Disease Patients

- 2016 PRECISION trial
  - Trend toward increased risk of nonselective agents (naproxen, ibuprofen) vs celecoxib
  - Did not reach statistical significance
- 2013 Meta analysis of > 300,000 patients (Lancet. 2013;382(9894):769)
  - In patients at high cardiovascular risk (baseline risk of 2% per year), the increased number of major vascular events for patients taking diclofenac or ibuprofen was estimated at 7-8 excess events per 1000 persons per year, including 2 fatal events. Coxibs, diclofenac, and ibuprofen increased the absolute annual excess risk of a major vascular event to a similar degree in these patients; naproxen did not increase such risk.

Adverse Cardiovascular Effects with NSAIDs After Myocardial Infarction

- Danish Registry 62,000 patients post MI (2002-2011)
- Patients on ASA, clopidogrel, oral anticoagulant or combination
- 34% received at least one prescription for NSAID (>90% nonselective)
- Median follow up 3.5 years

- Cardiovascular events in 30%
- NSAIDs increased risk: Hazard Ratio 1.4 (11.2 vs 8.3 events/100 person-yrs.)

Cardiac Issues 2017

JAMA. 2015 Feb;313(8):805-14

Adverse Cardiovascular Effects with NSAIDs After Heart Failure Admission

- Danish Observational study (1995-2004)
- 107,000 patients who survived a first admission for heart failure
- 34% received at least one prescription for NSAID (>90% nonselective)

- Adjusted risk (hazard ratio) for re-hospitalization

  Diclofenac: 1.35 Ibuprofen: 1.16 Naproxen 1.18 (ns)

- Adjusted risk (hazard ratio) for death

  Diclofenac: 2.08

  Ibuprofen (>1200 mg/d): 1.31*

Cardiac Issues 2017

Adverse Cardiovascular Effects with COX-2 Selective Inhibitors

- All of the COX-2 Selective Inhibitors appear to increase risk of ischemic events in a dose dependent fashion.
- All have been removed from the US market except celecoxib

What We Know: Adverse Cardiovascular Effects with COX-2 Selective Inhibitors

- 2013 Meta-analysis (Lancet. 2013;382(9894):769)
  - Trend toward higher risk with celecoxib vs placebo (RR 1.36)
  - Risk appears to be dose dependent

- Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) (N Engl J Med 2016; 375: 2519-29)
  - 24, 081 patient with arthritis
  - 75% had no known cardiovascular disease but did have at least 1 risk factor (HTN or DM)
  - Compared safety of
    - Celecoxib 100-200 mg bid
    - Naproxen sodium 375 -500 mg bid

What We Know: Adverse Cardiovascular Effects with COX-2 Selective Inhibitors

- PRECISION trial results
  - Celecoxib CV safety was non inferior to either non selective naproxen or ibuprofen
  - Celecoxib appears to be safer than either of these as far as GI side effects
  - Celecoxib renal safety profile was better than that of ibuprofen but not significantly different from naproxen

- But…
  - The mean dose of celecoxib in PRECISION was juts over 200 mg per day

N Engl J Med 2016; 375: 2519-29.

Thank You!