



# Common Drugs With Cardiovascular Risk: What You Need to Know

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# Introduction:

- Many common medications have potential cardiovascular side effects.
- These medications can be safely used, in the appropriate patients.
- Will review a number of medications recently in medical and popular press.

## The Leader

SUNY Fredonia's student newspaper: Online

Good drugs go bad: not always, but usually

# Good Drugs, Bad Doctors



## **Good Drugs and Bad Drugs: What's the Difference?**

## Introduction:

## Specific Agents:

Proton Pump Inhibitors (and Clopidogrel)

Azithromycin

Pioglitazone (Actos)

NSAIDs

COX-2 Inhibitors

## Format:

Define Interaction Issue

Prescribing Recommendations

## Proton Pump Inhibitors (and Plavix)

- Plavix reduces major CV events compared with placebo or aspirin.
- Dual antiplatelet therapy with Plavix/ASA reduces major CV events in patient with ischemic heart disease.
- Prolonged dual antiplatelet therapy is standard of care in patients after DES.

# Proton Pump Inhibitors (and Plavix)

- Antiplatelet agents increase risk of bleeding (prior GI bleeding, older age, use steroids/anticoagulants, or NSAIDs).
- PPIs reduce risk of upper GI bleeding compared with no therapy.
- However, potential interactions between PPIs and Plavix have emerged. A significant association between PPI use and Plavix has been inconsistently demonstrated.
- The proposed mechanism is PPI inhibition of the CYP<sub>450</sub> 2C<sub>19</sub>-mediated metabolic bioactivation of clopidogrel.

## Plavix and PPIs: What to do?

- Empiric use of PPIs should be avoided in patients treated with Clopidogrel.
- PPIs should only be considered in high-risk patients (history of gastrointestinal bleeding or ulcers, and those receiving concomitant anticoagulant therapy). PPIs to use are dexlansoprazole, lansoprazole, or pantoprazole.
- Also consider use of H<sub>2</sub>-receptor antagonists or antacids.

# Azithromycin and ↑(Sudden) Death

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Azithromycin and the Risk of Cardiovascular Death

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# Azithromycin and ↑(Sudden) Death

- Other macrolide antibiotics are associated with QT prolongation and increased arrhythmias.
- Retrospective (1992-2006) analysis of Tennessee Medicaid patients who took Azithromycin. Comparison groups took Amoxicillin, Levaquin, Cipro, or no Rx.
- 10 day post-Rx filling observation (5d Rx drug)
- Large # of prescriptions:
  - Azithromycin 347,795
  - Amoxicillin 1,348,672
  - Ciprofloxacin 264,626
  - Levaquin 193,306
  - No Abx 1,391,180 (Propensity matched)

# Azithromycin and ↑(Sudden) Death

<u>Drug</u>	<u>Deaths</u>	<u>Death Rate/million</u>
Azithromycin	29/22	85.2
Amoxicillin	42/29	24
No Antibiotic	41/33	24

- 2.88 x ↑ risk of sudden death
- 1.86x ↑ risk death by any cause
- ↑ 47 deaths per million.
- Risk Factors: Diabetes, CAD, Valve disease, CHF, PAD, use of certain medications – Digoxin, ACE-I, β-blockers

## What to do?

- Avoid indiscriminate use of antibiotics.
- Avoid Azithromycin in patients with established CV disease, especially cardiomyopathy/CAD/CHF.
- Avoid use in higher risk individuals
- Consider use of alternative antibiotic agents

# Pioglitazone (Actos) and CHF

- Thiazolidinediones (TZDs) have been associated with increased fluid retention.
- Rezulin pulled from market due to liver toxicity.
- Actos remains but has been associated with CHF.
  - 1.7-2.1 fold increase CHF after 24 weeks Rx.
  - 2.1 fold increase in HF resulting in hospitalization/death
  - 4-6% patients develop peripheral edema.
  - Observational studies: Increased weight gain and fluid retention.

# Pioglitazone (Actos) and CHF

- Mechanisms:
  - Renal Na<sup>+</sup> retention – stimulation sodium reabsorption in collecting tubule.
  - ? Aldosterone mediated effect
- Recommendations:
  - ↓↓ EF, no CHF – low dose TZD to start
  - ↓↓ EF, Class I-II CHF - low dose TZD to start
  - Class III-IV CHF – Avoid TZD use
  - If fluid retention occurs, assess for CHF.
  - If fluid retention, no evidence CHF, consider stopping medication.



# NSAIDs/COX-2 and Cardiac Events

- NSAIDs/COX-2 commonly used to treat pain and inflammation.
- However, these may have several negative effects on the CV system:
  - Interference with ASA effects.
  - Increased CV risk/events
  - Exacerbation of heart failure.
  - Cause (worsening) HTN control

# NSAIDs/COX-2 and Cardiac Events

- Use of NSAIDs with concomitant ASA may attenuate beneficial effects of ASA
  - Ibuprofen given 2 hours before/after ASA decreased platelet inhibition.
  - Similar effects after a single dose Naproxen.
  - NSAIDs compete for common COX-1 binding site.
- MD Health Study: 2.9x ↑ MI NSAIDs ≥ 60 days.



# NSAIDs/COX-2 and Cardiac Events

- NSAIDs and COX-2 increase CV risk:
  - NSAIDs – Absolute risk low, ↑ with dose.
    - Low risk/CAD pts - MI/CVA Ibuprofen (2.26), Diclofenac (1.6), Naproxen (1.23).
    - Unclear in patient with RA & CAD
  - COX-2 – ↑ Risk which vary depending upon agent and dose:
    - ↑ risk celebrex 1.35, Vioxx 2.12, Naproxen 0.82.
    - No known ↑ risk in patients with arthritis.
    - Effect occurs shortly after starting drug.

# NSAIDs/COX-2 and Cardiac Events

## ■ CAD

- NSAIDs: ↑ risk death, recurrent MI 1.5x (least Naproxen)
- COX-2 – ↑ CV events, non-cardiac pts.: Vioxx (2.6x), Celebrex (1.4x)
- COX-2 - ↑ risk in known CV disease w/ Celebrex (1.9) – Risk developed with 7d of treatment

# NSAIDs/COX-2 and Cardiac Events

- Worsening CHF
  - NSAIDs:
    - ↑(re)hospitalization CHF Diclofenac (1.35), Ibupro(1.16)
    - ↑ death diclofenac (2.1), Ibuprofen (>1200 mg 1.31), Naproxen (>500 mg 1.22),
    - ↑ afterload from vasoconstriction – Can also occur with ASA>325 mg. Reverses ACE-I/ARB effect.
  - COX-2:
    - ↑ Rates hospitalization CHF – Vioxx 2.7x, Celebrex 1.4x
    - ↑ Mortality – Vioxx, Celebrex (1.7 – 2.1x).
    - ↑ Risk renal failure when given to CHF patients.

# NSAIDs/COX-2 and Cardiac Events

- HTN
  - NSAID use associated with ↑ BP.
  - COX-2 can ↑ BP – Vioxx > Celebrex

## NSAIDs/COX-2: What to do?

- Factor in CV risk prior to NSAID Rx.
- Avoid use S/P CABG.
- Stop NSAID/COX-2 in patients with MI, CHF.
- Use lowest dose for shortest time.
- Use in caution with HTN – may exacerbate HTN
- (ACRheumatology) Consider risk/benefits NSAIDs - Naproxen NSAID of choice.

# Conclusions:

- Many common medications have potential cardiovascular side effects.
- These medications can be safely used, but with appropriate care.

# Thank you

