Deconstructing Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

AOASM OMED15
October 18, 2015
Orlando, FLA
Abbreviations

ASA – Acetylsalicylic Acid (Aspirin)
COX – Cyclooxygenase
MI – Myocardial Infarction
tNSAID – traditional non-steroidal anti-inflammatory drug
RCT – Randomized Clinical Trial
PG – Prostaglandin
PGI₂ – Prostacyclin
TxA₂ – Thromboxane
USPTFS – US Prevention Services Task Force
Evolution of NSAIDs

A rheumatologist is a gastroenterologist’s best friend
Ulcers
GI Bleeding
'Normal'
Arachidonic Acid
Cell Membrane Phospholipids
Joints
Connective Tissue
Swelling
Edema
Pain
Inflammation
COX
Salicylate
PGE$_2$
Normal Gastric Mucosa

1899 A-spirin
Salicylate

∼1975
Diclofenac
Piroxicam
Naproxen
Ibuprofen
Indomethacin

Gastric mucosa

COX
Discovery ~ 1976

- Thromboxane (TxA₂)
- Prostacyclin (PGI₂)

Platelet:endothelial interface

Cardiologists enter the story: “Paradise Lost”
Mechanism of Action

• At anti-inflammatory doses, aspirin is a pro-drug # salicylate, a reversible COX inhibitor.
• Aspirin itself is an irreversible inhibitor because it acetylates COX.
• tNSAIDs are reversible COX inhibitors with distinctive chemical & pharmacokinetic traits.

Do these nuances have any clinical significance?
A single, daily low-dose aspirin (81 mg) has a durable (days) anti-thrombotic effect due to unique chemical features of acetylsalicylic acid, platelets & mesenteric portal circulation.
Low dose minimizes gastric ulcer risk but confers a **durable systemic anti-thrombotic effect**

- Aspirin inhibits COX irreversibly
- **Platelets have no nucleus**
- Recovery requires platelet turnover
Does aspirin ‘prevent’ heart attacks?

Models, Clinical Trials, Recommendations
Blood Flow in Coronary (or Cerebral) Vessels Reflects the ‘Balance’ of Thrombotic & Antithrombotic Mediators
ISIS-2 2nd International Study of Infarct Survival

17,187 cases of suspected acute MI randomized into 4 arms.
Primary endpoint: 5 week vascular mortality.

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<tr>
<th>P</th>
<th>A</th>
<th>S</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>160 mg 1 month</td>
<td>Streptokinase</td>
<td>Both</td>
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</table>
FDA & USPSTF recently reached different conclusions about aspirin’s benefits/risk in primary prevention of patients with heightened baseline risk of heart attack.

Possible reasons?
## U.S. Preventive Services Task Force

**Actuarial perspective**

**Gain** = 33-60 life years

<table>
<thead>
<tr>
<th>Age</th>
<th>Benefit Number Prevented</th>
<th>Risk Number Caused</th>
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<tbody>
<tr>
<td><strong>50-59</strong></td>
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<tr>
<td><strong>CVD Risk</strong></td>
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<tr>
<td>10%</td>
<td>22.5 MI</td>
<td>28.4 Serious GI Bleeding</td>
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<tr>
<td></td>
<td>8.4 Stroke Ischemic</td>
<td>2.3 Strokes Hemorrhagic</td>
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<tr>
<td>20%</td>
<td>28.6 MI</td>
<td>24.8 Serious GI Bleeding</td>
</tr>
<tr>
<td></td>
<td>9.2 Stroke Ischemic</td>
<td>2.1 Strokes Hemorrhagic</td>
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<td></td>
<td>Colon Cancer</td>
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55 year old men, ≥ 2 risk factors: Risk of CVD death over next 20 years is ~ 20%
With the exception of Aspirin, since 2005 All other NSAIDs have had a Black Box warning for cardiovascular risks.

Why?
tNSAIDS

- Indole Acetic Acids: Indomethacin, sulindac
- Heteroaryl Acetic Acids: Diclofenac, ketorolac
- Aryl Propionic Acids: Ibuprofen, Naproxen, Flurbiprofen, Oxaprozin
- Anthranilic Acids: Mefenamic acid
- Enolic Acids: Pirox-, tenox-, melox-icam
- Alkanones: Nabumetone
Inflammation induces COX-2 expression; COX-2 converts AA into PGE\(_2\), worsening symptoms.
Are Selective COX-2 Inhibitors (Coxibs) The ‘Elusive’ Gastric Sparing NSAIDs?

~ 1996
- More COX-1 Selectivity
- More COX-2 Selectivity

Selectivity is a relative trait

- ~ 300-fold selective
  - Ibuprofen
  - Naproxen
  - Celecoxib
  - Diclofenac
  - Rofecoxib
  - Valdecoxib

- ~ 10-30-fold selective
  - Ketorolac (parenteral)
  - Salicylate (Equal)
Arachidonic Acid

Joints

Pain

Inflammation

Connective Tissue

COX-1

PGE_2

Gastric mucosa

COX-1 sparing

COX-2 selective

Rofecoxib

Celecoxib

COX- Selective Inhibitors

PGE_2

‘Normal’
Clinical Trials of Coxibs as Gastric Sparing NSAIDs
<table>
<thead>
<tr>
<th>Rofecoxib</th>
<th>Celecoxib</th>
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<tbody>
<tr>
<td><strong>VIGOR Vioxx Gastrointestinal Outcomes Research</strong></td>
<td><strong>CLASS Celecoxib Long-term Arthritis Safety Study</strong></td>
</tr>
<tr>
<td>RA (8076 enrolled)</td>
<td>OA &amp; RA (7968 enrolled)</td>
</tr>
<tr>
<td>Comparator: Naproxen (2 x 500 mg)</td>
<td>Comparators: Ibuprofen &amp; Diclofenac</td>
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**Endpoint: Fewer Gastrointestinal Events**
Do Coxibs Confer Risk of Cardiovascular Toxicity?

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<th>Q:CV T</th>
<th>?</th>
<th>A:A</th>
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**APTC** endpoint: Composite endpoint used in aspirin studies to get enough statistical power. MI, ischemic stroke, death from CV or unexplained causes.
After VIGOR & CLASS, four ongoing clinical trials provided a glimpse at cardiovascular safety of COXIBS. These were randomized, placebo-controlled, long-term trials for prevention of colorectal polyp recurrence & Alzheimer’s progression.
Rofecoxib APPROVe Adenomatous Polyp Prevention on Vioxx 25 mg CV risk ↑ RR .
Celecoxib

APC
Adenoma Prevention
Celecoxib

mg

mg

*CV risk↑

RR .

CV risk vs. placebo

CELECOXIB

ADAPT
Alzheimer's Disease
Anti-inflammatory Prevention Trial

CV risk vs. placebo

Celecoxib

Naproxen
Blood Flow in Coronary (or Cerebral) Vessels Reflects The ‘Balance’ of Thrombotic & Antithrombotic Mediators
The ‘imbalance’ model about cardiovascular risk of coxibs (or tNSAIDs) applies **ONLY** to ischemic thrombotic events (MI, stroke, death from MI, stroke) = APTC.
For patient safety each type of clinically relevant CV event matters INDEPENDENT of 'Imbalance' Model, FitzGerald Hypothesis, etc...

<table>
<thead>
<tr>
<th>Cardio/cerebrovascular events</th>
<th>MI (34)</th>
<th>Stroke (24)</th>
<th>CHF (18)</th>
<th>TIA (27)</th>
<th>CV death/MI (39)</th>
<th>CV death/MI/stroke/CHF (79)</th>
<th>CV death/MI/stroke/CHF/TIA (105)</th>
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<tr>
<td>13 (2.19)</td>
<td>13 (2.01)</td>
<td>7 (1.23)</td>
<td>7 (0.85)</td>
<td>10 (1.35)</td>
<td>8 (1.80)</td>
<td>7 (1.05)</td>
<td>3 (0.73)</td>
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<td>10 (2.38)</td>
<td>7 (2.19)</td>
<td>15 (2.52)</td>
<td>8 (1.51)</td>
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<td>11 (2.41)</td>
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**Aspirin**

- Aspirin use at baseline (45) | 14 (8.40) | 15 (9.58) | 16 (7.55) |
- No aspirin use at baseline (60) | 14 (4.30) | 25 (7.87) | 21 (4.87) |
Does cardiovascular risk observed with rofecoxib & celecoxib indicate a coxib ‘class’ effect?
2005 FDA ‘Yes’:

Other coxibs and all NSAIDs may confer a cardiovascular risk.
Does cardiovascular risk observed in trials with rofecoxib & celecoxib & valdecoxib validate the ‘Imbalance’ (FitzGerald) Hypothesis?
Much has been made of a numerical excess of adverse CV events in the treatment arm of CABG 1, without qualifying that this is partly attributable to randomization of patients in the ratio 2 drug: 1 placebo. Furthermore, the CABG I trial has been ‘misinterpreted’. The trial tested valdecoxib analgesic efficacy (opioid sparing effect) – it was not designed, nor was it intended to evaluate cardiovascular safety. The only significant ‘serious adverse event’ in CABG 1 was sternal wound healing – NOT cardiovascular events.
CABG 2 Trial Design

Post-CABG Surgery

3 days i.v.
- Parecoxib
  - PLACEBO
  - PLACEBO
7 days p.o.
- Valdecoxib
  - PLACEBO
  - Valdecoxib
  - PLACEBO
Three deaths occurred among patients given placebo & valdecoxib. These deaths occurred in patients who had not yet begun treatment with valdecoxib. It is imprudent/inadvisable to draw any mechanistic conclusions from Intent To Treat Analysis.
Where are we now?
Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee

February 10-11, 2014

Nonsteroidal anti-inflammatory drugs and cardiovascular thrombotic risk
July 09, 2015
FDA strengthens warning that non-aspirin anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes

<table>
<thead>
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<th>Retail</th>
<th>Dosing</th>
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<tr>
<td>Ibuprofen</td>
<td>( t^{1/2} = 2 \text{ hrs}, 2-3 \text{ tablets, tid, qid} )</td>
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<tr>
<td>Naproxen</td>
<td>( t^{1/2} = 14 \text{ hrs}, 1-2 \text{ tablets, bid} )</td>
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Current NSAID class labeling implies that CV thrombotic risk is not substantial with short treatment courses. Some epidemiological studies conducted since 2005 suggest that there is no, or minimal, latency period prior to the onset of CV thrombotic risk. Does the weight of evidence support reconsideration of advice regarding the latency of CV thrombotic risk?

Yes= 14 No=11 Abstain= 0
Do the available data support a conclusion that naproxen has a lower risk of CV thrombotic events as compared to the other NSAIDs?

Yes= 9 No=16 Abstain= 0
Prospective Randomized Evaluation of Celecoxib Integrated Safety Vs Ibuprofen Or Naproxen

PRECISION Randomized Clinical Trial Design

Established or at high risk for CVD

Screen

Diagnosis of symptomatic OA or RA

-3 wks.

Rand

M1 M2 M4 M8 M12 M18 M24 M30 M36 M42

Visit 1 2 3 4 5 6 7 8 9 10 11 12

Celecoxib 100-200 mg twice daily

Ibuprofen 600-800 mg three times daily

Naproxen 375-500 mg twice daily

18-mo minimum follow-up

Visits every 6 months

CVD, cardiovascular disease
ClinicalTrials.gov Identifier: NCT00346216
• High risk CV patients studied for first time.

• Full GI protection using a proton pump inhibitor.

• ASA permitted as indicated.

• >50,000 patient-years exposure >> than the meta-analysis of all prior trials comparing celecoxib to ibuprofen or naproxen.

• All CV, GI, & renal endpoints prospectively adjudicated.
Grateful thanks to Dr. John Dougherty, DO, FACOFP, FAOASM, FAODME, Senior Associate Dean for Clinical Affairs & GME, Professor Clinical Education/GME for inviting me to speak. W. Joshua Cox, DO, FACOFP, Chairman, Primary Care Medicine for helpful comments.