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
Gastric mucosa
1899 A-spirin
DICLOFENAC
PIROXICAM
NAPROXEN
IBUPROFEN
INDOMETHACIN
∼1975
Discovery ~ 1976

• Thromboxane (TxA₂)
• Prostacyclin (PGI₂)

Platelet:endothelium

Cardiologists enter the story: “Paradise Lost”

The mind is its own place, and in itself can make a heaven of hell, a hell of heaven.

John Milton
Paradise Lost
Arachidonic Acid

Blood Platelets

Vascular Endothelium

Gastric mucosa

COX

Thromboxane

Prostaglandin E2 (PGE₂)

Vasoconstriction

Aggregation

Thrombotic

Vessel-blood

Joints

Prostacyclin

PGE₂

Swelling

Edema

Gastric

Pain

Protection

Inflammation

Vasoconstriction

Aggregation

Anti-thrombotic

Vasoconstriction

Aggregation

Anti-thrombotic

Vasodilation

Vascular Endothelium

Interface
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
‘Imbalance” Model:

Blood Flow in Coronary (or Cerebral) Vessels Reflects The ‘Balance’ of Thrombotic & Antithrombotic Mediators
Clinical Trial
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.

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Aspirin 160 mg 1 month</th>
<th>Streptokinase</th>
<th>Both</th>
</tr>
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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?
<table>
<thead>
<tr>
<th>Age 50-59</th>
<th>Benefit Number Prevented</th>
<th>Risk Number Caused</th>
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<tbody>
<tr>
<td>CVD Risk</td>
<td>MI</td>
<td>Stroke Ischemic</td>
</tr>
<tr>
<td>10%</td>
<td>22.5</td>
<td>8.4</td>
</tr>
<tr>
<td>20%</td>
<td>28.6</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Actuarial perspective Gain = 33-60 life years
55 year old men, \( \geq 2 \) risk factors: Risk of CVD death over next 20 years is \( \sim 20\% \)

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<td>24.8</td>
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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
COX-1 ‘constitutive’; COX-2 inducible

Inflammation induces COX-2 expression; COX-2 converts AA into PGE$_2$, worsening symptoms

Knee

Induced: COX-2
Constitutive: COX-1

Connective Tissue

PGE$_2$

worse
Erythema
Edema
Pain
Are Selective COX-2 Inhibitors (Coxibs) The ‘Elusive’ Gastric Sparing NSAIDs?

~ 1996
More COX-1 Selectivity

Rofecoxib
Valdecoxib

Celecoxib
Diclofenac

More COX-2 Selectivity

Selectivity is a relative trait

~300-fold selective

~10-30-fold selective

Ibuprofen
Naproxen

Ketorolac (parenteral)

Salicylate (Equal)
Arachidonic Acid

Joints
Connective Tissue

COX-1

COX-2

PGE$_2$

Pain

Inflammation

Gastric mucosa

COX-1

PGE$_2$

‘Normal’

COX-2 Selective Inhibitors
Rofecoxib
Celecoxib

Normal

COX-1 sparing = Gastric sparing
Clinical Trials of Coxibs as Gastric Sparing NSAIDs
<table>
<thead>
<tr>
<th><strong>Rofecoxib</strong></th>
<th><strong>Celecoxib</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>VIGOR Vioxx Gastrointestinal Outcomes Research</td>
<td>CLASS Celecoxib Long-term Arthritis Safety Study</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>
</tr>
</tbody>
</table>

**Endpoint: Fewer Gastrointestinal Events**
Do Coxibs Confer Risk of Cardiovascular Toxicity?

**Q:** CV Toxicity?  **A:** Aspirin precedent

**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.

What did these trials show?
Rofecoxib

APPROVe
Adenomatous Polyp Prevention on Vioxx
25 mg
CV risk↑
RR 1.5

Withdrawn
‘Imbalance” Model Re-Visited
GA FitzGerald Model

Blood Flow in Coronary (or Cerebral) Vessels Reflects The ‘Balance’ of Thrombotic & Antithrombotic Mediators
“Imbalance” Model & Coxib CV Risk

**NONE** of the clinical trials mentioned was designed to test a model, nor ‘powered’ to reach statistically reliable conclusions about cardiovascular risks of coxibs (or tNSAIDs).

The ‘imbalance’ model about cardiovascular risk of coxibs (or tNSAIDs) applies **ONLY** to ischemic thrombotic events (MI, stroke, death from MI, stroke) = **APTC endpoint**
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 (62)</th>
<th>CV death/MI/stroke/ CHF (79)</th>
<th>CV death/MI/stroke/ CHF/ TIA (105)</th>
<th>Aspirin</th>
<th>No aspirin use at baseline (60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8 (1.80)</td>
<td>7 (1.05)</td>
<td>3 (0.73)</td>
<td>8 (1.55)</td>
<td>11 (2.41)</td>
<td>17 (3.26)</td>
<td>20 (4.00)</td>
<td>28 (5.54)</td>
<td>14 (8.40)</td>
<td>14 (4.30)</td>
</tr>
<tr>
<td></td>
<td>13 (2.19)</td>
<td>10 (2.38)</td>
<td>8 (1.51)</td>
<td>9 (2.20)</td>
<td>13 (2.19)</td>
<td>23 (4.54)</td>
<td>31 (6.05)</td>
<td>40 (8.25)</td>
<td>15 (9.58)</td>
<td>25 (7.87)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13 (2.01)</td>
<td></td>
<td></td>
<td></td>
<td>16 (7.55)</td>
<td>21 (4.87)</td>
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</table>
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?
Furthermore, the CABG I trial has been ‘misinterpreted’. The trial tested valdecoxb analgesic efficacy (opioid sparing effect) – It was not designed, nor powered 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
- Valdecoxib
- PLACEBO
It is imprudent/ inadvisable to draw any Mechanistic conclusions from Intent To Treat Analysis.

The mind is its own place, and in itself can make a heaven of hell, a hell of heaven.

John Milton
Paradise Lost

Image by Gustave Doré, Depiction of Satan c. 1866

"Three deaths occurred among patients given placebo & valdecoxib…. these deaths occurred in patients who had not yet begun treatment with valdecoxib."
Were 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>
<tr>
<th>Retail</th>
<th>Dosing</th>
</tr>
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<tbody>
<tr>
<td>Ibuprofen</td>
<td>$t^{1/2} = 2\text{ hrs}, 2-3\text{ tablets, tid, qid}$</td>
</tr>
<tr>
<td>Naproxen</td>
<td>$t^{1/2} = 14\text{ hrs}, 1-2\text{ tablets,bid}$</td>
</tr>
</tbody>
</table>
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

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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.