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
1899 A-\text{spirin}

\begin{itemize}
\item Diclofenac
\item Piroxicam
\item Naproxen
\item Ibuprofen
\item Indomethacin
\end{itemize}

\begin{itemize}
\item COX
\item PGE_2
\item Swelling
\item Edema
\item Pain
\item Inflammation
\end{itemize}

\begin{itemize}
\item Normal
\item Gastric Mucosa
\end{itemize}
Discovery ~ 1976

- Thromboxane (TxA$_2$)
- Prostacyclin (PGI$_2$)

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

COX

Thromboxane

Prostacyclin

COX

PGE$_2$

Joints

Gastric mucosa

Vessel-blood

interface

Gastric Protection

Swelling Edema Pain

Inflammation

Vasodilation

Aggregation

Anti-thrombotic

Thrombotic

Vasoconstriction

Aggregation
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
‘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>
</thead>
</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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CVD</td>
<td>MI, Stroke Ischemic, Colon Cancer</td>
</tr>
<tr>
<td>10%</td>
<td></td>
<td>22.5, 8.4, 13.9</td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td>28.6, 9.2, 12.2</td>
</tr>
</tbody>
</table>

Actuarial perspective
Gain = 33-60 life years
55 year old men, ≥ 2 risk factors: Risk of CVD death over next 20 years is ∼ 20% 

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<tr>
<td><strong>CVD Risk</strong></td>
<td><strong>MI</strong></td>
<td><strong>Serious GI Bleeding</strong></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>
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With the exception of Aspirin, since 2005, all other NSAIDs have had a Black Box warning for cardiovascular risks.

Why?
**COX-1 ‘constitutive’; COX-2 inducible**

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

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

~10-30-fold selective

Selectivity is a relative trait

More COX-2 Selectivity

Salicylate (Equal)

Ibuprofen
Naproxen

Ketorolac (parenteral)
Arachidonic Acid

Joints
Connective Tissue

COX-1
COX-2

PGE₂
Pain

Inflammation

COX-2 Selective
Inhibitors
Rofecoxib
Celecoxib

Gastric mucosa

COX-1

PGE₂
‘Normal’
Clinical Trials of Coxibs as Gastric Sparing NSAIDs
<table>
<thead>
<tr>
<th>Rofecoxib</th>
<th>Celecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VIGOR</strong> Vioxx Gastrointestinal Outcomes Research</td>
<td><strong>CLASS</strong> 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?

<table>
<thead>
<tr>
<th>Q: CV Toxicity?</th>
<th>A: Aspirin precedent</th>
</tr>
</thead>
</table>

**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
Celecoxib

**APC**
Adenoma Prevention
Celecoxib
400 mg

800 mg
*CV risk↑
RR 3.4

**PreSAP**
Prevention of Colorectal
Sporadic Adenomatous
Polyps
Celecoxib 400 mg
CV risk vs placebo
‘1.0’

**ADAPT**
Alzheimers Disease
Anti-inflammatory
Prevention Trial
CV risk vs. placebo
‘1.0’
Celecoxib 400
Naproxen 440
‘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>
</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>
</tr>
<tr>
<td>Composite events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death/MI (39)</td>
<td>11 (2.41)</td>
<td>13 (2.19)</td>
<td>15 (2.52)</td>
<td></td>
</tr>
<tr>
<td>CV death/MI/stroke (62)</td>
<td>17 (3.26)</td>
<td>23 (4.54)</td>
<td>22 (3.74)</td>
<td></td>
</tr>
<tr>
<td>CV death/MI/stroke/ CHF (79)</td>
<td>20 (4.00)</td>
<td>31 (6.05)</td>
<td>28 (4.46)</td>
<td></td>
</tr>
<tr>
<td>CV death/MI/stroke/ CHF/ TIA (105)</td>
<td>28 (5.54)</td>
<td>40 (8.25)</td>
<td>37 (5.68)</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin use at baseline (45)</td>
<td>14 (8.40)</td>
<td>15 (9.58)</td>
<td>16 (7.55)</td>
<td></td>
</tr>
<tr>
<td>No aspirin use at baseline (60)</td>
<td>14 (4.30)</td>
<td>25 (7.87)</td>
<td>21 (4.87)</td>
<td></td>
</tr>
</tbody>
</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 CABG I trial has been ‘misinterpreted’. The trial tested valdecoxib 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

7 days p.o.
- Valdecoxib
- 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.

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

John Milton
Paradise Lost

“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>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>$t^{1/2} = 2 \text{ hrs, 2-3 tablets, tid, qid}$</td>
</tr>
<tr>
<td>Naproxen</td>
<td>$t^{1/2} = 14 \text{ hrs, 1-2 tablets, bid}$</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: NCT00348216
• 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.