Deconstructing Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

AOASM OMED15
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Orlando, FLA

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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
Discovery ~ 1976

- Thromboxane (TxA₂)
- Prostacyclin (PGI₂)

Platelet:endothelial interface

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

Image by Gustave Doré, Depiction of Satan, c. 1866
Arachidonic Acid

Blood Platelets

Vascular Endothelium

Vasodilation
Aggregation
Anti-thrombotic
Interface

Thrombotic

Vessel-blood

Joints

Gastric mucosa

Prostaglandin E2 (PGE2)

COX

Platelets Aggregation

Gastric Protection

Inflammation

Vasorelaxation

Prostacyclin

Swelling Edema Pain

COX

Thromboxane

Vessel-blood 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.

| Placebo | **Aspirin** 160 mg 1 month | Streptokinase | Both |
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>
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<tbody>
<tr>
<td></td>
<td>CVD Risk</td>
<td>MI</td>
</tr>
<tr>
<td>10%</td>
<td></td>
<td>22.5</td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td>28.6</td>
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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>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>

* Indicates lifetime events per 1000 men taking aspirin.
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
Induced: COX-2
Constitutive: COX-1

Connective Tissue

Knee

AA → Induced: COX-2

PGE$_2$

Constitutive: COX-1

worse
Erythema
Edema
Pain

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?
More COX-1 Selectivity

More COX-2 Selectivity

Selectivity is a relative trait

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

~10-30-fold selective

Ibuprofen
Naproxen
Ketorolac (parenteral)

Salicylate (Equal)
Arachidonic Acid

Joints

Connective Tissue

COX-1

COX-2

PGE$_2$

Pain

Inflammation

COX-2 Selective Inhibitors

Rofecoxib

Celecoxib

Gastric mucosa

COX-1

PGE$_2$

‘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?

**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
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**
Alzheimer’s 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) 8 (1.80)</th>
<th>13 (2.19)</th>
<th>13 (2.01)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke (24)</td>
<td>7 (1.05)</td>
<td>10 (2.38)</td>
<td>7 (1.23)</td>
</tr>
<tr>
<td>CHF (18)</td>
<td>3 (0.73)</td>
<td>8 (1.51)</td>
<td>7 (0.85)</td>
</tr>
<tr>
<td>TIA (27)</td>
<td>8 (1.55)</td>
<td>9 (2.20)</td>
<td>10 (1.35)</td>
</tr>
<tr>
<td>Composite events</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>
</tr>
<tr>
<td>CV death/MI/stroke (62)</td>
<td>17 (3.26)</td>
<td>23 (4.54)</td>
<td>22 (3.74)</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>
</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>
</tr>
<tr>
<td>Aspirin</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>
</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>
</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’ hypothesis (FitzGerald)?
Furthermore CABG I trial has been ‘misinterpreted’. The trial tested valdecoxiax 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
"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

Image by Gustave Doré, Depiction of Satan c. 1866
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>
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<th>Retail</th>
<th>Dosing</th>
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<tr>
<td>Ibuprofen</td>
<td>$t^{1/2} = 2$ hrs, 2-3 tablets, tid, qid</td>
</tr>
<tr>
<td>Naproxen</td>
<td>$t^{1/2} = 14$ hrs, 1-2 tablets, bid</td>
</tr>
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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
• 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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Chairman, Primary Care Medicine for helpful comments.