The Vioxx Story

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Group Meeting Presentation
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Vioxx (Rofecoxib): What is it?

- Nonsteroidal anti-inflammatory drug (NSAID)
- Selective cyclooxygenase-2 (COX-2) inhibitor (coxib)
- Used in treatment of:
  - Osteoarthritis
  - Acute pain
  - Primary dysmenorrhea
- Marked by Merck & Co.
Cyclooxygenases (COX): What do they do?

• Begin biosynthetic cascade to convert polyunsaturated fatty acids to prostaglandins and thromboxane

Prostaglandains: What do they do?

• **Functions:**
  – Promote pain and inflammation
  – Protect stomach and intestinal lining
  – Have anti-coagulation effect on platelets

COX-1 and COX-2: A Comparison

• COX-1
  – Constitutively expressed
  – Involved in production of prostaglandins to mediate housekeeping bodily functions (ex. platelet aggregation)
  – Widely found throughout GI tract (maintain GI mucosa)

• COX-2
  – Primarily inducible enzyme (activated by cytokines, etc.)
  – Found in leukocytes, synoviocytes, and CNS—role in inflammation, fever, and pain
  – Mostly undetectable in GI tract

Traditional NSAIDs: An Overview

- **What do they do?**
  - Block prostaglandin formation

- **How do they work?**
  - Act by inhibiting COX-1 and -2

- **What are the effects?**
  - Analgesic, antipyretic, and anti-inflammatory (COX-2 inhibition)
  - GI irritation and formation of potentially life threatening GI ulcers (COX-1 inhibition)

COX-2 Inhibitors: The Appeal

• COX-2 enzyme located in areas commonly involved in inflammation, but not in stomach

• COX-2 inhibition → anti-inflammatory with lower gastric toxicity

• Examples of COX-2 inhibitors
  – Celecoxib (Celebrex): available in US (Pfizer)
  – Rofecoxib (Vioxx): withdrawn in 2004 (Merck)
  – Valdecoxib (Bextra): withdrawn in 2005 (Pfizer)
COX-2 Inhibitors: Structural Features

- SAR studies show requirement of *cis*-stilbene with 4-methylsulfonyl or sulfonamide for COX-2 specificity

Fig. 2. Origin of different classes of cyclooxygenase 2 (COX-2) inhibitors. Abbreviation: APHS, D-acetyloxyphenylhept-2-ynyl sulfide.

Rofecoxib (Vioxx): Synthesis

Celecoxib (Celebrex): Synthesis

The Vioxx Story: The History at a Glance

• **May 1999**: FDA approves Vioxx

• **Nov 2000**: Vioxx Gastrointestinal Outcomes Research (VIGOR) Study published
  – Showed lower number of GI events but greater number of heart attacks in patients taking Vioxx than naproxen

• **April 2002**: Vioxx label changed in US due to VIGOR data

• **Sept 2004**: Merck withdraws Vioxx after Adenomatous Polyp Prevention of Vioxx (APPROVe) Study
  – Showed Vioxx patients had higher risk of heart attacks after 18 months

The Vioxx Story: The Road to FDA Approval

- **Dec 1994**: Merck opens Investigational New Drug (IND) for osteoarthritis and acute pain

- **Nov 1998**: Merck submits New Drug Application (NDA) for Vioxx
  - Included ~5000 subjects exposed to rofecoxib from 1 day to 86 weeks (12.5 and 25 mg daily for chronic use, 50 mg daily for >6 months)
  - Included two 6 week placebo and ibuprofen-controlled studies
  - No cardiovascular signal observed in original NDA application
The Vioxx Story: The Road to FDA Approval

• **April 1999**: Arthritis Advisory Committee (AAC) meets to consider efficacy and safety of 12.5 to 25 mg dose → recommends approval

• **May 1999**: FDA approves Vioxx for acute pain, dysmenorrhea, and osteoarthritis
The Vioxx Story: The Road to FDA Approval

• Statement of Sandra Kweder, M.D. (Deputy Director of the Office of New Drugs at the Center for Drug Evaluation and Research (CDER), US FDA) before the Senate Committee on Finance:
  – “Vioxx received a six-month priority review because the drug potentially provided a significant therapeutic advantage over existing approved drugs due to fewer gastrointestinal side effects, including bleeding. A product undergoing a priority review is held to the same rigorous standards for safety, efficacy, and quality that FDA expects from all drugs submitted for approval.”
The Vioxx Story: The Next Step

• Statement of Sandra Kweder, M.D.:
  – “In the clinical trials conducted before approval, the risk of gastrointestinal (GI) side effects was determined through the use of endoscopy. At the time that FDA approved Vioxx, the available evidence from these endoscopy studies showed a significantly lower risk of gastrointestinal ulcers, a significant source of serious side effects such as bleeding and death, in comparison to ibuprofen.”
The Vioxx Story: VIGOR Study

- **Jan 1999**: Merck launches Vioxx Gastrointestinal Outcomes Research (VIGOR) Study
  - Compare number of upper GI events in patients with rheumatoid arthritis taking rofecoxib vs. naproxen
  - 8076 patients received either 50 mg of rofecoxib daily or 500 mg of naproxen twice daily
  - “This study was designed to provide longer term clinical outcome data to confirm the shorter term endoscopy findings and to evaluate overall safety.” (Sandra Kweder, M.D.)

- **March 2000**: VIGOR study completed

- **Nov 2000**: VIGOR study published in *NEJM*
VIGOR Study Results: The Good

• Patients treated with rofecoxib experienced significantly less upper GI events

• Rofecoxib and naproxen had similar efficacies against rheumatoid arthritis

VIGOR Study Results: The Good

Figure 1. Cumulative Incidence of the Primary End Point of a Confirmed Upper Gastrointestinal Event among All Randomized Patients.

Bombardier, C. M.D., et. al. NEJM 2000, 343, 1520.
### Table 4. Incidence of Gastrointestinal Events in the Treatment Groups.

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Rofecoxib Group (N=4047)</th>
<th>Naproxen Group (N=4029)</th>
<th>Rofecoxib Group (N=4047)</th>
<th>Naproxen Group (N=4029)</th>
<th>Relative Risk (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed upper gastrointestinal events</td>
<td>56</td>
<td>121</td>
<td>2.1</td>
<td>4.5</td>
<td>0.5 (0.3–0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complicated confirmed upper gastrointestinal events</td>
<td>16</td>
<td>37</td>
<td>0.6</td>
<td>1.4</td>
<td>0.4 (0.2–0.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Confirmed and unconfirmed upper gastrointestinal events†</td>
<td>58</td>
<td>132</td>
<td>2.2</td>
<td>4.9</td>
<td>0.4 (0.3–0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complicated confirmed and unconfirmed upper gastrointestinal events‡</td>
<td>17</td>
<td>42</td>
<td>0.6</td>
<td>1.6</td>
<td>0.4 (0.2–0.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>All episodes of gastrointestinal bleeding</td>
<td>31</td>
<td>82</td>
<td>1.1</td>
<td>3.0</td>
<td>0.4 (0.3–0.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*CI denotes confidence interval.
†The analysis includes 13 events that were reported by investigators but were considered to be unconfirmed by the end-point committee.
‡The analysis includes six events that were reported by investigators but that were considered to be unconfirmed by the end-point committee.
VIGOR Study Results: The Not So Good

• Result: Incidence of myocardial infarction significantly higher in rofecoxib group than naproxen group (0.4% vs. 0.1%)

• Explanation: Naproxen has a coronary protective effect rofecoxib does not have because rofecoxib is a selective COX-2 inhibitor

• “VIGOR did not have a placebo group because to do so would have meant patients with rheumatoid arthritis would have been randomized to receive no pain relief...The study also excluded subjects taking low dose aspirin for cardiovascular (CV) prevention because use of aspirin might have contributed to increased rates of GI bleeding in the study and confound the results. However, the exclusion of patients on low dose aspirin may have influenced CV events in the study, since low dose aspirin has been shown to reduce CV risk.” (Sandra Kweder, M.D.)

Bombardier, C. M.D., et. al. NEJM 2000, 343, 1520.
The Vioxx Story: The Years Post-VIGOR Study

- **Aug 2001**: Study in *JAMA* questions safety of Vioxx and validity of naproxen hypothesis (Mukherjee, D. M.D., et. al. *JAMA* 2001)

- **Sept 2001**: FDA recommends inclusion of balanced info regarding Vioxx safety and de-emphasis of GI safety advantage in Vioxx label

- **Oct 2001**: Label negotiations initiated by FDA

- **April 2002**: Label changes including results of VIGOR study and caution about potential risk for cardiovascular (CV) thrombotic events with Vioxx approved
The Vioxx Story: FDA Warning About VIGOR

• **Sept 2001**: FDA warning letter to Merck
  
  “You have engaged in a promotional campaign for Vioxx that minimizes the potentially serious cardiovascular findings that were observed in the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, and thus, misrepresents the safety profile for Vioxx...You assert that Vioxx does not increase the risk of MIs and that the VIGOR finding is consistent with naproxen’s ability to block platelet aggregation like aspirin. That is a possible explanation, but you fail to disclose that your explanation is hypothetical, has not been demonstrated by substantial evidence, and that there is another reasonable explanation, that Vioxx may have pro-thrombotic properties.”

The Vioxx Story: The Years Post-VIGOR Study

• **2002-2004**: Various epidemiologic studies suggest increased risk for CV events with Vioxx

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**TABLE 1**

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N (TOTAL)</th>
<th>N (ROFECOXIB)*</th>
<th>RELATIVE RISK</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solomon et al⁶</td>
<td>54,475</td>
<td>941</td>
<td>1.40</td>
<td>.005</td>
</tr>
<tr>
<td>Ray et al⁷</td>
<td>378,776</td>
<td>24,132</td>
<td>1.93</td>
<td>.024</td>
</tr>
<tr>
<td>Mamdani et al²⁴</td>
<td>166,964</td>
<td>12,156</td>
<td>1.00</td>
<td>NS</td>
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<td>Mamdani et al²⁵</td>
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<td>&lt; .05</td>
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* Rofecoxib use of 1–30 days (Solomon et al⁶), new use of rofecoxib > 25 mg (Ray et al⁷), any use of rofecoxib (both of the Mamdani et al studies²⁴,²⁵), and current use of rofecoxib > 25 mg (Graham et al⁵).

¹End points were myocardial infarction (Solomon et al⁶, Mamdani et al²⁴), a composite of myocardial infarction and cardiovascular death (Ray et al⁷), admission for congestive heart failure (Mamdani et al²⁵), and a composite of myocardial infarction and sudden cardiac death (Graham et al⁵). Comparator groups were celecoxib users (Solomon et al⁶, Mamdani et al²⁵) and nonusers of nonsteroidal anti-inflammatory drugs (Ray et al⁷, Mamdani et al²⁴, Graham et al⁵).

The Vioxx Story: The Years Post-VIGOR Study

• Testimony of David J. Graham, MD, MPH to US Senate Committee on Finance
  – “I worked with Kaiser Permanente in California to perform a large epidemiologic study....We had planned to present these data at the International Conference on Pharmacoepidemiology, in Bordeaux, France. We concluded that high-dose Vioxx significantly increased the risk of heart attacks and sudden death and that the high doses of the drug should not be prescribed or used by patients. This conclusion triggered an explosive response from the Office of New Drugs, which approved Vioxx in the first place and was responsible for regulating it post-marketing. The response from senior management in my Office, the Office of Drug Safety, was equally stressful. I was pressured to change my conclusions and recommendations, and basically threatened that if I did not change them, I would not be permitted to present the paper at the conference.”
The Vioxx Story: The Years Post-VIGOR Study

- **2002-2004**: Various epidemiologic studies suggest increased risk for CV events with Vioxx.
- **Aug 2004**: FDA approves Vioxx for treatment of juvenile rheumatoid arthritis.

### Table 1: Epidemiologic studies of rofecoxib and cardiovascular risk

<table>
<thead>
<tr>
<th>Study</th>
<th>N (Total)</th>
<th>N (ROFECOXIB)</th>
<th>Relative Risk</th>
<th>P-value</th>
</tr>
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• **Nov 2002**: Merck proposes analysis of CV thrombotic events in three placebo-controlled studies:
  – APPROVe: Does 3 year rofecoxib treatment reduce risk of recurrent sporadic adenomatous colon polyps?
  – VICTOR: Does Vioxx have a maintenance role in colorectal cancer patients after potentially curative therapy?
  – Prostate Cancer Prevention study: Does 6 year rofecoxib treatment influence incidence of developing prostate cancer?
APPROVe Study: The Final Blow

- **Sept 28, 2004**: Merck requests emergency meeting with FDA upper management
  - Merck shares data from APPROVe trial
  - Found that long-term use (>18 months) was associated with an increased risk of cardiovascular events

- **Sept 30, 2004**: Merck publically announced product withdrawal of Vioxx
APPROVe Study: The Published Results

- 2586 patients with history of colorectal adenomas received either 25 mg rofecoxib daily or placebo

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Rofecoxib Group</th>
<th>Placebo Group</th>
<th>Difference in Rate (95% CI)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. at Risk</td>
<td>No. of Events</td>
<td>Rate/100 Patient-yr</td>
<td>No. at Risk</td>
</tr>
<tr>
<td>Confirmed event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1287</td>
<td>46</td>
<td>3059</td>
<td>1.50</td>
</tr>
<tr>
<td>Month 0–18</td>
<td>1287</td>
<td>22</td>
<td>1656</td>
<td>1.33</td>
</tr>
<tr>
<td>Month 19–36</td>
<td>989</td>
<td>24</td>
<td>1403</td>
<td>1.71</td>
</tr>
</tbody>
</table>

| APTC end point |                 |               |                        |             |               |                        |                           |                        |
| Overall       | 1287            | 34            | 3070                   | 1.11        | 1299          | 18            | 3334                   | 0.54                    | 0.57 (0.12 to 1.02)     | 2.06 (1.16 to 3.64)    |
| Month 0–18    | 1287            | 14            | 1658                   | 0.84        | 1299          | 12            | 1769                   | 0.68                    | 0.17 (–0.42 to 0.75)    | 1.25 (0.58 to 2.69)    |
| Month 19–36   | 994             | 20            | 1412                   | 1.42        | 1083          | 6             | 1565                   | 0.38                    | 1.03 (0.34 to 1.73)     | 3.69 (1.43 to 11.24)   |

* CI denotes confidence interval, and APTC Antiplatelet Trialists’ Collaboration.

• Reference made to VIGOR study:
  – “A recent meta-analysis suggested that the magnitude of any cardioprotective effect of naproxen is unlikely to account entirely for these findings”

• Quote from meta-analysis study: (Jüni, P. et. al. Lancet, 2004)
  – “Our findings indicate that rofecoxib should have been withdrawn several years earlier. The reasons why manufacturer and drug licensing authorities did not continuously monitor and summarize the accumulating evidence need to clarified.”

Behind the Scenes: Questionable Procedures

- **Merck 1996-7 clinical trial**: Reported increase in urinary metabolites of prostacyclin but not thromboxane metabolites in healthy volunteers taking rofecoxib
  - Fitzgerald hypothesis: Suppression of prostacyclin but not thromboxane by selective COX-2 inhibitors “might mediate a risk of thrombosis from COX-2 inhibitors in predisposed individuals.”

- But...no intervention studies included in Vioxx’s NDA were designed to evaluate cardiovascular risk

- And...studies did not have standardized procedure to collect and adjudicate cardiovascular outcomes

Behind the Scenes: VIGOR Study

- **Nov 1999**: 79% greater risk of death or serious CV event found in one treatment group → safety board allows study to continue

- **Dec 1999**: Study still shows higher CV events in one group → board recommends analysis plan be developed to examine serious CV events

- Internal memo at Merck from Edward Scolnick, Merck’s chief scientist:
  - “It is a shame but it is a low incidence and it is mechanism based as we worried it was. [Merck employees/consultants] were right about the metabolite meanings, ie, urine [prostacyclin] data.”

VIGOR Study: Questionable Procedures

- No cardiologist on data safety monitoring board
- Near trial end, head of safety board given 2 year consulting contract and discloses family ownership in Merck shares of $70,000 (no potential conflict of interest disclosed previously)
- No standard operating procedure for collecting info on CV event
- Different termination dates for GI and CV event data acquisition (GI events counted 1 month longer), procedure not disclosed
- 3 heart attacks not disclosed in paper occurred in rofecoxib group in month after stopped counting CV events
- Conclusion about protective naproxen effect, yet no accepted evidence for naproxen strong cardioprotective effect

Behind the Scenes: Issues with Publications

- **Dec 2005**: NEJM issues “Expression of Concern” stating “inaccuracies and deletions” in VIGOR manuscript “call into question the integrity of the data” → ask authors to submit correction

  - Stated objective: Access tolerability of rofecoxib compared to naproxen for treatment of osteoarthritis
  - Later concluded ADVANTAGE study was seeding trial developed by Merck marketing division to promote Vioxx when it became available (“marketing framed as science”)

The Vioxx Story: The Legal Fallout

• **Aug 2005**: TX jury finds Merck liable in first Vioxx liability case

• **Jul 2006**: NJ jury rules in favor of Merck in its seventh Vioxx liability case (had won 3 and lost 3 before NJ case)

• **Nov 2007**: Merck says it will pay $4.85 billion to end thousands of Vioxx lawsuits
  – Believed to be largest drug settlement ever

Are All Selective COX-2 Inhibitors Bad?: An E.J. Corey Study

- Purpose: Describe chemical property of rofecoxib that makes it different from other available COX-2 inhibitors
  - Why does rofecoxib use increase cardiovascular risks but not other COX-2 inhibitors?

Conclusion: Rofecoxib ionizes under physiological conditions to anion 5 that readily reacts with O₂ to form the potentially toxic maleic anhydride derivative 6

- Property not shared by two most used COX-2 inhibitors, celecoxib and valdecoxib