Cardiovascular Risk of Celecoxib in 6 Randomized Placebo-controlled Trials: The Cross Trial Safety Analysis

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DISCLOSURES

No Disclosures

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Observational studies and randomized controlled trials have reported increased cardiovascular risk associated with cyclooxygenase-2 (cox-2) inhibitors (coxibs) 1,2,3,4

Strong biologic basis for this risk supported by abundant basic research 5,6,7

Most clinical studies compared coxibs with active comparators in short-term arthritis trials

5McAddam et al. PNAS 1999; 6Fitzgerald NEJM 2001; 7Fitzgerald et al. NEJM 2004
In December 2004, interim results from the Adenoma Prevention with Celecoxib (APC) trial results led to stopping drug in that trial and in 5 other long-term trials comparing celecoxib to placebo:

- The Prevention of Sporadic Adenomatous Polyps (PreSAP) trial
- The Alzheimer’s Disease Anti-inflammatory Prevention Trial (ADAPT)
- The MA-27 Breast Cancer Trial,
- The Celecoxib Diabetic Macular Edema (CDME) trial
- The Celecoxib/Selenium Trial.

FDA hearing resulted in Black Box Warning.

Celecoxib is the only available cox-2 inhibitor in US.

1 Arber et al. NEJM 2006; 2 ADAPT Invest. PLOS 2006
Low Event Rates Lead to Challenges in Risk Assessment with Coxibs

- Low precision of the estimates
- Inability to test observational and RCT data suggesting
  - coxib-associated CV risk may be dose related
  - dose and interval may be important in CV risk.¹
- Inability to assess whether CV risk associated with celecoxib varies by baseline CV risk

¹Solomon et al Circulation 2006
Objective

- To understand more fully the cardiovascular risk profile associated with long-term use of celecoxib
  - NCI commissioned and funded analysis of long-term placebo controlled trials
Selection of Studies

- Randomized, double-blind, placebo-controlled trials
- Planned follow-up of at least 3 years
- Source documentation available for adjudication
- 4 trials + APC and PreSAP fulfilled these criteria:
  - ADAPT
  - MA-27
  - CDME
  - Celecoxib/Selenium Trial
Methodology

- Each study submitted patient-level data:
  - Baseline data
  - Outcomes
  - Adverse events
- A blinded adjudication team identified all potential cardiovascular events from broad list of SAEs and AEs
- Requested source documentation for all relevant events
- All potential cardiovascular events were adjudicated by two reviewers masked to treatment allocation
  - Categorized all deaths
  - Adjudicated all non-fatal events

Endpoint Definitions: Solomon et al. NEJM 2005
The following endpoints were adjudicated:

- Death (cardiovascular or non-cardiovascular)
- Myocardial Infarction
- Stroke
- Hospitalization for heart Failure
- Thromboembolic event
- Other cardiovascular

Primary endpoint:

- CV death, MI, stroke, heart failure or thromboembolic event
Statistical Analysis

- Intention-to-treat

- Time-to-event analyses for each study
  - Calculated incidence of each outcome, rate (per 1000 pt-yrs) by Rx group
  - Cox models and KM curves

- Pooled (meta) analysis:
  - Estimated hazard ratios calculated from the average of the log-hazard ratio for each individual trial weighted by the inverse of its variance
  - Sensitivity of method assessed by standard Mantel-Haenszel pooled odds ratios and Cox models stratified by study.
  - Analyses adjusted for baseline cardiovascular risk

- Pooled analyses assessed overall risk and dosing regimen-related risk
Studies were grouped according to dose regimen:
- 400mg once daily (2 studies)
- 200mg twice daily (3 studies)
- 400mg twice daily (2 studies)

We tested for interaction between dose regimen and celecoxib risk.

We created a 3-category risk score using a modified Framingham Risk model conforming to the availability of data from these studies:
- Low: No known risk factor
- Moderate: One of following, age > 75, hypertension, hyperlipidemia, current smoker, low-dose ASA
- High: Diabetes, prior CV disease, or ≥ 2 risk factors in “moderate” category

We tested for interaction between baseline risk and celecoxib-related risk.
## Placebo-Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Sponsor</th>
<th>Disease being Studied</th>
<th>Celecoxib Dose</th>
<th>Planned follow-up time</th>
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</thead>
<tbody>
<tr>
<td>APC</td>
<td>2035</td>
<td>NCI and Pfizer</td>
<td>Colorectal polyps</td>
<td>Celecoxib 200mg BID, celecoxib 400mg BID, or placebo</td>
<td>3+ Years</td>
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<tr>
<td>PreSAP</td>
<td>1561</td>
<td>Pfizer</td>
<td>Colorectal Polyps</td>
<td>Celecoxib 400mg QD or placebo</td>
<td>3+ Years</td>
</tr>
<tr>
<td>MA27</td>
<td>1635</td>
<td>NCI, NCI Canada, &amp; Pfizer</td>
<td>Breast Cancer Recurrence</td>
<td>celecoxib 400 mg BID or placebo</td>
<td>3+ Years</td>
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<tr>
<td>ADAPT</td>
<td>1809</td>
<td>NIA</td>
<td>Alzheimer’s disease and cognitive decline</td>
<td>Celecoxib 200mg BID or Naproxen sodium 220 mg BID, or placebo</td>
<td>Up to 7 years</td>
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<tr>
<td>CDME</td>
<td>86</td>
<td>NEI</td>
<td>Diabetic Retinopathy</td>
<td>Celecoxib 200mg BID or placebo</td>
<td>3+ Years</td>
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<tr>
<td>Cel/Sel</td>
<td>824</td>
<td>NCI</td>
<td>Colorectal polyps</td>
<td>Celecoxib 400 mg QD or placebo</td>
<td>3-5 Years</td>
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</tbody>
</table>
## Baseline Characteristics (%)

<table>
<thead>
<tr>
<th></th>
<th>ADAPT</th>
<th>APC</th>
<th>CDME</th>
<th>MA27</th>
<th>PreSAP</th>
<th>Cel/Sel</th>
<th>Total</th>
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<tbody>
<tr>
<td># enrolled</td>
<td>1809</td>
<td>2035</td>
<td>86</td>
<td>1635</td>
<td>1561</td>
<td>824</td>
<td>7950</td>
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<td>Pt-Years</td>
<td>3530</td>
<td>6234</td>
<td>101</td>
<td>695</td>
<td>4141</td>
<td>1369</td>
<td>16070</td>
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<td>Age, mean (SD)</td>
<td>75 ± 4</td>
<td>59 ± 10</td>
<td>59 ± 9</td>
<td>64 ± 9</td>
<td>60 ± 10</td>
<td>63 ± 9</td>
<td>64 ± 10</td>
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<tr>
<td>Male</td>
<td>54</td>
<td>68</td>
<td>62</td>
<td>0</td>
<td>66</td>
<td>68</td>
<td>50</td>
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<td>White race</td>
<td>97</td>
<td>92</td>
<td>67</td>
<td>94</td>
<td>89</td>
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<td>Diabetes</td>
<td>7.4</td>
<td>9.5</td>
<td>100</td>
<td>6.1</td>
<td>10</td>
<td>7.5</td>
<td>9.2</td>
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<td>HTN or med</td>
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<td>41</td>
<td>62</td>
<td>34</td>
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<td>36</td>
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<td>Hyperlipidemia or med</td>
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<td>38</td>
<td>55</td>
<td>17</td>
<td>17</td>
<td>33</td>
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<td>Current smoker</td>
<td>3</td>
<td>17</td>
<td>?</td>
<td>?</td>
<td>24</td>
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<td>14</td>
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<td>Low-dose ASA use</td>
<td>50</td>
<td>31</td>
<td>62</td>
<td>14</td>
<td>17</td>
<td>45</td>
<td>31</td>
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<td>Prior CV event</td>
<td>13</td>
<td>14</td>
<td>1.2</td>
<td>7</td>
<td>13</td>
<td>14</td>
<td>12</td>
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<tr>
<td>Low CV risk</td>
<td>14</td>
<td>24</td>
<td>0</td>
<td>50</td>
<td>32</td>
<td>19</td>
<td>28</td>
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<td>Moderate CV risk</td>
<td>26</td>
<td>29</td>
<td>0</td>
<td>23</td>
<td>31</td>
<td>31</td>
<td>27</td>
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<tr>
<td>High CV risk</td>
<td>59</td>
<td>47</td>
<td>100</td>
<td>27</td>
<td>37</td>
<td>51</td>
<td>45</td>
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<td>Treatment</td>
<td>Placebo</td>
<td>Celecoxib</td>
<td>Hazard Ratio</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>-----------</td>
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<td></td>
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<tr>
<td>PreSAP</td>
<td>12/628 (7.2)</td>
<td>23/933 (9.4)</td>
<td>1.3 (0.6, 2.5)</td>
<td></td>
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<td></td>
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<tr>
<td>Cel/Sel</td>
<td>8/410 (11.8)</td>
<td>7/414 (10.3)</td>
<td>0.9 (0.3, 2.4)</td>
<td></td>
<td></td>
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<tr>
<td><strong>400mg QD Pooled</strong></td>
<td><strong>20/1038 (8.6)</strong></td>
<td><strong>30/1347 (9.6)</strong></td>
<td><strong>1.1 (0.6, 2.0)</strong></td>
<td></td>
<td></td>
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<tr>
<td>200mg BID</td>
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<tr>
<td>ADAPT</td>
<td>18/1083 (8.6)</td>
<td>18/725 (12.8)</td>
<td>1.5 (0.8, 2.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APC</td>
<td>8/679 (3.9)</td>
<td>20/685 (9.7)</td>
<td>2.5 (1.1, 5.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>200mg BID Pooled</strong></td>
<td><strong>29/1809 (6.9)</strong></td>
<td><strong>38/1450 (10.8)</strong></td>
<td><strong>1.8 (1.1, 3.1)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400mg BID</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APC</td>
<td>8/679 (3.9)</td>
<td>27/671 (13.4)</td>
<td>3.6 (1.6, 8.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA-27</td>
<td>3/817 (8.7)</td>
<td>6/818 (17.2)</td>
<td>1.8 (0.4, 7.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>400mg BID pooled</strong></td>
<td><strong>11/1496 (4.6)</strong></td>
<td><strong>33/1489 (13.9)</strong></td>
<td><strong>3.1 (1.5, 6.1)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CDME Not included in this table because of extremely low event rates*
Hazard Associated with Celecoxib at Various Doses
Stratified by Study and low-dose ASA use and Adjusted for Baseline CV Risk

Celecoxib Regimen

- 400 mg bid
- 200 mg bid
- 400 mg qd
- Overall

Hazard Ratio
CV Death, MI, Stroke, HF or thrombo-embolic event

- Overall: 1.6 (1.1, 2.3)
- 400 mg qd: 1.1 (0.6, 2.0)
- 200 mg bid: 1.8 (1.1, 3.1)
- 400 mg bid: 3.1 (1.5, 6.1)

Dose-regimen effect
P = 0.0005

Solomon et al. Circulation 2008
## Composite Outcomes (Hazard ratio and 95% CI)

<table>
<thead>
<tr>
<th></th>
<th>400mg QD</th>
<th>200mg BID</th>
<th>400mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death</td>
<td>0.5 (0.2, 1.7)</td>
<td>1.8 (0.5, 6.2)</td>
<td>6.5 (0.8, 54)</td>
</tr>
<tr>
<td>+ MI</td>
<td>1.0 (0.5, 2.1)</td>
<td>2.1 (1.0, 4.1)</td>
<td>3.4 (1.2, 9.6)</td>
</tr>
<tr>
<td>+ Stroke</td>
<td>1.0 (0.5, 1.9)</td>
<td>1.6 (0.9, 3.0)</td>
<td>2.9 (1.3, 6.6)</td>
</tr>
<tr>
<td>+ HF</td>
<td>1.1 (0.6, 2.1)</td>
<td>1.7 (1.0, 3.1)</td>
<td>2.7 (1.3, 5.6)</td>
</tr>
<tr>
<td>+ Embolic event</td>
<td>1.1 (0.6, 2.0)</td>
<td>1.8 (1.1, 3.1)</td>
<td>3.1 (1.5, 6.1)</td>
</tr>
<tr>
<td>Any CV Event</td>
<td>1.3 (0.9, 1.9)</td>
<td>1.4 (1.0, 1.8)</td>
<td>1.6 (1.1, 2.3)</td>
</tr>
</tbody>
</table>

Stratified by study and baseline aspirin use and adjusted for baseline risk

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Celecoxib Regimen and Baseline Cardiovascular Risk

Baseline Risk – Dose Regimen Interaction p = 0.034

<table>
<thead>
<tr>
<th>Regimen</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>3.5 (1.9, 6.4)</td>
</tr>
<tr>
<td>400 bid</td>
<td>2.3 (1.5, 3.4)</td>
</tr>
<tr>
<td>200 bid</td>
<td>1.5 (1.2, 1.9)</td>
</tr>
<tr>
<td>400 qd</td>
<td>1.7 (0.9, 3.2)</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>1.4 (1.0, 2.2)</td>
</tr>
<tr>
<td>400 bid</td>
<td>1.2 (1.0, 1.5)</td>
</tr>
<tr>
<td>200 bid</td>
<td>0.9 (0.3, 2.6)</td>
</tr>
<tr>
<td>400 qd</td>
<td>0.9 (0.4, 1.9)</td>
</tr>
<tr>
<td>Low Risk</td>
<td>1.0 (0.7, 1.4)</td>
</tr>
<tr>
<td>400 bid</td>
<td></td>
</tr>
<tr>
<td>200 bid</td>
<td></td>
</tr>
<tr>
<td>400 qd</td>
<td></td>
</tr>
</tbody>
</table>

Hazard Ratio
CV Death, MI, Stroke, HF or Thromboembolic Event

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Prespecified Subgroups

- Male
- Female
- White
- Non-White
- Low Dose ASA
- No Low Dose ASA
- CV Event History
- No CV Event
- Hypertension
- No Hypertension
- Hyperlipidemia
- No Hyperlipidemia
- Diabetes
- No Diabetes
- Current Smoker
- Non-Smoker

Hazard Ratio

P-Interaction

- p = 0.37
- p = 0.64
- p = 0.54
- p = 0.89
- p = 0.17
- p = 0.09
- p = 0.40
- p = 0.57

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Limitations and Caveats

- None of the trials included in this analysis was designed or powered with the intent of assessing cardiovascular risk.

- Doses tested higher than those typically used in osteoarthritis patients.
  - recommended doses in rheumatoid arthritis, acute pain and dysmenorrhea, FAP.
  - These data provide the strongest evidence of a dose-related risk

- While our data support differential risk based on dosing interval, wide confidence intervals suggest we cannot rigorously exclude hazard at the 400mg once daily dose.

- These data do not address the cardiovascular risk of doses lower than those tested or of other non-selective NSAIDs.
Conclusions (1)

• A pooled analysis of six randomized trials comparing celecoxib to placebo, with over 16,000 patient-years of follow-up, shows an overall increase in cardiovascular risk, with evidence for differences in risk based on the dose and dose-regimen of celecoxib.

• The data showed evidence of an interaction between baseline cardiovascular risk and the effect of celecoxib, suggesting that patients at highest baseline risk had an increased relative risk for celecoxib-related adverse cardiovascular events.
Conclusions (2)

- Our observation that baseline risk influences the cardiovascular risk associated with celecoxib may provide a measure of comfort in prescribing the drug in patients with very low baseline risk, and would argue for more caution in prescribing the drug in patients with higher baseline risk.

- Since celecoxib remains the only coxib available in the United States, and is the most commonly used coxib worldwide, these data should help guide rational clinical decisions regarding celecoxib use.