COX 2 Inhibitors and Cardiovascular risk

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CME Meeting 18/4/05
Background

- **NSAIDs**
  - Non specific COX inhibitor
  - Analgesia
  - Use limited by GI toxicity

- **2 isoenzymes**
  - **COX-1**
    - Constitutive
    - Involved in platelet activation, GI protection and renal function
  - **COX-2**
    - Inducible and produced in response to tissue damage and inflammatory response to injury
COX-2 Inhibitors

- Parecoxib
- Celecoxib
- Meloxicam
- Rofecoxib

Widespread use for analgesia

BUT

- Rofecoxib withdrawn because of increased risk cardiovascular events
Cardiovascular risk

- Proposed mechanisms
  - Prothrombotic state
    - Selective inhibition of COX-2 isoenzyme leads to imbalance between Thromboxane A\(_2\) and Prostacyclin levels
  - Worsening Hypertension
    - Independent cardiovascular risk factor
    - Due to renal effects of COX-2 inhibitors
  - COX-2 expressed in atherosclerotic lesions
    - Role uncertain
Efficacy and Safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery.


Multicentre, prospective, placebo-controlled, double-blind, randomised

462 patients undergoing CABGS

14 days treatment, 30 day follow up

Randomised to 2 groups (2:1 ratio)
  - Parecoxib (40mg bd), valdecoxib (40mg bd)
  - Placebo

Endpoints
  - Efficacy – pain scores, amount of morphine used
  - Safety – Adverse events, serious adverse events
Inclusion Criteria

- <77 years of age
- BMI < 40kg/m²
- Weight > 55kg
- LVEF > 35%
- NYHA Class I-III
- Well controlled HT
- Lack of psychological illness
Exclusion Criteria

- Emergency Surgery
- Recent MI (<48 hrs)
- IDDM or uncontrolled diabetes
- Altered LFTs
- Renal Impairment
- Coagulopathy
- Recent TIA/stroke (6 months)
- History of substance abuse
- PUD
- Allergy to drugs

Intra-operatively

- Complicated Course
- Bypass time > 3 hours
- Insertion of intra-aortic balloon pump

Post-operative

- 3+ inotropic infusions
- Arrhythmia
- New q-wave MI
- Chest tube output > 500mL
- Cardiac index < 1.5L/min
- T°C < 36 or > 38
- Hb < 9 g/dL
- Cr > 0.106 mmol/L
**Anaesthesia**

- Induction
  - Fentanyl and/or midazolam, Isoflurane, Muscle relaxant
- Maintenance
  - Isoflurane and/or propofol, Fentanyl, Midazolam, Pancuronium

**ICU**

- Sedation with propofol, morphine or midazolam
- Analgesia as needed
- Aspirin 80-325mg
- Extubation within 15 hours

**Study drug for 14 days total**
Results - Efficacy

- Parecoxib/valdecoxib – superior pain relief with reduction in morphine use
  - P=0.015 (1\textsuperscript{st} 24 hours)
  - P=0.020 (24-48 hours)
  - P=0.023 (72-96 hours)
Results – Safety

Adverse events

- Similar numbers of adverse events in control and treatment groups 89.4% vs 89.1%, p>0.95

Serious adverse events

- 9.9% control vs 19% treatment, p=0.015
- 4 deaths in treatment group vs none in control, p=0.309
- Serious wound infection, 3.2% vs 0%, p=0.035
- Myocardial infarction, 1.6% vs 0.7%, p=0.669
- Cerebrovascular complications, 2.9% vs 0.7% p=0.177
- Renal events, 1.9% vs 0%, p=0.017
Limitations

- Marginally powered to detect 2-fold difference in SAEs (68%)
- Not powered to detect differences in specific SAEs
- Single dosage regime and duration assessed.

Conclusions

- Superior pain relief over PCA
- Higher incidence serious side effects
- Needs further evaluation in large scale trial
Complications of Cox-2 Inhibitors parecoxib and valdecoxisib after cardiac surgery


Prospective, randomised, double-blind placebo-controlled study
Sponsor-initiated
1671 patients undergoing CABGS
10 days treatment, 30 days follow up
Randomised to 3 groups
- Parecoxib 40mg then 20mg bd/Valdecoxib 20mg bd
- Placebo/Valdecoxib 20mg bd
- Placebo

Endpoints
- Frequency of predefined adverse events
  - Cardiovascular events, renal failure/dysfunction, GI ulceration, wound healing complications
Inclusion criteria

- Elective primary CABGS
- Age 18-80
- NYHA I-III
- LVEF > 35%
- BMI < 40 kg/m$^2$
- Weight > 55kg
Exclusion Criteria
- Recent MI (< 7 days)
- IDDM or uncontrolled diabetes
- Coagulopathy
- Recent TIA/stroke (<3 mths)
- Recent DVT/PE (< 3 mths)
- PUD (< 2 months)
- Receipt of contrast
- CABGS without bypass
- Concommitant valvular or vascular surgery
- Bypass time > 3.5 hrs
- Insertion of intra-aortic balloon pump
- 2+ inotropic infusions
- Arrhythmia
- New q-wave MI
- Chest tube output > 500mL
- Cardiac index < 1.5L/min
- New neurological deficit
- Hb < 8 g/dL
- Cr > 0.159 mmol/L
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>67.1±6.6</td>
<td>67.6±9.1</td>
<td>63.0±9.1</td>
</tr>
<tr>
<td>Age ≥55 yr — no. (%)</td>
<td>229 (39.1%)</td>
<td>206 (36.1%)</td>
<td>223 (41.1%)</td>
</tr>
<tr>
<td>Male sex / n. (%)</td>
<td>477 (81.7%)</td>
<td>476 (86.2%)</td>
<td>473 (85.6%)</td>
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<tr>
<td>Race or ethnic group — no. (%)</td>
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<tr>
<td>White</td>
<td>514 (91.8%)</td>
<td>521 (93.3%)</td>
<td>524 (94.4%)</td>
</tr>
<tr>
<td>Black</td>
<td>14 (2.5%)</td>
<td>10 (1.8%)</td>
<td>6 (1.1%)</td>
</tr>
<tr>
<td>Asian</td>
<td>24 (4.3%)</td>
<td>15 (2.7%)</td>
<td>11 (2.0%)</td>
</tr>
<tr>
<td>Not listed</td>
<td>3 (0.5%)</td>
<td>10 (1.8%)</td>
<td>6 (1.1%)</td>
</tr>
<tr>
<td>Height — cm</td>
<td>172.0±8.3</td>
<td>173.6±9.3</td>
<td>172.2±8.7</td>
</tr>
<tr>
<td>Weight — kg</td>
<td>84.8±14.1</td>
<td>84.3±14.9</td>
<td>84.4±14.6</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>28.3±5.9</td>
<td>28.7±6.0</td>
<td>28.4±4.0</td>
</tr>
<tr>
<td>Body-mass index ≥30 — no. (%)</td>
<td>154 (29.3%)</td>
<td>184 (33.1%)</td>
<td>167 (30.1%)</td>
</tr>
<tr>
<td>Medical history — n. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>487 (87.0%)</td>
<td>483 (86.3%)</td>
<td>491 (88.3%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>406 (72.4%)</td>
<td>422 (75.2%)</td>
<td>411 (74.1%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>43 (7.7%)</td>
<td>47 (7.6%)</td>
<td>32 (5.8%)</td>
</tr>
<tr>
<td>Coronary artery atherosclerosis</td>
<td>317 (52.3%)</td>
<td>313 (51.5%)</td>
<td>314 (55.3%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>221 (39.5%)</td>
<td>248 (44.2%)</td>
<td>241 (42.3%)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>17 (3.0%)</td>
<td>24 (4.3%)</td>
<td>20 (3.6%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>418 (74.0%)</td>
<td>423 (76.1%)</td>
<td>438 (78.6%)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>47 (8.4%)</td>
<td>46 (8.3%)</td>
<td>49 (8.8%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>20 (3.5%)</td>
<td>21 (3.8%)</td>
<td>18 (3.2%)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>11 (2.0%)</td>
<td>10 (1.8%)</td>
<td>12 (2.2%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>138 (24.6%)</td>
<td>137 (24.2%)</td>
<td>169 (28.8%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>17 (3.0%)</td>
<td>27 (4.9%)</td>
<td>9 (1.6%)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD.
† Patients chose one of these four options.
<table>
<thead>
<tr>
<th>Table 3: Incidence of and Risk Ratios for Predefined Adverse Events and Death among Patients Who Received the Assigned Treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Events</strong></td>
</tr>
<tr>
<td><strong>Risk Ratio</strong></td>
</tr>
<tr>
<td><strong>Death</strong></td>
</tr>
<tr>
<td><strong>Surgical wound events</strong></td>
</tr>
<tr>
<td><strong>Superficial incisional SSI</strong></td>
</tr>
<tr>
<td><strong>Deep incisional SSI</strong></td>
</tr>
<tr>
<td><strong>Organ or space SSI</strong></td>
</tr>
<tr>
<td><strong>Wound-healing complications</strong></td>
</tr>
<tr>
<td><strong>Death</strong></td>
</tr>
</tbody>
</table>

*Some patients had multiple counts for an event. CDX denotes confidence interval, and SSI surgical site infection.
1. P<0.05 for the comparison with the placebo group.
2. P<0.05 for the comparison with the flurazepam group.
3. Benelium or hyperkalemia was the only type of renal event that occurred.
4. Serum or standard view was documented by means of retroscopy.
- Kaplan-Meier Estimates of the time to a cardiovascular event
Conclusions

- Short term COX-2 inhibition is associated with significant risk of thromboembolic events in patients at high risk for such events.
Celecoxib and cardiovascular risk

- Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention.

Scott D. Solomon, M.D., John J.V. McMurray, M.D., Marc A. Pfeffer, M.D., Ph.D., Janet Wittes, Ph.D., Robert Fowler, M.S., Peter Finn, M.D., William F. Anderson, M.D., M.P.H., Ann Zauber, Ph.D., Ernest Hawk, M.D., M.P.H., Monica Bertagnolli, M.D., for the Adenoma Prevention with Celecoxib (APC) Study Investigators

Celecoxib and cardiovascular risk

- Multicentre, prospective double-blind randomised placebo-controlled
- To evaluate the efficacy of celecoxib for the prevention of adenomatous polyps
- 2035 patients
- 2.8 to 3.1 years follow up
- Ages 32 to 88 with history of colonic adenoma
Celecoxib and cardiovascular risk

- Randomised to 3 groups
  - Placebo
  - Celecoxib 200mg bd
  - Celecoxib 400mg bd
- Adverse events classified as cardiovascular and non-cardiovascular
- Cardiovascular events categorized in blinded fashion according to pre-specified scheme
- Analysis
  - Intention to treat
  - Cox models to estimate hazard ratios
# Celecoxib and cardiovascular risk

## Table 1. Baseline Characteristics of the Patients.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N=679)</th>
<th>Celecoxib, 200 mg Twice Daily (N=685)</th>
<th>Celecoxib, 400 mg Twice Daily (N=671)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>59.7±9.7</td>
<td>59.7±9.4</td>
<td>59.9±9.4</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>473 (69.7)</td>
<td>460 (67.2)</td>
<td>454 (67.7)</td>
</tr>
<tr>
<td>History of cardiovascular events — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>70 (4.3)</td>
<td>77 (3.2)</td>
<td>31 (4.6)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>14 (2.1)</td>
<td>20 (2.9)</td>
<td>13 (1.9)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>14 (2.1)</td>
<td>6 (0.9)</td>
<td>11 (1.6)</td>
</tr>
<tr>
<td>Angina</td>
<td>51 (7.5)</td>
<td>50 (7.3)</td>
<td>42 (6.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>277 (40.8)</td>
<td>287 (41.9)</td>
<td>260 (38.7)</td>
</tr>
<tr>
<td>Diabetes — no. (%)†</td>
<td>61 (9.0)</td>
<td>66 (9.6)</td>
<td>64 (9.5)</td>
</tr>
<tr>
<td>Current smoker — no. (%)</td>
<td>122 (18.0)</td>
<td>119 (17.4)</td>
<td>96 (14.3)</td>
</tr>
<tr>
<td>Aspirin use — no. (%)</td>
<td>213 (31.4)</td>
<td>201 (29.3)</td>
<td>200 (29.8)</td>
</tr>
<tr>
<td>Use of lipid-lowering drug — no. (%)</td>
<td>184 (27.1)</td>
<td>188 (27.4)</td>
<td>191 (28.5)</td>
</tr>
</tbody>
</table>

* Plus—minus values are means ±SD. There were no significant differences among the groups.

† Data were missing for one patient in the placebo group.
Celecoxib and cardiovascular risk

<table>
<thead>
<tr>
<th>End Point*</th>
<th>Placebo (N=679)</th>
<th>Celecoxib, 200 mg Twice Daily (N=685)</th>
<th>Celecoxib, 400 mg Twice Daily (N=671)</th>
<th>Both Celecoxib Groups (N=1356)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes</td>
<td>1 (0.1)</td>
<td>3 (0.4)</td>
<td>6 (0.9)</td>
<td>9 (0.7)</td>
</tr>
<tr>
<td>Death from cardiovascular causes or non-fatal MI</td>
<td>4 (0.6)</td>
<td>12 (1.8)</td>
<td>15 (2.2)</td>
<td>27 (2.0)</td>
</tr>
<tr>
<td>Death from cardiovascular causes, non-fatal MI, or stroke</td>
<td>6 (0.9)</td>
<td>15 (2.2)</td>
<td>30 (4.5)</td>
<td>35 (2.6)</td>
</tr>
<tr>
<td>Death from cardiovascular causes, non-fatal MI, stroke, or heart failure</td>
<td>7 (1.0)</td>
<td>16 (2.3)</td>
<td>23 (3.4)</td>
<td>39 (2.9)</td>
</tr>
<tr>
<td>Death from cardiovascular causes, non-fatal MI, stroke, heart failure, or angina</td>
<td>11 (1.6)</td>
<td>18 (2.6)</td>
<td>25 (3.7)</td>
<td>43 (3.2)</td>
</tr>
<tr>
<td>Death from cardiovascular causes, non-fatal MI, stroke, heart failure, or angina or need for a cardiovascular procedure</td>
<td>17 (2.5)</td>
<td>31 (4.6)</td>
<td>57 (8.1)</td>
<td>57 (4.2)</td>
</tr>
</tbody>
</table>

Hazard ratio (95% confidence interval):

- Death from cardiovascular causes: 3.0 (0.8-10.4) to 4.3 (0.6-35.4)
- Death from cardiovascular causes or non-fatal MI: 3.0 (1.0-9.3) to 3.9 (1.3-11.3) to 3.4 (1.2-9.7)
- Death from cardiovascular causes, non-fatal MI, or stroke: 3.3 (1.0-6.3) to 5.0 (1.3-7.0)
- Death from cardiovascular causes, non-fatal MI, stroke, heart failure, or angina: 2.3 (0.9-5.5) to 3.4 (1.4-7.8) to 2.8 (1.3-6.3)

* MI denotes myocardial infarction.
### Celecoxib and Cardiovascular Risk

#### Table 3. Incidence of Individual Cardiovascular and Fatal Events.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo (N=679)</th>
<th>Celecoxib, 200 mg Twice Daily (N=685)</th>
<th>Celecoxib, 400 mg Twice Daily (N=681)</th>
<th>Both Celecoxib Groups (N=1356)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause</td>
<td>6 (0.9%)</td>
<td>5 (0.9%)</td>
<td>9 (1.3%)</td>
<td>15 (1.1%)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>1 (0.1%)</td>
<td>3 (0.4%)</td>
<td>6 (0.9%)</td>
<td>9 (0.7%)</td>
</tr>
<tr>
<td>Death from noncardiovascular causes</td>
<td>3 (0.7%)</td>
<td>3 (0.4%)</td>
<td>3 (0.4%)</td>
<td>6 (0.4%)</td>
</tr>
<tr>
<td>Nonfatal cardiovascular events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3 (0.4%)</td>
<td>9 (1.3%)</td>
<td>9 (1.3%)</td>
<td>18 (1.3%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (0.4%)</td>
<td>3 (0.4%)</td>
<td>3 (0.7%)</td>
<td>8 (0.6%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2 (0.3%)</td>
<td>1 (0.1%)</td>
<td>4 (0.6%)</td>
<td>5 (0.4%)</td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>1 (0.1%)</td>
<td>3 (0.4%)</td>
<td>4 (0.6%)</td>
<td>7 (0.1%)</td>
</tr>
<tr>
<td>Resuscitation after sudden cardiac arrest</td>
<td>0</td>
<td>0</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>5 (0.7%)</td>
<td>4 (0.6%)</td>
<td>2 (0.3%)</td>
<td>6 (0.4%)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>9 (1.3%)</td>
<td>4 (0.6%)</td>
<td>7 (1.0%)</td>
<td>11 (0.8%)</td>
</tr>
<tr>
<td>Cardiovascular procedure</td>
<td>7 (1.0%)</td>
<td>9 (1.3%)</td>
<td>6 (0.9%)</td>
<td>15 (1.1%)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (1.3%)</td>
<td>11 (1.6%)</td>
<td>14 (2.1%)</td>
<td>25 (1.8%)</td>
</tr>
</tbody>
</table>
Celecoxib and cardiovascular risk

Kaplan-Meier Estimates of the risk of the composite end point of death from cardiovascular causes, myocardial infarction, stroke or heart failure among patients who received celecoxib (200mg twice daily or 400mg twice daily) or placebo.
Celecoxib and cardiovascular risk

**Conclusion**

- Celecoxib use was associated with dose-related increase in the composite end-point of death from cardiovascular causes.
- Based on small number of events
- Trial not designed or statistically powered to detect cardiovascular risk
Conclusion

- Risk of cardiovascular events increased
  - Parecoxib/valdecoxib in high risk patients
  - Celecoxib
- Most likely a class effect