### Additional file 2: Summary of evidence of cardiovascular events with coxibs

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Population</th>
<th>Main outcomes</th>
<th>Statistical outcome</th>
<th>Exposure</th>
<th>Duration, patient years of exposure, patient years per patient</th>
<th>Mortality</th>
<th>APTC endpoint (fatal and non-fatal MI and stroke, plus cardiovascular death)</th>
<th>MI</th>
<th>Non-fatal MI</th>
<th>Stroke</th>
<th>Non-fatal Stroke</th>
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</thead>
<tbody>
<tr>
<td><strong>Large randomised trials</strong></td>
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<tr>
<td>Bombardier et al. N Engl J Med 2000 343: 1520-1528</td>
<td>Randomised trial powered for PUB outcome, comparing 50 mg rofecoxib with 1000 mg naproxen daily</td>
<td>8,076 patients with RA, at least 50 years</td>
<td></td>
<td>Significant increased risk of MI with rofecoxib</td>
<td>0.067/100 py (0.5%)</td>
<td>0.03/100 py (0.4%)</td>
<td>0.013/100 py (0.1%)</td>
<td>0.27/100 py (0.2%)</td>
<td>N 0.27/100 py (0.2%)</td>
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<tr>
<td>Silverstein et al. JAMA 2000 284: 1247-1259</td>
<td>Randomised trial powered for PUB outcome, comparing 800 mg celecoxib with 2400 mg ibuprofen and 1000 mg diclofenac daily</td>
<td>8,959 patients with OA or RA, a/18 years</td>
<td></td>
<td>No significant difference</td>
<td>Duration 6 months</td>
<td>N 1348 py</td>
<td>C 0.5/100 py (110/3687)</td>
<td>N 0.5/100 py (11/3981)</td>
<td>N 0.5/100 py (10/13681)</td>
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<tr>
<td>Farkouh et al. Lancet 2004 364: 675-684</td>
<td>Randomised trial powered for PUB outcome, comparing 2400 mg lumiracoxib with 2400 mg ibuprofen and 1000 mg diclofenac daily</td>
<td>18,325 patients with OA, a/18 years</td>
<td></td>
<td>No significant difference</td>
<td>52 weeks</td>
<td>L 23/9156 (0.25%)</td>
<td>L 23/9156 (0.25%)</td>
<td>L 18/9156 (0.20%)</td>
<td>L 24/9156 (0.25%)</td>
<td>L 20/9156 (0.22%)</td>
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<tr>
<td>Cannon et al. Lancet 2006 online publication Nov 13: DOI:10.1016/S0140-6756(06)66856-9</td>
<td>Prespecified pooled analysis of three randomised trials powered for cardiovascular outcomes comparing etoricoxib 60 mg or 90 mg with diclofenac 150 mg daily</td>
<td>34,701 patients with OA or RA followed for an average of 18 months and &gt;50,000 patient years of observation</td>
<td></td>
<td>No significant difference</td>
<td>Median duration 19 months</td>
<td>L 23/25346 (0.91%)</td>
<td>N 17/9169 (0.19%)</td>
<td>L 18/9169 (0.15%)</td>
<td>N 23/9169 (0.24%)</td>
<td>N 20/9169 (0.19%)</td>
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</tbody>
</table>

**Meta-analyses of randomised trials**

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<tr>
<td>MacIntyre et al. Clin Ther 2005 27: 1156-1214</td>
<td>Meta-analysis of all lumiracoxib studies in arthritis longer than 1 week</td>
<td>22 RCTs in arthritis with 34,686 patients, 22,781 in trials of one year. Mean age 62 years, over 50% hypertension at baseline, 6% diabetess</td>
<td></td>
<td>No significant differences by type of comparator, duration, prospective adjudication, or dose of lumiracoxib</td>
<td>0.19 pyt placebo trials</td>
<td>L 1.1/100 py (15/1111)</td>
<td>L 1.3/100 py (17/7462)</td>
<td>L 0.45/100 py (8/7011)</td>
<td>L 0.30/100 py (4/7011)</td>
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<tr>
<td>Simon et al. Arthritis Rheum 2005 52: 5408</td>
<td>Meta-analysis of all celecoxib studies of 2 weeks to 3 years</td>
<td>41 RCTs, mainly in arthritis but including AS, back pain, and Alzheimer's disease 44,308 patients, 24,993 on celecoxib, 4,057 on placebo, 13,990 on NSAIDs</td>
<td></td>
<td>No significant difference by type of comparator, duration, or with celecoxib compared with NSAIDs</td>
<td>Placebo comparator 0.168 py (0.14 pyt) NSAID comparator 0.651 py (0.29 pyt)</td>
<td>P 1.1/100 py (6/4025)</td>
<td>C 0.87/100 py (11/7462)</td>
<td>C 0.68/100 py (4/4025)</td>
<td>P 0.1/100 py (6/4025)</td>
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<tr>
<td>White et al. Am J Ther 2004 11: 244-250</td>
<td>Meta-analysis of all valdecoxib studies of at least 4 weeks</td>
<td>RCTs for arthritis, with 7934 patients 4531 on valdecoxib, 1142 on placebo. 2001 on NSAIDs Mean age about 70 years, with 45% history of CV disease</td>
<td></td>
<td>No significant difference by dose, or by duration</td>
<td>Placebo 181 py (0.14 pyt)</td>
<td>P 0.001/100 py (0.01)</td>
<td>C 0.25/100 py (20/4025)</td>
<td>P 0.01/100 py (6/4025)</td>
<td>V 0.43/100 py (8/4025)</td>
<td>V 0.21/100 py (4/1851)</td>
<td>N 0.45/100 py (3/2821)</td>
<td>V 0.49/100 py (1/1851)</td>
</tr>
</tbody>
</table>

**Events per 100 py, number of events, or percentage**

- **Cardiovascular death**
  - Placebo: 0.27/100 py (7/4531)
  - Celecoxib: 0.87/100 py (11/7462)
  - NSAID: 0.68/100 py (4/4025)

- **Serious CV thrombotic event**
  - Placebo: 0.30/100 py (9/4531)
  - Celecoxib: 0.87/100 py (11/7462)
  - NSAID: 0.68/100 py (4/4025)

- **Non-fatal MI**
  - Placebo: 1.27/100 py (17/7462)
  - Celecoxib: 1.8/100 py (23/7462)
  - NSAID: 0.82/100 py (55/10469)

- **Non-fatal stroke**
  - Placebo: 0.51/100 py (30/19773)
  - Celecoxib: 1.0/100 py (57/19773)
  - NSAID: 0.92/100 py (72/12090)

- **Non-fatal MI and stroke**
  - Placebo: 1.3/100 py (17/7462)
  - Celecoxib: 1.8/100 py (23/7462)
  - NSAID: 0.82/100 py (55/10469)

- **Non-fatal MI or stroke**
  - Placebo: 2.6/100 py (37/19773)
  - Celecoxib: 3.0/100 py (33/11046)
  - NSAID: 2.5/100 py (30/12090)

- **Serious CV death**
  - Placebo: 0.47/100 py (1/2261)
  - Celecoxib: 0.9/100 py (5/5651)
  - NSAID: 0.5/100 py (3/614)

- **Total major CV events**
  - Placebo: 2.9/100 py (41/19773)
  - Celecoxib: 3.6/100 py (39/11046)
  - NSAID: 2.5/100 py (30/12090)
Meta-analysis of studies of other NSAIDs or placebo trials of at least 4 weeks

**Large observational studies**

  - Users of NSAID, coxib, or non-users. Total population about 167,000
  - Users of coxib and NSAIDs were more likely to have had a hospital admission in the past year, use more drugs (ACEI, aspirin, hypoglycaemic, COX2, diuretics, statins, lipid lowering drugs, and nitro) and have lower income status

  - Users of NSAID, coxib, or non-users. Total population about 378,000
  - Users of coxib and NSAIDs were more likely to have had a major event, with treatment in the last year, be taking a CV drug, or have more prescriptions

  - Patients predominantly >40 years

**Meta-analysis of studies of \( R = \) rofecoxib; \( C = \) celecoxib; \( E = \) etoricoxib; \( V = \) valdecoxib; \( L = \) lumiracoxib; \( N = \) NSAID; \( P = \) placebo; Ibu = ibuprofen; Nap = naproxen

- **Kearney et al. BMJ 2006 332: 1302–1308**

**Meta-analysis of all coxibs vs NSAID or placebo trials of at least 4 weeks

- **Kearney et al. BMJ 2006 332: 1302–1308**

- **Curtis et al. Arthritis Rheum 2003 48(suppl 9): 1600**

- **Konstant et al. Circulation 2001 104: 2280–2288**

**Meta-analysis of etoricoxib studies of at least 4 weeks


**Meta-analysis of rofecoxib studies of at least four weeks


- **Kearney et al. BMJ 2006 332: 1302–1308**

**Meta-analysis of etoricoxib studies of at least 4 weeks

- **Kearney et al. BMJ 2006 332: 1302–1308**