The PRECISION Trial

Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen

Steven E. Nissen MD MACC

Disclosure

Study Sponsor: Pfizer
Consulting: Many pharmaceutical companies

Companies are directed to pay any honoraria, speaking or consulting fees directly to charity so that neither income nor tax deduction is received.
Background

- Non-steroidal anti-inflammatory drugs (NSAIDs) are amongst the most widely prescribed class of drugs in the world with 100 million prescriptions in the US in 2013.

- NSAIDs inhibit cyclooxygenase (COX), which reduces pain and inflammation through inhibition of prostaglandins, but also has important vascular effects.

- The withdrawal of the selective COX-2 inhibitor, rofecoxib, raised questions about CV safety of these drugs, including the sole remaining COX-2 inhibitor in USA, celecoxib.
Objectives of the PRECISION Trial

• The primary objective was *non-inferiority* assessment of the cardiovascular risk of celecoxib vs. two widely used non-selective NSAIDs, naproxen and ibuprofen, in osteoarthritis and rheumatoid arthritis patients.

• Other objectives included comparative safety of celecoxib vs. these two NSAIDs for all-cause mortality, gastrointestinal and renal adverse events.
All members of the Executive Committee agreed not to accept payments for related work on NSAIDs from any maker of these drugs.
Osteoarthritis or rheumatoid arthritis patients with established CV disease or increased risk who required NSAIDs for ≥ 6 months for symptom relief

Celecoxib 100 mg b.i.d

Ibuprofen 600 mg t.i.d

Naproxen 375 mg b.i.d.

Esomeprazole 20-40 mg

Option to increase dosage for unrelieved symptoms to the maximum approved by local regulatory authorities

Event driven trial with a minimum follow up of 18 months
Adjudicated Endpoints

• For noninferiority, the primary analyses used the APTC endpoint: cardiovascular death, including hemorrhagic death; nonfatal myocardial infarction or nonfatal stroke.

• Superiority comparisons:

  – Major adverse cardiovascular events – APTC endpoint plus revascularization, hospitalization for unstable angina or TIA.

  – Major gastrointestinal events, including iron deficiency anemia of GI origin (HCT drop >10%, Hgb > 2 gms).

  – Major renal events (including hospitalization for renal failure).

  – Hospitalization for hypertension or CHF
Study Milestones and Drug Exposure

• 31,857 patients screened and 24,081 randomized at 926 global centers beginning October 23, 2006

• Drug exposure (all now generic in USA):
  – Celecoxib mean daily dose, 104 mg b.i.d.
  – Ibuprofen mean daily dose, 681 mg t.i.d.
  – Naproxen mean daily dose, 426 mg b.i.d.

• Mean drug exposure 20.3 months and mean follow up 34.1 months.
Noninferiority Criteria

• To establish noninferiority, the trial design required pairwise comparison of the drugs to meet four criteria:

  – An upper 97.5% confidence interval (CI) ≤ 1.33 for intention-to-treat (ITT) analysis

  – An upper 97.5% CI ≤ 1.40 for on-treatment analysis (defined as events occurring while the patient taking study drug and 30 days thereafter)

  – A HR ≤ 1.12 for both ITT and on-treatment populations
Rationale for ITT and On-Treatment Analyses

• Intention-to-treat (ITT) analysis is preferred in efficacy studies because it preserves the integrity of randomization and represents a conservative assessment of benefits.

• However, ITT analysis can dilute safety signals by including events occurring after patients stop the therapy.

• On-treatment analysis offers complementary insights in safety studies because it includes events occurring only while patients are actually taking study drugs.

• To ensure a rigorous safety assessment, we prespecified achieving noninferiority using both approaches.
### Selected Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Celecoxib N=8072</th>
<th>Ibuprofen N=8040</th>
<th>Naproxen N=7969</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.0</td>
<td>63.2</td>
<td>63.3</td>
</tr>
<tr>
<td>Female Gender</td>
<td>64.1%</td>
<td>64.4%</td>
<td>63.9%</td>
</tr>
<tr>
<td>White</td>
<td>75.0%</td>
<td>74.5%</td>
<td>74.4%</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>89.9%</td>
<td>89.6%</td>
<td>90.1%</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>10.1%</td>
<td>10.4%</td>
<td>9.9%</td>
</tr>
<tr>
<td>Secondary Prevention</td>
<td>23.1%</td>
<td>22.8%</td>
<td>22.4%</td>
</tr>
<tr>
<td>Prior aspirin use</td>
<td>45.8%</td>
<td>46.2%</td>
<td>45.8%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>35.2%</td>
<td>35.9%</td>
<td>34.7%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>20.9%</td>
<td>20.9%</td>
<td>20.5%</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>125.3</td>
<td>125.4</td>
<td>125.0</td>
</tr>
</tbody>
</table>
Noninferiority Analysis for Primary APTC Endpoint

Intention-to-Treat

- Cele vs. Ibu, HR 0.85 (0.70-1.04), $P<0.001^*$
- Cele vs. Nap, HR 0.93 (0.76-1.12), $P<0.001^*$
- Ibu vs. Nap, HR 1.08 (0.90-1.31), $P<0.02^*$

On-Treatment

- Cele vs. Ibu, HR 0.81 (0.65-1.02), $P<0.001^*$
- Cele vs. Nap HR 0.90 (0.71-1.15), $P<0.001^*$
- Ibu vs. Nap HR 1.12 (0.89-1.4), $P<0.025^*$

*Noninferiority p values
Superiority Analyses of Secondary Endpoints

Secondary and tertiary analyses should be viewed as hypothesis-generating, rather than conclusive, and are not adjusted for multiplicity.

We will present the ITT analyses as primary, but for completeness, also report on-treatment HRs and 95% CIs (without $P$ values) as a sensitivity analysis.
Time-to-Major Adverse Cardiovascular Event

Intention-to-Treat

On-Treatment

Cele vs. Ibu, HR 0.87 (0.75-1.01), $P=0.06$

Cele vs. Nap, HR 0.97 (0.83-1.12), $P=0.64$

Ibu vs. Nap, HR 1.11 (0.96-1.29), $P=0.15$

Cele vs. Ibu, HR 0.82 (0.69-0.97)

Cele vs. Nap, HR 0.95 (0.80-1.13)

Ibu vs. Nap, HR 1.17 (0.99-1.38)

Ibuprofen 15% higher (borderline significant)
Time-to-Death from Cardiovascular Causes

**Intention-to-Treat**

- Cele vs. Ibu, HR 0.84 (0.61-1.16), $P=0.30$
- Cele vs. Nap, HR 0.78 (0.57-1.07), $P=0.13$
- Ibu vs. Nap, HR 0.93 (0.69-1.26), $P=0.64$

**On-Treatment**

- Cele vs. Ibu, HR 0.64 (0.42-0.99)
- Cele vs. Nap, HR 0.69 (0.45-1.07)
- Ibu vs. Nap, HR 1.08 (0.73-1.60)
Time from Randomization to All-Cause Mortality

**Intention-to-Treat**

- Cele vs. Ibu, HR 0.92 (0.73-1.17), \(P=0.49\)
- Cele vs. Nap, HR 0.80 (0.63-1.00), \(P=0.052\)
- Ibu vs. Nap, HR 0.87 (0.70-1.09), \(P=0.22\)

Naproxen 25% higher (borderline significant)

**On-Treatment**

- Cele vs. Ibu, HR 0.68 (0.48-0.97)
- Cele vs. Nap, HR 0.65 (0.46-0.92)
- Ibu vs. Nap, HR 0.96 (0.70-1.31)
Time-to-Major Gastrointestinal Event

**Intention-to-Treat**

- Cele vs. Ibu, HR 0.65 (0.50-0.85), \(P=0.002\)
- Cele vs. Nap, HR 0.71 (0.54-0.93), \(P=0.01\)
- Ibu vs. Nap, HR 0.108 (0.85-1.39), \(P=0.53\)

**On-Treatment**

- Cele vs. Ibu, HR 0.44 (0.32-0.61)
- Cele vs. Nap, HR 0.45 (0.33-0.63)
- Ibu vs. Nap, HR 1.03 (0.80-1.34)
Time from Randomization to Serious Renal Event

**Intention-to-Treat**

- Cele vs. Ibu, HR 0.61 (0.44-0.85), \(P=0.004\)
- Cele vs. Nap, HR 0.79 (0.56-1.12), \(P=0.19\)
- Ibu vs. Nap, HR 1.29 (0.95-1.76), \(P=0.10\)

**On-Treatment**

- Cele vs. Ibu, HR 0.54 (0.37-0.80)
- Cele vs. Nap, HR 0.66 (0.44-0.97)
- Ibu vs. Nap, HR 1.21 (0.86-1.70)

Ibuprofen 64% higher
Patients with an Event (%)

**Intention-to-Treat**

- Cele vs. Ibu, HR 0.78 (0.69-0.87), \( P < 0.001 \)
- Cele vs. Nap, HR 0.87 (0.77-0.99), \( P = 0.03 \)
- Ibu vs. Nap, HR 1.13 (1.01-1.26), \( P = 0.04 \)

**Post Hoc: Any Adjudicated CV, GI or Renal Event**

<table>
<thead>
<tr>
<th></th>
<th>Ibuprofen</th>
<th>Naproxen</th>
<th>Celecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen 28% higher</td>
<td>(NNH - 59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen 15% higher</td>
<td></td>
<td>(NNH - 117)</td>
<td></td>
</tr>
</tbody>
</table>

**On-Treatment**

- Cele vs. Ibu, HR 0.69 (0.61-0.79)
- Cele vs. Nap, HR 0.78 (0.68-0.90)
- Ibu vs. Nap, HR 1.13 (0.997-1.28)
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>N=8030 Celecoxib</th>
<th>N=7990 Ibuprofen</th>
<th>N=7933 Naproxen</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not taking low-dose Aspirin</td>
<td>0.78 (0.58, 1.04)</td>
<td>81</td>
<td>102</td>
<td></td>
<td>0.40</td>
</tr>
<tr>
<td>Taking low-dose Aspirin</td>
<td>0.93 (0.71, 1.20)</td>
<td>107</td>
<td>116</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not taking low-dose Aspirin</td>
<td>0.83 (0.61, 1.11)</td>
<td>81</td>
<td>97</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Taking low-dose Aspirin</td>
<td>1.03 (0.79, 1.35)</td>
<td>107</td>
<td>104</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not taking low-dose Aspirin</td>
<td>1.06 (0.80, 1.35)</td>
<td>102</td>
<td>97</td>
<td></td>
<td>0.80</td>
</tr>
<tr>
<td>Taking low-dose Aspirin</td>
<td>1.40 (1.09, 1.86)</td>
<td>116</td>
<td>104</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Selected Investigator-Reported Adverse Effects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Celecoxib N=8030</th>
<th>Ibuprofen N=7992</th>
<th>Naproxen N=7933</th>
<th>Celecoxib vs. Ibuprofen P value</th>
<th>Celecoxib vs. Naproxen P value</th>
<th>Ibuprofen vs. Naproxen P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>2.8%</td>
<td>5.5%</td>
<td>4.2%</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increased BP</td>
<td>2.3%</td>
<td>3.1%</td>
<td>2.5%</td>
<td>0.001</td>
<td>0.29</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9.7%</td>
<td>13.0%</td>
<td>11.0%</td>
<td>&lt;0.001</td>
<td>0.006</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>1.8%</td>
<td>3.4%</td>
<td>1.9%</td>
<td>&lt;0.001</td>
<td>0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Constipation</td>
<td>3.4%</td>
<td>4.3%</td>
<td>5.2%</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>0.02</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8.0%</td>
<td>6.8%</td>
<td>7.2%</td>
<td>0.004</td>
<td>0.05</td>
<td>0.38</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>3.6%</td>
<td>3.4%</td>
<td>2.8%</td>
<td>0.45</td>
<td>0.006</td>
<td>0.04</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2.4%</td>
<td>3.2%</td>
<td>3.0%</td>
<td>0.003</td>
<td>0.01</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Adjudicated hospitalization for hypertension, celecoxib vs. ibuprofen HR 0.60 (0.36-0.99), P=0.04
Limitations-1

• Adherence and retention were lower than other CV outcome trials (although similar to other pain studies):
  – Patients with chronic painful conditions frequently experience unrelieved symptoms and switch therapies or leave the trial.

• The dose of celecoxib was moderate (100 mg twice daily).
  – The trials that provided signals suggesting harm studied supratherapeutic doses of celecoxib (up to 800 mg daily)
Rates of Drug Discontinuation and Non-Retention

<table>
<thead>
<tr>
<th>Months Since Randomization</th>
<th>Percentage of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ibuprofen</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>6</td>
<td>0.06</td>
</tr>
<tr>
<td>12</td>
<td>0.16</td>
</tr>
<tr>
<td>18</td>
<td>0.25</td>
</tr>
<tr>
<td>24</td>
<td>0.33</td>
</tr>
<tr>
<td>30</td>
<td>0.39</td>
</tr>
<tr>
<td>36</td>
<td>0.45</td>
</tr>
<tr>
<td>42</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Patients Discontinuing Treatment: 68.8%

Patients Discontinuing Follow up: 27.4%
Limitations-2

• The results reflect the relative safety of these 3 drugs and not the more than 20 other currently-marketed NSAIDs.

• No direct inferences are possible regarding the effects of NSAIDs compared with placebo.

• These data do not provide conclusive evidence regarding the safety of intermittent treatment or use of low-dose over-the-counter preparations.
Conclusions: Celecoxib vs. Naproxen

- Numerically fewer APTC events occurred with celecoxib than naproxen, meeting all 4 noninferiority criteria ($P<0.001$)

- In ITT analyses, chronic treatment with prescription doses of naproxen, compared with celecoxib, was associated with:
  - Higher rates of gastrointestinal adverse events and a borderline significant increase in all-cause mortality.

- In the on-treatment sensitivity analysis, naproxen showed:
  - Higher rates of all-cause mortality and major gastrointestinal and renal events.
Conclusions: Celecoxib vs. Ibuprofen

• Numerically fewer APTC events occurred with celecoxib than ibuprofen, meeting all 4 noninferiority criteria ($P<0.001$)

• In ITT analyses, chronic treatment with prescription doses of ibuprofen, compared with celecoxib, was associated with:
  – Higher rates of gastrointestinal and renal adverse events

• In the on-treatment sensitivity analysis, ibuprofen showed:
  – Higher rates of MACE, cardiovascular death, all-cause mortality and major gastrointestinal and renal events.
Additional Conclusions

• These findings challenge the widely-held view that naproxen provides superior cardiovascular safety.

• Results were consistent regardless of baseline administration of aspirin. Gastrointestinal safety differences were evident despite prophylactic use of esomeprazole.

• Between drug differences should be viewed as hypothesis-generating, rather than conclusive, given multiplicity issues and the challenges of adherence and retention in the trial.

• These findings will require careful review by global health authorities to determine what changes in labeling or regulatory status of these drugs are warranted.
Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis

Steven E. Nissen, M.D., Neville D. Yeomans, M.D., Daniel H. Solomon, M.D., M.P.H., Thomas F. Lüscher, M.D., Peter Libby, M.D., M. Elaine Husni, M.D., David Y. Graham, M.D., Jeffrey S. Borer, M.D., Lisa M. Wisniewski, R.N., Katherine E. Wolski, M.P.H., Qiuqing Wang, M.S., Venu Menon, M.D., Frank Ruschitzka, M.D., Michael Gaffney, Ph.D., Bruce Beckerman, M.D., Manuela F. Berger, M.D., Weihang Bao, Ph.D., and A. Michael Lincoff, M.D., for the PRECISION Trial Investigators*

ABSTRACT

BACKGROUND
The cardiovascular safety of celecoxib, as compared with nonselective nonsteroidal antiinflammatory drugs (NSAIDs), remains uncertain.
A Final Thought

After the withdrawal of rofecoxib, there ensued a rush to judgment about the cardiovascular safety of COX-2 inhibitors. Fueled by the controversy, investigators and some expert commentary used observational data, small RCTs and theoretical concerns to “confirm” what they expected. The PRECISION trial demonstrates the hazards inherent in prejudgment about the risks and benefits of therapies based upon expectations and indirect methods. These findings serve as an important warning to the medical community that we may arrive at erroneous conclusions when we fail to follow a systematic and unbiased approach to scientific and public health questions.