PROSPECTIVE RANDOMIZED EVALUATION OF CÉLECOXIB INTEGRATED SAFETY VERSUS IBUPROFEN OR NAPROXEN AMBULATORY BLOOD PRESSURE MEASUREMENT TRIAL
Declaration of interest

Study Sponsor: Pfizer
Executive committee members agreed not to accept any financial payments related to NSAIDs from any manufacturer of NSAIDs throughout the duration of the trial, including the trial’s sponsor

Served on Steering Committees/Speakerbureau for:
Abbott, Bayer, Biotronik, Cardiorentis, Fresenius, Merck, Novartis, Servier, Zoll
• Non-steroidal anti-inflammatory drugs (NSAIDs) are amongst the most widely prescribed drugs in the world with more than 100 million prescriptions in the United States and Europe

• NSAIDs reduce pain and inflammation through the suppression of prostaglandin synthesis, by inhibiting the enzyme cyclooxygenase (COX), but may also exert cardiovascular off-target effects

• One fourth of the world’s population aged over 35 years has arthritis
  • of these, almost half have *or are at high risk of* cardiovascular disease, particularly hypertension
PRECISION-ABPM: **Objective**

- Even relatively small changes in blood pressure may impact cardiovascular morbidity and mortality
- Current labeling of all NSAIDs include warnings regarding potential risk of cardiovascular events and increase in blood pressure
- Therefore, the primary objective of PRECISION-ABPM was to compare the COX-2 inhibitor celecoxib vs two widely used non-selective NSAIDs, naproxen and ibuprofen, in patients with arthritis and either known CAD or at relatively high cardiovascular risk
- Primary endpoint was the change from baseline in 24-hour mean systolic blood pressure after 4 months treatment
OA or RA patients with established CV disease or at increased CV risk who required NSAIDs for ≥ 6 months for symptom relief

- Celecoxib 100 mg BID
- Ibuprofen 600 mg TID
- Naproxen 375 mg BID

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

- Esomeprazole 20-40 mg
### Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Celecoxib (100-200mg BID)</th>
<th>Ibuprofen (600-800mg TID)</th>
<th>Naproxen (375-500mg BID)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 146 )</td>
<td>( n = 151 )</td>
<td>( n = 147 )</td>
</tr>
<tr>
<td>Age, years</td>
<td>62.1 ± 10.1</td>
<td>61.9 ± 9.7</td>
<td>61.4 ± 10.3</td>
</tr>
<tr>
<td>Sex m/f, %</td>
<td>70/76</td>
<td>72/79</td>
<td>63/84</td>
</tr>
<tr>
<td>Race: White/Black/Other, %</td>
<td>81/13/6</td>
<td>80/17/3</td>
<td>81/16/2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>32.6 ± 7.0</td>
<td>32.7 ± 6.9</td>
<td>31.9 ± 6.6</td>
</tr>
<tr>
<td>OA/RA, %</td>
<td>92/8</td>
<td>91/9</td>
<td>94/6</td>
</tr>
<tr>
<td>Baseline aspirin, %</td>
<td>49</td>
<td>49</td>
<td>46</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>125.1 ± 9.41</td>
<td>125.5 ± 10.63</td>
<td>125.3 ± 9.93</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>74.6 ± 7.43</td>
<td>74.2 ± 8.72</td>
<td>74.8 ± 7.52</td>
</tr>
<tr>
<td>Laboratory tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.6 ± 1.92</td>
<td>7.4 ± 1.63</td>
<td>7.5 ± 2.08</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.9 ± 0.21</td>
<td>0.9 ± 0.23</td>
<td>0.9 ± 0.20</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73m²</td>
<td>79.8 ± 18.28</td>
<td>79.8 ± 18.25</td>
<td>79.6 ± 18.16</td>
</tr>
</tbody>
</table>

## PRECISION-ABPM: Co-Medication

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Celecoxib (100-200mg BID) n = 146</th>
<th>Ibuprofen (600-800mg TID) n = 151</th>
<th>Naproxen (375-500mg BID) n = 147</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Drug (mean dose/day)</td>
<td>208 (34)</td>
<td>2031 (237)</td>
<td>852 (98)</td>
</tr>
<tr>
<td>Any concomitant medication, %</td>
<td>85</td>
<td>89</td>
<td>87</td>
</tr>
<tr>
<td>Agents acting on the RAAS, %</td>
<td>59</td>
<td>67</td>
<td>59</td>
</tr>
<tr>
<td>Beta-Blocker, %</td>
<td>29</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Ca Channel Blockers, %</td>
<td>23</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Diuretics, %</td>
<td>32</td>
<td>41</td>
<td>32</td>
</tr>
<tr>
<td>Peripheral Vasodilators, %</td>
<td>8</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

PRECISION-ABPM: Change in Ambulatory 24-h Systolic Blood Pressure from Baseline at 4 Months

Celecoxib (n = 146) vs. Ibuprofen (n = 151) vs. Naproxen (n = 147)

LS, least squares. SBP, systolic blood pressure

PRECISION-ABPM: Hourly Ambulatory Systolic BP Over 24 Hours at Baseline and at 4 Months

Celecoxib  Δ at month 4 p=0.80  
Ibuprofen  Δ at month 4 p<0.001  
Naproxen   Δ at month 4 p=0.12
PRECISION-ABPM: Patients with Baseline Normotensive Blood Pressure Who Developed Hypertension at 4 months

New hypertension defined as mean 24-hour SBP ≥ 130 and/or DBP ≥ 80 mmHg

PRECISION: Time to First Hospitalization for Hypertension

Celecoxib vs Ibuprofen, HR 0.59 (95% CI, 0.36-0.99), P = .04
Celecoxib vs Naproxen, HR 0.69 (95% CI, 0.41-1.17), P = .17
Ibuprofen vs Naproxen, HR 1.17 (95% CI, 0.74-1.84), P = .51

No. at Risk:
Celecoxib 8072 7841 7674 7558 7456 7317 7236 7082 7013 6908 6639 6446 6240 6240 5990 5832 5673
Ibuprofen 8040 7797 7599 7458 7347 7218 7135 7002 6931 6830 6536 6331 6105 5833 5704 5544
Naproxen 7969 7772 7607 7439 7360 7223 7145 7020 6942 6847 6537 6358 6148 5874 5713 5543
PRECISION: Cardiovascular and All Cause Mortality

**A. Death from Cardiovascular Causes - Intention to Treat Population**

- Celecoxib vs Ibuprofen, HR: 0.84 (95% CI: 0.61-1.16), P=0.30
- Celecoxib vs Naproxen, HR: 0.78 (95% CI: 0.51-1.20), P=0.12
- Ibuprofen vs Naproxen, HR: 0.93 (95% CI: 0.69-1.26), P=0.64

**B. Death from Cardiovascular Causes - On Treatment Population**

- Celecoxib vs Ibuprofen, HR: 0.64 (95% CI: 0.42-0.95), P=0.04
- Celecoxib vs Naproxen, HR: 0.69 (95% CI: 0.45-1.07), P=0.10
- Ibuprofen vs Naproxen, HR: 1.08 (95% CI: 0.79-1.48), P=0.70

**C. All Cause Mortality - Intention to Treat Population**

- Celecoxib vs Ibuprofen, HR: 0.82 (95% CI: 0.73-1.11), P=0.46
- Celecoxib vs Naproxen, HR: 0.88 (95% CI: 0.63-1.20), P=0.30
- Ibuprofen vs Naproxen, HR: 0.87 (95% CI: 0.70-1.09), P=0.22

**D. All Cause Mortality - On Treatment Population**

- Celecoxib vs Ibuprofen, HR: 0.68 (95% CI: 0.48-0.97), P=0.03
- Celecoxib vs Naproxen, HR: 0.99 (95% CI: 0.66-1.48), P=0.95
- Ibuprofen vs Naproxen, HR: 0.96 (95% CI: 0.76-1.21), P=0.78

Nissen, et al. NEJM 2016
PRECISION-ABPM: Limitations

- Regulatory restrictions limited the dose of celecoxib to 200 mg daily for osteoarthritis patients who comprised the majority enrolled; however, symptom relief was similar with all 3 NSAIDs.

- The results reflect the relative safety of these 3 drugs, but provide no information about the other currently-marketed NSAIDs.

- These data do not provide conclusive evidence regarding the safety of intermittent treatment or use of low-dose over-the-counter preparations.

- No direct inferences are possible regarding the effects of NSAIDs compared with placebo.
PRECISION-ABPM: Conclusions

- Prescription-strength Ibuprofen was associated with a significant increase of systolic blood pressure, and a higher incidence of new-onset hypertension when compared with the COX-2 selective inhibitor celecoxib.

- PRECISION-ABPM adds to the evidence about the adverse cardiovascular effects of NSAIDs, particularly ibuprofen, and confirms that they should be used only after consulting a healthcare professional.

- Clinicians need to weigh the potential hazards of worsening blood pressure control and its clinical sequelae against the arthritis-mitigating benefits associated with the use of NSAIDs, particularly ibuprofen.
Merci

Prof. Dr. med. Dr. h.c. Frank Ruschitzka, FRCP (Edin.)
PRECISION-ABPM: Distribution of Changes from Baseline in Ambulatory Systolic BP at 4 Months

Analysis of distribution: Cochran Mantel Haenszel (CMH) test with adjustment for region.

PRECISION-ABPM: Change in Awake and Sleep Systolic Blood Pressure from Baseline at 4 Months

LS, least squares. SBP, systolic blood pressure.

PRECISION-ABPM: Change in Mean 24-h Pulse Pressure from Baseline at 4 Months

- LS, least squares. PP, pulse blood pressure.

Celecoxib (n = 146) vs. Ibuprofen (n = 151) vs. Naproxen (n = 147).

Celecoxib vs. Ibuprofen: P<0.001
Celecoxib vs. Naproxen: P=0.058
Naproxen vs. Ibuprofen: P=0.011

PRECISION: Gastrointestinal and Renal Events

A. Serious Gastrointestinal Events - Intention-to-Treat Population

B. Serious Gastrointestinal Events - On-Treatment Population

C. Renal Events - Intention-to-Treat Population

D. Renal Events - On-treatment Population

Nissen, et al. NEJM 2016