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LETTER TO THE EDITOR

# Comment on: "Coxibs Refocus Attention on the Cardiovascular Risks of Non-Aspirin NSAIDs"

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Dear Editors,

In a recent issue of the *American Journal of Cardiovascular Drugs*, Thomas et al. [1] analyzed the cardiovascular safety of cyclo-oxygenase (COX)-2 inhibitors (coxibs). In the Recommendations section of the paper, the authors stated that, based on the results of the PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen) trial [2], celecoxib at moderate doses is not inferior to ibuprofen or naproxen in terms of cardiovascular safety. The PRECISION investigators seem to imply that celecoxib is a 'cardiovascular safe' drug, and we would like to challenge this statement with a more detailed analysis of the PRECISION trial.

On the recommendation of the US FDA after the doubts raised over the cardiovascular safety of the coxibs, Pfizer performed the PRECISION trial [2], proposing as its primary objective "To assess the effects of celecoxib 100–200 mg twice daily (bid) and ibuprofen 600–800 mg three times daily (tid) compared with naproxen 375–500 mg bid on the first occurrence of Anti-Platelet Trialists Collaboration (APTC) composite cardiovascular endpoint [cardiovascular death, including hemorrhagic death, non-fatal myocardial infarction (MI), non-fatal stroke] in subjects with osteoarthritis or rheumatoid arthritis (RA), and pre-existing cardiovascular disease (CVD) or at high risk for developing CVD. Cardiovascular effects of celecoxib 100–200 mg bid will also be compared with ibuprofen 600–800 mg three times daily" [3]. According to the authors' conclusion, "at moderate doses, celecoxib was found to be noninferior to ibuprofen or naproxen with regard to cardiovascular safety", implying that their results validate the safe use of celecoxib at the same level as naproxen or ibuprofen.

The PRECISION investigators concluded that their trial confirmed the primary hypothesis of non-inferiority [3]. However, we consider that the possibility of several biases in the design and development of the trial do not allow its results to be considered a reliable answer to the research question of the trial.

Coxibs would find a place in therapeutics if they showed equal anti-inflammatory and analgesic efficacy and fewer gastrointestinal adverse effects without increasing cardiovascular harm compared with naproxen. Let us examine each of these aspects in the PRECISION trial.

## 1 Anti-Inflammatory and Analgesic Efficacy: Were Comparable Doses Used?

The therapeutic effects and adverse event profile of traditional non-steroidal anti-inflammatory drugs (NSAIDs) and coxibs are dose dependent. For this reason, the comparison of adverse events between pharmacologic agents is only interpretable if therapeutically equivalent doses are used.

The PRECISION trial investigated celecoxib 200–400 mg/day compared with naproxen 750–1000 mg/day and

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ibuprofen 1800–2400 mg/day in patients with osteoarthritis or RA. Patients started treatment with the lowest dose and increased it as needed.

Since 200 mg/day is the maximum approved dose of celecoxib for osteoarthritis in several countries, including the USA [2], more than 90% of the population studied did not exceed that dose. As a result, the average dose of celecoxib (209 mg/day) used was practically equal to the minimum dose, whereas those of naproxen (852 mg/day) and ibuprofen (2045 mg/day) showed that a great number of patients used the higher dose. This difference was reflected in a lower analgesic effect with celecoxib than with naproxen [2] and in a slightly higher percentage of treatment discontinuation due to insufficient clinical response among those completing the protocol [764/5853 for celecoxib (13.1%) versus 661/5849 for naproxen (11.3%)] [4].

In conclusion, it is possible that the anti-inflammatory and analgesic doses used were not equivalent, which complicates the interpretation of adverse event rates.

## 2 Cardiovascular Adverse Events

In the PRECISION trial, 45% of patients were using aspirin up to 325 mg/day because they had previous CVD or were at high cardiovascular risk. The published report does not clarify further use of this drug. Considering that COX-1 is irreversibly inhibited by aspirin, this effect cancels the COX-2 selectivity of celecoxib, which is suspected of increasing cardiovascular risk, biasing the outcome toward an absence of difference between both groups.

The initial protocol established that the upper limit of the 95% confidence interval (CI) of one tail for the hazard ratio of the primary outcome in the intention-to-treat (ITT) analysis comparing celecoxib and ibuprofen versus naproxen should not exceed 1.33. For the on-treatment analysis (in which follow-up ended 30 days after the final suspension of the drug under study), the initial margin was set at 1.33 but then changed to 1.40 since the rate of cardiovascular events was lower than expected [3].

However, a 33 or 40% increase in cardiovascular events is not clinically irrelevant. Many well established cardiovascular risk factors produce effects of this magnitude and, conversely, the benefits of statins, antihypertensives, or antiplatelet agents are approximately in this order. In fact, the cardiovascular risk of celecoxib (at a typical dose of 400 mg/day) compared with placebo is estimated at a relative risk of 1.36 (95% CI 1.0–1.84; $p = 0.05$) in the most comprehensive meta-analysis available [5], an effect size that coincides with the chosen Delta and that, therefore, would be considered 'acceptable damage' from the trial design itself.

In the PRECISION trial, 68.8% of patients stopped taking the study drug, continuing their own anti-inflammatory treatment outside the protocol, which biases the results towards an absence of difference between the groups studied and thus favors a spurious verdict of 'non-inferiority' [2].

If withdrawal from treatment biases the results toward absence of difference, the high loss of follow-up (27.4%) may produce further biases in either direction. The observed primary outcome rates for the celecoxib, naproxen, and ibuprofen groups were 2.3, 2.5, and 2.7%, respectively, in the ITT analysis and 1.7, 1.8, and 1.9%, respectively, in the on-treatment analysis. These minimal differences between groups that support the conclusion of non-inferiority of celecoxib could be substantially modified in either direction. In other words, for each patient who experienced a cardiovascular event in the trial (2.5%), more than ten patients were lost at follow-up (27.4%). Therefore, the final results—if they could be known—may clearly tip the balance in one direction or another.

Given these biases, the PRECISION results cannot be taken as evidence of non-inferiority of cardiovascular risk between celecoxib and ibuprofen or naproxen.

## 3 Gastrointestinal Adverse Events: Late Changes in Endpoints During Trial Implementation

Although gastrointestinal adverse events are clinically relevant, they were not chosen as primary endpoints. It should be noted that, by specification of the protocol, all patients received esomeprazole during the trial [3], which may bias the results of the trial and mask serious adverse events.

The published trial protocol, in its final version dated July 2016, defined one primary outcome, five secondary outcomes, and ten tertiary outcomes in addition to other 'exploratory analysis' of variables. The gastrointestinal secondary outcome measures the incidence of "clinically significant gastrointestinal events" (CSGE), defined as the first occurrence of either gastroduodenal hemorrhage; gastric outlet obstruction; gastroduodenal, small bowel, or large bowel perforation; large bowel hemorrhage; small bowel hemorrhage; acute gastrointestinal hemorrhage of unknown origin, including presumed small bowel hemorrhage or symptomatic gastric or duodenal ulcer. Tertiary outcomes were the composite result of symptomatic high gastrointestinal ulceration, moderate to severe abdominal symptoms and withdrawal from the trial due to gastrointestinal adverse events, and first occurrence of clinically significant gastrointestinal iron deficiency anemia (CSGIDA) [3].

In the trial, no statistically significant differences were found between the three drugs in the secondary CSGE outcome; however, in the tertiary CSGIDA outcome, celecoxib had fewer events than naproxen or ibuprofen. The published trial report presented a "composite outcome of serious gastrointestinal events" as the main gastrointestinal result, adding CSGE and CSGIDA, and found the combination results significantly lower in the celecoxib group than in the naproxen or ibuprofen groups [2].

This new composite variable was not previously informed. A letter signed by the chief statistician of the trial confirmed that the decision to add CSGIDA to the CSGE outcome was made before the unblinding of the trial results but does not mention the reasons for the change [3]. It would have been preferable to stick to the published statistical analysis plan.

## 4 Conclusion

Given the problems identified in the design, development, and implementation of the PRECISION trial, we consider that the cardiovascular non-inferiority status of celecoxib compared with naproxen, as stated by Thomas et al. [1], is questionable because of several biases that reduce the possible differences between drugs studied in that trial. Therefore, celecoxib should not be considered a 'cardiovascular safe' medicine when compared with other treatments such as ibuprofen or naproxen.

**Compliance with Ethical Standards**

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