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# Editorial: gastrointestinal safety of COX-2 selective and non-selective NSAIDs - the impact of the PRECISION trial. Authors' reply

N.D. Yeomans, D.Y. Graham

We enjoyed Dr. Laine's editorial[1] on the PRECISION trial whose primary goal was to compare the relative cardiovascular safety of celecoxib with ibuprofen and naproxen in patients who were at increased cardiovascular risk. We found no evidence of a cardioprotective effect of naproxen (which has been mooted[2]), as the three drugs appeared similar.[3] Importantly, the conclusions cannot be extended to other NSAIDs and, because there was no placebo group, only relative safety of these drugs could be assessed.

The overarching goal of PRECISION was to examine safety of these NSAIDs from a multisystem perspective. The occurrence of adjudicated GI events from stomach to colon

was among the additional pre-specified endpoints. The editorial focuses on this latter publication.[4]

PRECISION ambitiously set out to randomise 20,000 or more patients to celecoxib, ibuprofen or naproxen and follow them for up to 42 months. While we agree that the dropout rate was disappointing, it is noteworthy that the mean duration of treatment was nevertheless 20 months with follow-up of 34 months – an unequalled total patient-years of observation in an RCT comparing a currently licensed coxib with nonselective NSAIDs. One of the reassuring findings was how uncommon serious GI events were, even among patients randomised to the nonselective NSAIDs. We suspect this is probably due to the almost 100% use of high dose PPI which is sufficient to maintain intragastric pH above 4 for 50-60% of each day.[5] It remains unclear whether lower PPI doses would have been equally beneficial. Although it has been suggested that anaemia may be more common in NSAID users who take PPIs, the studies Laine refers to used an enteric-coated NSAID, diclofenac, which may accentuate small bowel injury *via* localized and prolonged contact with the intestine.

Laine also points out that, while iron deficiency anaemia was less frequent on celecoxib in the ITT group, a significant difference in the other GI events was only evident in the modified-ITT group which is restricted to the subjects who developed an endpoint while actually taking study drug or during the following 30 days. This highlights one of the weaknesses of ITT analyses in RCTs that primarily set out to examine adverse events rather than efficacy of treatments – something we addressed in the paper.

One of the interesting subgroup analyses (admittedly *post hoc*) in PRECISION showed that celecoxib was especially effective among rheumatoid arthritis patients taking steroids. This result was similar to that seen in a prior analysis of the results of the VIGOR trial, which included previously unreported data showing that the GI significant safety benefits of rofecoxib over naproxen in rheumatoid arthritis were limited to patients also taking steroids.[6, 7]

Finally, the dose of celecoxib taken by most patients in PRECISION was lower than in many earlier studies. As always, the aim of NSAID treatment should be to use the lowest

doses with the durations limited to the time needed to control symptoms, which is especially true in osteoarthritis where symptoms are often intermittent.


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