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Randomised clinical trial: gastrointestinal events in arthritis patients treated with celecoxib, ibuprofen or naproxen in the PRECISION trial

Short Title: Gastrointestinal events in PRECISION trial

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The trial sponsor (Pfizer) participated in protocol development with the Executive Committee and in consultation with the FDA. The sponsor assisted with data collection and maintained the trial database, which was transferred to the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) at trial conclusion for statistical analysis, and where the data were available to all authors. The sponsor shared operational responsibilities with C5Research and several contract research organisations. The manuscript was written by the authors and provided to the sponsor for comment, but the final content was decided by the authors.

Summary

Background: We evaluated GI safety of celecoxib compared with two nonselective (ns) NSAIDs, as a secondary objective of a large trial examining multiorgan safety.
Methods: This randomised, double-blind controlled trial analyzed 24,081 patients. Osteoarthritis or rheumatoid arthritis patients, needing ongoing NSAID treatment, were randomized to receive celecoxib 100-200 mg b.d., ibuprofen 600-800 mg t.d.s. or naproxen 375-500 mg b.d. plus esomeprazole, and low-dose aspirin or corticosteroids if already prescribed. Clinically significant GI events (CSGIE - bleeding, obstruction, perforation events from stomach downwards or symptomatic ulcers) and iron-deficiency anaemia (IDA) were adjudicated blindly.
Results: Mean treatment and follow-up durations were 20.3 and 34.1 months. While on-treatment or 30 days after, CSGIE occurred in 0.34%, 0.74% and 0.66% taking celecoxib, ibuprofen and naproxen. Hazard ratios (HR) were 0.43 (95% CI 0.27-0.68, P=0.0003) celecoxib vs. ibuprofen and 0.51 (0.32-0.81, P=0.004) vs naproxen. There was also less IDA on celecoxib: HR 0.43 (0.27-

0.68, P=0.0003) vs ibuprofen; 0.40 (0.25-0.62, P<0.0001) vs naproxen. Even taken with low-dose aspirin, fewer CSGIE occurred on celecoxib than ibuprofen [HR 0.52 (0.29-0.94), P=0.03], and fewer IDA vs. naproxen [0.42 (0.23-0.77, P=0.005)]. Corticosteroid use increased total GI events and CSGIE. Helicobacter sero-status had no influence.

Conclusions: Arthritis patients taking NSAIDs plus esomeprazole have infrequent clinically significant gastrointestinal events. Co-prescribed with esomeprazole, celecoxib has better overall GI safety than ibuprofen or naproxen at these doses, despite treatment with low-dose aspirin or corticosteroids.

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Key words: nonsteroidal anti-inflammatory drugs; gastrointestinal adverse events; cyclo-oxygenase-2 inhibitors; gastrointestinal bleeding; anaemia.

1. INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for relieving pain and inflammation in patients with osteoarthritis (OA) and rheumatoid arthritis (RA). However, their use associates with gastrointestinal (GI) haemorrhage in about 0.2 to 12 per 100 patient years annually, depending on the patient's level of GI risk. [1, 2] NSAIDs damage the GI mucosae partly by blocking production of protective prostaglandins synthesized via cyclo-oxygenase (COX)-1, whereas prostaglandins that mediate inflammation arise mainly from the isoform COX-2.[3] These findings spurred the development of selective NSAIDs (coxibs) that preferentially inhibit COX-2. The first coxibs to market were rofecoxib and celecoxib.

Several randomised controlled trials (RCT) have demonstrated a substantially lower incidence of gastroduodenal ulcers detected by endoscopy in patients treated for up to 6 months with rofecoxib or celecoxib compared with nonselective (ns) NSAIDs.[4, 5] Two large RCTs investigated the more important endpoint – ulcer complications. The VIGOR study compared rofecoxib with naproxen in patients with RA, and found a reduction in complicated ulcer events in those treated with rofecoxib. The CLASS study compared celecoxib with ibuprofen and diclofenac with regard to upper GI ulcer complications, and found a statistically significant benefit for celecoxib only when patients taking low-dose aspirin were omitted[7] It thus raised the question of whether the beneficial effects of celecoxib on ulcer clinical events might be mitigated with the concurrent use of aspirin – a group that was excluded from the VIGOR trial, and either excluded from or minimally represented in more recent RCTs comparing celecoxib with nsNSAIDs.[1, 8, 9] Adding to

uncertainty, a meta-analysis of available RCTs in 2011 found no difference in upper GI events with coxibs compared with nsNSAIDS if a proton pump inhibitor (PPI) were also taken.[10] Thus, questions remain about the GI benefits of a coxib versus nsNSAIDs, particularly in patients taking low-dose aspirin – often required by arthritis patients to manage their cardio- or cerebro-vascular co-morbidities.

Concerns about cardiovascular harm by coxibs led to the withdrawal of rofecoxib by its manufacturer in 2004. The US Food and Drug Administration (FDA) permitted the continued marketing of celecoxib, but mandated a safety trial whose primary endpoint was the rate of serious cardiovascular events compared with those during treatment with two commonly used nsNSAIDs, in patients at increased cardiovascular risk. The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial demonstrated that celecoxib in moderate doses was non-inferior to ibuprofen or naproxen in cardiovascular safety.[11] This companion paper reports a prespecified secondary analysis of the adjudicated events due to damage to stomach, intestine, or colon in patients treated with the coxib compared with the nsNSAIDs. It also examines the influence of co-administered aspirin or corticosteroids, and *Helicobacter pylori (H. pylori)* infection, on the incidence of these events.

2. METHODS

2.1 Study design

PRECISION was a randomised, multi-centre, double-blind, parallel-arm active-controlled trial, designed to detect non-inferiority for its primary cardiovascular endpoint. It was carried out in 923 centres in the United States, Canada, Australia, Brazil, Colombia, Costa Rica, Mexico, Panama, Peru, Philippines, Taiwan, Hong Kong, and Ukraine between October 2006 and April 2016. The trial could not be performed in Europe because of restrictions placed on prescribing of coxibs by the European Medicines Agency. The protocol is available on request from the corresponding author, and the detailed design has been published previously.[12] Ethical approval was obtained from either a central ethical review board or the human research ethics committee at each centre.

A blinded multidisciplinary Executive Committee supervised the trial. The committee members did not accept any financial payments related to NSAIDs (including from the trial sponsor) for the duration of the trial. An independent unblinded data-monitoring committee reviewed data throughout the trial to assess safety. The online appendix lists members of the committees.

2.2 Patients

We enrolled patients aged 18 years or older, with a clinical diagnosis of osteoarthritis (OA) or rheumatoid arthritis (RA) for at least the previous six months, who required daily treatment with NSAIDs for arthritis pain as judged by patient and physician. Patients who received adequate relief with paracetamol/acetaminophen alone were ineligible. A principal inclusion criterion was that patients have established cardiovascular disease or be at high risk for developing it. Detailed inclusion/exclusion criteria are listed in the previous publication. The major exclusion criteria relevant to the gastrointestinal endpoints were: (i) diagnosis or treatment of oesophageal, gastric or duodenal ulcer in the 60 days before randomization; (ii) history of gastrointestinal perforation, obstruction or bleeding within 6 months before randomization; (iii) inflammatory bowel disease, recent diverticulitis or diverticulosis with prior known bleeding; (iv) treatment with aspirin at a dose >325 mg/d (those taking lower doses were encouraged to continue); and (v) treatment with warfarin or other vitamin K antagonist anticoagulants. Patients with RA were permitted treatment with oral corticosteroids (up to prednisolone 20 mg/d equivalent) or disease-modifying anti-rheumatic drugs provided dosing had been stable. Patients gave written informed consent to the study.

2.3 Randomization and masking

Patients were randomised in a 1:1:1 ratio to receive celecoxib, ibuprofen or naproxen, stratified by study centre, arthritis type (OA or RA), and aspirin use for cardiovascular prophylaxis. The randomised allocation was via an interactive voice response system. Blinding was via triple dummy allocation with placebo tablets or capsules matched to each active drug by size, color, smell, taste, and appearance.

2.4 Procedures

Study drugs were assigned in these doses: celecoxib 100 mg twice daily, ibuprofen 600 mg three times daily or naproxen 375 mg twice daily. If required for control of arthritis symptoms at subsequent visits, dosage escalation was permitted to celecoxib 200 mg twice daily (for RA, and in those countries permitting this dose for OA), ibuprofen 800 mg three times daily or naproxen 500 mg twice daily. Esomeprazole (20 to 40 mg daily) was provided to all patients (though investigators were permitted to replace this with a histamine-2 receptor antagonist at their

discretion). Gastroprotection was provided to all patients since their cardiac risk factors or disease put them at greater hazard should they experience a large GI bleed.

H. pylori serology was performed at baseline (at central laboratories for each region), together with routine haematologic, clinical safety chemical and other analyses listed in the previous publication. Patients had subsequent visits at 1, 2, 4, 8, and 12 months, then 6-monthly till 42 months unless discontinued earlier. Patients enrolled toward the end of study had an opportunity for at least 18 months of follow-up.

2.5 Adjudicated Outcomes

The primary outcome of the parent study (reported elsewhere[11]) was the first occurrence of an adverse event that met the Antiplatelet Trialists Collaboration (APTC) criteria – death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke. Secondary outcomes were major adverse cardiac events and clinically significant gastrointestinal events (CSGIE) (detailed definitions in the online appendix). The prespecified events that constituted CSGIE were: gastroduodenal haemorrhage; gastric outlet obstruction; gastroduodenal, small or large bowel perforation; small bowel haemorrhage; large bowel haemorrhage; acute gastrointestinal haemorrhage of unknown origin, including presumed small bowel haemorrhage; and symptomatic gastric or duodenal ulcer. The haemorrhage endpoints required observation of overt bleeding or endoscopic evidence of recent haemorrhage. A tertiary GI endpoint was clinically significant iron-deficiency anaemia (IDA) of proven or presumed gastrointestinal origin, defined as a fall in haemoglobin ≥2 g/dl or haematocrit ≥10% points from baseline, with biochemical evidence of iron deficiency, and no clinical evidence of acute gastrointestinal haemorrhage. A second tertiary endpoint was ‘composite GI events’: the first occurrence of any of symptomatic upper GI ulcer, moderate to severe abdominal symptoms or withdrawal from study drug due to GI related adverse events. Prespecified exploratory endpoints were time to first CSGIE according to aspirin usage, age, *H. pylori* and arthritis type. A further prespecified analysis combined CSGIE and IDA (as ‘total GI events’). The full list of adjudicated GI outcomes with detailed criteria for each is in the online appendix.

An expert Clinical Events Committee at the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) which included Board Certified (or Board Eligible) gastroenterologists assessed primary, secondary or tertiary outcomes that investigators identified as a suspected endpoint. The committee members were unaware of the treatment assigned. The online appendix

lists their names. Adverse events other than the adjudicated outcomes were monitored and published in the online appendix to the publication that reported the primary cardiovascular endpoint.[11]

2.6 Statistical analysis

The sample size calculation for the primary (cardiovascular) endpoint was described in the companion paper;[11] it estimated a requirement for about 20,000 patients to accumulate the requisite number of primary cardiovascular endpoints. Since the adjudicated gastrointestinal events were secondary and tertiary outcomes, no prospective power calculations were performed. The protocol prespecified a maximum 43-month study period, with a minimum follow-up of 18 months for those enrolled towards the end of the study, with censoring of data from event-free patients after 30 months in the ITT population and 43 months in the modified intention-to-treat (MITT) population. Both populations were prespecified for analysis: the ITT consisted of all randomised patients irrespective of whether they received or were still taking allocated drug; in the MITT, adjudicated events were recorded while patients actually received the study NSAID and for 30 days after. The main comparisons were times-to-event for the major gastrointestinal outcomes per treatment. For comparison with other studies, event rates were also converted to patient-years using treatment duration, or the time to first event for subjects who had an event. Additional prespecified comparisons were performed per treatment with low-dose aspirin and *H. pylori* status (the statistical analysis plan specified this to be only in the MITT population). Also in this population, the influence of corticosteroids in patients with RA was examined in a post hoc analysis. A Cox proportional hazards model with adjustment for stratification factors (investigator region, arthritis type and aspirin use at baseline) was used to calculate hazard ratios (HR) and 95% confidence intervals (CI), using SAS software, version 9.4. Statistical significance, $p<0.05$ for comparisons between treatment groups, or $p<0.10$ for treatment group by other subgroups (aspirin use or *H. pylori* serology or corticosteroid use) interaction was based on nominal P-values. The use of $P<0.10$ for the interaction tests is exploratory. A two-sided P value of <0.05 indicated statistical significance in superiority comparisons, without adjustment for multiple comparisons. The prespecified Statistical Analysis Plan is available on request to the corresponding author. The trial was registered at ClinicalTrials.gov, number NCT00346216.

3. RESULTS

3.1 Patient population

We screened 31,857 patients for a total of 24,222 who underwent randomization between 23 October 2006 and 30 June 2014, of whom 141 were excluded from analysis (106 determined to be fraudulently enrolled plus 35 enrolled more than once). Thus 24,081 patients could be included in the ITT analysis and 23,953 in the MITT analysis. The study profile is shown in Figure S1 (Supporting Information).

The three treatment groups had similar major demographic variables, use of low-dose aspirin, arthritis type, *H. pylori* status, smoking, and history of peptic ulcer (Table 1). Esomeprazole was provided for gastroprotection, and was taken by 98.9% of patients in each treatment group (dispensed for ≥90% of the on-treatment period in 95.4, 95.8 and 96.0% of celecoxib, ibuprofen and naproxen groups respectively). The mean esomeprazole dose was 27 mg/d in each group. The groups had similar mean (±SD) durations of treatment and follow-up (in months): 20.8 ±16.0 and 34.2 ±13.4 (celecoxib), 19.6 ±16.0 and 33.8 ±13.6 (ibuprofen), and 20.5 ±15.9 and 34.2 ±13.3 (naproxen). The proportions who discontinued study drug before the maximum 42-month end date (excluding deaths) were 66.7%, 69.6% and 67.2% in the celecoxib, ibuprofen and naproxen groups (P<0.001). Although patients were to continue to be followed per protocol after ceasing randomised drug, 27.5%, 28.2% and 26.6% did not complete the study. The reasons for noncompletion of the full protocol (3.5 years on treatment unless a trial endpoint required withdrawal) were 'patient no longer willing / withdrawal of consent' (3795 patients), 'lost to follow-up' (1741 patients), and 'other' (1071 patients).

3.2 Secondary and Tertiary Prespecified Endpoints

The major gastrointestinal endpoint was Clinically Significant Gastrointestinal Events (CSGIE). These occurred infrequently in all treatment groups. In the ITT analysis set, where patients may or may not have been taking their allocated drug for many months, confidence intervals of the Hazard Ratios overlapped unity for each of the three treatment comparisons (Table 2). In the MITT analyses, CSGIE occurred about half as often in those taking celecoxib compared with ibuprofen or naproxen: 0.19 vs 0.44 and 0.38 MITT events per 100 patient-years. Figure 1A shows the time-to-event curves. Hazard Ratios (and 95% CI) were 0.43 (0.27-0.68) for celecoxib versus ibuprofen (P=0.0003) and 0.51 (0.32-0.81) for celecoxib versus naproxen (p=0.004).

Iron deficiency anaemia of gastrointestinal origin (IDA), an adjudicated prespecified tertiary endpoint, also occurred less often in the celecoxib group compared with the nsNSAIDs, in both analysis sets (Table 2). In the MITT population the rates were: 0.19 vs 0.44 and 0.48 per 100

patient-years, with HR 0.43 (0.27-0.68) for celecoxib versus ibuprofen (P=0.0003) and 0.40 (0.25-0.62) for celecoxib versus naproxen (P<0.0001) (Figure 1B). CSGIE and IDA were detected with similar frequencies in the ibuprofen and naproxen groups: CSGIE, HR 1.16 (0.80-1.69, P=0.42); IDA, HR 0.91 (0.64-1.29, P=0.59). The numbers of patients who reached an IDA endpoint with haemoglobin concentration <10.0 g/dl were small: 4 (0.05%), 18 (0.2%) and 14 (0.2%) in the celecoxib, ibuprofen and naproxen groups (P=0.01).

The frequencies with which the individual adjudicated components of CSGIE occurred in the ITT and MITT populations are in Table 2. In addition to the differences in IDA noted above, significantly fewer symptomatic gastric or duodenal ulcers occurred in the celecoxib group than the ibuprofen group (ITT and MITT) or the naproxen group (MITT population only), and this component contributed most to the statistically significant differences in CSGIE between treatments. Overt gastrointestinal bleeding events were infrequent in all groups: less than 1 per 1000 patient years at any adjudicated anatomical site. Adding together the bleeding events from all sites (Table 2) gives numbers needed to harm of 769, 417 and 625 annually on celecoxib, ibuprofen or naproxen.

Table S1 provides data for the composite tertiary endpoint of symptomatic ulcers, abdominal symptoms and GI related withdrawals. The MITT population experienced fewer composite events on celecoxib than on either nsNSAID; in ITT, the difference reached significance only for celecoxib vs. naproxen.

3.3 Exploratory Endpoints: effects of low-dose aspirin, corticosteroids and *H. pylori*

The effects of concomitant treatment with low-dose aspirin on gastrointestinal events in the MITT population (the population specified for this analysis in the SAP) are shown in Figure 2A (and Fig. S2 and Table S2 in the online appendix). Commensurate with their elevated cardiac risk, almost 50% of patients in PRECISION took aspirin, and CSGIE occurred in them more often than in those who did not take aspirin (P=0.036). Less than 5% of patients who were not taking aspirin at baseline were started on it later in the study.

Fifty-six percent of RA patients took corticosteroids at baseline, and this treatment's effect was examined in a post hoc analysis of the MITT population. Those receiving steroids experienced more than twice as many adjudicated GI events as those who did not (Figure 2C and Table S2).

The effect of *H. pylori* infection (assessed by baseline serology) was a prespecified exploratory endpoint for the MITT analysis. Serology positive patients experienced similar rates of both CSGIE and IDA compared with uninfected patients (Figure 2B and TableS2).

Figure 2 shows forest plots and interaction statistics for the subgroup analyses for aspirin, *H. pylori* status and corticosteroid use. The exploratory level of significance set for interactions ($P<0.1$) was reached for two comparisons: total GI events and IDA for the comparison of celecoxib with ibuprofen in the presence of aspirin. No other tests for interaction reached this threshold.

3.4 Other endpoints

Older patients more often had CSGIE and IDA events. Those aged <63 years (the median age) constituted 46.9% of the whole MITT population; CSGIE occurred in 0.33% aged < 63 compared with 0.79% aged ≥63 ($P<0.0001$), while IDA events occurred in 0.42% and 0.82% respectively ($P<0.0001$). Each of the three treatment groups showed this pattern of more CSGIE and IDA in older patients.

Investigator-reported adverse events (other than adjudicated outcomes) that occurred in 3% or more of the patients in any treatment group are reported in the online appendix to the companion publication.[11] The only ones that differed by >1 percentage point between treatment groups were constipation (less frequent on celecoxib), diarrhoea (more frequent on celecoxib), increased blood creatinine (more frequent on ibuprofen), and arthralgia (less frequent on ibuprofen).

4. DISCUSSION

In this large trial, where patients took their allocated NSAID for an average of close to two years, and nearly all took esomeprazole, there was a notably low incidence of clinically significant GI injury in all three treatment arms. In the ITT population, CSGIE occurred at rates (per 100 patient years) of 0.32 in the celecoxib, 0.43 in the ibuprofen and 0.33 in the naproxen groups (table 2), and the differences were not significant. In the MITT population, the rates of CSGIE were lower than observed in ITT and about twice as high on the nsNSAIDs as on celecoxib. In both the ITT and MITT populations, numbers needed to harm by a CSGIE event were never less than 200 per annum.

In the ITT population, celecoxib associated with about half as many episodes of iron-deficiency anaemia of GI origin as either ibuprofen or naproxen in arthritis patients treated with a

concomitant PPI, while the differences in CSGIE were not significant. In the MITT population, celecoxib associated with significant reductions in both clinically significant GI events and iron-deficiency anaemia, the former being driven mainly by a reduction in the incidence of symptomatic ulcers.

We consider the MITT analyses more appropriate than ITT since the MITT events occurred while patients were *actually taking* their allocated study drug or in the month thereafter. The ITT analysis – while usually the more appropriate in efficacy studies, because it can take account of efficacy failures due to patients for any reason stopping their drug – is not well suited to a harms study such as PRECISION since patients in the ITT population could have taken other NSAIDs for as long as thirty months.

Our ITT results, in which complicated upper GI ulcer events were similar between the treatment arms, are comparable to the ITT findings in the pragmatic SCOT trial in Europe. In that trial, arthritis patients without serious cardiovascular disease were randomised to continue an nsNSAID or switch to celecoxib. Follow up of almost 8000 patients was slightly longer than in PRECISION, but the adjudicated GI endpoints (death or hospitalization from an upper GI ulcer complication) were not significantly different between the treatment arms. [9] The study was open-label and had the limitation that endpoints were obtained by data linkage rather than regular adjudicated follow-up. This, plus its substantially smaller patient population, may have accounted for the failure in SCOT to detect a difference between treatment groups in their on-treatment analysis. Two other studies, the CONDOR and GI-REASONS trials, used composite endpoints to capture both upper and lower GI injury, similar to the main GI endpoint in PRECISION. During six months treatment, each trial observed substantially fewer CSGIE in patients randomised to celecoxib than to the comparator nsNSAIDs.[1, 8]

In contrast to these low rates of serious GI events in PRECISION, the CONCERN trial from Hong Kong recently reported upper gastrointestinal bleeding in 6% and 12% of patients taking celecoxib 200 mg/d or naproxen 1000 mg/d for 18 months, despite all being given a PPI. [2] The two studies are very complementary, though. Patients enrolled in PRECISION had low to average risk for GI complications: recent GI bleeding was an exclusion, and few had a peptic ulcer history. By contrast, CONCERN enrolled patients with very high GI risk – those who had already bled from a gastroduodenal ulcer, had their ulcer healed and then were restarted on an NSAID. Chan et al. have shown previously that such patients have a high likelihood of future bleeding after

resumption of NSAIDs.[13] Considering the PRECISION and CONCERN trials in tandem provides a more complete picture of the GI event risks when patients take these NSAIDs.

PRECISION and CONCERN are also the first RCTs comparing a COX-2 selective with nsNSAIDs that have demonstrated significantly fewer GI events on a coxib than an nsNSAID, even in patients who took low-dose aspirin. In PRECISION, there was a suggestive ($P<0.1$) interaction between aspirin, celecoxib and ibuprofen, which diminished but did not abolish the reduction of total GI events by the coxib. However, there was not a significant interaction between aspirin, celecoxib and naproxen: with or without aspirin, less GI events overall occurred on the coxib. Patients taking aspirin were excluded from the six-month VIGOR, CONDOR and GI-REASONS trials,[1, 8, 14] and constituted only 12% of participants in the SCOT trial in Europe.[9] A recent network meta-analysis, which found peptic ulcers and their complications to occur least often in patients who took a coxib plus a PPI, did not evaluate the effects of aspirin.[15] Other RCTs, which permitted aspirin and used similar endpoints to ours (the CLASS, SUCCESS I and TARGET studies), failed to show statistically significant GI benefit when aspirin was taken concurrently; importantly, each of those trials specifically excluded the use of PPIs.[7, 16, 17] Our findings mirror those of a large retrospective cohort study in Quebec Province, which reported hazard ratios (and CI) of 1.00 for nsNSAIDs alone (reference group), 0.41 (0.33-0.50) for celecoxib, 1.01 (0.81-1.25) for celecoxib plus aspirin, and 1.63 (1.29-2.05) for nsNSAIDs plus aspirin.[18] While the risk of confounding in cohort studies, the lack of blinded adjudication of events, and possible confounding by over-the-counter aspirin use makes reliance on those findings more uncertain, the similarity to the PRECISION results lends credence to their validity.

We found that CSGIE occurred about three times more often in the RA patients taking corticosteroids, but there was not a significant interaction between them and the NSAID treatment groups. This increased GI event rate that we demonstrated in an RCT is in agreement with some prior epidemiological data, which reported 4-5 times higher risk of upper GI bleeding in patients taking steroids combined with nsNSAIDs.[19, 20]

Similar to our findings, the CONDOR and GI-REASONS trials reported 42-77% less anaemia of presumed GI origin on celecoxib than the comparator nsNSAIDs. One difference between those trials and PRECISION is that we required biochemical evidence of iron-deficiency (i.e. decreased ferritin or iron saturation), whereas the former studies probably included some patients with recent acute bleeding. Perhaps because of the almost universal use of a PPI, the rate of iron-deficiency

anaemia did not exceed 0.5 per 100 patient years in any of the three treatment arms in PRECISION, and few patients had haemoglobin levels below 10 g/dl.

Earlier studies of the GI adverse effects of NSAIDs have focused on peptic ulcers and their complications, but it is now known (from capsule video-endoscopy) that small intestinal damage is frequent,[21] as is colonic damage.[22] Consequently, recent trials comparing the effects of coxibs and nsNSAIDs have used the composite endpoint we chose for PRECISION.[23] However, acute bleeding events from large or small bowel were very uncommon in PRECISION, and did not exceed 1 per 1000 patient years on any treatment. There is some evidence that celecoxib produces less intestinal erosions and small ulcers than naproxen.[24] Thus the more than fifty percent reduction (compared with the nsNSAIDs) in iron-deficiency anaemia which we found in coxib-treated patients not taking aspirin may be a result of fewer subclinical ulcers and erosions in the small bowel, as well as in the stomach and duodenum.

Whether *H. pylori* contributes to NSAID GI injury has been controversial, with some studies reporting that eradication of the infection before starting NSAID treatment markedly reduced subsequent ulcer complications.[25] However, others found seemingly paradoxical evidence of protection against NSAID ulcers.[26] Our findings suggest that any effect is clinically unimportant in a population such as that in PRECISION, as patients with or without serologic evidence of infection had similar rates of GI events, including iron-deficiency anaemia. However, *H. pylori* serology does not necessarily indicate current infection if patients have recently received treatment. The co-treatment with esomeprazole might mitigate any deleterious effect of *H. pylori*: not only do PPIs suppress the contribution of gastric acid to NSAID ulcer pathogenesis, PPIs also markedly suppress growth of *H. pylori*.[27]

In keeping with previous studies,[28] older patients developed more GI injury than younger ones: about twice as many aged ≥63 developed iron-deficiency anaemia or had a CSGIE. This very population more often needs treatment with an anti-inflammatory for arthritis and more likely has cardiovascular disease.

The major strengths of this study include its very large patient population, the long duration of NSAID treatment and the blinded adjudication of many prespecified GI adverse events. It is also the first to have used the endpoint of *iron-deficiency* anaemia as an indicator of chronic GI injury. Other recent studies that have used anaemia of GI origin as an endpoint have not required evidence of iron deficiency, so are likely to have included instances of acute self-limited bleeding.

The population studied is also very relevant to the population that requires NSAID treatment, many of whom will be at increased risk of cardiovascular disease due to age, obesity and diabetes. Since the individuals enrolled often need low-dose aspirin, and PRECISION participants were stratified for aspirin use, the findings will inform the management of patients with these multiple comorbidities. Similarly, as many patients with RA receive corticosteroids, our findings should assist rheumatologists and their patients to weigh the relative safety of these three NSAIDs in that setting. The results of this trial may prompt re-evaluation of the current guidelines which recommend testing and treating for *H. pylori* before prescribing NSAIDs.[29] Our data suggest that concomitant PPI treatment may render such routine screening unnecessary.

A limitation of the study is the number of patients who were unwilling to continue their assigned treatment for the planned 42 months. While the mean treatment duration of 20 months is longer than similar RCTs in patients taking multiple NSAIDs, it is shorter than anticipated by the protocol. This limitation reflects real world circumstances, particularly for patients with osteoarthritis, where the need for pain treatment fluctuates with time and with the activity of their disease. Since patients were aware that the primary purpose of PRECISION was to determine whether one of the drugs they might receive increases the risk of heart attacks, anxiety about this may have contributed to some not wishing to continue for such a long period. The conclusions we have drawn about the relative GI safety of the three drugs in those taking aspirin, versus those who did not, requires consideration that aspirin use was not randomised. It should also be noted that the testing of interactions was exploratory; it set a significance level that increased the risk of type I error to partly compensate for the reduced statistical power inherent in subgroup analyses. Moreover, the conclusions apply only to the doses of the agents used and in patients taking a proton pump inhibitor. The celecoxib dose was lower than had been used in many of the earlier studies with the drug, but is now that specified as the maximum for osteoarthritis in most countries. The companion paper reported that pain relief with these doses was comparable in patients treated with celecoxib and ibuprofen, though marginally greater in those taking naproxen.[11] This study's conclusions apply only to these three NSAIDs, since NSAIDs vary in their pharmacology and toxicities and the behavior of other members of the nsNSAID class may differ.

In conclusion, PRECISION studied the integrated safety and efficacy of three commonly used NSAIDs, from two pharmacologic groups, which in a very large number of patients at increased cardiovascular risk has provided information about their safety and efficacy across four major

systems: cardiovascular, renal, gastrointestinal and rheumatological. The overall gastrointestinal event rates were reassuringly low, in all treatment arms. Exploratory testing of interactions in subgroups suggests that aspirin may reduce celecoxib's advantage over ibuprofen. Finally, the analysis of the gastrointestinal events, in patients who were actually taking their allocated treatments (rather than in the ITT population where they may have changed to other treatments for extended periods) validates the original tenet of the COX-1 / COX-2 hypothesis—selective inhibition of COX-2 should damage the GI tract less— even in patients who take corticosteroids or are infected with *H. pylori* but also take a PPI.

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AUTHORSHIP

Guarantor of the article: Neville D. Yeomans

Author contributions: NDY was responsible for writing the manuscript and worked together with DYG, MEH, DHS, TS, JV, QW, LMW and KEW on the initial drafts. SEN chaired the Executive Committee; NDY, DYG, MEH, DHS, JSB, PL, AML and TFL were its members; all contributed to the initial design and the ongoing management of the trial. QW and KEW were responsible for the statistical analyses, aided by WB who finalized the statistical analysis plan (before unblinding the study) and validated the results. LMW provided academic study management, and TS and JV were members of the blinded gastrointestinal events adjudication committee. CW contributed to the overall management of the trial and checked the manuscript for accuracy along with WB. All authors approved the final manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information will be found online in the supporting information tab for this article.

Table 1: Baseline characteristics of patients (Intention-to-Treat population)

Characteristic	Celecoxib Group (N=8072)	Ibuprofen Group (N=8040)	Naproxen Group (N=7969)
Age (years)	63.0 ± 9.5	63.2 ± 9.4	63.3 ± 9.4
Female	5175 (64.1%)	5174 (64.4%)	5096 (63.9%)
Race			
White	6058 (75.0%)	5991 (74.5%)	5926 (74.4%)
Black	1090 (13.5%)	1108 (13.8%)	1134 (14.2%)
Asian	164 (2.0%)	173 (2.2%)	172 (2.2%)
Unspecified or other	760 (9.4%)	768 (9.6%)	737 (9.2%)
Body-mass index	32.7 ± 7.3	32.5 ± 7.4	32.6 ± 7.3
Low-dose aspirin use	3701 (45.8%)	3712 (46.2%)	3652 (45.8%)
Corticosteroid use	471 (5.8%)	454 (5.6%)	448 (5.6%)
Arthritis type			
Osteoarthritis	7259 (89.9%)	7208 (89.7%)	7178 (90.1%)
Rheumatoid arthritis	813 (10.1%)	832 (10.3%)	791 (9.9%)
H. pylori sero-positive†	2443 (30.3%)	2385 (29.7%)	2364 (29.7%)
Smoker (current)	1689 (20.9%)	1680 (20.9%)	1631 (20.5%)
Peptic ulcer history	264 (3.3%)	247 (3.1%)	251 (3.1%)

†*H. pylori* serology missing in 200

4 patients. Data are n (%) or mean ± SD

Table 2: Clinically Significant Gastrointestinal Events (CSGIE) and iron-deficiency anaemia

Intention-to-Treat Population									
				Celecoxib vs Ibuprofen		Celecoxib vs Naproxen		Ibuprofen vs Naproxen	
Outcome n (%), n per 100 patient years	Celecoxib N = 8072	Ibuprofen N= 8040	Naproxen N=7969	Adjusted HR‡ (95% CI)	P value‡	Adjusted HR‡ (95% CI)	P value‡	Adjusted HR‡ (95% CI)	P value‡
CSGIE:	55 (0.68%), 0.32	72 (0.90%), 0.42	56 (0.70%), 0.33	0.76 (0.53, 1.08)	0.12	0.97 (0.67, 1.40)	0.86	1.27 (0.90, 1.81)	0.17
Gastroduodenal haemorrhage	11 (0.14%), 0.06	17 (0.21%), 0.06	9 (0.11%), 0.05	0.64 (0.30, 1.38)	0.26	1.22 (0.51, 2.94)	0.67	1.89 (0.84, 4.24)	0.12
Gastric outlet obstruction	1 (0.01%), 0.01	1 (0.01%), 0.01	0 (0.00%), 0.00	1.00 (0.06, 15.94)	1.00	-	-	-	-
Gastroduodenal small or large bowel perforation	8 (0.10%), 0.05	8 (0.10%), 0.05	10 (0.13%), 0.06	1.00 (0.38, 2.67)	0.99	0.79 (0.31, 2.00)	0.62	0.81 (0.32, 2.04)	0.65
Large bowel haemorrhage	15 (0.19%), 0.09	14 (0.17%), 0.08	9 (0.11%), 0.05	1.06 (0.51, 2.20)	0.88	1.67 (0.73, 3.82)	0.23	1.57 (0.68, 3.64)	0.29
Small bowel haemorrhage	2 (0.02%), 0.01	2 (0.02%), 0.01	0 (0.00%), 0.00	1.00 (0.14, 7.06)	1.00	-	-	-	-
Acute GI haemorrhage	7 (0.09%), 0.04	5 (0.06%), 0.03	9 (0.11%), 0.05	1.39 (0.44, 4.38)	0.57	0.78 (0.29, 2.08)	0.61	0.55 (0.19, 1.65)	0.29
Symptomatic gastric or duodenal ulcer	15 (0.19%), 0.09	29 (0.36%), 0.17	20 (0.25%), 0.12	0.51 (0.28, 0.96)	0.04	0.73 (0.37, 1.42)	0.35	1.40 (0.79, 2.47)	0.25
Iron-deficiency anaemia	33 (0.41%), 0.19	64 (0.80%), 0.38	69 (0.87%), 0.41	0.51 (0.33, 0.77)	0.002	0.47 (0.31, 0.71)	0.0003	0.92 (0.65, 1.29)	0.62
Modified Intention-to-Treat Population†									
				Celecoxib vs Ibuprofen		Celecoxib vs Naproxen		Ibuprofen vs Naproxen	
Outcome n (%), n per 100 patient years	Celecoxib N = 8030	Ibuprofen N= 7990	Naproxen N=7933	Adjusted HR‡ (95% CI)	P value‡	Adjusted HR‡ (95% CI)	P value‡	Adjusted HR‡ (95% CI)	P value‡
CSGIE:	27 (0.34%), 0.19	59 (0.74%), 0.44	52 (0.66%), 0.38	0.43 (0.27, 0.68)	0.0003	0.51 (0.32, 0.81)	0.004	1.16 (0.80, 1.69)	0.42
Gastroduodenal haemorrhage	7 (0.09%), 0.05	12 (0.15%), 0.09	6 (0.08%), 0.04	0.56 (0.22, 1.42)	0.22	1.16 (0.39, 3.44)	0.80	2.05 (0.77, 5.46)	0.15

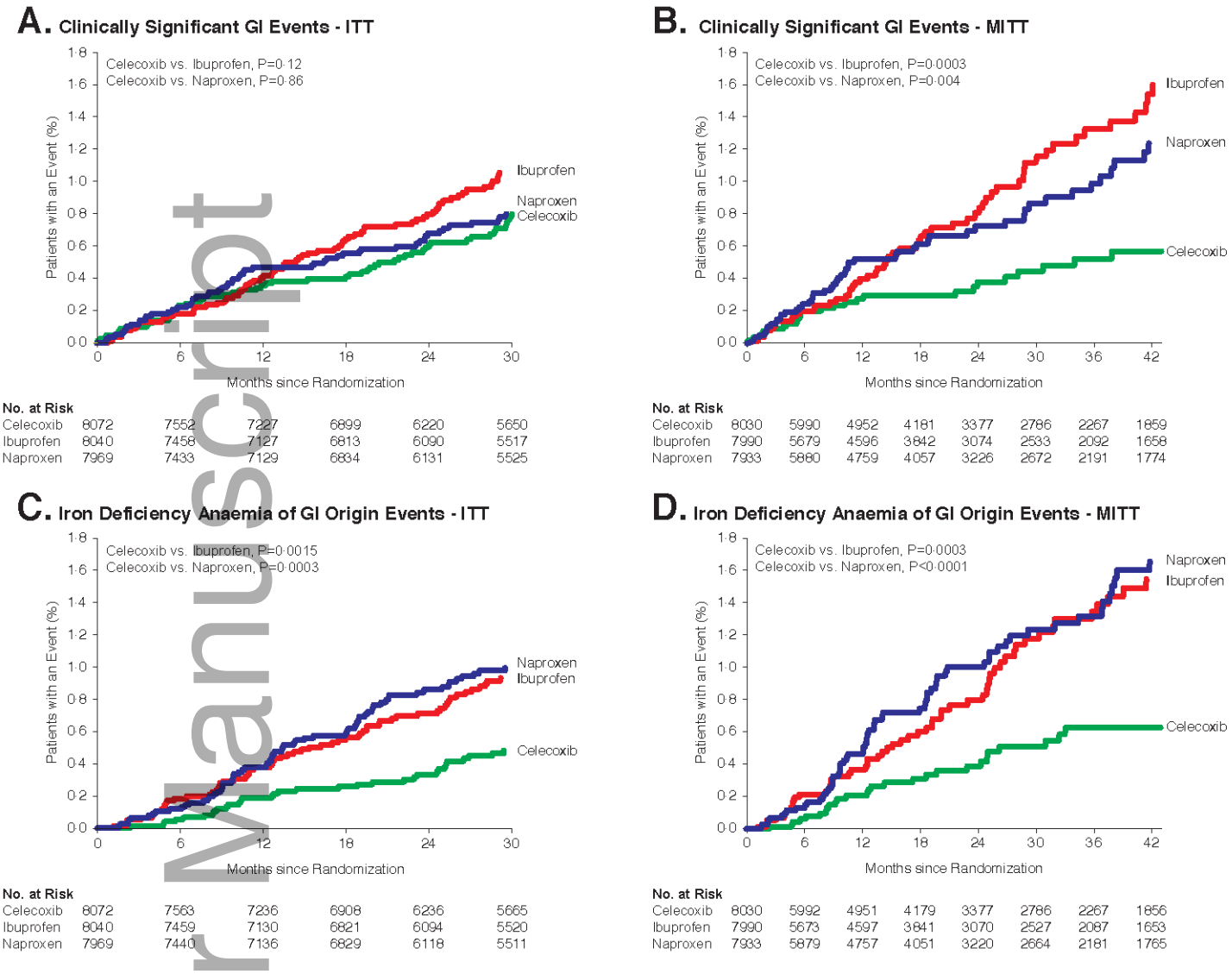
Gastric outlet obstruction	1 (0.01%), 0.01	2 (0.03%), 0.02	0 (0.00%), 0.00	0.45 (0.04, 5.00)	0.52	-	-	-	-
Gastroduodenal small or large bowel perforation	5 (0.06%), 0.04	6 (0.08%), 0.05	8 (0.10%), 0.06	0.80 (0.24, 2.61)	0.69	0.61 (0.20, 1.87)	0.39	0.79 (0.27, 2.27)	0.66
Large bowel haemorrhage	8 (0.10%), 0.06	10 (0.13%), 0.08	10 (0.13%), 0.07	0.76 (0.30, 1.92)	0.55	0.79 (0.31, 2.00)	0.61	1.04 (0.43, 2.50)	0.93
Small bowel haemorrhage	1 (0.01%), 0.01	2 (0.03%), 0.02	0 (0.00%), 0.00	0.48 (0.04, 5.26)	0.55	-	-	-	-
Acute GI haemorrhage	2 (0.02%), 0.01	6 (0.08%), 0.05	7 (0.09%), 0.05	0.31 (0.06, 1.53)	0.16	0.28 (0.06, 1.35)	0.11	0.88 (0.29, 2.61)	0.81
Symptomatic gastric or duodenal ulcer	8 (0.10%), 0.06	22 (0.28%), 0.17	22 (0.28%), 0.16	0.34 (0.15, 0.77)	0.009	0.35 (0.16, 0.79)	0.01	1.03 (0.57, 1.86)	0.93
Iron-deficiency anaemia	27 (0.34%), 0.19	58 (0.73%), 0.44	66 (0.83%), 0.48	0.43 (0.27, 0.68)	0.0003	0.40 (0.25, 0.62)	<0.0001	0.91 (0.64, 1.29)	0.59

†Events while patients on allocated treatment or up to 30 days later. ‡By Cox proportional-hazards model with adjustment for stratification factors: investigator region, arthritis type and aspirin use at baseline. Some patients had more than one CSGIE component during treatment, thus columns do not always total (since CSGIE endpoint reached as soon as first component event recorded).

Legends to Figures

Figure 1: Kaplan-Meier curves for Clinically Significant Gastrointestinal Events and iron-deficiency anaemia of gastrointestinal origin events by treatment allocation. P-values calculated using Cox proportional hazards model with adjustment for stratification factors: investigator region, arthritis type and aspirin use at baseline.

Figure 2: Interaction testing in subgroup analyses for adjudicated GI endpoints.



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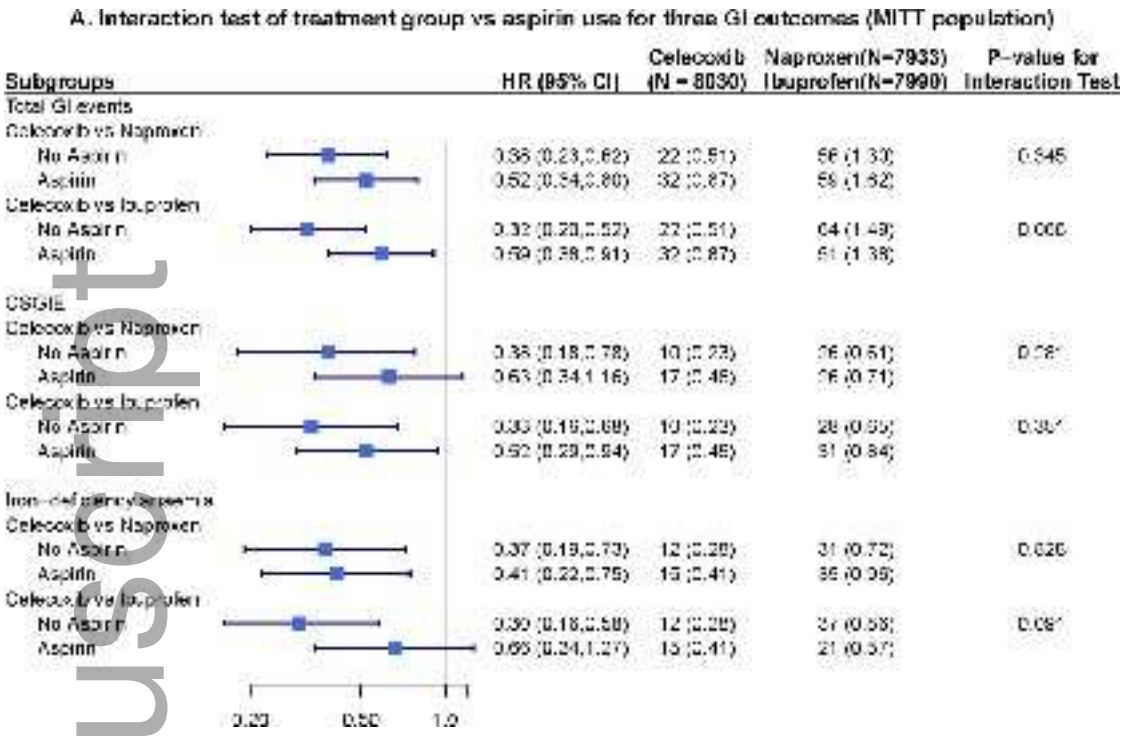

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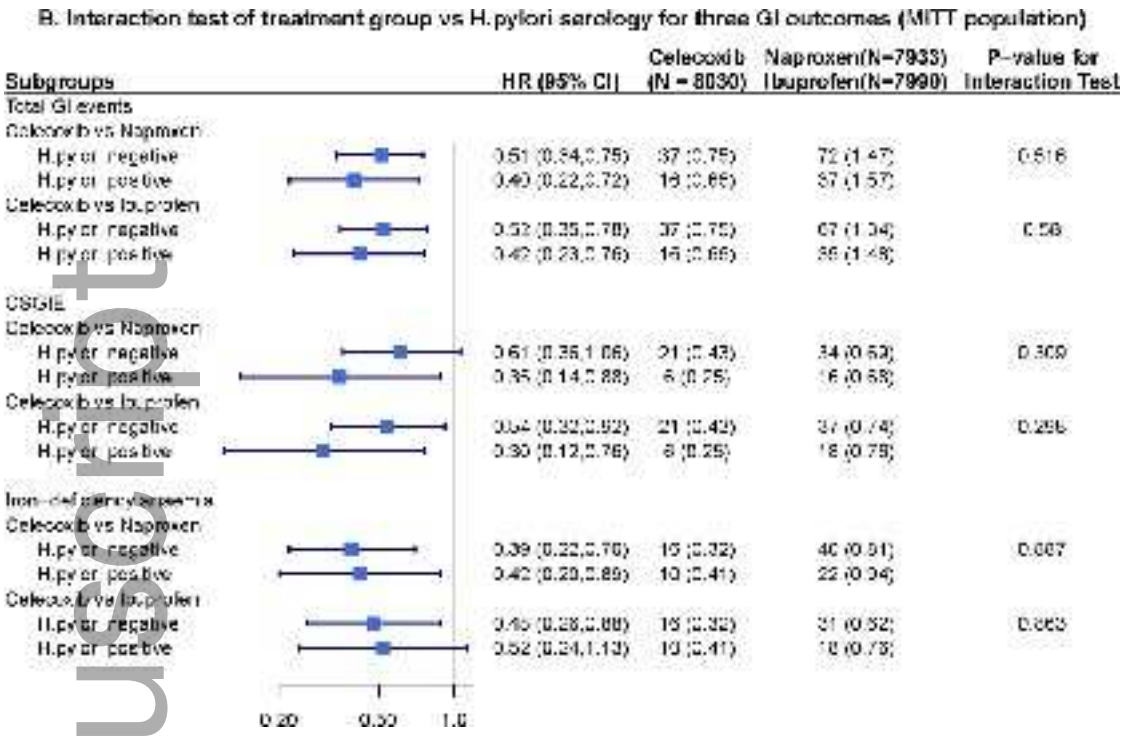

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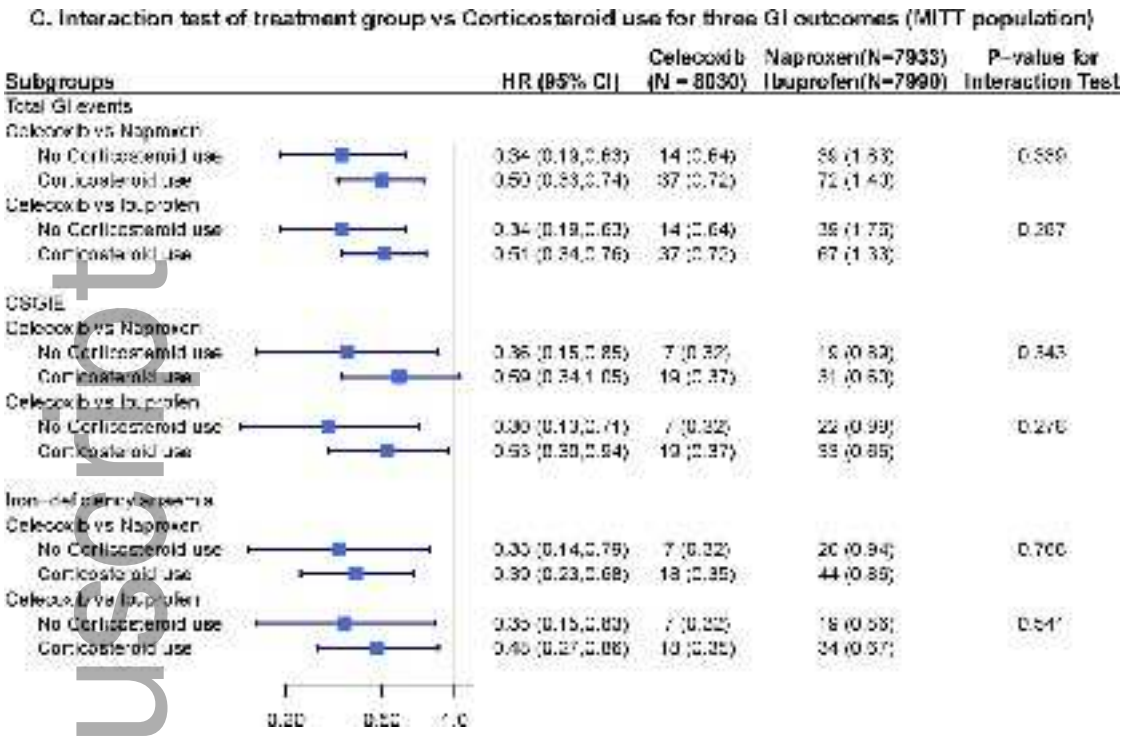

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