

Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial



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Summary

Background Cyclo-oxygenase (COX)-2-selective non-steroidal anti-inflammatory drugs (NSAIDs) and non-selective NSAIDs plus a proton-pump inhibitor (PPI) have similar upper gastrointestinal outcomes, but risk of clinical outcomes across the entire gastrointestinal tract might be lower with selective drugs than with non-selective drugs. We aimed to compare risk of gastrointestinal events associated with celecoxib versus diclofenac slow release plus omeprazole.

Methods We undertook a 6-month, double-blind, randomised trial in patients with osteoarthritis or rheumatoid arthritis at increased gastrointestinal risk at 196 centres in 32 countries or territories. Patients tested negative for *Helicobacter pylori* and were aged 60 years and older or 18 years and older with previous gastroduodenal ulceration. We used a computer-generated randomisation schedule to assign patients in a 1:1 ratio to receive celecoxib 200 mg twice a day or diclofenac slow release 75 mg twice a day plus omeprazole 20 mg once a day. Patients and investigators were masked to treatment allocation. The primary endpoint was a composite of clinically significant upper or lower gastrointestinal events adjudicated by an independent committee. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00141102.

Findings 4484 patients were randomly allocated to treatment (2238 celecoxib; 2246 diclofenac plus omeprazole) and were included in intention-to-treat analyses. 20 (0.9%) patients receiving celecoxib and 81 (3.8%) receiving diclofenac plus omeprazole met criteria for the primary endpoint (hazard ratio 4.3, 95% CI 2.6–7.0; $p < 0.0001$). 114 (6%) patients taking celecoxib versus 167 (8%) taking diclofenac plus omeprazole withdrew early because of gastrointestinal adverse events ($p = 0.0006$).

Interpretation Risk of clinical outcomes throughout the gastrointestinal tract was lower in patients treated with a COX-2-selective NSAID than in those receiving a non-selective NSAID plus a PPI. These findings should encourage review of approaches to reduce risk of NSAID treatment.

Funding Pfizer Inc.

Introduction

Present approaches to reduce risk of upper gastrointestinal adverse events associated with non-steroidal anti-inflammatory drugs (NSAIDs) recommend use of a non-selective NSAID plus a proton-pump inhibitor (PPI) or a cyclo-oxygenase (COX)-2 selective NSAID alone.^{1–3} Although these guidelines, which are based on previous work by ourselves and others,^{4–7} suggest that both strategies reduce risk to the upper gastrointestinal tract, they do not address gastrointestinal adverse events originating beyond the duodenum. Although NSAID use is associated with injury to the small bowel and colon,^{4, 8–10} leading to overt bleeding, ulceration, occult blood loss, or development of anaemia, evidence suggests that COX-2 selective NSAIDs are associated with fewer mucosal lesions of the small bowel than are non-selective NSAIDs plus a PPI.^{11,12} Prespecified prospective trials directly comparing clinically relevant sequelae of these strategies throughout the gastrointestinal tract are not available.

To address the absence of a comprehensive yet clinically practical endpoint, we proposed a composite

endpoint of clinically significant events throughout the gastrointestinal tract (referred to in the protocol as clinically significant upper or lower gastrointestinal events) as a common platform for comparison of future clinical trials of gastrointestinal safety.¹³ This endpoint was designed to assess several potential outcomes relevant to clinical practice, ranging from discontinuation of treatment due to presumed significant occult blood loss to admission to hospital for life-threatening complications. We also included presumed significant occult gastrointestinal blood loss in the definition of the endpoint because this outcome is relevant in view of the number of patients at risk and the potential downstream clinical implications and economic effect.

Since damage to the small bowel and colon is not acid-dependent,^{14,15} we postulated that the risk of clinical outcomes across the entire gastrointestinal tract associated with celecoxib would be lower than that associated with diclofenac plus omeprazole. To address this hypothesis, we aimed to compare treatment with celecoxib and diclofenac plus omeprazole in patients

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with osteoarthritis and rheumatoid arthritis at increased gastrointestinal risk.

Methods

Study design and patients

We undertook a double-blind, triple-dummy, parallel-group randomised trial at 196 active (having recruited more than one patient) centres in 32 countries or territories. One site was excluded because it did not comply with International Conference on Harmonisation Good Clinical Practice guidelines. The protocol was approved by local institutional review boards; all participants provided written informed consent.

Patients with a clinical diagnosis of osteoarthritis or rheumatoid arthritis were eligible if they were expected to need regular NSAID treatment for at least 6 months. Enrolment included those aged 60 years or older with or without a history of gastroduodenal ulceration or gastrointestinal haemorrhage. Patients aged between 18 years and 59 years were enrolled if they had a documented history of gastroduodenal ulceration or gastrointestinal haemorrhage more than 90 days before screening. Patients also had to test negative for *Helicobacter pylori* at the screening visit or have confirmed eradication of the infection at a rescreening visit.

Patients were excluded if they had concomitant use of antiplatelet or anticoagulant drugs, ischaemic heart disease, heart failure, peripheral arterial disease, cerebrovascular disease, gastrointestinal haemorrhage or active gastroduodenal ulceration less than 90 days before screening, inflammatory bowel disease, gastric surgery besides a patch repair, erosive oesophagitis, gastric-outlet obstruction, or active malignant disease. Other exclusion criteria were alcohol and substance misuse, allergy to diclofenac, celecoxib, omeprazole, or sulphonamides, serum alanine transaminase or aspartate transaminase concentrations more than 1.5 times and serum creatinine concentration more than 1.2 times the upper limit of normal (according to the central laboratory definition), and a haemoglobin concentration lower than 115 g/L.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to receive either celecoxib 200 mg twice a day (Pfizer Inc, New York, NY, USA) or diclofenac slow release 75 mg twice a day (Novartis Pharmaceuticals UK Ltd, Camberley, UK) plus omeprazole 20 mg once a day (AstraZeneca LP, Westborough, MA, USA) for 6 months. Patients were stratified first by individual investigator sites and then according to history of gastroduodenal ulceration (yes or no). A computer-generated randomisation schedule (block size four; generated by the Pfizer Global Research and Development randomisation group) was used, with concealed allocation of study drugs in consecutively numbered, sealed bottles. Patients and investigators were masked to treatment allocation.

Procedures

After providing informed consent, patients underwent physical examination and laboratory testing at screening (visit 1). Eligible patients returned at visit 2 and were randomly assigned to treatment groups. Patients could take antacids and non-NSAID analgesic drugs, including paracetamol up to 4 g per day and histamine-2-receptor antagonists no more than 3 days per week. Corticosteroids (prednisolone ≤ 10 mg daily), disease-modifying antirheumatic drugs, or biological treatments were only allowed if patients had been taking a stable dose for 12 or more weeks at randomisation. After randomisation, doses could be adjusted if clinically indicated for disease management; however, patients were not allowed to start treatment with any of these agents during the study. NSAIDs other than study drugs, other antiulcer drugs, cytotoxic agents, lithium, and iron supplements were prohibited.

Patients returned to the clinic at months 1, 2, 3, and 6. At every visit, drug compliance, use of concomitant drugs, safety, Patient's Global Assessment of Arthritis,¹⁶ haemoglobin concentrations, and biochemical markers were assessed. Any patient taking less than 80% or more than 120% of the allocated dose of study drug was regarded as non-compliant. Safety was assessed on the basis of physical examination, laboratory tests, and adverse events and serious adverse events. Patient's Global Assessment of Arthritis¹⁶ was measured on a Likert scale of 1–5, where 1 was very good and 5 very poor. A final visit occurred at month 6, unless the patient discontinued treatment early.

The primary endpoint was a composite of clinically significant events occurring throughout the gastrointestinal tract. Definitions of the endpoint criteria were described by Chan and colleagues¹³ and are shown in the webappendix. Components of the primary endpoint were gastroduodenal, small-bowel, or large-bowel haemorrhage; gastric-outlet obstruction; gastroduodenal, small-bowel, or large-bowel perforation; clinically significant anaemia of defined gastrointestinal or presumed occult gastrointestinal origin (including possible blood loss from the small bowel); and acute gastrointestinal haemorrhage of unknown origin (including presumed small-bowel haemorrhage). Clinically significant anaemia was defined in the protocol as a decrease in haemoglobin of 20 g/L or more, or a decrease in haematocrit of at least 10 percentage points.¹⁷

Patients with suspected gastrointestinal events were asked to return for an event visit, at which the protocol recommended that three faecal occult blood tests and gastroscopy be done. If the investigator could not identify a source of upper gastrointestinal blood loss, colonoscopy was recommended. Patients without an identified source would undergo investigations per protocol to exclude non-gastrointestinal origin and further endoscopic or radiological investigations, as deemed appropriate by the local investigator. Members of an independent masked adjudication committee decided whether the primary

For the International Conference on Harmonisation Good Clinical Practice guidelines see <https://www.ich.org>

For the study protocol see <http://www.clinicaltrials.gov/ct2/show/NCT00141102?term=A3191084&rank=1>

See Online for webappendix

endpoint was attained in accordance with the predefined criteria (webappendix). If the source of bleeding was identified, the event was adjudicated as clinically significant anaemia of defined gastrointestinal origin. Without a source, if no clinical or laboratory evidence of a non-gastrointestinal source of anaemia was identified, the event was adjudicated as clinically significant anaemia of presumed occult gastrointestinal origin, including possible small-bowel blood loss.

Key secondary endpoints were Patients' Global Assessment of Arthritis (obtained at every visit),¹⁶ clinically significant events throughout the gastrointestinal tract plus symptomatic ulcers (defined as ulcer on endoscopy in a patient with dyspepsia), moderate-to-severe abdominal symptoms, and withdrawal due to gastrointestinal adverse events.

An independent data safety and monitoring committee oversaw the overall safety of the trial. From October, 2005, serious cardiovascular adverse events were adjudicated by an independent masked cardiovascular event committee. Potential cardiovascular events were classified as primary, according to the Anti-Platelet Trialists Collaboration criteria (acute myocardial infarction, stroke, and cardiovascular deaths)¹⁸ or secondary, predefined as unstable angina, coronary revascularisation, transient ischaemic attack, venous and peripheral arterial vascular thrombotic events, and congestive heart failure.

Statistical analysis

SAS (version 8.02) was used for all analyses. With an assumed rate of the primary endpoint at month 6 of 1·1% for celecoxib and 2·3% for diclofenac plus omeprazole,¹⁹ and a drop-out rate of roughly 20%, a sample size of 4402 would achieve 80% power to detect the treatment difference at a 5% level of significance using the χ^2 test.

Only events confirmed by the adjudication committee were included in the analysis. The primary and secondary analyses were by intention to treat, including all patients randomly allocated to treatment. We assessed the primary endpoint using a life-table (actuarial) extension of the Mantel-Haenszel method,²⁰ stratified by region and history of gastroduodenal ulceration (yes or no). Patients who discontinued treatment during the study or who completed the study with no events were censored. Predefined regions were western Europe, South America, Asia, and eastern Europe. We computed rates of the primary endpoint at month 6 in each group and the rate difference between the two treatment groups using Zhang and Klein's method.²¹ We analysed changes from baseline in the Patients' Global Assessment of Arthritis¹⁶ using a generalised linear model, with last measurements carried forward.

A planned interim analysis was undertaken by the data safety and monitoring committee after 50% of patients completed the trial. Using a group sequential approach, we intended to stop the trial early for superiority if there was an overwhelming body of evidence. On reviewing the interim data, the data safety and monitoring

committee did not recommend changes in study conduct; hence, the adjusted nominal level of significance for the final analysis was set to 0·049.

This study is registered at ClinicalTrials.gov, number NCT00141102.

Role of the funding source

Authors employed by Pfizer (MB and HN) participated in monitoring of study progress and collection and analysis of data. The sponsor did not participate in adjudication of potential gastrointestinal and cardiovascular events. FC, AL, JS, and JG had full access to all data and had final responsibility for the decision to submit for publication.

Results

Between Oct 31, 2005, and May 11, 2009, 8098 potentially eligible patients were screened; 4484 patients were enrolled and were included in intention-to-treat analyses (2238 celecoxib, 2246 diclofenac plus omeprazole; figure 1, table 1). Predominant reasons for screening failure were *H pylori* infection (2476 patients, 75%) and low baseline haemoglobin (217, 6%). 876 patients initially infected with *H pylori* were successfully treated and then randomly allocated to celecoxib (444, 51%) and diclofenac plus omeprazole (432, 49%). Median duration of study treatment was 176 days (range 1–318) in the celecoxib group and 175 days (1–225) in the

	Celecoxib (n=2238)	Diclofenac slow release plus omeprazole (n=2246)
Women	1848 (83%)	1822 (81%)
Osteoarthritis	1884 (84%)	1890 (84%)
Age		
Mean	65 (7·8; 26–89)	65 (7·6; 25–93)
60 years or older	1940 (87%)	1969 (88%)
Ethnicity		
White	1238 (55%)	1212 (54%)
Black	49 (2%)	57 (3%)
Asian	299 (13%)	311 (14%)
Hispanic	462 (21%)	464 (21%)
Other	190 (8%)	202 (9%)
Region of origin		
Western Europe	450 (20%)	447 (20%)
South America	878 (39%)	874 (39%)
Asia	291 (13%)	297 (13%)
Eastern Europe	619 (28%)	628 (28%)
Haemoglobin (g/L)	140 (11; 99–188)	140 (11; 103–189)
Haematocrit (%)	41% (3·5; 29·0–59·4)	41% (3·5; 31·0–55·0)
History of gastroduodenal ulcer or ulcer bleeding	421 (19%)	424 (19%)
Previous <i>Helicobacter pylori</i> infection	478 (21%)	486 (22%)
Comorbidity*	1447 (65%)	1553 (69%)

Data are n (%) or mean (SD; range). *Comorbidities included cardiovascular diseases (excluding coronary heart disease and heart failure), diabetes mellitus, hypertension, chronic lung diseases, chronic liver diseases, deep vein thrombosis, kidney diseases, and history of anaemia.

Table 1: Patient baseline characteristics

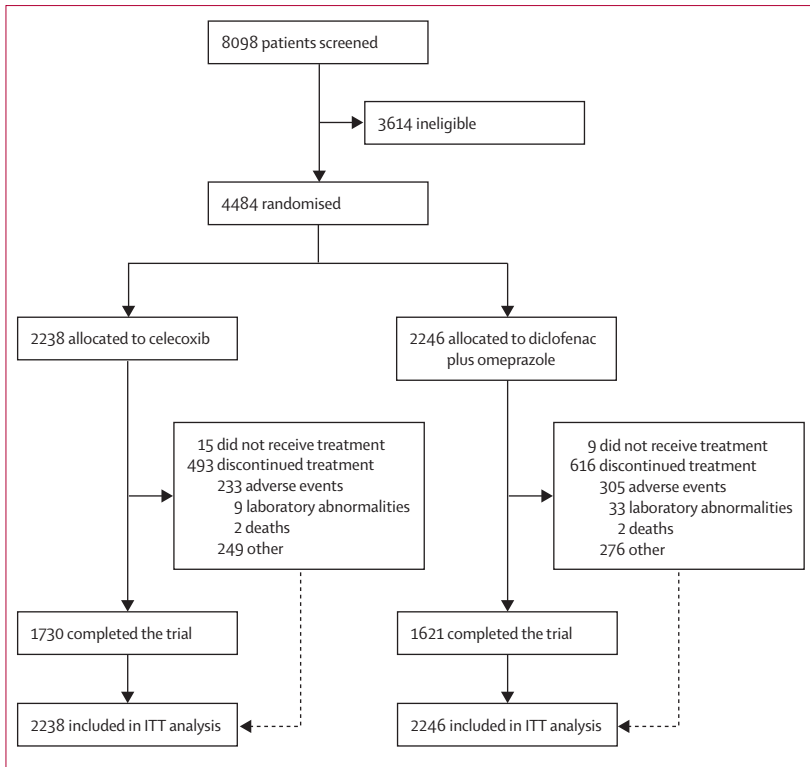


Figure 1: Trial profile
ITT=intention-to-treat.

diclofenac plus omeprazole group. 493 (22%) patients in the celecoxib group discontinued treatment early (42 discontinuations related to study drug), as did 616 (27%) patients in the diclofenac plus omeprazole group (83 related to study drug). 2193 (98%) patients in the celecoxib group and 2179 (97%) in the diclofenac

plus omeprazole group had drug adherence between 80% and 120%.

Site investigators reported 253 potential endpoint cases to the gastrointestinal adjudication committee for assessment (71 in the celecoxib group and 182 in the diclofenac plus omeprazole group). The committee identified 20 primary endpoints in patients receiving celecoxib and 81 in patients taking diclofenac plus omeprazole. With a Cox proportional hazard model, the proportion of patients reaching the primary endpoint during the 6-month study period was 0.9% (95% CI 0.5–1.3) in the celecoxib group and 3.8% (2.9–4.3) in the diclofenac plus omeprazole group (difference 2.9%, 2.0–3.8%; $p < 0.0001$) (table 2, figure 2). The hazard ratio was 4.3 (2.6–7.0) in favour of celecoxib. The main driving force behind the primary endpoint was a haemoglobin decrease of 20 g/L or more (table 2). Fewer patients in the celecoxib group than in the diclofenac plus omeprazole group had a significant decrease in haemoglobin (15 vs 77 patients). Of the 92 patients who had a decrease of 20 g/L or more with or without defined lesions, 50 had haemoglobin concentrations lower than 115 g/L (which was the central laboratory definition of anaemia for both sexes); five (10%) were in the celecoxib group and 45 (90%) were in the diclofenac plus omeprazole group.

63 patients had events that were judged by the committee to be clinically significant anaemia of presumed occult gastrointestinal origin, including possible blood loss from the small bowel. Of these patients, 56 (89%) had a gastroscopy, 27 (43%) had a colonoscopy, and seven (11%) had neither; an alternative explanation was not identified for any of these patients, thus the possibility remains that the small bowel was the source of bleeding. 152 potential gastrointestinal events

	Celecoxib (n=2238)	Diclofenac slow release plus omeprazole (n=2246)
Clinically significant events through the GI tract, total	20	81
Gastroduodenal haemorrhage	3	3
Gastric outlet obstruction	0	0
Gastroduodenal, small-bowel, or large-bowel perforation	0	0
Small-bowel haemorrhage	0	0
Large-bowel haemorrhage	1	1
Clinically significant anaemia of defined GI origin		
Total	5	24
Gastroduodenal ulcer or erosions	5	20
Early gastric cancer	0	1
Lower GI bleeding*	0	1
Lower GI ulcer or erosions	0	2
Acute GI haemorrhage of unknown origin, including presumed small-bowel haemorrhage	1	0
Clinically significant anaemia of presumed occult GI origin including possible small-bowel blood loss	10	53

Data are number of patients. GI=gastrointestinal. *Endoscopic assessment of anaemia revealed bleeding angiodysplasia in the colon of one patient in the diclofenac plus omeprazole group.

Table 2: Primary endpoint and components

were adjudicated as not reaching the primary endpoint. 51 of these events were in the celecoxib group (18 [35%] were anaemia due to non-gastrointestinal causes and 33 [65%] did not meet prespecified criteria) and 101 were in the diclofenac plus omeprazole group (26 [26%] were anaemia due to non-gastrointestinal causes and 75 [74%] did not meet prespecified criteria).

Least-squares mean change from baseline to visit 6 in Patient's Global Assessment of Arthritis¹⁶ showed an improvement of 0.75 (0.02) in the celecoxib group and 0.77 (0.02) in the diclofenac plus omeprazole group ($p=0.41$). For the secondary composite endpoint of clinically significant events throughout the gastrointestinal tract plus symptomatic ulcers, fewer events were reported for patients who received celecoxib (25 patients, 1%) than for patients who received diclofenac plus omeprazole (92, 5%; $p<0.0001$). The number of patients with moderate-to-severe abdominal symptoms at month 6 was 336 (16%) for the celecoxib group and 384 (19%) for the diclofenac plus omeprazole group ($p=0.03$). 114 (6%) patients in the celecoxib group and 167 (8%) in the diclofenac plus omeprazole group withdrew early because of gastrointestinal adverse events ($p=0.0006$).

Table 3 shows a summary of adverse events. Two patients in each group died. Reported causes of death were pulmonary embolism and bronchopneumonia in the celecoxib group and two cases of cardiac arrest in the diclofenac plus omeprazole group. 28 potential cardiovascular events were assessed by the adjudication committee; 21 treatment-related events were confirmed in 20 patients. 11 were primary Anti-Platelet Trialists Collaboration events; six of these were in the celecoxib group and five were in the diclofenac plus omeprazole group (two myocardial infarctions and three strokes in each group, plus one pulmonary embolism [the cardiovascular death] in the celecoxib group). Nine confirmed events were secondary: one unstable angina, two transient ischaemic attacks, one peripheral arterial event, and four cases of venous thrombosis in the celecoxib group and one transient ischaemic attack in the diclofenac plus omeprazole group.

Discussion

In this population of patients with osteoarthritis or rheumatoid arthritis who were not using antiplatelet and anticoagulant drugs, the rate of clinically significant gastrointestinal events was four times higher in those receiving diclofenac plus omeprazole than in those receiving celecoxib. As in our previous trial, rates of upper gastrointestinal bleeding did not differ between treatment groups.⁴ However, we noted large differences for the likelihood of clinically significant blood loss from the gastrointestinal tract. For patients with substantial decreases in haemoglobin and defined lesions, our data support the contribution of the upper gastrointestinal tract as a potential site of blood loss. Notably, the frequency of upper gastrointestinal ulcers or erosions

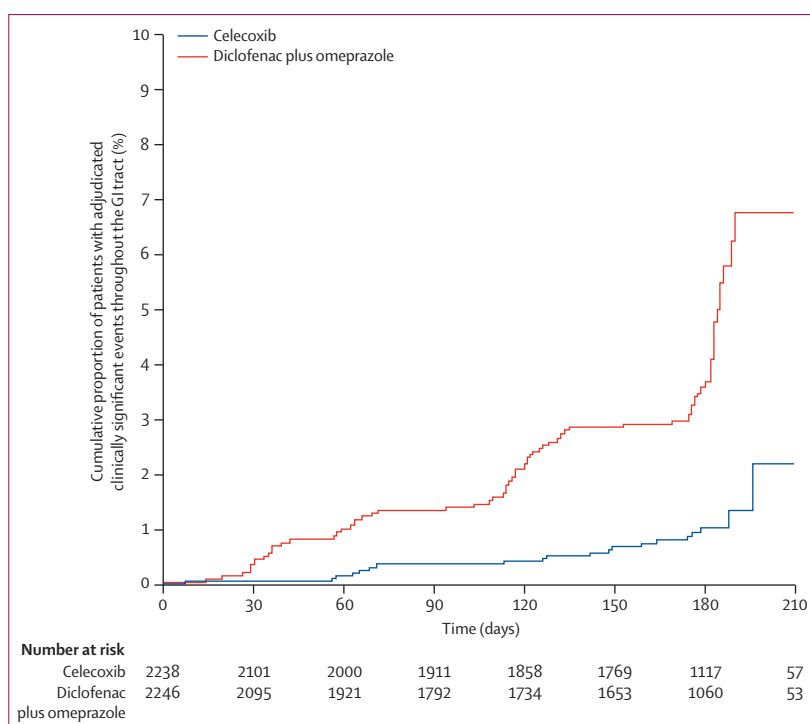


Figure 2: Cumulative proportion of patients with adjudicated clinically significant events throughout the gastrointestinal tract

Numbers at risk on day 180 are the number of patients who had not yet returned for the final visit (because a time window was allowed for this scheduled visit). Proportions of patients with the primary endpoint were estimated on the basis of the Cox-proportional model, as described by Zhang and Klein.²¹ GI=gastrointestinal.

	Celecoxib (n=2223)*	Diclofenac slow release plus omeprazole (n=2237)*
Patients with AEs†		
All	1137 (51%)	1287 (58%)
Treatment-related	562 (25%)	736 (33%)
Patients with SAEs‡		
All	61 (3%)	61 (3%)
Treatment-related	13 (1%)	8 (<1%)
Patients who had dose reduced or temporarily discontinued because of AEs		
All	130 (6%)	210 (9%)
Treatment-related	48 (2%)	103 (5%)

Data are n (%). AE=adverse event. SAE=serious adverse event. *Patients who could be assessed for AEs. †An AE is defined as any untoward medical occurrence in a patient administered a product or medical device (the event need not necessarily have a causal association with the treatment or usage). ‡An SAE is defined as any untoward medical occurrence at any dose that results in death, is life threatening, or results in a congenital abnormality or birth defect.

Table 3: Summary of adverse events

associated with haemoglobin decreases was significantly higher in the diclofenac plus omeprazole group than in the celecoxib group. These results confirm our previous findings in patients with high gastrointestinal risk.²²

Reductions in haemoglobin in the absence of a defined lesion were more than five times more likely for patients receiving diclofenac plus omeprazole than for those receiving celecoxib. We recognise that this component of the primary endpoint was affected by the clinical

judgment of the masked adjudication committee. Their adjudication was on the basis of endoscopic and radiological assessment and consideration of non-gastrointestinal sources of haemoglobin reduction. A decrease in haemoglobin is an important yet poorly recognised finding because occult blood loss was not a predefined event in previous trials. Unlike overt bleeding, occult gastrointestinal blood loss does not necessarily lead to hospital admission, as in our study. However, one should not underestimate the relevance of a significant decrease in haemoglobin because in clinical practice this finding often leads to further investigation and premature discontinuation of treatment. Results of epidemiological studies have consistently shown that even mildly low or low-normal haemoglobin concentrations were independently associated with increased risk of frailty, poor functional outcomes, admission to hospital, and mortality.^{23–25}

In support of the primary analysis, treatment with celecoxib was associated with a lower rate of moderate-to-severe abdominal symptoms and withdrawal because of gastrointestinal adverse events than was treatment with diclofenac plus omeprazole. These small but significant differences contradict the results of a recent meta-analysis²⁶ suggesting that co-therapy with non-selective NSAIDs plus a PPI was better tolerated than was a COX-2 selective NSAID alone. This meta-analysis, however, was hampered by scarcity of head-to-head data for comparison of COX-2 selective NSAIDs versus non-selective NSAIDs plus a PPI.

This trial has important strengths. First, we directly and rigorously compared two widely advocated strategies to reduce NSAID-associated gastrointestinal risk. Second, unlike previous trials of gastrointestinal outcomes that focused only on upper gastrointestinal events, we used a comprehensive composite endpoint to cover many facets of gastrointestinal outcomes that are relevant to clinical practice, ranging from discontinuation of treatment due to decreases in haemoglobin to admission to hospital because of complications. Third, our findings will affect clinical practice because they show the importance of clinical awareness of decreasing haemoglobin associated with NSAID use, even if the patient is without apparent clinical disease.

Our study had limitations. First, we excluded patients taking aspirin. Although this criterion reduced the confounding effect of aspirin in the gastrointestinal mucosa, our results cannot be extrapolated to patients at cardiovascular risk using aspirin, for whom we advocate alternative treatment approaches.¹ Second, the adjudication of presumed occult gastrointestinal bleeding was a diagnosis by exclusion rather than by direct confirmation of the source of blood loss. Thus, we cannot say with certainty that the bleeding site was the gastrointestinal tract, let alone the small bowel. However, because we used masked adjudication, we believe that any misclassification of presumed occult gastrointestinal bleeding should have been equally distributed between

the two groups. When we excluded this limitation by comparing only (post hoc) the other components of the primary endpoint, the overall significant difference between treatments was maintained, favouring celecoxib ($p=0.0035$). Third, our study was not powered nor designed to assess the difference in cardiovascular outcomes between treatment groups. Furthermore, censoring of data because of potential gastrointestinal events reduced duration of treatment exposure and thus the likelihood of development of cardiovascular events, especially in the diclofenac plus omeprazole group. As a consequence, the cardiovascular data should be interpreted with caution because they might not show the true cardiovascular hazard of the two treatments.

COX-2 selective NSAIDs were developed to provide anti-inflammatory therapy; avoiding COX-1 inhibition and sparing the enzyme in the gut supports mucosal integrity. Several large outcome studies^{19,27,28} have shown reductions in upper gastrointestinal tract ulceration and complications for patients using these drugs compared with non-selective NSAIDs. Although PPIs effectively reduce upper gastrointestinal ulceration,^{4,5} the CONDOR trial, by directly comparing these strategies for gastrointestinal risk reduction in a large randomised trial, has provided a new understanding of the gastrointestinal effect of these two seemingly similar treatment approaches.

Since guidelines recommend that selection of NSAID therapy be driven by consideration of both cardiovascular and gastrointestinal effects of treatment,^{29–31} CONDOR has provided new data relevant to patients requiring anti-inflammatory therapy who are at increased gastrointestinal but not increased cardiovascular risk. In this population, the gastrointestinal outcomes of a COX-2 selective NSAID were quite different to those of a non-selective NSAID plus a PPI. Further understanding of the cardiovascular outcomes of these two strategies of gastrointestinal risk reduction requires the results of ongoing trials that have been designed directly to address that important clinical question. The findings of the CONDOR trial should encourage guideline committees to review their treatment recommendations for arthritis patients.

Contributors

FKLC proposed the research idea to the sponsor, and the protocol was developed by FKLC, AL, JS, and JLG. An independent executive committee provided input and oversight throughout the study. A steering committee undertook governance of the study, and the safety of the trial, including the recommendation of the results of the interim analysis, were assessed by an independent data safety and monitoring committee. Two independent masked committees adjudicated potential gastrointestinal and cardiovascular events (see webappendix). MFB monitored and oversaw the study progress and coordinated work between investigators and various committees. Data analysis was done by HN, and MFB and HN were responsible for data interpretation. The report was prepared by the authors, with editorial support. All authors read, revised, and approved the final report.

Conflicts of interest

FKLC, JLG, AL, and JS are all consultants to Pfizer. FKLC is the International Associate Editor of the American Journal of Gastroenterology and has also served as a consultant for Eisai, Takeda, and

Otsuka. He has received grants from Pfizer and has been paid lecture fees (including service on speakers' bureaus) by Pfizer, AstraZeneca, and Takeda. JLG reports having served as a consultant to AstraZeneca, TAP, Takeda, Novartis, Pozen, Logical Therapeutics, Proctor and Gamble, PLX, Wyeth, Astellas, Amgen, Given, GlaxoSmithKline, and Merck, and has received grant support and honoraria from Pfizer, AstraZeneca, TAP, Takeda, Novartis, Pozen, Logical Therapeutics, Amgen, and Given. He has also been paid lecture fees (including service on speakers' bureaus) by AstraZeneca, TAP, Takeda, Novartis, Pozen, Logical Therapeutics, and Given. AL reports having received grants and lecture fees from Pfizer and AstraZeneca, and having been involved in the steering committee of studies conducted by Pfizer (CONDOR) and AstraZeneca (Energy and Gades Studies). JS reports serving as a consultant to AstraZeneca, Takeda, Pozen, Bayer, Novartis, and Nicox and has received a grant from AstraZeneca. He has also been paid lecture fees (including service on speakers' bureaus) by AstraZeneca and Takeda. MFB and HN are both currently employees of Pfizer Inc and own Pfizer stock.

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