Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison

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Summary

Background Upper gastrointestinal safety of cyclo-oxygenase (COX)-2 selective inhibitors versus traditional non-steroidal anti-inflammatory drugs (NSAIDs) has not been assessed in trials that simulate standard clinical practice. Our aim was to assess the effects of these drugs on gastrointestinal outcomes in a population that includes patients taking gastrointestinal protective therapy.

Methods A prespecified pooled intent-to-treat analysis of three double-blind randomised comparisons of etoricoxib (60 or 90 mg daily) and diclofenac (150 mg daily) in 34 701 patients with osteoarthritis or rheumatoid arthritis was done for upper gastrointestinal clinical events (bleeding, perforation, obstruction, or ulcer) and the subset of complicated events (perforation, obstruction, witnessed ulcer bleeding, or significant bleeding). We also assessed such outcomes in patients who were taking concomitant proton pump inhibitors (PPIs) or low-dose aspirin. These trials are registered with ClinicalTrials.gov, with the numbers NCT00092703, NCT00092742, and NCT00250445.

Findings Overall upper gastrointestinal clinical events were significantly less common with etoricoxib than with diclofenac (hazard ratio [HR] 0·69, 95% CI 0·57–0·83; p=0·0001). There were significantly fewer uncomplicated gastrointestinal events with etoricoxib than there were with diclofenac (0·57, 0·45–0·74; p<0·0001); there was no difference in complicated events (0·91, 0·67–1·24; p=0·561). PPIs were used concomitantly for at least 75% of the study period by 13 862 (40%) and low-dose aspirin by 11 418 (33%) patients; treatment effects did not differ significantly in these individuals.

Interpretation There were significantly fewer upper gastrointestinal clinical events with the COX-2 selective inhibitor etoricoxib than with the traditional NSAID diclofenac due to a decrease in uncomplicated events, but not in the more serious complicated events. The reduction in uncomplicated events with etoricoxib is maintained in patients treated with PPIs and is also observed with regular low-dose aspirin use.

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Introduction

Traditional non-steroidal anti-inflammatory drugs (NSAIDs) significantly increase the risk of upper gastrointestinal clinical events such as bleeding ulcers by about two to five times compared with no NSAID therapy.[1] Strategies used to decrease the risk of NSAID-associated upper gastrointestinal clinical events include medical co-therapy with misoprostol or proton pump inhibitors (PPIs), or the use of cyclo-oxygenase (COX)-2 selective inhibitors.

PPIs are most frequently used as co-therapy with traditional NSAIDs,[2] although no large clinical outcome studies have assessed this strategy. However, randomised trials in patients with complicated ulcers indicate that PPIs significantly decrease recurrent ulcer complications compared with *Helicobacter pylori* therapy in *H pylori*-positive patients taking naproxen[3] and compared with placebo in patients taking low-dose aspirin.[4]

The incidences of upper gastrointestinal clinical events have been shown to be significantly less with COX-2 selective inhibitors than traditional NSAIDs in randomised gastrointestinal outcomes trials of 12 weeks to 12 months duration.[5–8] However, none of these trials simulated real-world practice because gastrointestinal protective therapies—eg, PPIs—were not allowed. Thus, the effect of COX-2 selective inhibitors versus traditional NSAIDs in patients taking PPIs is unknown.

Another area of controversy relates to the use of COX-2 selective inhibitors plus low-dose aspirin. Endoscopic trials indicate that the combination of a COX-2 selective NSAID and low-dose aspirin has an ulcer incidence comparable with a traditional NSAID,[9] but still lower than the rate with a traditional NSAID plus low-dose aspirin.[10,11] An observational cohort study reported a significantly lower rate of upper gastrointestinal complications with COX-2 selective inhibitors than with traditional NSAIDs in low-dose aspirin users.[12] However, subgroup analyses from randomised outcomes trials of COX-2 selective inhibitors versus traditional NSAIDs have not identified

significant reductions in upper gastrointestinal clinical events with low-dose aspirin use.[5,7,8]

Although upper gastrointestinal clinical events raise greater concern among physicians, upper gastrointestinal symptoms such as dyspepsia are the most common side-effects that occur with NSAID use. Dyspepsia is reported weekly in up to about 30% of patients taking NSAIDs regularly, and in up to 15% daily.[13] Furthermore, dyspepsia is the most common reason for discontinuation of NSAID therapy.[14] Among patients without ulcers, PPIs have shown significant benefit in relief or prevention of NSAID-associated upper gastrointestinal symptoms.[15–17] COX-2 selective inhibitors have also been reported to induce less dyspepsia than traditional NSAIDs.[18–22] However, the relative benefit of traditional NSAIDs versus COX-2 selective inhibitors on upper gastrointestinal symptoms in PPI users has not been studied in a clinical trial.

The MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term) programme provides a randomised comparison of the COX-2 selective inhibitor etoricoxib and the traditional NSAID diclofenac in 34701 osteoarthritis and rheumatoid arthritis patients followed for a mean duration of 18 months.[23,24] The primary endpoint was thrombotic cardiovascular events, but upper gastrointestinal clinical events were also a predefined endpoint. Our aim was to assess upper gastrointestinal outcomes in a setting that simulated real-world practice, in which patients with gastrointestinal risk factors were encouraged to use protective PPI therapy and those with cardiovascular risk were encouraged to use low-dose aspirin.

	Criteria
Perforation*	Perforation due to non-malignant gastric or duodenal ulcer confirmed by endoscopy, surgery, radiography (intraperitoneal air or contrast extravasation), or autopsy
Obstruction*	Postprandial nausea and vomiting for ≥24 h and evidence of narrowing of the distal stomach, pylorus, or duodenum due to a non-malignant ulcer documented by endoscopy, surgery, radiography, or autopsy
Complicated bleeding*	1 Health-care provider-witnessed haematemesis, melaena, haematochezia, or nasogastric aspirate with blood or coffee grounds material; 2 Active upper gastrointestinal bleeding documented by endoscopy, angiography, or surgery; 3 Occult blood-positive stool associated with significant bleeding† and with a documented upper gastrointestinal lesion judged by the health-care provider to be the source of the bleeding; or 4 Patient-reported haematemesis, melaena, or haematochezia associated with significant bleeding† and a documented upper gastrointestinal lesion judged by the health-care provider to be the source of the bleeding
Uncomplicated bleeding‡	1 Occult blood-positive stool associated with a documented upper gastrointestinal lesion judged by the health-care provider to be the source of the bleeding and stigmata of recent bleeding (visible vessel, pigmented spot, or clot in ulcer base) at endoscopy but no significant bleeding†; or 2 Patient-reported haematemesis, melaena, or haematochezia associated with a documented upper gastrointestinal lesion judged by the health-care provider to be the source of the bleeding and stigmata of recent bleeding at endoscopy but no significant bleeding†
Uncomplicated ulcer‡	Gastric or duodenal ulcer documented on clinical assessment by endoscopy, surgery, upper gastrointestinal contrast radiography, or autopsy

*Complicated event. †Hypotension, orthostatic changes in heart rate (>20 bpm) or blood pressure (>20 mm Hg systolic or 10 mm Hg diastolic), haemoglobin drop ≥20 g/L, or transfusion. ‡Uncomplicated event.

Table 1: **Prespecified criteria for upper gastrointestinal clinical events**

	Etoricoxib group (n=17412)	Diclofenac group (n=17289)
Age (years)	63·2 (8·5)	63·2 (8·5)
<65 years	10178 (58%)	10127 (59%)
≥65 to <75 years	5201 (30%)	5261 (30%)
≥75 years	2033 (12%)	1901 (11%)
Sex (female)	12925 (74%)	12823 (74%)
Osteoarthritis	12533 (72%)	12380 (72%)
Rheumatoid arthritis	4878 (28%)	4909 (28%)
Cigarette smoker	2034 (12%)	2037 (12%)
Low-dose aspirin use	6030 (35%)	5976 (35%)
PPI use	6742 (39%)	6664 (39%)
Traditional NSAID use	14209 (82%)	14174 (82%)
COX-2 selective inhibitor use	4873 (28%)	4939 (29%)
Systemic corticosteroid use	2685 (15%)	2705 (16%)
Methotrexate use	2762 (16%)	2831 (16%)
Other DMARD use	2246 (13%)	2208 (13%)
History of upper gastrointestinal event	1127 (6%)	1133 (7%)

Data are mean (SD) or n (%). DMARD=disease modifying antirheumatic drug. NSAID=non-steroidal anti-inflammatory drug. PPI=proton pump inhibitor.

Table 2: **Selected baseline characteristics in intention-to-treat population**

Methods

Study design and patients

The design of the MEDAL programme and the results for cardiovascular outcomes have been presented in detail elsewhere.[23,24] In brief, this study was done between June, 2002, and May, 2006, at 1380 sites in 46 countries. The MEDAL programme was prospectively designed to pool data from three randomised, double-blind clinical trials: the MEDAL study, the Etoricoxib *vs* Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness (EDGE) study, and the EDGE II study. Similar entry criteria and study medications across these three long-term studies made them suitable for pooling. The ethics committee for each study site approved the trial at that site and all patients provided written informed consent before participation.

Eligibility for the MEDAL programme has been described previously.[24] Briefly, patients with osteoarthritis or rheumatoid arthritis aged 50 years or over were eligible for enrolment if they had a clinical diagnosis of osteoarthritis of the knee, hip, hand, or spine, or a clinical diagnosis of rheumatoid arthritis that satisfied at least four of seven of the American Rheumatism Association 1987 revised criteria,[25] and in the judgment of the investigator, would require chronic therapy with an NSAID.

Procedures

Patients that met the entry criteria were randomly assigned to treatment with etoricoxib or diclofenac, as previously described.[23]

Low-dose aspirin (≤100 mg/day) was strongly recommended for cardiovascular prophylaxis in patients with established cardiovascular, peripheral arterial, or

cerebrovascular disease and was also encouraged for patients with diabetes. Use of medical co-therapy (PPIs or misoprostol) was also strongly recommended for patients at high risk of upper gastrointestinal clinical events (ie, age >65 years; history of gastrointestinal ulcer or haemorrhage; concurrent use of corticosteroid, anticoagulant, or antiplatelet therapy). If low-dose aspirin or a PPI or misoprostol was not given to a patient meeting these criteria, investigators were contacted and required to state their reasons for not providing the medication. For the MEDAL study, omeprazole (20 mg) and low-dose aspirin were provided free of charge; low-dose aspirin was provided free of charge in the EDGE and EDGE II trials. Patients returned for visits every 4 months and a scheduled telephone contact was made between visits. Patient compliance with study medication was assessed by pill count. An independent data and safety monitoring board monitored emerging safety data from all three trials at regular intervals.

The primary endpoint for the MEDAL programme was thrombotic cardiovascular events with the primary hypothesis that etoricoxib was non-inferior to diclofenac in thrombotic cardiovascular events in the per-protocol population.[23,24] Upper gastrointestinal clinical and complicated events were prespecified endpoints, but were not the primary endpoint.

Potential upper gastrointestinal clinical events (bleeding, perforation, obstruction, ulcer diagnosed on clinical work-up) were identified through active surveillance of reported adverse events, and were adjudicated by an independent blinded committee by use of predefined criteria (table 1). The subset of complicated events included those with perforation, obstruction, and complicated bleeding, whereas uncomplicated events included uncomplicated bleeding and uncomplicated ulcer (table 1). Patients with both a complicated and uncomplicated event (n=4; bleeding ulcer with synchronous uncomplicated ulcer) were counted in the overall clinical event patient group and the complicated event patient subgroup, but not the uncomplicated event patient subgroup.

Statistical analysis

Rates of upper gastrointestinal clinical events and complications per 100 patient-years with their 95% CI were prespecified determinations. The 95% CI for the rates per 100 patient-years were calculated with the Poisson distribution assumption. To better characterise the observed treatment effects, a post-hoc calculation of the hazard ratios (HR) with 95% CI was done with a Cox model with a term for treatment effect and stratification factor for baseline low-dose aspirin use. The proportional hazard assumption was tested by inclusion of treatment-by-log (time) as a factor in the model. Kaplan-Meier time-to-event curves were generated and truncated when the number of patients remaining at risk was less than 500. The MEDAL programme was event-driven and continued until at least 635 confirmed thrombotic cardiovascular events had occurred; the number of upper gastrointestinal events was not prespecified and was determined by the time required to accrue the necessary cardiovascular events. Hence, no power calculations were done for any of the upper gastrointestinal analyses. All analyses were done in the intention-to-treat population of all patients randomised followed until 14 days after discontinuation of study medication.

Subgroup analyses were done for concomitant use of low-dose aspirin or PPI co-therapy, or both, with both very liberal definitions and more restrictive definitions

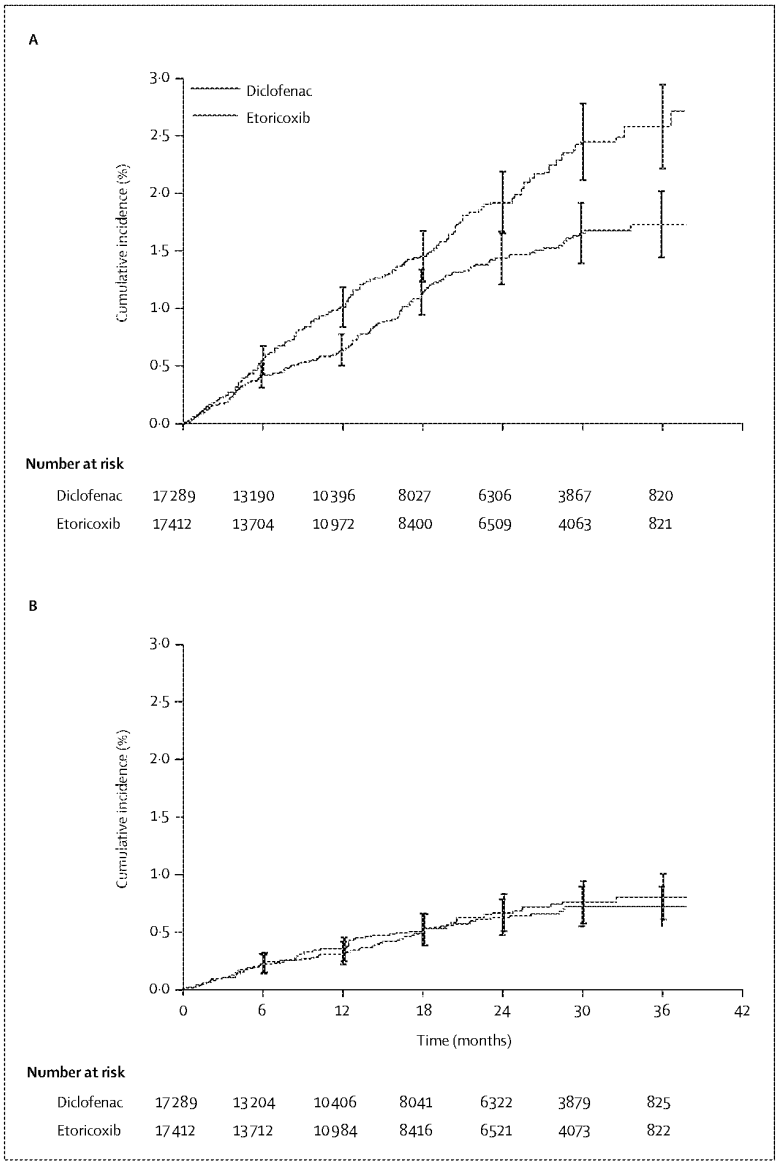

Figure: **Time-to-event analyses in intention-to-treat population**
(A) Cumulative incidence of all upper gastrointestinal clinical events. (B) Cumulative incidence of upper gastrointestinal complicated events. Error bars are 95% CI.

	Etoricoxib (n=17 412)		Diclofenac (n=17 289)		Hazard ratio (95% CI)
	n (%)	Rate*	n (%)	Rate*	
Patients with any clinical event	176 (1·01%)	0·67	246 (1·42%)	0·97	0·69 (0·57–0·83)
Patients with complicated events	78 (0·45%)	0·30	82 (0·47%)	0·32	0·91 (0·67–1·24)
Perforation†	5 (0·03%)	0·02	11 (0·06%)	0·04	
Obstruction	2 (0·01%)	0·01	2 (0·01%)	0·01	
Bleeding	72 (0·41%)	0·27	72 (0·42%)	0·28	
Gastric ulcer	40 (0·23%)	0·15	26 (0·15%)	0·10	
Duodenal ulcer	17 (0·10%)	0·06	23 (0·13%)	0·09	
Gastric and duodenal ulcer	4 (0·02%)	0·02	5 (0·03%)	0·02	
Anastomotic ulcer	1 (0·01%)	0·00	1 (0·01%)	0·00	
Other source	10 (0·06%)	0·04	17 (0·10%)	0·07	
Patients with uncomplicated events	98 (0·56%)	0·37	164 (0·95%)	0·65	0·57 (0·45–0·74)
Bleeding‡	6 (0·03%)	0·02	4 (0·02%)	0·02	
Ulcer	92 (0·53%)	0·35	161 (0·93%)	0·63	
Gastric ulcer	57 (0·33%)	0·22	110 (0·64%)	0·43	
Duodenal ulcer	27 (0·16%)	0·10	35 (0·20%)	0·14	
Gastric and duodenal ulcer	8 (0·05%)	0·03	16 (0·09%)	0·06	

*Events per 100 patient-years. †Four patients with perforation also had bleeding reported. ‡One patient with uncomplicated bleeding from a Mallory-Weiss tear also had an uncomplicated gastric ulcer identified.

Table 3: **Upper gastrointestinal clinical events in intention-to-treat population**

of concomitant therapy. The first definition was prespecified to capture all patients who took even modest amounts of concomitant therapy: use of low-dose aspirin for at least 10% of the study period, and use of US prescription doses of any PPI (omeprazole ≥20 mg, lansoprazole ≥15 mg, rabeprazole ≥20 mg, pantoprazole ≥40 mg, esomeprazole ≥20 mg daily) for more than 20% of the study period consecutively or for 30 consecutive days. The data analysis plan allowed for additional exploratory analyses with regard to co-therapies, and therefore a more restrictive definition was developed after unblinding to better investigate the specific effect of regular aspirin or PPI use on upper gastrointestinal outcomes. This definition of regular use required concomitant therapy for at least 75% of the study period (and for patients with an event, ≥75% in the period before the event); 75% was chosen because it was the prespecified definition of compliance for the study drug in the MEDAL programme. Concomitant use of other anti-ulcer medications (prescription strength histamine$_2$-receptor antagonists, misoprostol, and sucralfate) was also recorded. The subgroup analyses were done by adding terms for the subgroup factor and its interaction with treatment to the Cox model. A p value of 0·05 or less was deemed to be significant. Subgroup analyses do not have the same

	Regular PPI use		No regular PPI use		Regular aspirin use		No regular aspirin use	
	Etoricoxib (n=6951)	Diclofenac (n=6911)	Etoricoxib (n=10 461)	Diclofenac (n=10 378)	Etoricoxib (n=5745)	Diclofenac (n=5673)	Etoricoxib (n=11 667)	Diclofenac (n=11 616)
Age >65 years	2876 (41%)	2808 (41%)	3695 (35%)	3699 (36%)	2735 (48%)	2721 (48%)	3836 (33%)	3786 (33%)
Sex (female)	5311 (76%)	5311 (77%)	7614 (73%)	7512 (72%)	3977 (69%)	3961 (70%)	8948 (77%)	8862 (76%)
History of upper gastrointestinal event	728 (10%)	747 (11%)	399 (4%)	386 (4%)	377 (7%)	388 (7%)	750 (6%)	745 (6%)
Corticosteroid use	1239 (18%)	1257 (18%)	1446 (14%)	1448 (14%)	669 (12%)	674 (12%)	2016 (17%)	2031 (17%)
Aspirin use	3116 (45%)	3081 (45%)	2914 (28%)	2895 (28%)	5546 (97%)	5501 (97%)	484 (4%)	475 (4%)
Established atherosclerotic cardiovascular disease	976 (14%)	991 (14%)	1038 (10%)	1019 (10%)	1449 (25%)	1447 (26%)	565 (5%)	563 (5%)
Diabetes	823 (12%)	836 (12%)	987 (9%)	1019 (10%)	946 (16%)	956 (17%)	864 (7%)	899 (8%)
Cigarette smoker	799 (11%)	809 (12%)	1235 (12%)	1228 (12%)	628 (11%)	629 (11%)	1406 (12%)	1408 (12%)
Hypertension	3613 (52%)	3644 (53%)	4496 (43%)	4577 (44%)	3608 (63%)	3605 (64%)	4501 (39%)	4616 (40%)

Data are n (%).

Table 4: **Baseline risk factors in patients with and without PPI use or low-dose aspirin use for at least 75% of the study period**

power as did the analysis of the primary endpoint and thus should be interpreted with appropriate caution.

Discontinuations due to upper gastrointestinal symptoms consistent with dyspepsia and reflux were assessed for patients in the intent-to-treat population, and subgroup analyses were done related to the use of PPIs as well as to the use of low-dose aspirin. The definition of dyspepsia included pain or discomfort in the upper abdomen (including epigastric or stomach) or nausea, whereas reflux included reports of heartburn, oesophagitis, oesophageal burning or discomfort, gastro-oesophageal reflux disease, and hiatal hernia. Because reports of mild gastrointestinal adverse events are extremely common and might be variably reported from different sites and investigators, we chose to assess discontinuations as a marker of clinically meaningful upper gastrointestinal symptoms—ie, symptoms that were more likely to have adversely affected patient quality of life. Discontinuations due to any gastrointestinal adverse event were also assessed as a prespecified endpoint.

Role of the funding source

The MEDAL programme was designed cooperatively by the sponsor (Merck Research Laboratories) and the programme steering committee, which consists of experts in gastroenterology, cardiovascular medicine, rheumatology, pharmacology, statistical sciences, and epidemiology. The sponsor monitored the study, collected data, and did statistical analysis. An independent confirmation of the statistical analyses was done by Frontier Science Foundation (Madison, WI, USA), under the supervision of C Morton Hawkins and David DeMets (MEDAL programme steering committee member). All authors had full access to data and statistical analyses and wrote the manuscript. The corresponding author had final responsibility for the decision to submit the manuscript for publication.

Results

34701 patients were enrolled in the MEDAL programme (23504 in the MEDAL study, 7111 in EDGE, and 4086 in EDGE II), including 24913 (72%) with osteoarthritis and 9787 (28%) with rheumatoid arthritis. Baseline characteristics were much the same in the two study groups (table 2). Etoricoxib and diclofenac had similar efficacy for treatment of arthritis as measured by global assessment of disease status and discontinuations for lack of efficacy.

The figure shows the Kaplan-Meier estimates for upper gastrointestinal clinical events and complicated events. The cumulative incidence rates with etoricoxib compared with diclofenac satisfied the proportional hazard assumption, indicating a constant hazard ratio over time. The number of patients with upper gastrointestinal clinical events and the rates per 100 patient-years are shown in table 3. Upper gastrointestinal clinical events were significantly less frequent with etoricoxib than they were with diclofenac (HR 0·69, 95% CI 0·57–0·83; p=0·0001), although there was no difference in the subset of complicated events (0·91, 0·67–1·24; p=0·561). The major difference between study groups was in uncomplicated ulcers, with rates of 0·35 (95% CI 0·28–0·43) per 100 patient-years for etoricoxib and 0·63 (0·54–0·74) per 100 patient-years for diclofenac.

A breakdown of the component events is shown in table 3. Perforation (16 patients) and obstruction (four patients) were uncommon. The most common event was an uncomplicated ulcer (253 patients) followed by complicated or uncomplicated upper gastrointestinal bleeding (154 patients). The complication of upper gastrointestinal bleeding was due to gastric or duodenal ulcers in 117 (81%) cases (including two patients with anastomotic ulcers); other sources included erosions (n=11), vascular ectasias (3), cancer (1), Mallory-Weiss tears (2), varices (3), and oesophageal ulcer (1); causes were unknown or there was insufficient work-up in six cases. Gastric ulcers were almost twice as common as duodenal ulcers as a source of bleeding and were over twice as common among the uncomplicated ulcers.

The rate of upper gastrointestinal clinical events was also assessed related to concomitant use of PPIs or low-dose aspirin. Concomitant low-dose aspirin was used during at least 10% of the study by 6454 (37%) individuals in the etoricoxib group and 6367 (37%) in the diclofenac

	Etoricoxib		Diclofenac		Hazard ratio (95% CI)
	n/N (%)	Rate*	n/N (%)	Rate*	
Patients with any clinical event					
Aspirin use (p=0·19†)					
Yes	100/5752 (1·7%)	1·14	124/5680 (2·2%)	1·46	0·78 (0·60–1·01)
No	76/11 660 (0·65%)	0·43	122/11 609 (1·1%)	0·72	0·60 (0·45–0·80)
PPI use (p=0·36†)					
Yes	68/6950 (0·98%)	0·56	106/6906 (1·5%)	0·91	0·62 (0·45–0·83)
No	108/10 462 (1·0%)	0·76	140/10 383 (1·3%)	1·02	0·74 (0·58–0·95)
Patients with complicated events					
Aspirin use (p=0·92†)					
Yes	50/5752 (0·87%)	0·57	52/5680 (0·92%)	0·61	0·93 (0·63–1·36)
No	28/11 660 (0·24%)	0·16	30/11 609 (0·26%)	0·18	0·90 (0·53–1·50)
PPI use (p=0·28†)					
Yes	24/6950 (0·35%)	0·20	32/6906 (0·46%)	0·27	0·72 (0·42–1·22)
No	54/10 462 (0·52%)	0·38	50/10 383 (0·48%)	0·36	1·03 (0·70–1·52)
Patients with uncomplicated events					
Aspirin use (p=0·26†)					
Yes	50/5752 (0·87%)	0·57	72/5680 (1·3%)	0·85	0·67 (0·47–0·96)
No	48/11 660 (0·41%)	0·27	92/11 609 (0·79%)	0·54	0·50 (0·35–0·71)
PPI use (p=0·97†)					
Yes	44/6950 (0·63%)	0·36	74/6906 (1·1%)	0·63	0·57 (0·39–0·83)
No	54/10 462 (0·52%)	0·38	90/10 383 (0·87%)	0·66	0·58 (0·41–0·81)

PPI=proton pump inhibitor. *Events per 100 patient-years. †Treatment-by-subgroup interaction.

Table 5: **Upper gastrointestinal clinical events related to concomitant use of low-dose aspirin or PPIs for at least 75% of the study period in intention-to-treat population**

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