

Gastrointestinal Side Effects of Etoricoxib in Patients with Osteoarthritis: Results of the Etoricoxib versus Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness (EDGE) Trial

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ABSTRACT. Objective. To compare the gastrointestinal (GI) tolerability, safety, and efficacy of etoricoxib and diclofenac in patients with osteoarthritis (OA).

Methods. In total, 7111 patients (mean age 64 yrs) diagnosed with OA were enrolled in a randomized, double-blind trial. Patients received etoricoxib 90 mg qd (n = 3593) or diclofenac sodium 50 mg tid (n = 3518). Gastroprotective agents and low-dose aspirin were prescribed per treatment guidelines. The primary endpoint was the cumulative rate of discontinuations due to clinical and laboratory GI adverse experiences (AE). General safety was assessed, including adjudication of thrombotic cardiovascular (CV) safety data. Efficacy was evaluated using the least-square (LS) mean change from baseline patient global assessment of disease status (PGADS; 0–4 point scale).

Results. Mean (SD, maximum) duration of treatment was 9.3 (4.4, 16.5) and 8.9 (4.5, 16.6) months in the etoricoxib and diclofenac groups, respectively. The cumulative discontinuation rate due to GI AE was significantly lower with etoricoxib than diclofenac [9.4 vs 19.2 events per 100 patient-years (PY), respectively; hazard ratio (HR) 0.50 (95% CI 0.43, 0.58; p < 0.001). Rates of thrombotic CV events were similar with etoricoxib and diclofenac [1.25 vs 1.15 events per 100 PY, respectively; HR 1.07 (95% CI 0.65, 1.74)]. The incidence of patients who discontinued due to hypertension-related AE was significantly higher with etoricoxib compared to diclofenac (2.3% vs 0.7%; p < 0.001), although few AE were severe (3 etoricoxib, 1 diclofenac). Etoricoxib and diclofenac treatment resulted in similar improvements in PGADS from baseline of –0.78 (95% CI –0.80, –0.75) and –0.75 (95% CI –0.77, –0.72), respectively.

Conclusion. Treatment with etoricoxib 90 mg was associated with significantly better GI tolerability compared to diclofenac in this population of patients with OA. Etoricoxib 90 mg, a dose 50% higher than indicated for OA, resulted in more discontinuations due to hypertension-related AE. (J Rheumatol 2007;34:408–20)

Key Indexing Terms:

ETORICOXIB

DICLOFENAC

OSTEOARTHRITIS

GASTROINTESTINAL

TOLERABILITY

Osteoarthritis (OA) is one of the most common disabilities present in the elderly population and is projected to be the fourth leading cause of disability on a worldwide basis by the

year 2020¹. The primary objective of treatment for patients with OA is to manage symptoms, including pain and inflammation, and to improve quality of life^{2,3}. For patients who

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require effective pain and symptom relief, nonsteroidal antiinflammatory drugs (NSAID) are often prescribed. Lack of efficacy is the leading cause for switching treatment to other members of the NSAID class⁴. The use of traditional NSAID can be limited due to their inherent toxicity to the upper and lower gastrointestinal (GI) tract^{5,6}. Specifically, use of traditional NSAID is associated with upper GI intolerance (often characterized under the general term of dyspepsia), which is not necessarily related to GI mucosal injury or serious upper GI events (i.e., perforations, ulcers, or bleeds)⁷⁻⁹. Dyspeptic symptoms can occur in a significant proportion (~25%) of patients being treated with traditional NSAID⁷. Patients experiencing GI symptoms may be prescribed gastroprotective agents (GPA) to alleviate their symptoms, or may discontinue and/or switch treatment^{10,11}. Hepatotoxicity due to NSAID therapy occurs at a much lower rate than dyspeptic symptoms, but is also associated with treatment switching¹².

Selective inhibitors of COX-2 (coxibs) such as etoricoxib were developed to reduce the risk of GI adverse experiences (AE)^{13,14}. A combined analysis of 9 randomized, double-blind, efficacy studies of the coxib etoricoxib, across its development program, suggested reduced rates of discontinuation of etoricoxib or of GPA use due to dyspeptic symptoms during the first 6 months of use compared to traditional NSAID^{15,16}. To further evaluate this, our current study was designed with the primary objective of evaluating the GI "tolerability" of etoricoxib 90 mg qd compared to diclofenac 50 mg tid, in patients with OA, using the primary endpoint of treatment discontinuations due to clinical and laboratory GI AE. GI tolerability was assessed by determining the rates of treatment discontinuation arising from the development of the GI signs, symptoms, or laboratory abnormalities associated with NSAID use. The trial was not designed to formally test treatment differences related to GI safety (i.e., rates of perforations, ulcers, or bleeds).

MATERIALS AND METHODS

The protocol for our study was approved by the institutional review boards of each study site. All patients provided written informed consent prior to their participation in the study. Patients initiated treatment between June and November of 2002. For administrative reasons, there was a predefined end-of-study period for all patients between October 15 and November 1, 2003.

Patients. Patients with OA were eligible if they were ≥ 50 years of age, with a clinical diagnosis of OA of the knee, hip, hand, or spine, and in the judgment of the investigator, would require chronic therapy with a traditional NSAID or coxib. Patients with a history of myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention more than 6 months preceding enrollment in the study could participate.

Patients who had any of the following were excluded: morbid obesity; significantly impaired renal function (creatinine clearance < 30 ml/min or serum creatinine > 2.0 mg/dl); uncontrolled hypertension (sitting diastolic blood pressure > 95 mm Hg or sitting systolic blood pressure > 165 mm Hg); stroke or transient ischemic attack within the previous 6 months; GI malabsorption; active hepatitis or hepatic disease; congestive heart failure (CHF) with symptoms at rest or with minimal activity; unstable angina; bleeding diathesis; inflammatory bowel disease; evidence of active GI bleeding; history of leukemia, lymphoma, melanoma, or myeloproliferative disease, or other

malignancy within the past 5 years that had not been successfully treated; required therapy with warfarin, heparin, high-dose aspirin (> 100 mg/day), nonstudy NSAID or coxib, or the combination of ticlopidine or clopidogrel plus low-dose aspirin; or allergy or hypersensitivity to aspirin, other traditional NSAID, or coxibs. In addition, patients who used H2-receptor antagonists, antacids, or proton pump inhibitors at prescription or over-the-counter doses for more than 4 consecutive days within 1 month prior to the screening visit were excluded. Patients were also excluded who used misoprostol or sucralfate within 3 days prior to study start.

Study design. This was a randomized, double-blind, active-comparator-controlled, multicenter study (Sponsor protocol number 061) to compare the GI tolerability of etoricoxib and diclofenac. The EDGE trial is a component of the larger MEDAL Program, which consists of 3 studies: EDGE; EDGE II (NCT00250445); and MEDAL (NCT00092742)¹⁹. The trial was designed to run for about 18 months with an enrollment period of about 5 months. Based on the predefined end-of-study period for all patients and time between screening and enrollment, the maximum duration of treatment for a patient could range from 11 to 16 months.

Following screening, patients discontinued their prestudy OA medication and returned to the clinical research center within 2 to 10 days. Patients who completed this prestudy washout period were stratified according to low-dose aspirin use and randomized using a computer-generated randomization schedule, in a 1:1 ratio, to etoricoxib 90 mg qd or diclofenac sodium 50 mg tid. Study medication was supplied in 2 coded study bottles, labeled bottle A (containing etoricoxib 90 mg tablets or matching placebo) and bottle B (containing diclofenac sodium 50 mg tablets or matching placebo). Patients were instructed to take one tablet in the morning from bottles A and B and one tablet in the afternoon and evening from bottle B. Acetaminophen (up to 2600 mg per day) served as rescue pain medication. If acetaminophen failed, non-aspirin, non-NSAID analgesic alternatives (e.g., narcotic analgesic) could be taken for a maximum of 3 doses per day for up to 7 days per month.

Safety and efficacy data were collected during clinic visits (screening, randomization, and at 1, 4, 8, and 12 months of therapy, and at end of study). The investigators identified and evaluated AE based on patient reports, physical examination, and laboratory assessments. Telephone contacts to monitor compliance and facilitate patient retention occurred monthly between visits (Months 2, 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, and 16 for patients remaining in the study). Pill counts furnished a measure of compliance. Patients contacted the investigator if they desired to discontinue treatment, or an investigator could recommend discontinuation. Study sites contacted patients who discontinued early by telephone every 4 months, at 12 months, and at the predefined end of study period, to identify any potential serious thrombotic cardiovascular (CV) AE (thrombotic CV events) or deaths. Patients underwent physical examination, including vital signs, collection of laboratory samples, and an electrocardiogram at Month 12 or the end-of-study visit. Patient follow-up included collection of data regarding any serious AE that may have occurred within 28 days subsequent to the last dose of study medication. Data from these time periods were tracked and are displayed separately.

All potential thrombotic CV events and deaths, regardless of cause, and upper and lower GI events were adjudicated by separate expert case review committees that were blinded to treatment assignment according to described criteria^{6,17}.

Permitted and excluded medications. GPA, including proton pump inhibitors, H2-receptor antagonists, and antacids, were permitted after enrollment in the study. It was recommended that investigators consider proton pump inhibitors for patients with one or more risk factors for NSAID-induced gastropathy according to current treatment guidelines¹⁸. Excluded medications consisted of warfarin and heparin; use of more than one antiplatelet agent; aspirin > 100 mg/day; or nonstudy traditional NSAID or coxibs. Patients could take low-dose aspirin (75–100 mg/day) for CV prophylaxis. For purposes of subgroup analyses for thrombotic CV event analyses, aspirin use was defined as any patient who took any dose of aspirin, clopidogrel, clopidogrel bisulfate, ticlopidine, and ticlopidine HCl for at least 50% of the time while on study therapy, and did not start any of these medications after a confirmed thrombotic CV event.

Primary endpoint

GI tolerability assessment. The primary endpoint of this trial was GI tolerability defined as the cumulative rate of discontinuation due to GI AE. Each investigator was responsible for determining the appropriate action to be taken with their patients following a GI AE (i.e., no action, stop then restart therapy, or discontinue therapy). The primary endpoint included 2 components: (1) discontinuations due to clinical GI AE consisting of all investigator-reported AE with terms that mapped to the GI system organ class (with the exception of a small number of oral and dental disorders not deemed clinically relevant); (2) discontinuations due to laboratory GI AE related to liver function abnormalities (all AE terms related to hepatic disorder, hepatic failure, hepatic function abnormality, hepatitis, jaundice, increased ALT, increased AST, or increased bilirubin).

To evaluate the consistency of the primary outcome we examined several prespecified patient subgroups including: low-dose aspirin use from baseline, continued GPA use (defined as use of GPA prior to randomization and continuing after randomization); new GPA use (defined as patients starting GPA after starting study medication and using GPA for > 30 consecutive days or > 20% of time while on study therapy); and patients sorted by age (< 65 yrs vs \geq 65 yrs), race, and sex. The risk of discontinuations, due to clinical GI AE, is influenced more by the prespecified risk factors (i.e., low-dose aspirin use, continued or new GPA use, or \geq 65 yrs of age) versus laboratory GI AE. Therefore, we also evaluated the 2 components of the combined GI AE primary endpoint (i.e., clinical GI AE and laboratory GI AE) separately in a post-hoc analysis.

Secondary endpoints

Assessment of CV adverse experiences. All investigator-reported thrombotic CV events in EDGE were adjudicated by an independent expert case review committee that was blinded to treatment assignment according to described criteria¹⁹. Thrombotic CV events were classified by vascular bed (i.e., cardiovascular, cerebrovascular, peripheral vascular) and by specific event type (e.g., myocardial infarction, ischemic cerebrovascular accident). Serious CV AE were also classified using the Anti-Platelet Trialists' Collaboration (APTC) criteria²⁰.

Assessment of clinical adverse experiences of interest for coxibs and traditional NSAID. Clinical AE of interest in relation to chronic therapy with coxibs or traditional NSAID were compared in EDGE. These endpoints included: discontinuations due to edema-related AE; discontinuations due to hypertension-related AE; AE of CHF, pulmonary edema, or cardiac failure; hepatic (clinical or laboratory in nature) AE, discontinuations due to clinical or laboratory hepatic AE; and discontinuations due to clinical and laboratory AE related to renal dysfunction. All episodes of CHF resulting in admission or emergency room visits were adjudicated by the cardiology adjudication subcommittee. Overall rates of clinical and laboratory AE were analyzed, including drug-related and serious AE, as well as discontinuations due to AE.

Efficacy assessment. Patient Global Assessment of Disease Status (PGADS; 4-point scale; 0 = very well, 1 = well, 2 = fair, 3 = poor, 4 = very poor) provided a measure of treatment efficacy.

Exploratory endpoints

Assessment of serious GI events. Serious upper GI AE [i.e., perforations, ulcers, bleeds (upper GI events)] and lower GI AE were adjudicated as described^{6,17}.

Statistical methods

Sample size. The sample size for the study was based on hazard ratio (HR) estimates of discontinuations due to clinical and laboratory GI AE derived from previous OA and rheumatoid arthritis trials of etoricoxib (sponsor protocols 007 and 010), rofecoxib (sponsor protocols 034 and 035), and celecoxib (CLASS study) compared to diclofenac²¹⁻²³. If the true HR for etoricoxib versus diclofenac was 0.7 (e.g., 5.0% vs 7.1%), then 3400 patients per treatment group provided 95% power for the study to detect a difference (2-sided test at $\alpha = 0.05$).

Analysis populations. We used the modified intention-to-treat (mITT) population for the primary analysis. This included patients who received at least one dose of study medication according to their randomized treatment assignment. A per-protocol confirmatory analysis excluded patients in the mITT population who had: < 75% compliance; concomitant NSAID use during > 10% of the study; aspirin use > 125 mg for > 10% of the study; active upper GI event at baseline; positive for fecal occult blood at baseline; ALT and/or AST > 80 U/l at baseline, and other prespecified violations.

Primary analysis. A Cox proportional hazards model with factors for treatment effect and baseline low-dose aspirin use strata (yes or no) provided an estimate of the HR and the corresponding 95% CI for etoricoxib compared to diclofenac. Kaplan-Meier estimates were used to calculate the cumulative incidence for each treatment group, and discontinuations due to GI AE per 100 patient-years (PY) were summarized. The study was considered to have proven its primary hypothesis if a significant ($p < 0.05$) reduction in the risk of discontinuation due to the aggregate of GI AE (primary endpoint) was found with etoricoxib compared to diclofenac. A log-rank test for time-to-event data supported the primary analytical approach.

Secondary analyses

Thrombotic CV events assessment. A Cox proportional hazards model with factors for treatment effect and baseline low-dose aspirin use strata was used to estimate the HR and corresponding 95% CI for thrombotic CV events with etoricoxib compared with diclofenac. The thrombotic CV event rates per 100 PY and corresponding 95% CI were determined.

Assessment of clinical AE of interest for coxibs and traditional NSAID. Fisher's exact test was used to compare the treatment groups in terms of the incidence of the 6 prespecified AE secondary endpoints listed above, which was confirmed with a Cox proportional hazards model.

Efficacy assessment. We evaluated data from patients with a baseline and at least one on-treatment efficacy measurement (PGADS) using an analysis of covariance (ANCOVA) model. This model included factors for treatment, baseline low-dose aspirin use strata, and baseline value as a covariate.

Exploratory and other safety assessments

Upper GI event assessment. Treatment group randomization did not account for new GPA or concurrent aspirin use. Due to this possible confounding, no formal hypotheses, objectives, or analyses of confirmed upper GI events were performed. The numbers of events were tabulated along with rates per 100 PY.

Lower GI event assessment. This study was not adequately powered to compare rates of lower GI AE. A comparison of rates of lower GI AE in patients receiving etoricoxib and diclofenac was prespecified to be formally assessed as part of the MEDAL Program¹⁹, which was adequately powered to assess this endpoint. Therefore, these data were included with that formal analysis and are not presented here.

General safety assessment. Overall rates of clinical and laboratory AE including drug-related AE, discontinuations due to AE, and serious AE were tabulated. Drug exposure or time at risk for an AE for each of the treatment groups was compared. Wilson's score method was used to calculate CI for differences between treatment groups^{24,25}. The incidence of other AE was summarized and assessed by clinical examination.

RESULTS

Patients. A total of 8711 patients were screened and 7111 randomized to treatment across 636 clinical centers (411 in the USA and 225 at sites outside the USA; Figure 1). Randomized patients received etoricoxib ($n = 3593$) or diclofenac ($n = 3518$). Baseline patient demographics and characteristics were similar between treatment groups, including prior use of coxibs, traditional NSAID, and non-narcotic analgesics (Table 1). The 2 treatment groups were also similar with regard to their

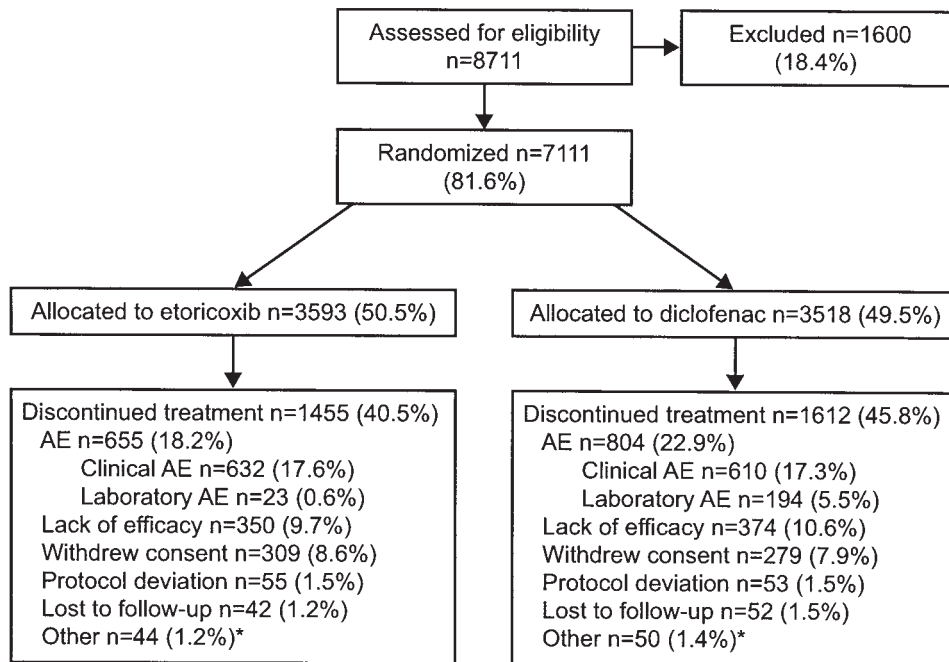


Figure 1. Patient accounting. AE: adverse experience; PGADS: Patient Global Assessment of Disease Status.
*Discontinued for reasons other than listed.

history of upper GI events (4% overall). Within the patients reporting a change in their arthritis medication in the year prior to enrollment, 56.8% of patients changed due to lack of efficacy, 13.0% due to side effects, and 6.5% due to lack of efficacy and side effects. Twenty-eight percent of patients were low-dose aspirin users and 38% were at increased risk for a thrombotic CV event. History of previously diagnosed hypertension in the treatment groups was similar (45% taking etoricoxib and 46% taking diclofenac).

Mean (SD; maximum) duration of treatment was 9.3 (4.4; 16.5) and 8.9 (4.5; 16.6) months in the etoricoxib and diclofenac groups, respectively. Significantly more patients discontinued study treatment with diclofenac than etoricoxib, both overall for any reason (45.8% vs 40.5%, respectively; $p < 0.05$) and specifically due to any AE (22.9% vs 18.2%, respectively; $p < 0.05$).

Primary endpoint

GI tolerability. Significantly fewer patients discontinued from the study due to GI AE (primary endpoint) with etoricoxib than diclofenac (Figure 2). The cumulative discontinuation rates per 100 PY were 9.41 (95% CI 8.33, 10.49) with etoricoxib and 19.23 (95% CI 17.71, 20.74) with diclofenac, with a HR of 0.5 (95% CI 0.43, 0.58; $p < 0.001$). The cumulative incidence curves for discontinuations due to GI AE for the 2 treatments separated early, continuing to diverge over the first 6 months, with the separation of the curves maintained over the duration of the study (Figure 2). A per-protocol analysis corroborated the primary mITT analysis.

A post-hoc analysis evaluated discontinuation rates due to

GI AE of a clinical or laboratory nature separately. For clinical GI AE, the discontinuation rates per 100 PY were 9.12 (95% CI 8.05, 10.19) with etoricoxib and 12.28 (95% CI 11.02, 13.55) with diclofenac, HR 0.75 (95% CI 0.64, 0.89; $p < 0.001$). For laboratory GI AE, the discontinuation rates per 100 PY were 0.29 (95% CI 0.09, 0.48) with etoricoxib and 6.88 (95% CI 5.91, 7.85) with diclofenac, HR 0.04 (95% CI 0.02, 0.09; $p < 0.001$; Figure 2). Although the magnitude of the hazard reductions in these individual components was different, differences in rates of discontinuation between treatments remained statistically significant. The difference in discontinuations due to clinical GI AE is primarily due to an incidence of general [25 (0.7%) vs 43 (1.2%)] and upper abdominal pain [33 (0.9%) vs 48 (1.4%)] and diarrhea [23 (0.6%) vs 46 (1.3%)] that was lower with etoricoxib than diclofenac, while the difference in discontinuations due to laboratory GI AE is primarily due to increases in ALT [8 (0.2%) vs 175 (5.0%)] and AST [6 (0.2%) vs 119 (3.4%)] observed with diclofenac. Three patients, all in the diclofenac group, discontinued due to increased bilirubin levels.

Further analyses across the prespecified subgroups indicated consistency of treatment effects across all groups, with no statistically significant treat-by-subgroup interaction. Etoricoxib treatment resulted in ~50% risk reduction, compared to diclofenac, for discontinuations due to GI AE, even in subgroups at increased risk for GI AE. These at-risk subgroups included: aspirin use HR 0.53 (95% CI 0.42, 0.68); continued GPA use HR 0.55 (95% CI 0.31, 0.96); newly initiated GPA use HR 0.51 (95% CI 0.33, 0.77); and age ≥ 65 years HR 0.47 (95% CI 0.38, 0.54). The HR for discontinua-

Table 1. Summary of baseline demographics and characteristics.

| Characteristic | Etoricoxib 90 mg, N = 3593, n (%) | Diclofenac 150 mg, N = 3518, n (%) |
|---|--------------------------------------|---------------------------------------|
| Age, mean, yrs (SD) | 63.7 (8.6) | 63.8 (8.5) |
| Sex, n (%) | | |
| Male | 982 (27.3) | 1030 (29.3) |
| Female | 2611 (72.7) | 2488 (70.7) |
| Race, n (%) | | |
| Caucasian | 3050 (84.9) | 3001 (85.3) |
| Black | 135 (3.8) | 132 (3.8) |
| Hispanic | 204 (5.7) | 206 (5.9) |
| Asian | 123 (3.4) | 103 (2.9) |
| Native American | 14 (0.4) | 8 (0.2) |
| Other | 67 (1.9) | 68 (1.9) |
| Body mass index, mean kg/m ² (SD) | 30.3 (6.6) | 30.2 (6.3) |
| Primary study joint, n (%) | | |
| Knee | 1904 (53.0) | 1880 (53.4) |
| Hand | 655 (18.2) | 648 (18.4) |
| Hip | 237 (6.6) | 259 (7.4) |
| Spine | 794 (22.1) | 731 (20.8) |
| Left shoulder | 3 (0.1) | 0 (0.0) |
| ACR functional class, n (%) | | |
| Class I | 968 (26.9) | 936 (26.6) |
| Class II | 2119 (59.0) | 2077 (59.0) |
| Class III | 506 (14.1) | 505 (14.4) |
| | Etoricoxib 90 mg N = 3593, n (%) | Diclofenac 150 mg N = 3518, n (%) |
| Prior antiinflammatory/antirheumatic products, n (%) | | |
| Rofecoxib | 593 (16.5) | 530 (15.1) |
| Celecoxib | 500 (13.9) | 473 (13.4) |
| Valdecoxib | 180 (5.0) | 182 (5.2) |
| Ibuprofen | 519 (14.4) | 551 (15.7) |
| Naproxen | 171 (4.8) | 186 (5.3) |
| Prior analgesic products, n (%) | | |
| Aspirin | 1054 (29.3) | 983 (27.9) |
| Acetaminophen | 877 (24.4) | 840 (23.9) |
| History of upper GI events (perforations, ulcers, bleeding), n (%) | 148 (4.1) | 142 (4.0) |
| Low-dose aspirin use, strata*, n (%) | | |
| User | 1027 (28.6) | 962 (27.3) |
| Nonuser | 2566 (71.4) | 2556 (72.7) |
| Increased risk for thrombotic cardiovascular event [‡] , n (%) | 1335 (37.2) | 1345 (38.2) |
| History of diagnosed hypertension prior to randomization, n (%) | 1627 (45.3) | 1609 (45.7) |

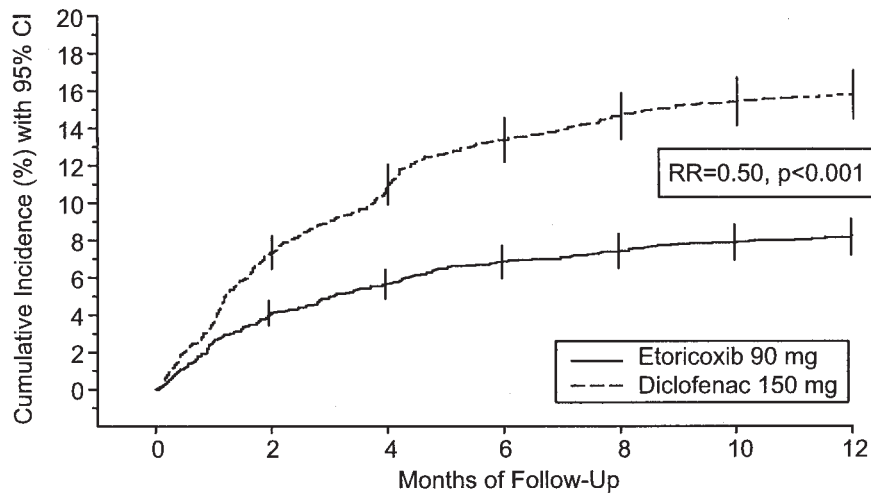
* Determined at baseline to require low-dose aspirin \leq 100 mg/day during the study. [‡] 2 or more CV risk factors for coronary artery disease (history of diabetes, hypercholesterolemia, hypertension, and tobacco use) or a history of symptomatic atherosclerotic CV disease. ACR: American College of Rheumatology, GI: gastrointestinal.

tion due to clinical GI AE were higher than for the combined endpoint. They indicated a consistent reduced risk for discontinuation among the at-risk groups following treatment with etoricoxib compared to diclofenac (Figure 3): aspirin use HR 0.76 (95% CI 0.58, 1.00); continued GPA use HR 0.66 (95% CI 0.37, 1.19); new GPA use HR 0.62 (95% CI 0.40, 0.96); and age \geq 65 yrs HR 0.66 (95% CI 0.53, 0.84).

Secondary endpoints

Thrombotic CV events. The rates of confirmed thrombotic CV, APTC criteria-based, and investigator-reported events in

patients receiving etoricoxib or diclofenac were similar (Table 2). Etoricoxib and diclofenac treatments associated with a similar rate of confirmed thrombotic CV events over time. HR for etoricoxib compared to diclofenac for the confirmed thrombotic CV event endpoint were 1.07 (95% CI 0.65, 1.74) and 1.02 (95% CI 0.64, 1.62) from within 14 days and within 28 days after treatment discontinuation. HR for APTC criteria-based and investigator-reported events were similar to the thrombotic CV event endpoint. No statistically significant treatment-by-subgroup interactions were identified in the following subgroups for the cardiovascular endpoints: age (\leq 65



| # at Risk | 0 | 2 | 4 | 6 | 8 | 10 | 12 |
|-------------------|------|------|------|------|------|------|------|
| Etoricoxib 90 mg | 3593 | 3135 | 2862 | 2616 | 2466 | 2351 | 1120 |
| Diclofenac 150 mg | 3518 | 2991 | 2687 | 2420 | 2246 | 2126 | 991 |

| Discontinued Due to GI Adverse Events (PY) | Etoricoxib 90 mg (N = 3593) Rate | Diclofenac 150 mg (N = 3518) Rate | Relative Risk (95% CI, p-value) |
|--|----------------------------------|-----------------------------------|---------------------------------|
| Total (5374 yrs) | 9.41 | 19.23 | 0.50 (0.43, 0.58; <0.001) |
| Clinical (5382 yrs) | 9.12 | 12.28 | 0.75 (0.64, 0.89; <0.001) |
| Laboratory (5396 yrs) | 0.29 | 6.88 | 0.04 (0.02, 0.09; <0.001) |

*Events per 100 patient years (PY). Includes adverse experiences up to and including end of study visit.

Figure 2. Kaplan-Meier plot of the cumulative rates of discontinuation due to GI adverse experiences in patients treated with etoricoxib or diclofenac.

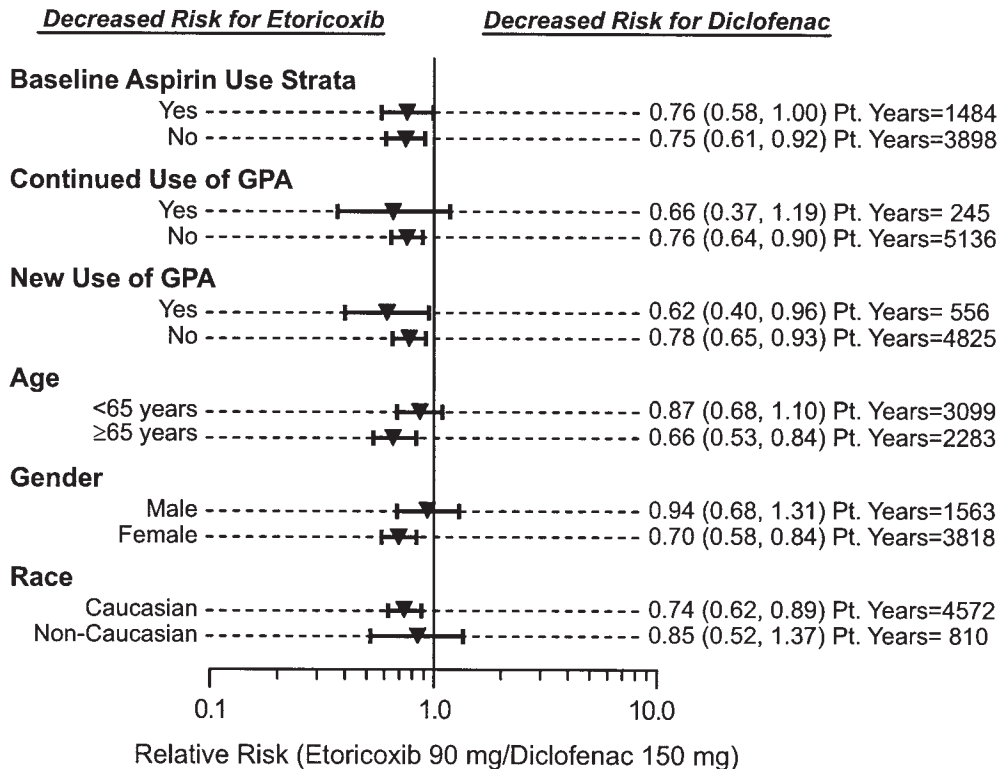


Figure 3. Relative risk for discontinuation due to a clinical GI adverse experience with etoricoxib compared to diclofenac (left, decreased risk with etoricoxib; right, decreased risk with diclofenac). Includes adverse experiences up to and including end of study visit.

Table 2. Thrombotic cardiovascular (CV) events. Total number of patients: etoricoxib 90 mg, N = 3593; diclofenac 150 mg, N = 3518.

| Analysis Approach | Treatment | n/PY* | Rate† (95% CI) |
|---------------------------------|-------------------|---------|-------------------|
| Confirmed thrombotic CV events | | | |
| Within 14 days** | Etoricoxib 90 mg | 35/2789 | 1.25 (0.87, 1.74) |
| | Diclofenac 150 mg | 30/2607 | 1.15 (0.78, 1.64) |
| Within 28 days§ | Etoricoxib 90 mg | 38/2926 | 1.30 (0.92, 1.78) |
| | Diclofenac 150 mg | 34/2740 | 1.24 (0.86, 1.73) |
| All events# | Etoricoxib 90 mg | 41/4109 | 1.00 (0.72, 1.35) |
| | Diclofenac 150 mg | 37/4030 | 0.92 (0.65, 1.27) |
| Confirmed APTC events | | | |
| Within 14 days | Etoricoxib 90 mg | 27/2792 | 0.97 (0.64, 1.41) |
| | Diclofenac 150 mg | 21/2608 | 0.81 (0.50, 1.23) |
| Within 28 days | Etoricoxib 90 mg | 28/2929 | 0.96 (0.64, 1.38) |
| | Diclofenac 150 mg | 24/2742 | 0.88 (0.56, 1.30) |
| All events | Etoricoxib 90 mg | 29/4111 | 0.70 (0.47, 1.01) |
| | Diclofenac 150 mg | 27/4034 | 0.67 (0.44, 0.97) |
| Investigator-reported CV events | | | |
| Within 14 days | Etoricoxib 90 mg | 59/2783 | 2.12 (1.61, 2.73) |
| | Diclofenac 150 mg | 56/2601 | 2.15 (1.63, 2.80) |
| Within 28 days | Etoricoxib 90 mg | 64/2919 | 2.19 (1.69, 2.80) |
| | Diclofenac 150 mg | 59/2734 | 2.16 (1.64, 2.78) |
| All events | Etoricoxib 90 mg | 69/4119 | 1.69 (1.31, 2.13) |
| | Diclofenac 150 mg | 63/4039 | 1.57 (0.21, 2.01) |

* n/PY: number of events per patient-years at risk. † Rate = number of events per 100 patient-years. ** Includes all events while on study drug and within 14 days of discontinuing study drug. § Includes all events while on study drug and within 28 days of discontinuing study drug. # All events regardless of time. APTC events: according to Anti-Platelet Trialists' Collaboration criteria.

yrs, > 65 yrs); sex; low-dose aspirin use at baseline; low-dose aspirin indicated; low-dose aspirin indicated or ≥ 2 CV risk factors; ≥ 2 CV risk factors; family history of CV disease; history of diabetes; history of hypercholesterolemia; history of hypertension; cigarette use; or concomitant aspirin use.

Thrombotic CV events occurred in all 3 vascular beds, with more cardiac than cerebrovascular or peripheral vascular events, irrespective of treatment group (Table 3A). Evaluation of individual events indicates that the absolute number of any of these events was small. There were numeric differences between treatments for some event types. For example, some events occurred at a higher rate in the etoricoxib group [e.g., myocardial infarction within 14 days of treatment discontinuation; HR 1.60 (95% CI 0.76, 3.36)] and some occurred at a higher rate in the diclofenac group [e.g., fatal and nonfatal ischemic cerebrovascular stroke within 14 days of treatment discontinuation; HR 0.60 (95% CI 0.17, 2.12)]. Although the confidence intervals include unity, suggestive of no significant difference, the number of events is limited, prohibiting a robust analysis by event type. APTC criteria events are presented in Table 3B for comparison.

Clinical AE of interest for coxibs and traditional NSAID. There were no significant differences between treatment groups in the incidence of patients who discontinued due to edema-related AE, AE related to renal dysfunction, or experience of confirmed CHF (Table 4). Only a small percentage of edema-related AE (1.9% taking etoricoxib and

1.4% taking diclofenac) were associated with significant weight gain (> 2 kg) at the time the AE was reported. The incidence of patients who discontinued due to hypertension-related AE was statistically significantly higher with etoricoxib compared to diclofenac (2.3% vs 0.7%; $p < 0.001$). Three serious AE of hypertension were reported in the etoricoxib group and one in the diclofenac group. Increases in blood pressure values were numerically greater in the etoricoxib group, with mean (SD) increases from baseline (i.e., at randomization) in systolic blood pressure of 4.1 (14.6) mm Hg and 1.4 (13.8) mm Hg observed in the etoricoxib and diclofenac groups, respectively. The percentage of patients who exceeded the predefined limits of change in systolic pressure (> 140 mm Hg and > 20 mm Hg greater than baseline) were 4.9% and 2.7% for etoricoxib and diclofenac, respectively. In contrast, etoricoxib use was associated with a significantly lower incidence of clinical and laboratory hepatic AE or discontinuation due to hepatic AE than use of diclofenac. There was an ~17-fold increase (5.0% vs 0.3%) in discontinuations due to hepatic AE with diclofenac compared to etoricoxib (Table 4). Of the patients treated with diclofenac who discontinued due to liver function tests, ~50% had elevations of 3-fold or greater over baseline, and ~10% had elevations of 10-fold or greater.

Efficacy. Mean (SD) PGADS values at baseline were 2.21 (0.94) and 2.25 (0.91) in the etoricoxib and diclofenac groups, respectively. Similar improvements ($p = 0.128$) in PGADS

values from baseline over the treatment period were observed for etoricoxib [least-square (LS) mean change = -0.78 (95% CI $-0.80, -0.75$)] and for diclofenac [LS mean change = -0.75 (95% CI $-0.77, -0.72$)].

Exploratory and other safety assessments

Upper GI events. There was no difference in the rates of confirmed upper GI events in the etoricoxib [1.11 events per 100 PY (95% CI 0.72, 1.50)] and diclofenac [1.11 events per 100 PY (95% CI 0.71, 1.51)] groups. The most commonly reported upper GI events in both treatment groups were gastric and duodenal ulcers and upper GI bleeding (Table 5). There was one perforation in the diclofenac treatment group.

Aspirin use appeared to increase the event rates in both groups, although there were no discernible differences in rates of upper GI events between treatment groups in aspirin users [etoricoxib 2.27 events per 100 PY (95% CI 1.26, 3.28); diclofenac 2.00 events per 100 PY (95% CI 0.96, 3.03)] and nonusers [etoricoxib 0.61 events per 100 PY (95% CI 0.27, 0.96); diclofenac 0.79 events per 100 PY (95% CI 0.39, 1.18)]. Since total patient exposure was limited and the number of events was small in these subgroups, these results should be interpreted with caution.

General safety

The overall incidence of clinical AE and drug-related clinical AE was generally similar between treatment groups (Table 4). The most commonly reported drug-related clinical AE were dyspepsia, hypertension, upper abdominal pain, diarrhea, peripheral edema, and nausea (Table 4). The most common clinical AE causing discontinuation (by treatment; etoricoxib vs diclofenac) included: dyspepsia (1.4% vs 1.2%), upper abdominal pain (0.9% vs 1.4%), and general abdominal pain (0.7% vs 1.2) (which are overlapping terms), hypertension (1.5% vs 0.5%), and diarrhea (0.6% vs 1.3%). There were 14 deaths during the study or within 14 days of discontinuation of study therapy; 8 (0.2%) etoricoxib patients (cerebral infarction, sudden death, cardiac arrest, cerebral hemorrhage, hemorrhagic shock, endocarditis, metastatic neoplasm, and pancreatic carcinoma), and 6 (0.2%) diclofenac patients (2 cerebral hemorrhages, sudden death, metastatic pancreatic carcinoma, renal cell carcinoma, and bone/brain/non-small cell lung cancer). One death in each treatment group (both due to cerebral hemorrhage) was considered by the investigators as possibly related to treatment. In addition, 5 patients [2 etoricoxib (sepsis diverticulitis and death cause unknown), 3 diclofenac (pancreatic carcinoma, cerebrovascular accident, and cardiogenic shock with myocardial infarction)] died after discontinuing the study drug for > 14 days but within the 28-day observation period.

Laboratory AE occurred more frequently with diclofenac than etoricoxib, including drug-related laboratory AE (11.3%, diclofenac; 3.0%, etoricoxib) (Table 4). The most common laboratory AE, and most common drug-related laboratory AE,

were increased ALT and AST. More patients discontinued treatment due to a laboratory AE with diclofenac (5.5%) than etoricoxib (0.6%). Few laboratory AE were serious in either treatment group (3 etoricoxib, 2 diclofenac), and no patient died due to a laboratory AE.

DISCUSSION

The EDGE trial directly compared the GI tolerability and general safety of clinically similar efficacious doses of etoricoxib and diclofenac in patients with OA²⁶. GI tolerability was assessed by determining the rates of treatment discontinuation arising from the development of the GI signs, symptoms, or laboratory abnormalities associated with NSAID use. The trial was not designed to formally test for treatment differences related to GI safety (i.e., perforations, ulcers, or bleeds).

Patients treated with etoricoxib 90 mg, a dose 50% higher than the currently recommended dose for OA, were at half the risk of discontinuing therapy due to the composite GI adverse event endpoint used in this study compared to those taking diclofenac 150 mg. Although this was driven by the relatively high rate of hepatotoxicity in the diclofenac treatment group, a statistically significant benefit was observed when considering clinical GI adverse effects only. Patients receiving etoricoxib 90 mg, however, were more likely to experience and discontinue due to hypertension-related AE than those receiving diclofenac.

Discontinuations due to GI side effects or the need for GI comedications add significant cost and inefficiencies to the management of patients with arthritis and other musculoskeletal disorders²⁷⁻³³. Patients with arthritis appear to be at the highest risk of switching NSAID therapy within the first 100 days of therapy due to lack of efficacy or poor tolerability³⁴. A retrospective cohort study of a general practitioners' database in the United Kingdom suggested that dissatisfaction with NSAID therapy is common, based on the frequency of switching between NSAID, and that the increased coadministration of GPA at the time of switching indicates that GI symptoms may be a contributing cause for this, along with a lack of efficacy⁴. Hence, from a clinical practice perspective, it is important to note that the cumulative incidence of discontinuations due to GI intolerance in the etoricoxib and diclofenac treatment groups in this trial separated early after initiation of treatment in a manner consistent with a prior pooled analysis of etoricoxib clinical studies¹⁵.

In addition to enrolling regular GPA and low-dose aspirin users, we allowed patients to use new GPA or initiate low-dose aspirin therapy during the study, in accordance with clinical guidelines. Due to these confounding factors, the lack of a difference in the incidence of upper GI events between treatment groups in this study was not unexpected. However, a pooled analysis of etoricoxib (≥ 60 mg) studies that restricted GPA use confirmed a lower risk of upper GI events after treatment with etoricoxib compared to the traditional NSAID diclofenac, ibuprofen, or naproxen¹³. The lower rates of upper

Table 3A. Confirmed thrombotic cardiovascular events by class: Events within 14 and 28 days of study treatment discontinuation.

| | Events Within 14 Days of Study Treatment Discontinuation | | | | Events Within 28 Days of Study Treatment Discontinuation | | | |
|---------------------------------------|--|-------------------|---|-------------------|--|-------------------|---|-------------------|
| | Etoricoxib 90 mg (N = 3593) 2789 PY | | Diclofenac 150 mg (N = 3518) 2607 PY | | Etoricoxib 90 mg (N = 3593) 2926 PY | | Diclofenac 150 mg (N = 3518) 2740 PY | |
| | n (%) | Rate (95% CI) | n (%) | Rate (95% CI) | n (%) | Rate (95% CI) | n (%) | Rate (95% CI) |
| Confirmed Adjudicated Events | | | | | | | | |
| Total patient events | 35 (0.97) | 1.25 (0.87, 1.74) | 30 (0.85) | 1.15 (0.78, 1.64) | 38 (1.06) | 1.30 (0.92, 1.78) | 34 (0.97) | 1.24 (0.86, 1.73) |
| Cardiac events | 27 (0.75) | 0.97 (0.64, 1.41) | 19 (0.54) | 0.73 (0.44, 1.14) | 28 (0.78) | 0.96 (0.64, 1.38) | 21 (0.60) | 0.77 (0.47, 1.17) |
| Acute myocardial infarction | 19 (0.53) | 0.68 (0.41, 1.06) | 11 (0.31) | 0.42 (0.21, 0.76) | 19 (0.53) | 0.65 (0.39, 1.01) | 13 (0.37) | 0.47 (0.25, 0.81) |
| Fatal acute myocardial infarction | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 1 (0.03) | 0.04 (0.00, 0.20) |
| Sudden cardiac death | 2 (0.06) | 0.07 (0.01, 0.26) | 1 (0.03) | 0.04 (0.00, 0.21) | 2 (0.06) | 0.07 (0.01, 0.25) | 1 (0.03) | 0.04 (0.00, 0.20) |
| Unstable angina pectoris | 6 (0.17) | 0.22 (0.08, 0.47) | 7 (0.20) | 0.27 (0.11, 0.55) | 7 (0.19) | 0.24 (0.10, 0.49) | 7 (0.20) | 0.26 (0.10, 0.53) |
| Peripheral vascular events | 3 (0.08) | 0.11 (0.02, 0.31) | 4 (0.11) | 0.15 (0.04, 0.39) | 4 (0.11) | 0.14 (0.04, 0.35) | 8 (0.23) | 0.29 (0.13, 0.58) |
| Peripheral arterial thrombosis | 0 | 0.00 | 1 (0.03) | 0.04 (0.00, 0.21) | 0 | 0.00 | 1 (0.03) | 0.04 (0.00, 0.20) |
| Peripheral venous thrombosis | 2 (0.06) | 0.07 (0.01, 0.26) | 0 | 0.00 | 2 (0.06) | 0.07 (0.01, 0.25) | 1 (0.03) | 0.04 (0.00, 0.20) |
| Pulmonary embolism | 1 (0.03) | 0.04 (0.00, 0.20) | 3 (0.09) | 0.12 (0.02, 0.34) | 2 (0.06) | 0.07 (0.01, 0.25) | 6 (0.17) | 0.22 (0.08, 0.48) |
| Cerebrovascular events | 7 (0.19) | 0.25 (0.10, 0.52) | 7 (0.20) | 0.27 (0.11, 0.55) | 8 (0.22) | 0.27 (0.12, 0.54) | 8 (0.23) | 0.29 (0.13, 0.58) |
| Fatal ischemic cerebrovascular stroke | 1 (0.03) | 0.04 (0.00, 0.20) | 0 | 0.00 | 1 (0.03) | 0.03 (0.00, 0.19) | 1 (0.03) | 0.04 (0.00, 0.20) |
| Ischemic cerebrovascular stroke | 3 (0.08) | 0.11 (0.02, 0.31) | 6 (0.17) | 0.23 (0.08, 0.50) | 4 (0.11) | 0.14 (0.04, 0.35) | 6 (0.17) | 0.22 (0.08, 0.48) |
| Transient ischemic attack | 3 (0.08) | 0.11 (0.02, 0.31) | 2 (0.06) | 0.08 (0.01, 0.28) | 3 (0.08) | 0.10 (0.02, 0.30) | 2 (0.06) | 0.07 (0.01, 0.26) |

*Rate = events per 100 patient-years (PY). Patients with multiple events may be counted more than once in different categories, but only once in each term.

GI events in EDGE compared to these pooled studies suggest that the current OA population was at lower absolute risk to experience an upper GI event, possibly due to GPA use, further reducing our ability to detect any potential treatment group differences¹³.

The 25-fold increased risk of discontinuations due to labo-

ratory GI AE observed with diclofenac compared to etoricoxib (inset, Figure 2) in the post-hoc analysis is reflective of the larger than expected rate with diclofenac and the low rate of discontinuations with etoricoxib. This was largely driven by diclofenac's greater incidence of hepatic AE. Hepatotoxicity is a known side effect of diclofenac that typically occurs after

Table 3B. Confirmed events by class, according to the Anti-Platelet Trialists' Collaboration (APTC) criteria: events within 14 and 28 days of study treatment discontinuation.

| Confirmed Adjudicated Events | Events Within 14 Days of Study Treatment Discontinuation | | | | Events Within 28 Days of Study Treatment Discontinuation | | | |
|---------------------------------------|--|-------------------|--------------------------------------|-------------------|--|-------------------|--------------------------------------|-------------------|
| | Etoricoxib 90 mg (N = 3593) 2792 PY | | Diclofenac 150 mg (N = 3518) 2608 PY | | Etoricoxib 90 mg (N = 3593) 2929 PY | | Diclofenac 150 mg (N = 3518) 2742 PY | |
| | n (%) | Rate* (95% CI) | n (%) | Rate (95% CI) | n (%) | Rate (95% CI) | n (%) | Rate (95% CI) |
| Total patient events | 27 (0.75) | 0.97 (0.64, 1.41) | 21 (0.6) | 0.81 (0.50, 1.23) | 28 (0.78) | 0.96 (0.64, 1.38) | 24 (0.68) | 0.88 (0.56, 1.30) |
| Cardiac events | 21 (0.58) | 0.75 (0.47, 1.15) | 12 (0.34) | 0.46 (0.24, 0.80) | 21 (0.58) | 0.72 (0.44, 1.10) | 15 (0.43) | 0.55 (0.31, 0.90) |
| Acute myocardial infarction | 19 (0.53) | 0.68 (0.41, 1.06) | 11 (0.31) | 0.42 (0.21, 0.75) | 19 (0.53) | 0.65 (0.39, 1.01) | 13 (0.37) | 0.47 (0.25, 0.81) |
| Fatal acute myocardial infarction | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 1 (0.03) | 0.04 (0.00, 0.20) |
| Sudden cardiac death | 2 (0.06) | 0.07 (0.01, 0.26) | 1 (0.03) | 0.04 (0.00, 0.21) | 2 (0.06) | 0.07 (0.01, 0.25) | 1 (0.03) | 0.04 (0.00, 0.20) |
| Cerebrovascular events | 4 (0.11) | 0.14 (0.04, 0.37) | 6 (0.17) | 0.23 (0.08, 0.50) | 5 (0.14) | 0.17 (0.06, 0.40) | 7 (0.20) | 0.26 (0.10, 0.53) |
| Fatal ischemic cerebrovascular stroke | 1 (0.03) | 0.04 (0.00, 0.20) | 0 | 0.00 | 1 (0.03) | 0.03 (0.00, 0.19) | 1 (0.03) | 0.04 (0.00, 0.20) |
| Ischemic cerebrovascular stroke | 3 (0.08) | 0.11 (0.02, 0.31) | 6 (0.17) | 0.23 (0.08, 0.50) | 4 (0.11) | 0.14 (0.04, 0.35) | 6 (0.17) | 0.22 (0.08, 0.48) |
| Hemorrhagic events | 2 (0.06) | 0.07 (0.01, 0.26) | 3 (0.09) | 0.12 (0.02, 0.34) | 2 (0.06) | 0.07 (0.01, 0.25) | 3 (0.09) | 0.11 (0.02, 0.32) |
| Fatal hemorrhagic stroke | 1 (0.03) | 0.04 (0.00, 0.20) | 2 (0.06) | 0.08 (0.01, 0.28) | 1 (0.03) | 0.03 (0.00, 0.19) | 2 (0.06) | 0.07 (0.01, 0.26) |
| Hemorrhagic stroke | 0 | 0.00 | 1 (0.03) | 0.04 (0.00, 0.21) | 0 | 0.00 | 1 (0.03) | 0.04 (0.00, 0.20) |
| Other hemorrhagic event | 1 (0.03) | 0.04 (0.00, 0.20) | 0 | 0.00 | 1 (0.03) | 0.03 (0.00, 0.19) | 0 | 0.00 |

* Rate = Events per 100 patient-year (PY); CI: confidence interval; Patients with multiple events may be counted more than once in different categories, but only once in each term.

1 to 6 months of use and requires periodic monitoring of liver enzymes^{35,36}. Elevations of ALT and AST > 3 times the upper limit of normal typically occur in 2–4% of patients receiving diclofenac³⁷. Differences between treatments in hepatic AE in our study were primarily due to higher rates of elevated AST

and ALT with diclofenac. However, only a few hepatic-related AE were classified as severe in nature. The mechanism leading to the idiosyncratic hepatotoxicity of diclofenac remains elusive, although several reactive metabolites have been suggested to be involved³⁸. The findings from our study

Table 4. Summary of adverse experiences (AE)*.

| | Etoricoxib 90 mg, N = 3593 n (%) | Diclofenac 150 mg, N = 3518 n (%) |
|--|--|---|
| Prespecified AE | | |
| Discontinued due to any edema-related AE | 32 (0.9) | 26 (0.7) |
| Discontinued due to any hypertension-related AE | 81 (2.3) | 23 (0.7) [‡] |
| Incidence of investigator-reported CHF | 14 (0.4) | 6 (0.2) |
| Incidence of confirmed CHF | 5 (0.1) | 4 (0.1) |
| Incidence of hepatic AE | 70 (1.9) | 417 (11.9) [‡] |
| Discontinued due to hepatic AE | 9 (0.3) | 176 (5.0) [‡] |
| Discontinued due to clinical or laboratory AE related to renal dysfunction | 15 (0.4) | 14 (0.4) |
| One or more AE | | |
| Clinical | 2736 (76.1) | 2617 (74.4) |
| Laboratory [†] | 219 (6.1) | 526 (15.0) |
| Drug-related AE | | |
| Clinical | 1407 (39.2) | 1306 (37.1) |
| Laboratory | 106 (3.0) | 396 (11.3) |
| Serious AE | | |
| Clinical | 300 (8.3) | 305 (8.7) |
| Laboratory | 3 (0.1) | 2 (0.1) |
| Discontinued due to AE [§] | | |
| Total | 655 (18.2) | 804 (22.9) |
| Clinical [#] | 632 (17.6) | 610 (17.3) |
| Laboratory | 23 (0.6) | 194 (5.5) |
| Discontinued due to drug-related AE [§] | | |
| Clinical | 461 (12.8) | 458 (13.0) |
| Laboratory | 20 (0.6) | 185 (5.3) |
| Most common drug-related clinical AE | | |
| Dyspepsia | 271 (7.5) | 236 (6.7) |
| Hypertension | 210 (5.8) | 95 (2.7) |
| Upper abdominal pain | 134 (3.7) | 181 (5.1) |
| Diarrhea | 92 (2.6) | 143 (4.1) |
| Peripheral edema | 126 (3.5) | 110 (3.1) |
| Nausea | 95 (2.6) | 131 (3.7) |
| Most common drug-related laboratory AE | | |
| ALT increased | 38 (1.1) | 336 (9.6) |
| AST increased | 33 (0.9) | 265 (7.5) |

* Includes adverse experiences up to and including 14 days post study period, unless otherwise noted. [†] One patient on etoricoxib and 5 patients on diclofenac did not have post-baseline laboratory tests. [‡] p < 0.001 based on Fisher's exact test vs etoricoxib. [§] Includes adverse experiences up to and including the end-of-study visit. [#] Includes 1 patient on diclofenac who discontinued due to an "other" type of clinical adverse experience, and 5 patients on etoricoxib and 3 patients on diclofenac who discontinued during the baseline period.

Table 5. Incidence of confirmed upper gastrointestinal (GI) events.

| | Etoricoxib 90 mg, N = 3593 | | Diclofenac 150 mg, N = 3518 | |
|---|-------------------------------|-------------------|--------------------------------|-------------------|
| | n (%) | Rate* | n (%) | Rate* |
| Patients with 1 or more upper GI events | 31 (0.86) | 1.11 (0.72, 1.50) | 29 (0.82) | 1.11 (0.71, 1.51) |
| Perforation | 0 | — | 1 (0.03) | 0.04 (0.00, 0.11) |
| Gastric ulcer | 21 (0.58) | 0.75 (0.43, 1.07) | 17 (0.48) | 0.65 (0.34, 0.96) |
| Duodenal ulcer | 10 (0.28) | 0.36 (0.14, 0.58) | 13 (0.37) | 0.50 (0.23, 0.77) |
| Obstruction | 0 | — | 0 | — |
| Upper GI bleed | 17 (0.47) | 0.61 (0.32, 0.90) | 13 (0.37) | 0.50 (0.23, 0.77) |

* Rate = events per 100 person-years (95% CI).

reinforce the importance of monitoring liver enzymes when treating patients with diclofenac.

Following a review of currently available data, the US Food and Drug Administration recently concluded that there is no clear evidence that coxibs confer a greater risk of CV events compared to traditional NSAID³⁹. In addition, they concluded that all NSAID, except aspirin, may carry an increased risk of CV events following longterm use and that this should be stated in their product labels⁴⁰. In contrast, the European Medicines Agency (EMA) recommended changes to the product labels of coxibs to reflect the increased thrombotic CV risk⁴¹. However, similar label changes were not requested for the traditional NSAID based on the EMA review of data on thrombotic CV risk with NSAID.

As the first available CV safety data set from the MEDAL Program, data representing ~5400 years of patient exposure were collected in the EDGE trial. Although rates of thrombotic CV events were similar between etoricoxib and diclofenac, this specific trial was not sufficiently powered on its own to detect a difference in CV risk between etoricoxib and diclofenac. However, results from the MEDAL Program, which enrolled > 34,000 patients with OA or rheumatoid arthritis, collecting data from over 50,000 PY of exposure, with maximum duration of treatment of ~40 months, have recently become available and provide a much more precise estimate of the CV risk of these 2 agents. In the MEDAL Program, rates per 100 patient-years of confirmed thrombotic CV events were comparable, 1.24 with etoricoxib and 1.30 with diclofenac, yielding a hazard ratio of 0.95 (95% CI 0.81, 1.11)⁴².

Hypertension is a common comorbid condition in patients with OA⁴³. Data from the third National Health and Nutrition Examination Survey⁴⁴ indicate that about 40% of adults with self-reported OA also have hypertension. Baseline characteristics of patients enrolled in our current study are consistent with these data. In EDGE, the rates of edema and congestive heart failure were generally similar between treatments; however, the incidence of hypertension-related AE and discontinuations due to hypertension-related AE were significantly higher with etoricoxib 90 mg compared to diclofenac 150 mg. Few hypertension AE reported during the study were considered serious. The results of the MEDAL program showed that the incidence of congestive heart failure with etoricoxib 90 mg and discontinuations due to hypertension with etoricoxib 60 mg and 90 mg were higher than with diclofenac⁴². However, since all NSAID have the potential to affect renal function to different extents, due to inhibition of renal prostaglandin biosynthesis, these data further emphasize the importance of monitoring blood pressure in all patients receiving chronic NSAID therapy.

In conclusion, in this randomized study of over 7000 patients with OA enrolled in a clinical practice setting, significantly fewer patients discontinued due to a laboratory or clinical GI AE following sustained treatment with etoricoxib 90 mg compared to diclofenac 150 mg.

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