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Cardiovascular safety and gastrointestinal tolerability of etoricoxib *vs* diclofenac in a randomized controlled clinical trial (The MEDAL study)

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Objective. To compare cardiovascular (CV) and other safety and efficacy parameters of etoricoxib 60 and 90 mg, and diclofenac 150 mg.
Methods. This double-blind study randomized OA patients to etoricoxib 90 mg, then to 60 mg once daily *vs* diclofenac 75 mg twice daily; RA patients were randomized to etoricoxib 90 mg once daily or diclofenac 75 mg twice daily. The primary endpoint was non-inferiority of etoricoxib *vs* diclofenac for thrombotic CV events (95% CI upper bound of hazard ratio <1.30). Other safety and efficacy parameters were evaluated in cohorts of patients based on etoricoxib dose and disease.
Results. A total of 23 504 patients were randomized with mean treatment duration from 19.4 to 20.8 months. The thrombotic CV risk hazard ratio (HR) (etoricoxib to diclofenac) was 0.96 (95% CI 0.81, 1.15), consistent with non-inferiority of etoricoxib to diclofenac. The cumulative gastrointestinal (GI)/liver adverse events (AEs) discontinuation rate was significantly lower for etoricoxib than diclofenac in each patient cohort; HR (95% CI) of 0.46 (0.39, 0.54), 0.52 (0.42, 0.63) and 0.49 (0.39, 0.62) for the 60 mg OA, 90 mg OA and RA cohorts. The maximum average change in systolic blood pressure (BP) with etoricoxib was 3.4–3.6 mmHg (diastolic BP: 1.0–1.5 mmHg), while diclofenac produced a maximum average change of 0.9–1.9 mmHg (diastolic BP: 0.0–0.5 mmHg). Both agents resulted in similar efficacy regardless of etoricoxib dose.
Conclusion. Long-term etoricoxib use is associated with a risk of thrombotic CV events comparable with that of diclofenac. Compared with diclofenac, etoricoxib demonstrated a greater risk of renovascular AEs, but a more favourable GI/liver tolerability profile.

Key words: NSAIDs, Rheumatoid arthritis, Osteoarthritis, COX-2 inhibitors, Cardiovascular safety, Gastrointestinal safety, Analgesia.

Introduction

NSAIDs are recommended as an integral part of a multimodal strategy to control pain and inflammation associated with OA and RA [1, 2]. Both traditional NSAIDs and selective cyclo-oxygenase-2 (COX)-2 inhibitors function via inhibition of the COX-2 isoenzyme, a rate-limiting enzyme in the prostaglandin biosynthetic pathway. Traditional NSAIDs also inhibit the COX-1 isoenzyme at therapeutically effective doses [3, 4], which is associated with upper gastrointestinal (GI) complications such as bleeding and symptomatic ulcers, and symptoms such as dyspepsia.

COX-2 selective NSAIDs such as etoricoxib arose from efforts to design NSAIDs that would spare COX-1 activity, thus reducing GI toxicity [5, 6]. Subsequent randomized controlled trials (RCTs) comparing selective COX-2 inhibitors and traditional NSAIDs have confirmed the success of this approach [7–11].

Data from RCTs and observational studies suggest that the long-term use of both selective COX-2 inhibitors and traditional NSAIDs with the possible exception of high-dose naproxen may be associated with an increased risk for thrombotic cardiovascular (CV) events when compared with placebo [12–15]. In addition to these analyses, results from the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme, the first CV outcomes programme prospectively designed to evaluate the relative thrombotic CV risk of a selective COX-2 inhibitor and a traditional NSAID, demonstrated no difference in risk of thrombotic CV events in arthritis patients on long-term therapy with etoricoxib or diclofenac [16].

The MEDAL programme consists of three component trials: (i) EDGE, (ii) EDGE II and (iii) the MEDAL study [16–19]. Here we report in detail the results from the largest component clinical trial of the MEDAL programme, the MEDAL study, which was the only component trial designed with sufficient power to determine relative thrombotic CV risk as a stand-alone RCT. The inclusion of both the 60 and 90 mg etoricoxib doses in the design of the MEDAL study and the large patient database from this individual trial also enables the evaluation of other important clinical issues related to etoricoxib dose: safety, including the effect of renovascular adverse events (AEs) on thrombotic CV outcomes, tolerability including GI AEs, and efficacy.

Methods

Institutional review boards for each study centre (1008 sites internationally) approved the study (sponsor protocol number 066). Patients provided written informed consent prior to study participation. This study was monitored by a Data and Safety Monitoring Board until completion. The primary therapy period for this study was from September 2002 to May 2006; the enrolment period was from September 2002 to September 2004.

Patient inclusion/exclusion

Patients were ⩾50 years of age, clinically diagnosed with either OA (knee, hip or spine) or RA (at least four of seven ARA 1987 revised criteria) [20] and required chronic NSAID therapy for at least 1.5 years.

Patients with uncontrolled hypertension, unstable angina, active hepatic disease, impaired renal function or any other potentially confounding concurrent medical conditions or

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conditions resulting in safety risk, were excluded. Pregnancy, nursing or planning pregnancy within the projected trial duration also led to exclusion.

In order to have a 'real-world' population, patients at risk for GI side-effects (i.e. age >65 years; prior history of GI ulcer or haemorrhage; concurrent use of corticosteroids, concurrent use of anti-coagulants) were allowed in the study. Patients with a history of CV disease were also allowed, with the exception of those with a history of stroke, transient ischaemic attack or myocardial infarction within 6 months of enrolment.

Study design

This was a randomized, double-blind, active-comparator-controlled, multicentre, parallel-group study. This study was designed to continue until the total number of confirmed thrombotic events reached at least 635 in the MEDAL programme as a whole with at least 490 confirmed events in the current study alone. The average duration of treatment was anticipated to be ~1.5 years. Upper GI clinical events were analysed as part of the overall MEDAL programme, as previously described [16, 21]. Patients who met screening criteria were randomized with concealed allocation to treatment in equal proportions with study site using a computer-generated randomization schedule. Allocation was concealed using an interactive voice response system (IVRS) method of study drug distribution, in which patient supplies were assigned to each site according to a computer-generated randomized allocation schedule and shipped according to individual component ID numbers. Study personnel utilized the IVRS to allocate patients, to assign drug to patients and to manage the distribution of clinical supplies. A double-dummy design along with coded study medications and matching-image placebo tablets of etoricoxib and matching-image placebo tablets of diclofenac were used to maintain blinding to treatment assignment [16, 17].

Study conduct

Following screening, qualified patients were instructed to discontinue their pre-study NSAID and return to the clinical research centre within 2–10 days. The first 4333 patients with OA and all patients with RA were randomized to receive etoricoxib 90 mg once daily or diclofenac 75 mg twice daily. Initial enrolment into this trial occurred primarily in the US. The study was amended to include etoricoxib 60 mg, the recommended dose for OA. Subsequent to the amendment, when enrolment occurred primarily outside of the US (i.e. Europe, Latin America and Asia) OA patients were randomized to etoricoxib 60 mg daily or diclofenac 75 mg twice daily. Acetaminophen (up to 2600 mg/day) was permitted as rescue medication.

Safety data were collected at screening, randomization, every 4 months thereafter and at end of study. Patient follow-up and compliance is described elsewhere [16, 17]. Physical examination, including vital signs, collection of laboratory samples and an electrocardiogram were performed at Month 12 and at the end-of-study visit. Serious AEs that may have occurred within 28 days of the last dose of study medication were collected for all patients. Due to the large size of the study, only serious AEs and AEs that resulted in discontinuation were collected.

Included and excluded study medications

Low-dose aspirin (≤100 mg/day) and anti-ulcer medication (proton-pump inhibitors or misoprostol) were recommended for prophylactic use; omeprazole was provided free of charge and investigators were reminded of current treatment guidelines on a case-by-case basis as previously described [16, 17].

Primary and secondary safety endpoints

This report focuses on the MEDAL study alone. The MEDAL study was the largest component trial of the MEDAL programme, which also included the EDGE and EDGE II studies [16, 21, 23]. The primary results from the entire pooled MEDAL programme, which included thrombotic CV safety and upper GI events, have been published elsewhere [16, 17].

Thrombotic CV safety was determined by evaluating thrombotic CV events, including both venous and arterial events (i.e. myocardial infarction, unstable angina pectoris, intracardiac thrombus resuscitated cardiac arrest, thrombotic stroke, cerebrovascular thrombosis, transient ischaemic attack, peripheral venous thrombosis, pulmonary embolism, peripheral arterial thrombosis and sudden or unexplained death). Potential CV endpoints were adjudicated by an outside panel of experts in cardiology, neurology and peripheral vascular disease blinded to study therapy. Additional secondary CV safety endpoints included the subset of confirmed arterial events only, and the Anti-Platelet Trialists' Collaboration (APTC) endpoint (myocardial infarction, stroke and vascular death) [17].

GI tolerability was assessed by evaluating discontinuations due to clinical or laboratory GI AEs over the first 12 months of treatment. This pre-defined endpoint included nearly all terms in the GI System Organ Class as well as laboratory AEs related to liver function abnormalities as previously described [16, 17]. All AEs reported by investigators with any one of these terms were included in this endpoint. An individual patient was only counted once in the GI System Organ Class; however, the same patient may be counted under different specific AE terms if more than one AE was reported for that individual patient. Discontinuations due to GI AEs were investigated further to examine discontinuation rates due to clinical GI AEs and laboratory GI/liver AEs separately.

Pre-specified general safety endpoints included: incidence of confirmed cases of congestive heart failure (CHF) resulting in hospitalization or emergency department visit, incidence of investigator-reported AEs of CHF, pulmonary oedema or cardiac failure; and discontinuations due to the following: oedema-related AEs; hypertension-related AEs; AEs related to renal dysfunction (clinical or laboratory).

Efficacy assessment

The Patient Global Assessment of Disease Status (PGADS) was administered at Months 4, 8, 12, and every 4 months including the discontinuation visit. Additionally, the Investigator Global Assessment of Disease Status (IGADS) was collected at Months 4, 12, 20, and every 8 months including the discontinuation visit. Both endpoints used a 5-point Likert scale; 0 = 'doing very well' to 4 = 'doing very poorly'. Differences of up to ±0.5 on this scale are not considered clinically meaningful [17, 22]. In this study, differences between the treatment groups would be considered clinically meaningful only if the 95% CI for the difference between treatment groups excluded the region from −0.5 or 0.5.

Sample size and data analysis

At an assumed confirmed thrombotic event rate of 1.6%/year (based on prior studies in arthritis), it was estimated that a total of ~21 544 patients would need to be enrolled in order to yield the required number of events within a 3-year time period. After the start of the study, the sample size was increased to ~23 504, in response to a less-than-expected overall rate of thrombotic CV events (1.3%/year) in the study population.

Assuming a true underlying hazard ratio (HR) of 1.00, 490 events were needed in order to have 83% power to yield the upper limit of the 95% CI for HR <1.30 (the pre-specified non-inferiority bound). The number of events needed was calculated using the Lachin–Foulkes method [23].

Statistical methods

Statistical methods are described here in brief as they have been described in detail elsewhere [16, 17]. Because this was a non-inferiority trial, primary analysis of thrombotic CV endpoints were based on a per-protocol approach. Specific exclusion criteria for the per-protocol analysis were based on non-compliance of the prime therapy (<75% of time on therapy) and the excess use of non-study NSAIDs and coxibs (>10% of time on therapy).

Intention-to treat (ITT; the analyses including all patients randomized) approach was used for non-CV endpoints and to corroborate the results of the per-protocol analysis of the primary CV endpoint [16, 17]. Three observation times were used between the trial start date: (i) 14 days following therapy discontinuation (all non-CV safety endpoints); (ii) 28 days following therapy discontinuation (thrombotic CV events); and (iii) up to the end of the study follow-up period and including all events regardless of time on therapy (thrombotic CV events).

For all CV and GI endpoints, survival analytical methods were used to evaluate the time to the first event during the study period. The analyses were based on a Cox proportional hazards model with treatment (etoricoxib/diclofenac) as a factor and baseline low-dose aspirin use as stratification factor. The efficacy parameters were summarized as the average change from baseline over the treatment period; the least square mean and CIs were based on analysis of covariance with treatment, baseline low-dose aspirin use and baseline value of efficacy parameter as covariates. The incidence of serious AEs, discontinuation due to AEs and other safety endpoints of interest were assessed as percent of patients with events, and difference in percent were computed using Wilson's score method. For the pre-specified general safety endpoints, the between-treatment difference was using Fisher's exact test.

Results

Patients

Of the 26 551 patients who were screened, 23 504 were randomized at 1008 international clinical centres to receive etoricoxib ($n = 11\,787$) or diclofenac ($n = 11\,717$). The number of patients in each treatment group by disease and dose are shown in Fig. 1. Baseline patient characteristics were similar among treatment groups (Table 1). Similar proportions of discontinuations for any reason were observed in each treatment group (Fig. 1).

The duration of treatment ranged from 0.3 to 42.3 months. The mean duration of treatment was similar in all treatment groups: 20.8 months for etoricoxib 60 mg and 20.2 months for diclofenac in the etoricoxib 60 mg OA cohort; 20.4 months for etoricoxib and 19.4 months for the diclofenac group in the etoricoxib 90 mg OA cohort; and 20.8 months for etoricoxib and 20.1 months for the diclofenac group in the RA cohort.

Safety and tolerability

Assessment of thrombotic CV risk. In the primary analysis, a total of 491 patients had confirmed thrombotic CV events; 246 on etoricoxib and 245 on diclofenac. As reported in Cannon *et al.* [16], the HR (95% CI) of thrombotic events for etoricoxib *vs* diclofenac was 0.96 (0.81, 1.15) (Table 2). The upper bound of the 95% CI was well below the pre-specified non-inferiority bound of 1.30. The rates of CV events were similar for etoricoxib and diclofenac in each of the three major vascular beds (cardiac, cerebrovascular and peripheral). The individual event with the highest rate of occurrence was acute myocardial infarction, which occurred at similar rates per 100 patient-years with etoricoxib (0.39; 95% CI 0.31, 0.49) and diclofenac (0.39; 95% CI 0.30, 0.49). The results were consistent across the three different pre-specified

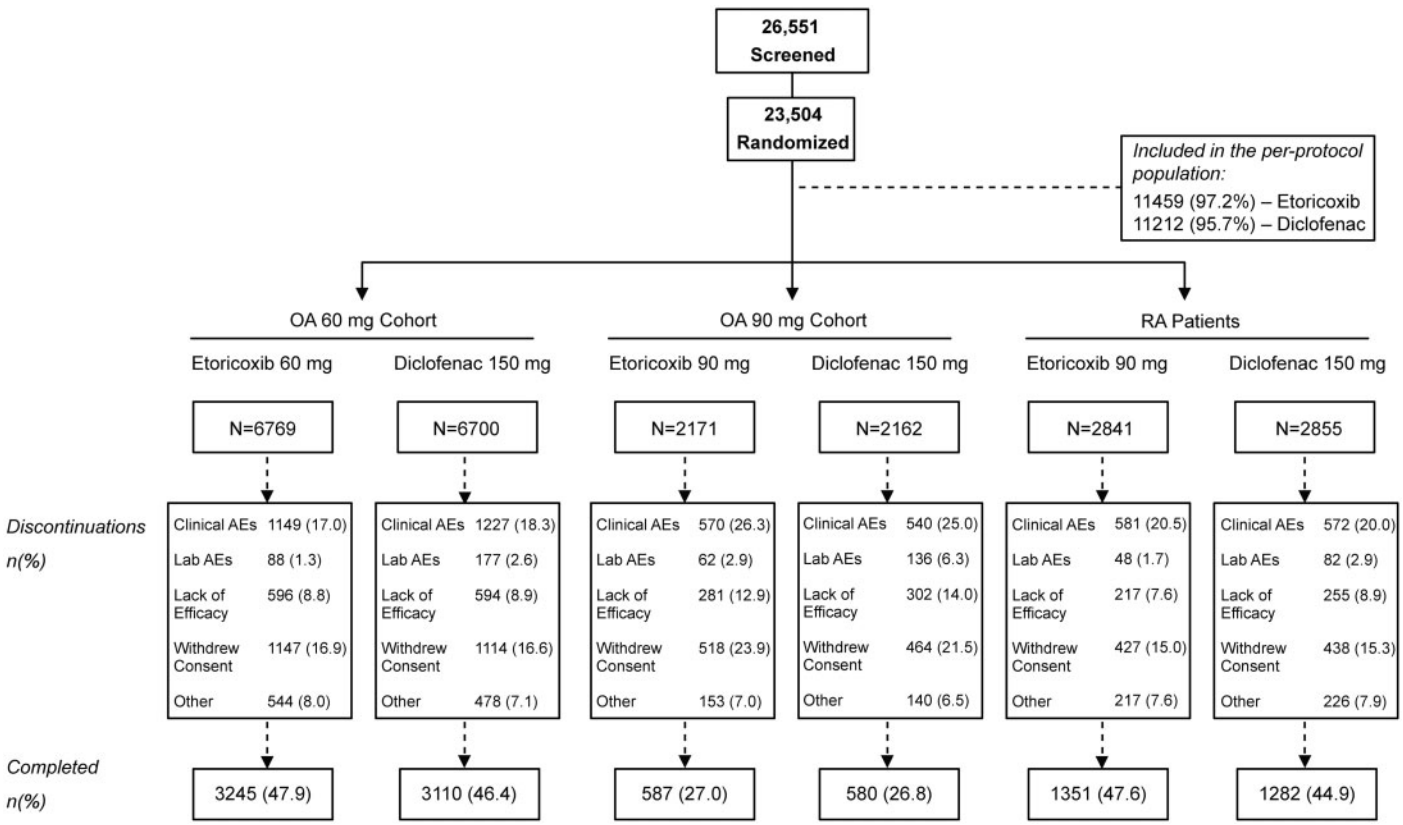

FIG. 1. Patient accounting. There were six enrolled patients receiving etoricoxib that were not included in analyses; one patient had a missing disease status and five RA patients had a treatment label of etoricoxib 60 mg.

TABLE 1. Summary of baseline demographics and characteristics

Characteristics	60 mg OA cohort		90 mg OA cohort		90 mg RA cohort	
	Etoricoxib 60 mg *N* = 6769	Diclofenac 150 mg *N* = 6700	Etoricoxib 90 mg *N* = 2171	Diclofenac 150 mg *N* = 2162	Etoricoxib 90 mg *N* = 2841	Diclofenac 150 mg *N* = 2855
Age, mean ± S.D., yrs	63.9 ± 8.5	64.0 ± 8.4	64.5 ± 8.8	64.2 ± 8.6	61.4 ± 8.2	61.4 ± 8.1
Gender, *n* (%)						
Female	4976 (73.5)	4953 (73.9)	1496 (68.9)	1514 (70.0)	2202 (77.5)	2244 (78.6)
Race, *n* (%)						
White	5454 (80.6)	5380 (80.3)	2082 (86.7)	1909 (88.3)	1959 (69.0)	2006 (70.3)
Black	205 (2.7)	209 (3.1)	142 (6.5)	125 (5.8)	119 (4.2)	109 (3.8)
Other	1130 (16.7)	1111 (16.6)	147 (6.8)	128 (5.9)	763 (26.9)	740 (25.9)
BMI, mean ± S.D., kg/m^2	29.7 ± 5.7	29.8 ± 5.6	31.2 ± 6.6	31.1 ± 6.7	28.0 ± 5.6	28.1 ± 5.6
History of upper GI events (perforations, ulcers and bleeding), *n* (%)	420 (6.2)	449 (6.7)	203 (8.4)	176 (8.1)	255 (9.0)	259 (9.1)
Baseline low-dose aspirin users, *n* (%)	2544 (37.6)	2505 (37.4)	1143 (52.6)	1173 (54.3)	913 (32.1)	952 (33.3)
Baseline PPI users, *n* (%)	3549 (52.4)	3514 (52.4)	1049 (48.3)	984 (45.5)	1698 (59.8)	1708 (59.8)
Increased-risk for thrombotic cardiovascular event,[a] *n* (%)	2682 (39.6)	2700 (40.3)	1049 (48.3)	1059 (49.0)	987 (34.7)	946 (33.1)
History of diagnosed hypertension, *n* (%)	3372 (49.8)	3445 (51.4)	1156 (53.2)	1117 (51.7)	1212 (42.7)	1246 (43.6)
History of dyslipidaemia, *n* (%)	2002 (29.6)	2033 (30.3)	990 (45.6)	964 (44.6)	668 (23.5)	589 (20.6)
Mean baseline systolic blood pressure, mm Hg	132.1	132.1	130.6	130.8	129.5	129.2
Mean baseline diastolic blood pressure, mm Hg	78.9	79.0	77.2	77.4	77.7	77.9

[a]History of symptomatic atherosclerotic CV disease or ≥2 CV risk factors (history of diabetes, hypertension, family history of CV disease, and current smokers).

TABLE 2. Rates of thrombotic cardiovascular events

Analysis approach	Treatment	*N*	*n*/PYR[a]	Rate[b] (95% CI)	HR (95% CI)
Thrombotic events					
Per-protocol	Etoricoxib	11 459	246/19 970	1.23 (1.08, 1.40)	0.96 (0.81, 1.15)
	Diclofenac	11 212	245/19 103	1.28 (1.13, 1.45)	
ITT (within 14 days)[c]	Etoricoxib	11 787	261/20 328	1.28 (1.13, 1.45)	0.96 (0.81, 1.14)
	Diclofenac	11 717	261/19 536	1.34 (1.20, 1.51)	
ITT (within 28 days)[c]	Etoricoxib	11 787	278/20 768	1.34 (1.19, 1.51)	1.00 (0.84, 1.20)
	Diclofenac	11 717	268/19 975	1.34 (1.19, 1.51)	
ITT (to end of study)[c]	Etoricoxib	11 787	394/31 256	1.26 (1.14, 1.39)	1.08 (0.94, 1.25)
	Diclofenac	11 717	363/31 057	1.17 (1.05, 1.30)	
Arterial thrombotic events					
Per-protocol	Etoricoxib	11 459	207/19 972	1.04 (0.90, 1.19)	0.99 (0.81, 1.20)
	Diclofenac	11 212	201/19 108	1.05 (0.91, 1.21)	
ITT (within 14 days)[c]	Etoricoxib	11 787	222/20 330	1.09 (0.95, 1.25)	0.99 (0.82, 1.19)
	Diclofenac	11 717	216/19 541	1.11 (0.96, 1.26)	
ITT (within 28 days)[c]	Etoricoxib	11 787	227/20 772	1.09 (0.96, 1.24)	0.99 (0.82, 1.19)
	Diclofenac	11 717	220/19 981	1.10 (0.96, 1.26)	
ITT (to end of study)	Etoricoxib	11 787	319/31 359	1.02 (0.91, 1.14)	1.06 (0.90, 1.24)
	Diclofenac	11 717	300/31 147	0.96 (0.86, 1.08)	
APTC events					
Per-protocol	Etoricoxib	11 459	166/19 981	0.83 (0.71, 0.97)	1.01 (0.81, 1.25)
	Diclofenac	11 212	158/19 119	0.83 (0.70, 0.97)	
ITT (within 14 days)[c]	Etoricoxib	11 787	174/20 341	0.86 (0.73, 0.99)	0.99 (0.80, 1.22)
	Diclofenac	11 717	169/19 553	0.86 (0.74, 1.00)	
ITT (within 28 days)[c]	Etoricoxib	11 787	178/20 785	0.86 (0.74, 0.99)	1.00 (0.81, 1.23)
	Diclofenac	11 717	171/19 995	0.86 (0.73, 0.99)	
ITT (to end of study)	Etoricoxib	11 787	265/31 469	0.84 (0.74, 0.95)	1.08 (0.90, 1.28)
	Diclofenac	11 717	245/31 243	0.78 (0.69, 0.89)	

[a]Patient-years at risk. [b]Number of events per 100 patient-years. [c]Events between trial start date and within specified days after study therapy discontinuation. *N*: total number of patients; *n*: the number of patients with events.

endpoints (all thrombotic, arterial and APTC) and across the per-protocol and ITT analyses (Table 2). The results for the subgroup of patients on low-dose aspirin are consistent with the results for the overall population with a hazard ratio (95% CI) of 0.89 (0.69, 1.14) for etoricoxib *vs* diclofenac, although a slightly greater numerical risk reduction for etoricoxib was observed compared with diclofenac in the subgroup of patients on low-dose aspirin compared with the overall MEDAL study population.

Assessment of GI tolerability. Significantly fewer etoricoxib patients ($P < 0.001$) discontinued treatment due to clinical GI AEs and laboratory GI/liver AEs combined, as well as clinical GI AEs and laboratory GI/liver AEs when analysed separately. The percent of patients discontinuing from clinical GI AEs and laboratory GI/liver AEs over the first year of treatment are reported in Table 3. The significantly lower rate of discontinuation due to clinical GI AEs, when analysed separately from laboratory GI/liver AEs, was evident by the first evaluation and maintained throughout the primary 12-month period of analysis (Fig. 2).

For clinical GI AEs, the difference in discontinuations was primarily due to a lower incidence of patient reports of abdominal discomfort, abdominal pain, upper abdominal pain, diarrhoea and gastric ulcers in patients receiving etoricoxib. For laboratory GI/liver AEs, the difference in discontinuations was primarily attributed to increase in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) observed in patients receiving diclofenac (Table 3). Consistent results were obtained for the pre-specified endpoint of discontinuations due to hepatic AEs; these have been reported elsewhere [20].

TABLE 3. Efficacy endpoints and safety endpoints of special interest

	60 mg OA cohort		90 mg OA cohort		90 mg RA cohort	
	Etoricoxib 60 mg *N* = 6769	Diclofenac 150 mg *N* = 6700	Etoricoxib 90 mg *N* = 2171	Diclofenac 150 mg *N* = 2162	Etoricoxib 90 mg *N* = 2841	Diclofenac 150 mg *N* = 2855
General safety, *n* (%)						
Serious AEs	1179 (17.4)	1202 (17.6)	456 (21.0)	422 (19.5)	607 (21.4)	540 (20.9)
Discontinuations due to AEs	1133 (16.7)	1208 (20.0)	565 (26.0)	532 (24.6)	573 (20.2)	567 (19.9)
Discontinuations due to GI AEs, *n* (%)[a]						
Overall discontinuations due to any clinical GI AE	213 (3.1)*	369 (5.5)	134 (6.2)*	195 (9.0)	96 (3.4)*	169 (5.9)
Overall discontinuations due to any laboratory GI/liver AE	9 (0.1)*	96 (1.4)	8 (0.4)*	71 (3.3)	6 (0.2)*	39 (1.4)
Efficacy endpoints						
Patient global assessment of disease status						
N (baseline mean)	6395 (2.27)	6294 (2.26)	2076 (2.22)	2073 (2.25)	2717 (2.13)	2723 (2.14)
Least squares (LS) mean change (95% CI)	−0.66 (−0.67, −0.64)	−0.61 (−0.63, −0.59)	−0.75 (−0.78, −0.72)	−0.67 (−0.70, −0.63)	−0.65 (−0.68, −0.62)	−0.58 (−0.60, −0.55)
Between-treatment group difference in LS mean change (95% CI)	−0.04 (−0.07, −0.02)		−0.08 (−0.13, −0.04)		−0.08 (−0.12, −0.04)	
Investigator global assessment of disease status						
N (baseline mean)	6523 (2.20)	6424 (2.17)	2054 (2.21)	2046 (2.24)	2751 (2.09)	2751 (2.10)
LS mean change (95% CI)	−0.69 (−0.71, −0.67)	−0.65 (−0.67, −0.63)	−0.74 (−0.77, −0.71)	−0.65 (−0.69, −0.62)	−0.68 (−0.71, −0.65)	−0.64 (−0.67, −0.61)
Between-treatment group difference in LS mean change (95% CI)	−0.04 (−0.06, −0.01)		−0.08 (−0.13, −0.04)		−0.04 (−0.08, 0.00)	

Pre-specified safety endpoints include adverse experiences up to and including 14 days post-study period, unless otherwise noted. [a]Only the most frequent AEs (occurring in ⩾0.1% of patients) are shown. *$P < 0.001$ based on Fisher's exact test.

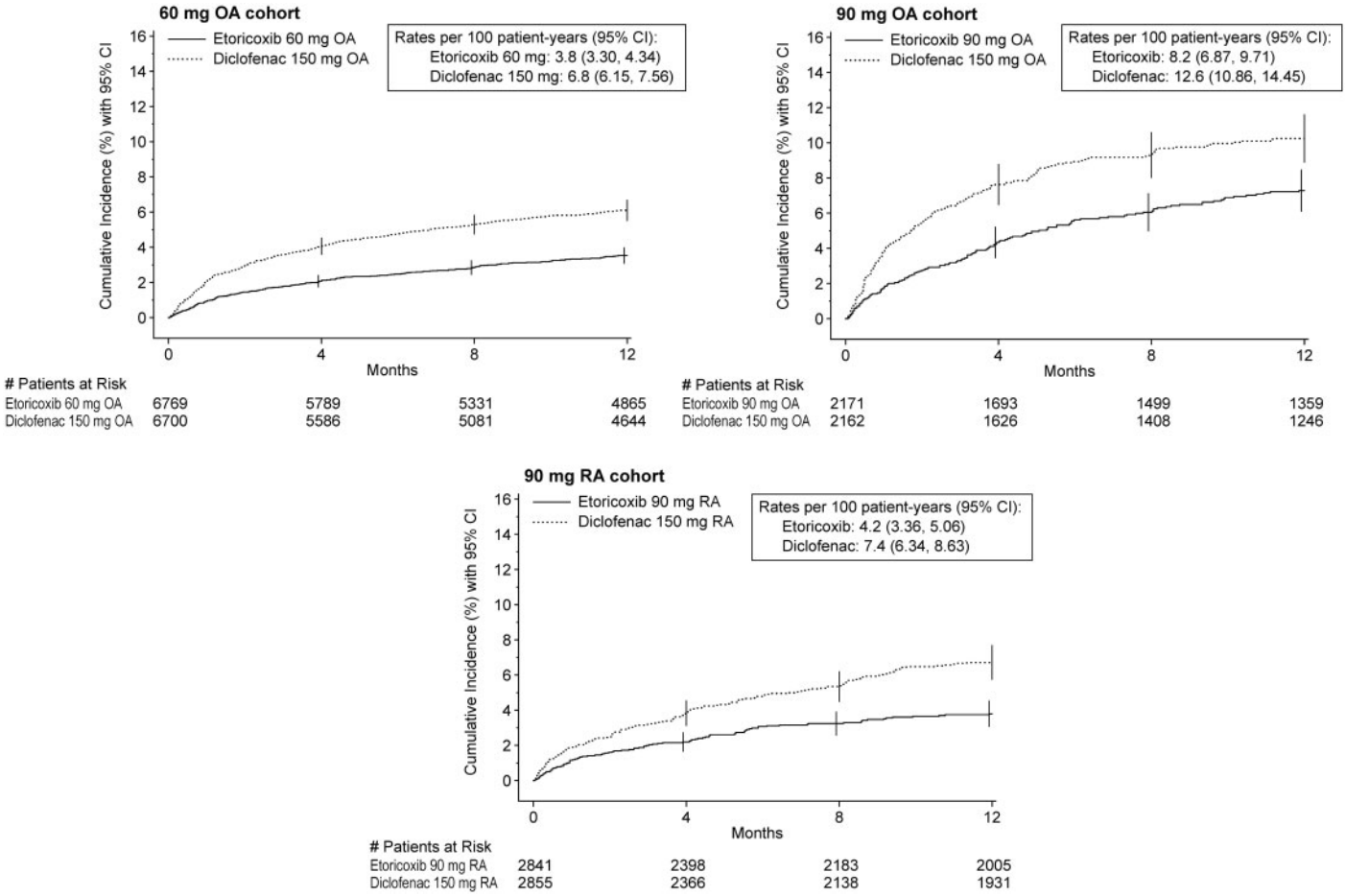

FIG. 2. Cumulative discontinuations due to clinical GI AEs within 12 months.

The incidence of serious GI AEs were similar for each treatment group: in the 60 mg OA cohort, 1.9% (etoricoxib 60 mg) and 2.1% (diclofenac 150 mg); in the 90 mg OA cohort, 2.9% (etoricoxib 90 mg) and 2.8% (diclofenac 150 mg); in RA cohort, 2.2% (etoricoxib 90 mg) and 2.4% (diclofenac 150 mg).

Pre-specified safety-related endpoints. Data on pre-specified safety-related endpoints in the MEDAL study were previously published as part of the presentation of the overall MEDAL programme [17]. These data are briefly summarized here to provide full context of GI, renovascular and hepatic AEs that

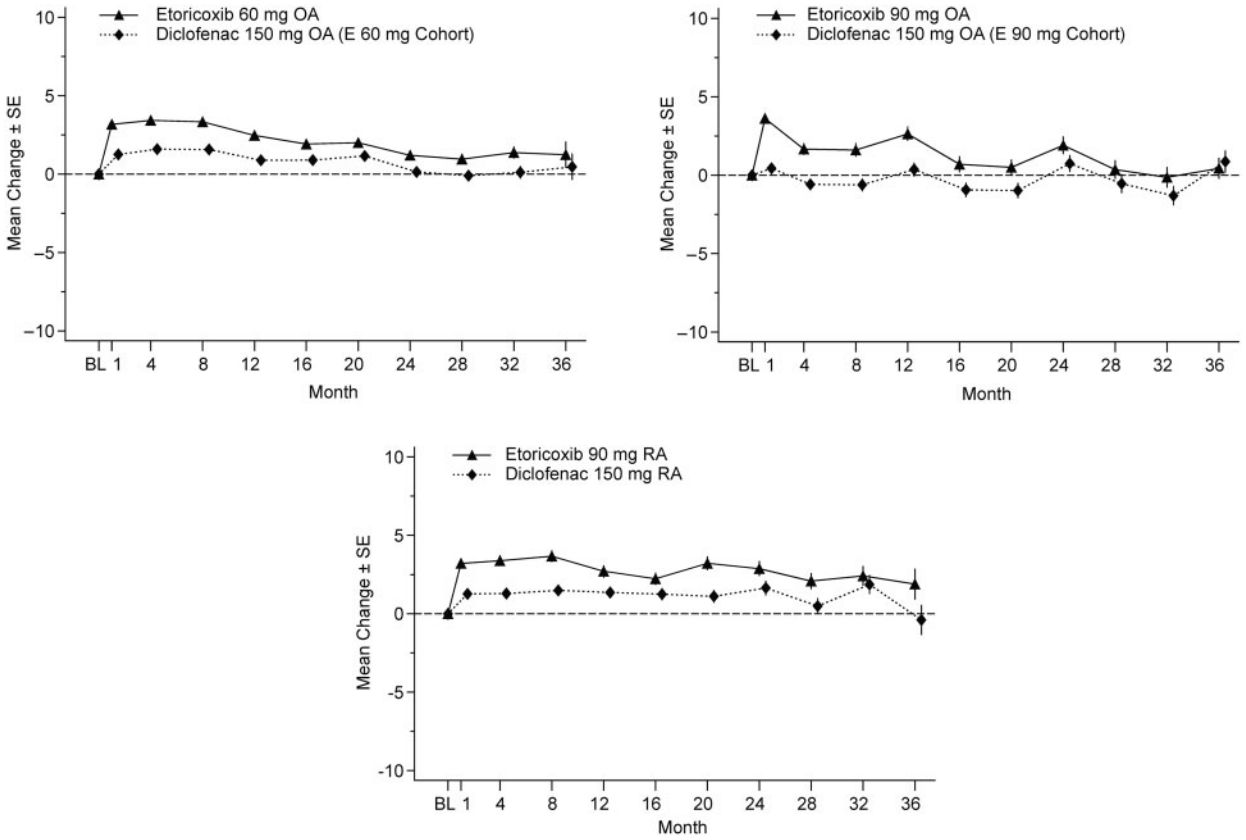

FIG. 3. Mean change in systolic blood pressure (mmHg) from baseline over time.

occurred in this individual trial. Discontinuations due to oedema-related AEs were low in all three cohorts, although more frequent in the etoricoxib treatment groups [17]. Etoricoxib was associated with a significantly greater number of hypertension-related discontinuations in all patient cohorts [17]. This effect appeared to be dose dependent; although significance testing was not done, the differences between the discontinuation rates with etoricoxib and diclofenac were greater in the 90 mg OA and RA cohorts than in the 60 mg OA cohort (Table 3). Among patients who discontinued due to hypertension, the following percentage had a pre-existing history of hypertension upon enrolling in this trial: in the 60 mg OA cohort, 66% (etoricoxib 60 mg) and 65% (diclofenac 150 mg); in the 90 mg OA cohort, 71% (etoricoxib 90 mg) and 46% (diclofenac 150 mg); and in the RA cohort, 65% (etoricoxib 90 mg) and 52% (diclofenac 150 mg). Confirmed cases of CHF, although rare and not significantly different between etoricoxib and diclofenac in any patient cohort, were numerically higher in the etoricoxib groups [17]. Additionally, the investigator-reported cases of CHF were significantly higher for etoricoxib 90 mg *vs* diclofenac, but not for etoricoxib 60 mg *vs* diclofenac in the OA cohorts; the incidence was 0.4% for both treatments in the 60 mg OA cohort, 1.1% (etoricoxib 90 mg) and 0.5% (diclofenac) in the 90 mg OA cohort, and 0.8 and 0.5% (diclofenac) in the RA cohort. Discontinuations due to clinical or laboratory AEs related to renal dysfunction were infrequent and similar for both etoricoxib 60 mg and diclofenac 150 mg OA and for both groups in the RA cohort [17].

General safety and tolerability. Serious clinical AEs and AEs that led to discontinuation were both similar between treatment groups (Table 3). There were 196 deaths (94 on etoricoxib and 102 on diclofenac) while on study therapy or within 14 days of discontinuation.

When compared with diclofenac, etoricoxib generally produced a greater average increase in the systolic blood pressure (BP) from baseline in the three study cohorts at Months 1, 12 and 36 (Fig. 3). In the 60 mg OA cohort, mean increase in systolic BP at Month 1 was 3.2 mmHg for etoricoxib 60 mg *vs* 1.3 mmHg for diclofenac. Mean increase in systolic BP at Month 12 was 2.5 mmHg for etoricoxib 60 mg *vs* 0.5 mmHg for diclofenac. Mean increase in systolic BP at Month 36 was 1.2 mmHg for etoricoxib 60 mg *vs* 0.5 mmHg for diclofenac. In the 90 mg OA cohort, systolic BP at Month 1 was 3.6 mmHg for etoricoxib 60 mg *vs* 0.4 mmHg for diclofenac. Mean increase in systolic BP at Month 12 was 2.6 mmHg for etoricoxib 60 mg *vs* 0.4 mmHg for diclofenac. Mean increase in systolic BP at Month 36 was 0.4 mmHg for etoricoxib 60 mg *vs* 0.9 mmHg for diclofenac. In the RA cohort, increase in mean systolic BP at Month 1 was 3.2 mmHg for etoricoxib 60 mg *vs* 1.3 mmHg for diclofenac. Mean increase in systolic BP at Month 12 was 2.7 mmHg for etoricoxib 60 mg *vs* 1.4 mmHg for diclofenac. Mean increase in systolic BP at Month 36 was 1.9 mmHg for etoricoxib 60 mg *vs* − 0.4 mmHg for diclofenac.

Mean increases from baseline in diastolic BP were also higher with etoricoxib compared with diclofenac at Months 1, 12 and 36. In the 60 mg OA cohort, mean increase in diastolic BP at Month 1 was 1.0 mmHg for etoricoxib 60 mg *vs* 0.2 mmHg for diclofenac. Mean increase in diastolic BP at Month 12 was 0.6 mmHg for etoricoxib 60 mg *vs* − 0.1 mmHg for diclofenac. Mean increase in diastolic BP at Month 36 was −0.4 mmHg for etoricoxib 60 mg *vs* − 0.5 mmHg for diclofenac. In the 90 mg OA cohort, diastolic BP at Month 1 was 1.5 mmHg for etoricoxib 60 mg *vs* − 0.2 mmHg for diclofenac. Mean increase in diastolic BP at Month 12 was 0.9 mmHg for etoricoxib 60 mg *vs* − 0.2 mmHg for diclofenac. Mean increase in diastolic BP at Month 36 was −0.6 mmHg for

etoricoxib 60 mg *vs* – 1.1 mmHg for diclofenac. In the RA cohort, increase in mean diastolic BP at Month 1 was 1.0 mmHg for etoricoxib 60 mg *vs* 0.1 mmHg for diclofenac. Mean increase in diastolic BP at Month 12 was 0.7 mmHg for etoricoxib 60 mg *vs* 0.1 mmHg for diclofenac. Mean increase in diastolic BP at Month 36 was 0.1 mmHg for etoricoxib 60 mg *vs* – 1.5 mmHg for diclofenac.

Efficacy

In each of the three cohorts, baseline measurements of PGADs and IGADs were similar among the etoricoxib and diclofenac treatment groups. In each case, patients had greater reductions in PGADs and IGADs on etoricoxib compared with diclofenac. These differences in reduction from baseline between treatments did not exceed the minimum pre-specified criterion to be considered clinically meaningful (Table 3).

Discussion

The MEDAL study, with 23 504 patients, is the largest and longest individual outcome study of NSAID use in arthritis patients. It was designed to evaluate the HR of thrombotic CV events for etoricoxib, a selective COX-2 inhibitor, and diclofenac a traditional NSAID both as a stand-alone study and as one of the three-component studies in the previously published MEDAL programme [16, 17]. A single traditional NSAID comparator was used for this trial to maximize power for evaluation of the CV endpoint [16, 27]. Diclofenac was chosen as the active comparator because it is the most widely used NSAID in the world, exhibits a lack of interference with the cardioprotective benefits of low-dose aspirin [24], and demonstrates significant COX-1 inhibition as shown by pharmacodynamic data and endoscopic ulcer trials [3].

As there are advantages to evaluating data from a stand-alone RCT, the MEDAL study was designed and adequately powered to assess the relative CV risk of these treatments. The HR was 0.96 (95% CI 0.81, 1.15), with the upper bound of the 95% CI being less than the pre-specified bound of 1.30, thus establishing the non-inferiority of the selective COX-2 inhibitor, etoricoxib and the traditional NSAID, diclofenac, with respect to CV risk. These results are consistent with those for the pooled MEDAL programme [16]. The results of the MEDAL study are also consistent with recent meta-analyses suggesting similar CV risk for selective COX-2 inhibitors and traditional NSAIDs other than high-dose naproxen [8, 14, 15]. In addition, the TARGET trial, a 1-year randomized comparison of lumiracoxib *vs* ibuprofen or naproxen in 20 244 OA patients also collected and adjudicated CV outcomes, although the study's primary endpoint was upper GI complications [8, 14, 15]. No significant differences were seen between lumiracoxib and the traditional NSAIDs, although a trend to fewer events with naproxen was present.

The incidence of thrombotic CV events is low, necessitating the pooling of data for different doses of etoricoxib and different patient groups to properly evaluate CV safety. On the other hand, the other safety and efficacy endpoints can be evaluated using patient cohorts separated by disease indication and etoricoxib dose. Enrolment of patients with OA into this study began in the US where patients were randomized to etoricoxib 90 mg or diclofenac 150 mg. The study was then amended to randomize OA patients to etoricoxib 60 mg as enrolment began outside of the US. As a result, the 90 mg OA cohort consisted primarily of patients from the US, and the 60 mg OA cohort patients from Europe, Latin America and elsewhere. While these differences in baseline patient characteristics make a direct comparison of etoricoxib 60 mg and etoricoxib 90 mg difficult, they also highlight important differences between patient populations in the US and those from Europe, Latin America or other geographic areas. In general, patients in the 90 mg OA cohort appeared to have more CV risk factors such as dyslipidaemia and a prior history of smoking as well as greater baseline use of low-dose aspirin and anti-platelet medication than patients in the 60 mg OA group.

NSAID-associated GI AEs interfere with treatment regimens often leading to discontinuation of medication leaving patients with inadequate pain relief. This inability to tolerate therapy may lead to additional physician involvement, endoscopies or radiological procedures, prescribing of gastroprotective agents or switching of therapy. In the MEDAL study, discontinuations due to clinical GI AEs occurred at a significantly lower rate in patients randomized to etoricoxib despite encouragements to co-administer appropriate gastroprotective agents. Etoricoxib also precipitated significantly fewer discontinuations due to laboratory GI/liver AEs such as elevated AST and ALT when compared with diclofenac. Although less common, patients prescribed NSAID therapy are also recognized to be at increased risk of upper GI events such as bleeding [21]. In the pooled MEDAL programme, significantly fewer uncomplicated upper GI events occurred with etoricoxib compared with diclofenac [21].

NSAID-associated renovascular effects are primarily driven by inhibition of renal prostanoid (i.e. PGI_2 and PGE_2) biosynthesis and subsequent reductions in renal function controlling salt and fluid balance [25, 26]. Although PGI_2 and PGE_2 are also thought to stimulate renin release, the net effect of their inhibition by NSAIDs is an increase in BP and fluid retention, particularly in patients with pre-existing low renin activity or hypertension [27, 28]. Because these effects are mechanism based, they may become more evident with higher dosing NSAID regimens. A meta-analysis of RCTs suggests that some traditional NSAIDs are associated with an average increase in mean arterial pressure as high as 3.6–6 mmHg [29]. In an analysis of pooled data from the etoricoxib development programme, naproxen demonstrated negligible effects on BP, while ibuprofen produced an increase in mean arterial pressure that was greater than that produced by etoricoxib 60 or 90 mg [30]. In the MEDAL study, the maximum average change in systolic BP with etoricoxib was 3.4–3.6 mmHg (diastolic BP: 1.0–1.5 mmHg), while diclofenac produced a maximum average change of 0.9–1.9 mmHg (diastolic BP: 0.0–0.5 mmHg).

Hypertension is an important risk factor for CV disease and in this study etoricoxib was associated with a significantly greater number of discontinuations due to hypertension-related AEs [16]. Similarly, the incidence of investigator-reported CHF and discontinuations due to oedema were significantly greater for etoricoxib 90 mg than diclofenac, but not for etoricoxib 60 mg *vs* diclofenac [16]. These results are generally consistent with the results from the EDGE and EDGE II studies [17, 18]. Although dose-related increases in hypertension, oedema and CHF were observed with etoricoxib, this did not translate into an increase in thrombotic CV events for either dose of etoricoxib over the study period [16].

Efficacy was evaluated to ensure that the comparison of safety endpoints was done in the context of effective clinical treatment. Consistent with previous findings, both etoricoxib doses and diclofenac provided similar, significant clinical benefits in the symptomatic treatment of OA and RA [6].

In summary, etoricoxib was associated with a thrombotic CV risk that was similar to that of diclofenac 150 mg with a better GI tolerability profile. Etoricoxib, however, was associated with an increase in discontinuations due to hypertension. Efficacy of etoricoxib 60 and 90 mg was comparable with that of diclofenac 150 mg in patients with OA and RA. The results of this study also demonstrate that in OA patients, the therapeutic effect and safety/tolerability profile of etoricoxib 60 mg (the recommended dose) and etoricoxib 90 mg was similar with the important exception of renovascular safety suggesting a better overall safety profile for etoricoxib 60 mg compared with the higher etoricoxib dose. Additionally, overall discontinuations due to clinical AEs and the incidence of serious clinical AEs were generally similar for all treatment groups and cohorts.

Rheumatology key messages

- The thrombotic cardiovascular risk for etoricoxib was similar to that of diclofenac, a traditional NSAID.
- While blood pressure increases and renovascular discontinuations were higher on etoricoxib, diclofenac demonstrated increased GI and hepatic adverse events.
- These data will assist physicians in choosing appropriate treatment for arthritis based on individual patients' risk factors.

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