Cardiovascular outcomes with 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 **Cyclo-oxygenase-2 (COX-2) selective inhibitors have been associated with an increased risk of thrombotic cardiovascular events in placebo-controlled trials, but no clinical trial has been reported with the primary aim of assessing relative cardiovascular risk of these drugs compared with traditional non-steroidal anti-inflammatory drugs (NSAIDs). The MEDAL programme was designed to provide a precise estimate of thrombotic cardiovascular events with the COX-2 selective inhibitor etoricoxib versus the traditional NSAID diclofenac.**

Methods **We designed a prespecified pooled analysis of data from three trials in which patients with osteoarthritis or rheumatoid arthritis were randomly assigned to etoricoxib (60 mg or 90 mg daily) or diclofenac (150 mg daily). The primary hypothesis stated that etoricoxib is not inferior to diclofenac, defined as an upper boundary of less than 1·30 for the 95% CI of the hazard ratio for thrombotic cardiovascular events in the per-protocol analysis. Intention-to-treat analyses were also done to assess consistency of results. These trials are registered at http://www.clinicaltrials.gov with the numbers NCT00092703, NCT00092742, and NCT00250445.**

Findings **34 701 patients (24 913 with osteoarthritis and 9787 with rheumatoid arthritis) were enrolled. Average treatment duration was 18 months (SD 11·8). 320 patients in the etoricoxib group and 323 in the diclofenac group had thrombotic cardiovascular events, yielding event rates of 1·24 and 1·30 per 100 patient-years and a hazard ratio of 0·95 (95% CI 0·81–1·11) for etoricoxib compared with diclofenac. Rates of upper gastrointestinal clinical events (perforation, bleeding, obstruction, ulcer) were lower with etoricoxib than with diclofenac (0·67 *vs* 0·97 per 100 patient-years; hazard ratio 0·69 [0·57–0·83]), but the rates of complicated upper gastrointestinal events were similar for etoricoxib (0·30) and diclofenac (0·32).**

Interpretation **Rates of thrombotic cardiovascular events in patients with arthritis on etoricoxib are similar to those in patients on diclofenac with long-term use of these drugs.**

Lancet 2006; 368: 1771–81

Published Online November 13, 2006 DOI:10.1016/S0140-6736(06)69666-9

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications in the world and are often taken long term by patients with osteoarthritis and rheumatoid arthritis. A major factor limiting use of NSAIDs is concern for the development of gastrointestinal complications such as bleeding. Cyclo-oxygenase-2 (COX-2) selective inhibitors were developed to decrease the risk of gastrointestinal tract injury and avoid the anti-platelet effect of traditional NSAIDs, and large outcome trials have shown a decrease in upper gastrointestinal complications with COX-2 selective inhibitors as compared with traditional NSAIDs.[1–3] However, randomised trials have shown an increased risk of thrombotic cardiovascular events with COX-2 selective inhibitors compared with placebo.[4–8] Comparable long-term, placebo-controlled trials in patients with arthritis assessing the risk of thrombotic cardiovascular events with traditional NSAIDs are not available, although results of observational studies suggest that some traditional NSAIDs (eg, diclofenac, ibuprofen) also increase cardiovascular risk compared with no NSAID therapy.[9–11] These safety data for COX-2 selective inhibitors and traditional NSAIDs raise concerns for patients with arthritis taking NSAIDs long term, and add a new element to decisions about the choice of therapy in these patients. Large, long-term prospective trials specifically designed to assess the cardiovascular risk with different agents have been called for to help inform these choices.[12,13] We designed the MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long Term) programme to assess the relative cardiovascular safety of two long-term anti-inflammatory treatments for patients with osteoarthritis and rheumatoid arthritis.[14] The aim was to estimate precisely the relative risk of thrombotic cardiovascular events with etoricoxib compared with the widely used traditional NSAID diclofenac, using a non-inferiority trial design. We sought to study a broad range of patients to simulate the general population of individuals with arthritis, enrolling patients with a range of cardiovascular risk factors (including pre-existing cardiovascular disease) and gastrointestinal risk factors.

Methods

Study design and patients

The design of the MEDAL programme has been presented in detail elsewhere.[14] 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 versus Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness (EDGE) study, and the EDGE II study. Similar entry criteria, including the same diseases and doses, 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. Worldwide regulatory agency review of the safety profile of COX-2 selective inhibitors and traditional NSAIDs occurred during the course of the EDGE II and MEDAL studies, resulting in changes in product labelling to point out the potential increased cardiovascular risk with use of these drugs. Hence, the written informed consent forms for MEDAL programme trials in progress at that time (EDGE II and MEDAL studies) were revised with reference to this potential increased risk, and patients resupplied consent.

The MEDAL programme's primary objective was to compare thrombotic cardiovascular events with etoricoxib and diclofenac during the long-term treatment of patients with osteoarthritis and rheumatoid arthritis. The prespecified primary analysis was based on pooling events from all three trials (91% power) and the prespecified secondary analysis was based on thrombotic cardiovascular events from the MEDAL study alone (83% power).[14]

Patients with osteoarthritis or rheumatoid arthitis aged 50 years or older 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,[15] and in the judgment of the investigator, would need chronic treatment with an NSAID. These patients were not candidates for paracetamol as first-line therapy because of the severity of their symptoms. Patients with a history of myocardial infarction, coronary artery bypass graft surgery, or percutaneous coronary intervention more than 6 months preceding enrolment were allowed to participate.

Procedures

Patients meeting entry criteria were randomly assigned with concealed allocation to treatment in equal proportions in each study site, using a different computer generated randomisation schedule for each of the three-component trials. In the MEDAL study, the first 4333 patients with osteoarthritis and all patients with rheumatoid arthritis received etoricoxib 90 mg once a day or diclofenac 75 mg twice a day. Subsequent patients with osteoarthritis enrolled in this study received etoricoxib 60 mg once a day or diclofenac 75 mg twice a day. In EDGE and EDGE II, patients received etoricoxib 90 mg once a day, diclofenac 50 mg three times a day (EDGE), or diclofenac 75 mg twice a day (EDGE II). A matching placebo design along with coded study medications provided blinding to treatment assignment.

Low-dose aspirin (≤100 mg per day) was recommended for prophylaxis in patients with established cardiovascular, peripheral arterial, or cerebrovascular disease.[16] Use of low-dose aspirin was also strongly encouraged for patients with diabetes.[17] Use of anti-ulcer medication (proton pump inhibitors or misoprostol) was recommended for patients at high risk of upper gastrointestinal clinical events (age >65 years; history of gastrointestinal ulcer or haemorrhage; concurrent use of corticosteroid, anticoagulant, or antiplatelet therapy).[18,19] Antihypertensive drugs were recommended as per the seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure guidelines in the MEDAL study.[20] For the MEDAL study, omeprazole and low-dose aspirin were prescribed free of charge; low-dose aspirin alone 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. Compliance with study medication was assessed by pill count. Patients who did not continue in the study were contacted every 6 months by telephone until the end of the study they had been enrolled in. All potential thrombotic cardiovascular events from the three trials were identified through active surveillance of reported adverse events, and were adjudicated by an independent blinded committee of clinical experts in cardiology, neurology, and peripheral vascular disease. Electrocardiograms done on all patients at randomisation, along with any electrocardiograms done during the trial, were compared to the electrocardiogram at the end of the study to look for evidence of silent myocardial infarction; these cases were also adjudicated.

The primary composite thrombotic cardiovascular endpoint was the first occurrence of the following fatal and non-fatal events: myocardial infarction (including silent 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. This composite primary endpoint[14] was inclusive of all thrombotic cardiovascular events, both venous and arterial, to be as comprehensive as possible. Myocardial infarction and ischaemic stroke are clinical events of great interest in this context[21,22] and accordingly, we prespecified secondary cardiovascular endpoints consisting of the subset of confirmed arterial events only and the Anti-Platelet Trialists' Collaboration endpoint (APTC; myocardial infarction, stroke, vascular death).[14,23]

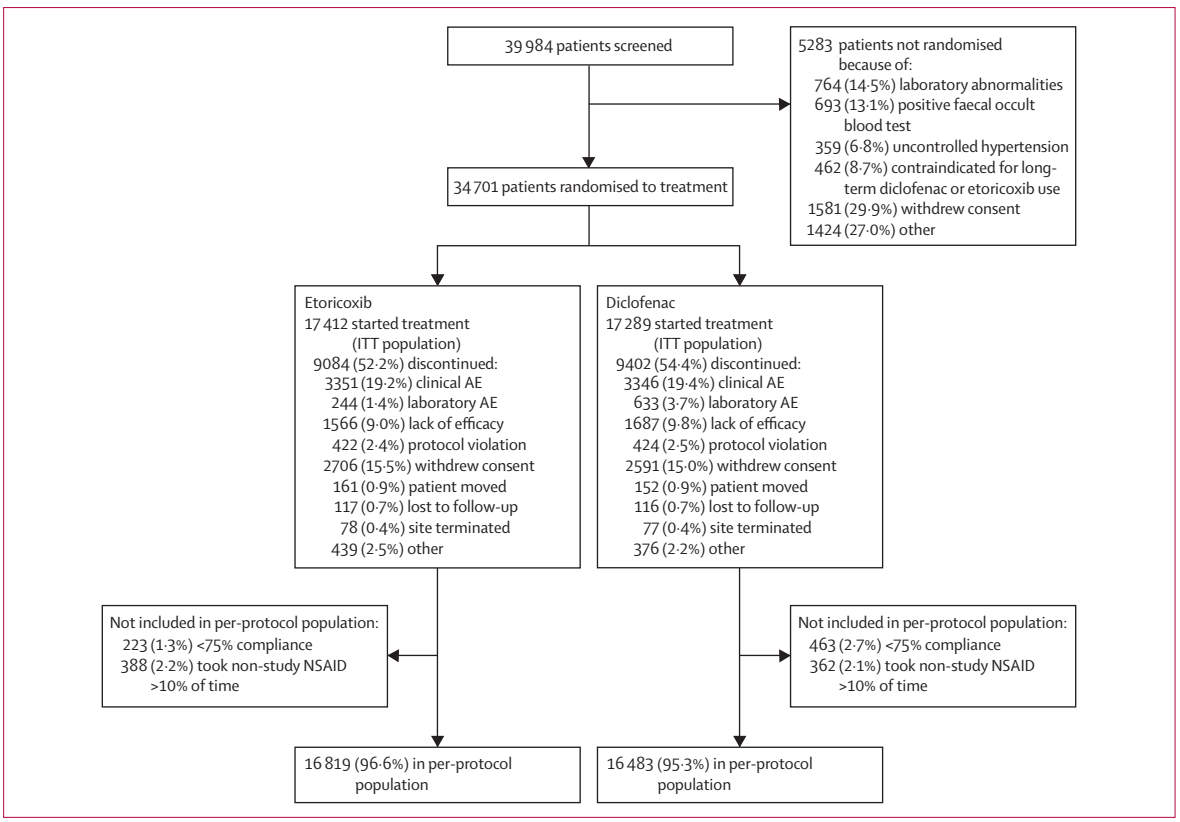

Figure 1: **Distribution of patients**
AE=adverse event.

In addition to cardiovascular events, prespecified safety endpoints also included discontinuations due to hypertension, oedema, renal dysfunction, gastrointestinal adverse events, and liver test abnormalities or other hepatic events. The cardiology adjudication subcommittee used prespecified criteria to adjudicate all episodes of congestive heart failure resulting in admission or emergency room visits. Results for these prespecified safety endpoints are presented by trial (ie, MEDAL study, EDGE, EDGE II). At all visits, patients were asked to rate their overall arthritis disease status (patient-reported global assessment of disease status) on a five-point scale (0=very well to 4=very poor) to assess the efficacy of the study medications.

Potential upper gastrointestinal clinical events were identified through active surveillance of reported adverse events, and were adjudicated by an independent blinded committee as previously described.[1,24] These events included bleeding from the oesophagus, stomach, or duodenum; perforation or obstruction from a non-malignant gastric or duodenal ulcer; or an ulcer documented on clinically indicated workup. They were confirmed by endoscopy, contrast radiography, surgery, or autopsy. Perforation, obstruction, and witnessed ulcer or significant bleeding were categorised as complicated events.[1] Potential lower gastrointestinal clinical events (bleeding, perforation, obstruction) were also identified through active surveillance of reported adverse events, and were adjudicated by the same independent blinded committee.[24] An independent data and safety monitoring board monitored emerging safety data from all three trials at regular intervals.[14]

Sample size and data analysis

The prespecified primary analysis was a comparison of all thrombotic cardiovascular events confirmed by the adjudication committee in the etoricoxib and diclofenac groups from the per-protocol populations of the three component studies combined. The definition of non-inferiority was an upper limit of the 95% CI of the hazard ratio (HR) for etoricoxib versus diclofenac of less than 1·30. As prespecified, to account for the interim analysis, the CI was adjusted to 95·87% to preserve the overall type I error of 0·05.[25] Assuming a true underlying HR of 1·0, 635 confirmed thrombotic cardiovascular events were needed to provide 91% power to yield the 95% CI upper limit of less than 1·30 for the primary endpoint HR. The Lachin-Foulkes method was used to calculate the number of events needed.[26]

The per-protocol population was used for the primary analysis, as recommended, to provide the more conservative approach for this non-inferiority assessment.[27–29]

	Etoricoxib (n=17 412)	Diclofenac (n=17 289)
Age, mean (SD)	63·2 (8·5)	63·2 (8·5)
<65 years	10 178 (58·5%)	10 127 (58·6%)
≥65 to <75 years	5201 (29·9%)	5261 (30·4%)
≥75 years	2033 (11·7%)	1901 (11·0%)
Sex		
Women	12 925 (74·2%)	12 823 (74·2%)
Arthritis type*		
Osteoarthritis	12 533 (72·0%)	12 380 (71·6%)
Rheumatoid arthritis	4878 (28·0%)	4909 (28·4%)
Weight in kg, mean (SD)	78·9 (18·6)	78·9 (18·5)
BMI in kg/m^2, mean (SD)	29·5 (6·1)	29·5 (6·0)
Ethnic group		
Asian	669 (3·8%)	662 (3·8%)
Black	646 (3·7%)	620 (3·6%)
Hispanic American	1441 (8·3%)	1425 (8·2%)
Multiracial	945 (5·4%)	909 (5·3%)
White	13 633 (78·3%)	13 609 (78·7%)
Other†	78 (0·5%)	64 (0·4%)
Diabetes	1810 (10·4%)	1855 (10·7%)
Hypertension‡	8109 (46·6%)	8221 (47·6%)
Dyslipidaemia‡	5097 (29·3%)	5034 (29·1%)
Current cigarette smoker	2034 (11·7%)	2037 (11·8%)
Established atherosclerotic CV disease§	2014 (11·6%)	2010 (11·6%)
≥2 CV risk factors¶ or established atherosclerotic CV disease	6586 (37·8%)	6639 (38·4%)
Low-dose aspirin use	6030 (34·6%)	5976 (34·6%)
Cardiac mediations		
β blocker	2806 (16·1%)	2837 (16·4%)
ACE inhibitor or ARB	4571 (26·3%)	4535 (26·2%)
Calcium channel blocker	2096 (12·0%)	2149 (12·4%)
Statin	2859 (16·4%)	2890 (16·7%)
Diuretic	3129 (18·0%)	3147 (18·2%)
Anti-arthritic medications		
COX-2 selective NSAID	4873 (28·0%)	4939 (28·6%)
Traditional NSAID	14 209 (81·6%)	14 174 (82·0%)
Paracetamol	10 852 (62·3%)	10 765 (62·3%)
High-dose aspirin	173 (1·0%)	185 (1·1%)
Glucocorticoid	2758 (15·8%)	2762 (16·0%)
DMARD‖	2246 (12·9%)	2208 (12·8%)

Data are number (%) unless otherwise specified. BMI=body-mass index. CV=cardiovascular. ACE=angiotension-converting enzyme. ARB=angiotensin-receptor blocker. *Data missing for one patient. †Includes Australoid, European, Indian, Melanesian, Native American, and Polynesian. ‡Clinical history at time of screening. §Includes clinical history of myocardial infarction, angina pectoris, cerebral vascular accident, transient ischaemic attack, angioplasty, carotid artery disease, peripheral vascular disease, or coronary artery bypass surgery. ¶Includes two or more of the following risk factors: history of hypertension, diabetes, dyslipidaemia, family history of CV disease, current cigarette smoking. ‖Disease-modifying antirheumatic drug.

Table 1: **Baseline characteristics**

It included observations for individual patients from the first day of therapy to 14 days after the last dose of study drug, and excluded patients if they took less than 75% of their study medication or took non-study NSAIDs more than 10% of the time while on study medication. As also recommended,[21,27] to evaluate the consistency of the results and provide greater confidence in the conclusions, we prespecified three supporting analyses for the primary endpoint. These included two modified intention-to-treat (ITT) analyses (all randomised patients who received at least one dose of study medication); one included all events that occurred from the first day of study treatment to 14 days after the last dose; the second included all events until 28 days after the last dose of study drug; the third was an ITT analysis that included all events from all patients from the first day of therapy until the end of each trial, including events in patients who discontinued study drug early and who might have been exposed to non-study interventions following discontinuation. The eligibility date for a thrombotic cardiovascular event to be included in this ITT analysis was 28 days after the last patient's last dose of study medication for each respective trial. The ascertainment date for potential thrombotic cardiovascular events to be submitted to the adjudication committee in order to be included in the ITT analysis was 42 days after the last patient's last dose of study drug.

The HR for confirmed thrombotic events for etoricoxib compared with diclofenac was calculated with a Cox proportional hazards model.[30] Treatment served as an explanatory factor and low-dose aspirin use at baseline as a stratification factor. Kaplan-Meier time-to-event curves were generated. Kaplan-Meier curves[31,32] were truncated when the number of patients remaining at risk was less than 500. This truncation did not affect statistical analysis or the Cox model results. The HR of thrombotic events was also assessed across a range of prespecified subgroup factors, which were checked for consistency of HR by testing the subgroup factor-by-treatment interaction with the Cox proportional hazards model. Subgroup analyses might have less power than an analysis based on the full dataset.

For analyses of discontinuations due to hypertension, oedema, renal dysfunction, gastrointestinal adverse events, and liver test abnormalities or other hepatic events, and for confirmed congestive heart failure, pair-wise comparisons by dose and disease (osteoarthritis or rheumatoid arthritis) were computed using Fisher's exact test, and the associated 95% CIs for the differences were calculated by Wilson's score method. Comparisons for the MEDAL study osteoarthritis data were made between the patients randomised to 60 mg etoricoxib and the group of patients randomised to diclofenac during the same period, and between patients randomised to 90 mg etoricoxib and its time-coincident diclofenac group, to account for the time and location of randomisation.

The rates of clinical upper gastrointestinal events, complicated upper gastrointestinal events, and lower gastrointestinal clinical events based on the MEDAL programme were prespecified endpoints, with post-hoc Cox model applied to clinical upper gastrointestinal events. In each individual study, anti-arthritic efficacy was expressed as the average change from baseline in

patient global assessment of disease status (scale 0–4), using an analysis of covariance model.[33,34]

This trial is registered at http://www.clinicaltrials.gov with the numbers NCT00092703 (EDGE), NCT00092742 (EDGE II), and NCT00250445 (MEDAL study).

Role of the funding source

The MEDAL programme was designed cooperatively by the sponsor (Merck Research Laboratories) and the programme steering committee, which consisted of experts in cardiovascular medicine, gastroenterology, 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). The authors had full access to data and statistical analyses and drafted the manuscript. The corresponding author had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the overall trial profile for the 34701 patients in the MEDAL programme. 23504 patients were randomised in the MEDAL study, 7111 in EDGE, and 4086 in EDGE II, including 24913 (72%) patients with osteoarthritis and 9787 (28%) with rheumatoid arthritis. Baseline characteristics were similar in both treatment groups (table 1). 14396 (41%) patients were aged 65 years or older; 3665 (11%) had diabetes; 10131 (29%) had dyslipidaemia; 16330 (47%) had hypertension; 4024 (12%) had established atherosclerotic cardiovascular disease, and 13225 (38%) had established atherosclerotic cardiovascular disease or two or more cardiovascular risk factors (hypertension, diabetes, dyslipidaemia, family history of cardiovascular disease, smoking); 12006 (35%) patients were using low-dose aspirin at baseline.

6769 patients were assigned to etoricoxib 60 mg once a day, 10643 to etoricoxib 90 mg once a day, and 3518 to diclofenac 50 mg three times a day, and 13771 to diclofenac 75 mg twice daily. The mean (SD) duration of exposure to study drug was 18·2 (11·7) months for etoricoxib and 17·7 (11·9) months for diclofenac; 21395 patients took the drug for 12 months or longer and 12854 for 24 months or longer. All patients randomised to treatment received at least one dose of study medication, so the predefined modified ITT population included all patients randomised (ie, a true ITT population). Overall mean treatment compliance was 98% (SD 7·4) for etoricoxib, and 96% (8·2) for diclofenac; compliance was less than 75% for 223 (1%) patients in the etoricoxib group and 463 (3%) in the diclofenac group. 1399 (4%) patients were excluded from the per-protocol population (figure 1), but included in all other analyses.

	Treatment	n	n/PYR	Rate (95% CI)*	HR (95% CI)
Thrombotic events					
Per-protocol	Etoricoxib	16819	320/25836	1·24 (1·11–1·38)	0·95 (0·81–1·11)
	Diclofenac	16483	323/24766	1·30 (1·17–1·45)	
ITT (within 14 days)	Etoricoxib	17412	345/26384	1·31 (1·17–1·45)	0·96 (0·83–1·11)
	Diclofenac	17289	345/25394	1·36 (1·22–1·51)	
ITT (within 28 days)	Etoricoxib	17412	366/27036	1·35 (1·22–1·50)	0·98 (0·85–1·14)
	Diclofenac	17289	357/26042	1·37 (1·23–1·52)	
ITT (to end of studies)	Etoricoxib	17412	495/39654	1·25 (1·14–1·36)	1·05 (0·93–1·19)
	Diclofenac	17289	468/39413	1·19 (1·08–1·30)	
Arterial thrombotic events					
Per-protocol	Etoricoxib	16819	272/25839	1·05 (0·93–1·19)	0·96 (0·81–1·13)
	Diclofenac	16483	272/24771	1·10 (0·97–1·24)	
ITT (within 14 days)	Etoricoxib	17412	297/26386	1·13 (1·00–1·26)	0·97 (0·83–1·14)
	Diclofenac	17289	293/25399	1·15 (1·03–1·29)	
ITT (within 28 days)	Etoricoxib	17412	305/27040	1·13 (1·00–1·26)	0·98 (0·83–1·15)
	Diclofenac	17289	300/26049	1·15 (1·03–1·29)	
ITT (to end of studies)	Etoricoxib	17412	407/39767	1·02 (0·93–1·13)	1·03 (0·89–1·18)
	Diclofenac	17289	394/39513	1·00 (0·90–1·10)	
APTC events					
Per-protocol	Etoricoxib	16819	216/25851	0·84 (0·73–0·95)	0·96 (0·79–1·16)
	Diclofenac	16483	216/24787	0·87 (0·76–1·00)	
ITT (within 14 days)	Etoricoxib	17412	231/26402	0·87 (0·77–1·00)	0·96 (0·80–1·15)
	Diclofenac	17289	232/25416	0·91 (0·80–1·04)	
ITT (within 28 days)	Etoricoxib	17412	237/27059	0·88 (0·77–0·99)	0·95 (0·80–1·14)
	Diclofenac	17289	239/26068	0·92 (0·80–1·04)	
ITT (to end of studies)	Etoricoxib	17412	332/39894	0·83 (0·75–0·93)	1·02 (0·87–1·18)
	Diclofenac	17289	325/39623	0·82 (0·73–0·91)	

PYR=patient-years at risk. *Per 100 PYR.

Table 2: **Incidence of thrombotic cardiovascular events**

Numbers and rates of thrombotic cardiovascular events, with HRs, are shown in table 2. The HR for the per-protocol comparison of thrombotic events in the two groups was 0·95 (95% CI 0·81–1·11), showing non-inferiority of etoricoxib to diclofenac according to the prespecified criterion (table 2). We noted consistency across the three different prespecified endpoints and across the per-protocol and ITT analyses. The prespecified secondary analysis, assessing confirmed thrombotic cardiovascular events in the per-protocol population of the MEDAL study alone, gave an HR of 0·96 (95% CI 0·81–1·15).

The Kaplan-Meier estimates over 36 months are shown in figure 2. The cumulative incidence of primary and secondary endpoints with etoricoxib compared with diclofenac satisfied the proportional hazard assumption, indicating a constant HR over time.

The HR for etoricoxib versus diclofenac for cardiac events, cerebrovascular events, and peripheral vascular events did not show any discernible difference between treatment groups (table 3). The most common thrombotic cardiovascular event was non-fatal or fatal myocardial infarction, with rates of 0·43 per 100 patient-years

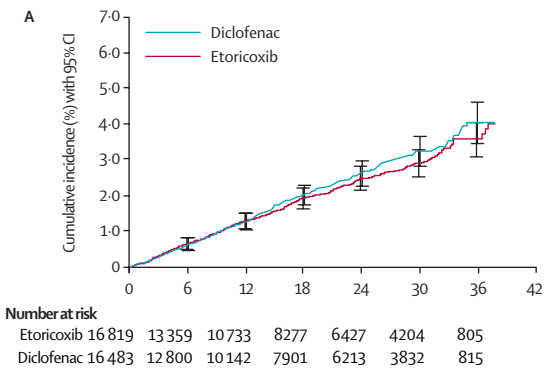

Figure 2: **Time-to-event per-protocol analysis**
(A) Cumulative incidence of thrombotic cardiovascular events. (B) Cumulative incidence of arterial thrombotic events. (C) Cumulative incidence of APTC[23] events (myocardial infarction, stroke, or vascular death).

in the etoricoxib group and 0·49 per 100 patient-years in the diclofenac group (per-protocol analysis). Rates of fatal thrombotic cardiovascular events were similar between the groups (0·17 per 100 patient-years in both groups). All-cause mortality rates were 0·48 per 100 patient-years for etoricoxib and 0·50 per 100 patient-years for diclofenac in the ITT population through 14 days after study drug discontinuation.

Analyses of thrombotic cardiovascular events by subgroups in the per-protocol population are shown in figure 3. We noted no significant treatment-by-subgroup interactions, including study, suggesting that the thrombotic cardiovascular risk of etoricoxib versus diclofenac did not differ across the subgroups analysed, including varying baseline cardiovascular risk and etoricoxib dose. Additionally, HRs were similar in patients with (HR 0·85, 95% CI 0·64–1·12) and without (1·00, 95% CI 0·83–1·20) previous use of COX-2 selective NSAID (treatment-by-subgroup interaction, p=0·344). Cardiovascular event rates varied on the basis of cardiovascular risk. For example, rates ranged from less than one event per 100 patient-years for patients with no established atherosclerotic cardiovascular disease and one or no cardiovascular risk factors, to more than three events per 100 patient-years in patients with established atherosclerotic cardiovascular disease.

Incidences of congestive heart failure and discontinuations for pre-specified adverse events are shown in figure 4 by study, etoricoxib dose, and disease (ITT analyses including events within 14 days of last dose of study drug). In the MEDAL study, a higher rate of congestive heart failure was seen with etoricoxib 90 mg than with diclofenac, but the difference was not significant; no difference was seen with etoricoxib 60 mg. Discontinuations because of oedema were significantly more frequent with 90 mg of etoricoxib than with diclofenac, but rates were similar for 60 mg of etoricoxib and diclofenac. Discontinuations because of hypertension were more frequent with both doses of etoricoxib than with diclofenac. Discontinuations due to gastrointestinal adverse events were significantly less frequent with etoricoxib than diclofenac, as were discontinuations due to liver test abnormalities or other hepatic events. Results for EDGE and EDGE II were consistent with the results of the MEDAL study (figure 4).

Rates of upper gastrointestinal clinical events were 0·67 (95% CI 0·57–0·77) per 100 patient-years with etoricoxib and 0·97 (0·85–1·10) per 100 patient-years with diclofenac, yielding an HR of 0·69 (0·57–0·83). However, rates of complicated upper gastrointestinal clinical events did not differ between the groups (0·30 etoricoxib *vs* 0·32 diclofenac per 100 patient-years). The rates of lower gastrointestinal clinical events were 0·32 per 100 patient-years (95% CI 0·25–0·39) for etoricoxib and 0·38 per 100 patient-years (0·31, 0·46) for diclofenac, yielding an HR of 0·84 (0·63–1·13).

Etoricoxib and diclofenac showed similar efficacy for treatment of arthritis. In the MEDAL study, the average changes from baseline (Likert units) in patient-reported global assessment of disease status were –0·67 (SD 1·02) for etoricoxib and –0·61 (1·02) for diclofenac. Efficacy results for EDGE and EDGE II were similar (data not shown). Discontinuations because of lack of efficacy were also similar between the groups (figure 1).

	Etoricoxib (N=16 819, 25 836 PY)*		Diclofenac (N=16 483, 24 766 PY)		HR (95% CI)
	n (%)†	Rate‡	n (%)†	Rate‡	
Patients with fatal thrombotic cardiovascular events	43 (0·26)	0·17 (0·12–0·22)	43 (0·26)	0·17 (0·13–0·23)	0·96 (0·63–1·46)
Patients with cardiac events	183 (1·09)	0·71 (0·61–0·82)	194 (1·18)	0·78 (0·68–0·90)	0·90 (0·74–1·10)
Non-fatal myocardial infarction	105 (0·62)	0·41 (0·33–0·49)	105 (0·64)	0·42 (0·35–0·51)	
Fatal myocardial infarction	6 (0·04)	0·02 (0·01–0·05)	17 (0·10)	0·07 (0·04–0·11)	
Sudden cardiac death	29 (0·17)	0·11 (0·08–0·16)	23 (0·14)	0·09 (0·06–0·14)	
Unstable angina pectoris	42 (0·25)	0·16 (0·12–0·22)	51 (0·31)	0·21 (0·15–0·27)	
Resuscitated cardiac arrest	2 (0·01)	0·01 (0·00–0·03)	1 (0·01)	0·00 (0·00–0·02)	
Cardiac thrombus	4 (0·02)	0·02 (0·00–0·04)	3 (0·02)	0·01 (0·00–0·04)	
Patients with cerebrovascular events	89 (0·53)	0·34 (0·28–0·42)	79 (0·48)	0·32 (0·25–0·40)	1·08 (0·80–1·46)
Non-fatal ischaemic cerebrovascular stroke	53 (0·32)	0·21 (0·15–0·27)	55 (0·33)	0·22 (0·17–0·29)	
Fatal ischaemic cerebrovascular stroke	6 (0·04)	0·02 (0·01–0·05)	2 (0·01)	0·01 (0·00–0·03)	
Cerebrovascular venous thrombosis	1 (0·01)	0·00 (0·00–0·02)	1 (0·01)	0·00 (0·00–0·02)	
Transient ischaemic attack	31 (0·18)	0·12 (0·08–0·17)	22 (0·13)	0·09 (0·06–0·13)	
Patients with peripheral vascular events	53 (0·32)	0·20 (0·15–0·27)	55 (0·33)	0·22 (0·17–0·29)	0·92 (0·63–1·35)
Non-fatal pulmonary embolism	17 (0·10)	0·07 (0·04–0·11)	25 (0·15)	0·10 (0·07–0·15)	
Fatal pulmonary embolism	1 (0·01)	0·00 (0·00–0·02)	0 (0·00)	0·00	
Non-fatal peripheral arterial thrombosis	5 (0·03)	0·02 (0·01–0·05)	4 (0·02)	0·02 (0·00–0·04)	
Fatal peripheral arterial thrombosis	1 (0·01)	0·00 (0·00–0·02)	1 (0·01)	0·00 (0·00–0·02)	
Peripheral venous thrombosis	29 (0·17)	0·11 (0·08–0·16)	27 (0·16)	0·11 (0·07–0·16)	

Patients with several events were listed for each of their specific diagnoses. PY=patient-years. *Etoricoxib combined 60 mg and 90 mg. †Crude incidence (n/Nx100); ‡Events per 100 patient-years.

Table 3: **Incidence of thrombotic cardiovascular event types in per-protocol population**

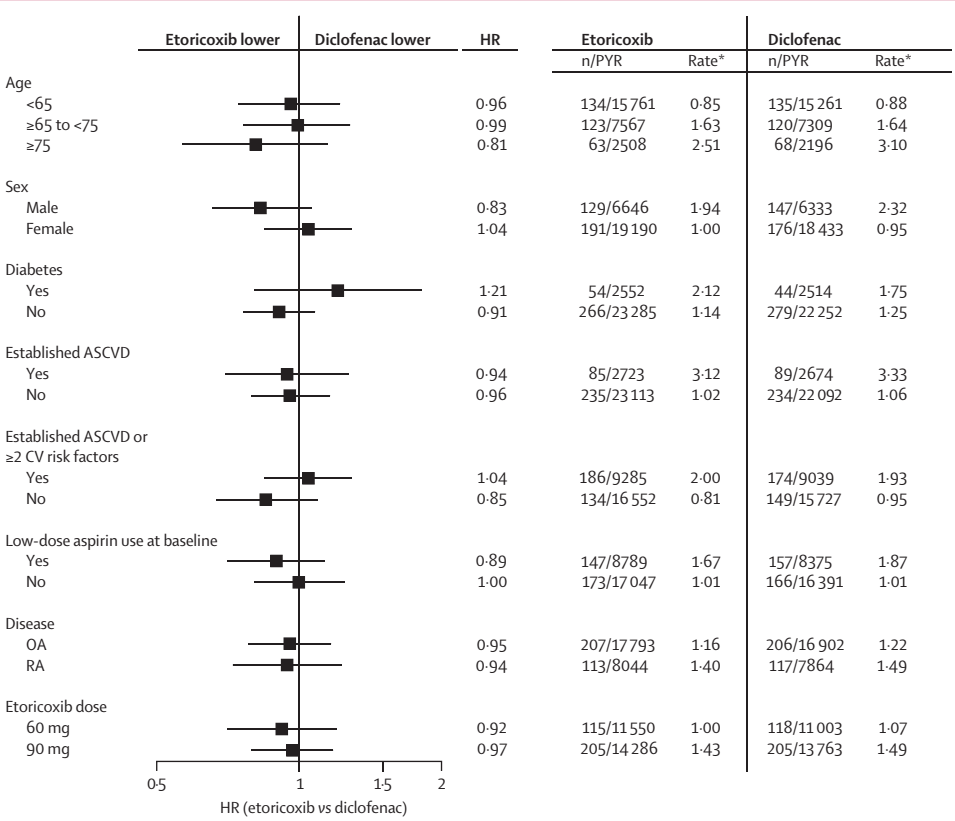

Figure 3: **Incidence of thrombotic cardiovascular (CV) events in prespecified subgroups, per-protocol population**
ASCVD=atherosclerotic cardiovascular disease. PYR=patient-years at risk. *Events per 100 patient-years.

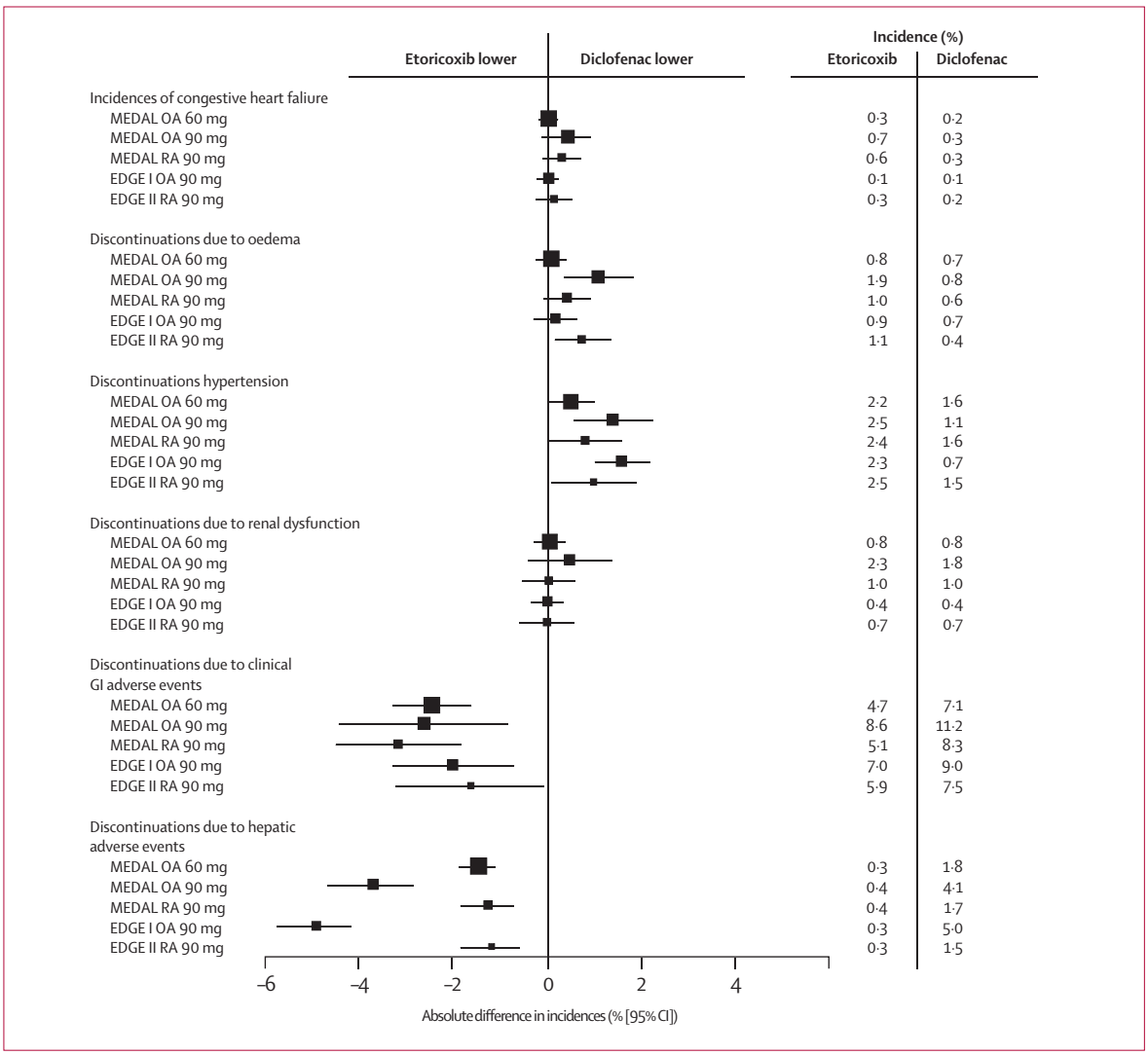

Figure 4: **Difference in incidences of prespecified renovascular and gastrointestinal (GI) endpoints from MEDAL study, EDGE, and EDGE II, by dose and disease**
Symbol areas represent the relative size of each group. OA=osteoarthritis. RA=rheumatoid arthritis.

Discussion

Our results show that patients with arthritis treated with the COX-2 selective NSAID etoricoxib and those given the traditional NSAID diclofenac have nearly identical rates of thrombotic cardiovascular events. The robustness of this finding was supported by consistency of results across several prespecified analyses. Furthermore, the similarity in rates was consistent across all subgroups assessed. The results of subgroup analyses suggest that cardiovascular risk factors and low-dose aspirin use do not affect the absence of difference in the relative risk of cardiovascular events for etoricoxib and diclofenac.

The MEDAL programme was designed with the primary aim of assessing thrombotic cardiovascular events with a COX-2 selective NSAID compared with a traditional NSAID. Enrolment of 34701 patients with treatment duration up to 3·5 years (mean duration 18 months, SD 11·8) allowed us to provide estimates of thrombotic cardiovascular events in patients with arthritis taking chronic NSAID therapy with greater precision than previous clinical trials. In addition to the large size, the worldwide distribution of patients and the inclusion of patients with a broad range of cardiovascular risk factors should simulate a real-world population of patients with arthritis. The annual incidence of thrombotic cardiovascular events in the overall MEDAL programme population was about 1·25%, and the absolute difference in event rates between treatments was less than one patient per 1000 treated for a year (–0·07 events per 100 patient years; 95% CI –0·26 to 0·13). On the basis of the 95% CI for this difference in the primary analysis, etoricoxib could be associated with at most an increase of 1·3 events (or a decrease of 2·6 events) per 1000 patients treated for a year compared with diclofenac.

The question of the relative cardiovascular and gastrointestinal safety of long-term treatment with COX-2 selective and traditional NSAIDs is important to patients, doctors, public-health officials, and regulatory agencies. The evidence that treatment with COX-2 selective NSAIDs is associated with an increased risk of cardiovascular events compared with placebo,[4–7] and the suggestion from observational studies and a meta-analysis of randomised clinical trials[8,10,35] of possible differences among traditional NSAIDs with respect to cardiovascular risk, raise the clinical issue of the different risk between COX-2 selective and traditional NSAIDs. Although randomised clinical trials have established that COX-2 selective NSAIDs reduce the risk of upper gastrointestinal clinical events,[1,3] large long-term outcome studies, such as the MEDAL programme, are needed to ascertain the relative risk of cardiovascular and gastrointestinal events of different agents in the NSAID class.

We chose to compare the COX-2 selective inhibitor etoricoxib and the traditional NSAID diclofenac. Etoricoxib is a highly selective COX-2 inhibitor, which does not inhibit COX-1 at clinical doses, causes significantly fewer gastroduodenal ulcers than traditional NSAIDs, is effective for the treatment of osteoarthritis and rheumatoid arthritis, and is currently approved in over 60 countries.[36–39] Diclofenac was selected as the traditional NSAID comparator in the MEDAL programme for several reasons.[14] First, diclofenac is the most widely prescribed NSAID in the world.[40] Additionally, unlike ibuprofen and naproxen,[41–45] diclofenac does not interfere with the antiplatelet effects of low-dose aspirin, which was used by about a third of patients in the MEDAL programme. Thus, diclofenac should not inhibit the cardioprotective effect of aspirin, although this notion has not been assessed in randomised clinical trials. Unlike etoricoxib or celecoxib, diclofenac inhibits COX-1 at clinical doses, although to a lesser degree than ibuprofen and naproxen.[36] Clinical evidence for COX-1 inhibition by diclofenac in the gastrointestinal tract is provided by endoscopic studies showing that diclofenac is associated with gastroduodenal ulcers at rates similar to those seen with ibuprofen and higher than those with COX-2 selective inhibitors.[46–48]

Diclofenac, like many traditional NSAIDs, does not provide sustained inhibition of COX-1 derived thromboxane-dependent platelet function.[42] Greater than 95% inhibition of thromboxane is necessary to affect platelet function.[49] Diclofenac achieves 87% inhibition of thromboxane at 2 h (time of peak plasma concentration), which decreases to 55% 6 h after dosing.[42] Etoricoxib, a COX-2 selective NSAID, produces no inhibition of thromboxane and thus has no effect on platelet aggregation over its clinical dose range.[38] Daily low-dose aspirin, by contrast, achieves long-term inhibition of thromboxane due to irreversible binding to COX-1,[42] making it an effective cardioprotective agent.[16,17]

Prostacyclin is a prostanoid that acts as a restraint on mediators of platelet activation, hypertension, and atherogenesis, including thromboxane A_2, which is generated in the platelet by COX-1.[50] Suppression of prostacyclin (and prostaglandin E_2) is the most thoroughly developed explanation for the cardiovascular hazard associated with NSAIDs.[50] Coincident inhibition of platelet COX-1-derived thromboxane would be expected to mitigate this hazard,[50,51] although clinical trials to directly address this question are not available.

Although the degree of COX-1 inhibition with diclofenac may not be enough to inhibit platelet aggregation, results of endoscopic studies suggest that it is sufficient to inhibit the gastrointestinal tract mucosal prostaglandins that protect the mucosa.[46–48] The difference in the extent of COX-1 inhibition[52] between etoricoxib and diclofenac presumably explains our finding of a significant difference in rates of upper gastrointestinal clinical events between the groups (even with 50% of patients receiving gastroprotective agents)—although this finding was driven by a difference in uncomplicated upper gastrointestinal events, not complicated gastrointestinal events. By contrast, the difference in COX-1 mediated thromboxane inhibition between diclofenac and etoricoxib is unlikely to translate into a difference in effective inhibition of platelet aggregation, and was not associated with a difference in rates of thrombotic cardiovascular events.

In clinical practice, the choice of anti-inflammatory agent needs to take into consideration the risk for thrombotic cardiovascular and gastrointestinal events, as well as congestive heart failure and other renovascular effects (eg, blood pressure, fluid retention), gastrointestinal tolerability (eg, dyspepsia), and efficacy. As shown in figure 4, the incidence of clinically important renovascular endpoints such as congestive heart failure (90 mg) and discontinuations because of hypertension (60 mg and 90 mg) was higher with etoricoxib than with diclofenac. We noted no difference in the incidence of discontinuation due to renal dysfunction, and a lower incidence of discontinuations due to gastrointestinal and hepatic adverse events was observed with etoricoxib than with diclofenac.

The MEDAL programme had some limitations. For example, it did not include a placebo group; long-term placebo-controlled trials in arthritic patients are not possible, because many patients in the placebo group would have breakthrough symptoms on placebo, and thus would require some type of anti-inflammatory treatment. Therefore, the absolute cardiovascular risks associated with etoricoxib and diclofenac cannot be ascertained from this trial. Another limitation is that the results observed with these two drugs cannot necessarily be extrapolated to other COX-2 selective or traditional NSAIDs. Only studies that directly compare drugs can provide definitive information on differences in cardiovascular and gastrointestinal outcomes. Such studies are

needed because an idiosyncratic absence or loss of NSAID effectiveness is a leading cause of patients switching treatment from one NSAID to another.[53]

The data from this large randomised clinical trial should help clinicians and patients, and will hopefully encourage guideline committees to continue developing recommendations for optimum treatment of patients with arthritis.

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See Online for webappendix

For the full list of participating investagators see webappendix.

Contributors

All authors read and approved the manuscript and contributed to its design, analysis or interpretation of data, and drafting and revision of the manuscript. H Krum joined the Steering Committee after the design of the programme but contributed to all other subsequent aspects as stated above. S P Curtis was the clinical leader of the programme and A Kaur was the programme's statistical science leader.

Conflict of interest statement

C P Cannon receives research grant support from Accumetrics, AstraZeneca, Merck, Merck/Schering-Plough Partnership, and Schering-Plough, and has spoken at symposia sponsored by and served on scientific advisory boards for Alnylam, AstraZeneca, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Merck, Merck/Schering-Plough Partnership, Pfizer, Sanofi-Aventis, Schering-Plough, and Vertex. G A FitzGerald receives financial support for investigator-initiated research from Bayer, Boehringer Ingelheim, and Merck, and serves as a consultant for Bayer, Boehringer Ingelheim, Cardiovascular Therapeutics, Genentech, Genome Institute of the Novartis Foundation, GlaxoSmithKline, Logical Therapeutics, Merck, NicOx, Novartis, Portala, and VIA Pharmaceuticals. H Krum has received research grant support, spoken at symposia, and served on scientific advisory boards for Merck, Pfizer, and Novartis in the area of COX-2 selective inhibitors. C Bombardier has received research support from Abbott, Amgen, Bristol-Myers Squibb, and Schering Canada, and served as a consultant for AstraZeneca, Hoffmann LaRoche, Merck, and Pfizer, and served on an advisory board for Merck. M E Weinblatt has received research support from Amgen, Abbott, Bristol-Myers Squibb, Genentech, and Millennium Pharmaceuticals, and served as a consultant for Abbott, Alza, Amgen, AstraZeneca, Biogen, Bristol-Myers Squibb, Canfite, Celgene, Centocor, Critical Therapeutics, Entremed, Human Genome Sciences, Genetech, Gilead, Eli Lilly, Merrimack, Merck, Millennium Pharmaceuticals, Novartis, Pfizer, Praecis, Rigel, Hoffmann LaRoche, Sanofi-Aventis, Serona, Scios, Synta, Wyeth, and VBL. D van der Heijde has received research support from Wyeth and served as a consultant for Abbott, Amgen, Centocor, Merck, Schering-Plough, and Wyeth. E Erdmann has received research support from Bayer and has served as a speaker, consultant, or advisory board member for Bayer, E Merck Germany, Merck, and Takeda. L Laine has received research support and served as a consultant for Pfizer, Novartis, Bayer, and Merck. S P Curtis, A Kaur, J A Bolognese, and A S Reicin are employees of Merck and own stock and/or hold stock options in the company.

Acknowledgments

We thank all the patients who participated, along with the doctors, nurses, coordinators, and staff who made the MEDAL programme clinical studies possible. We also thank Laurine Connors and Gary Swergold of Merck Research Laboratories for their significant contributions to the conduct and monitoring of the component clinical trials; Xiaohui Wang of Merck Research Laboratories for providing statistical programming support; and Paul Cavanaugh of Merck Research Laboratories for serving as the medical writer for this manuscript. Finally, we acknowledge the substantial contributions of the late Murray Selwyn of Merck Research Laboratories to statistical science support for this clinical trials programme. This research was supported by Merck and Co, Whitehouse Station, NJ, USA.

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