Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial

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Summary

Background **The potential for cyclo-oxygenase 2 (COX2)-selective inhibitors to increase the risk for myocardial infarction is controversial. The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) aimed to assess gastrointestinal and cardiovascular safety of the COX2 inhibitor lumiracoxib compared with two non-steroidal anti-inflammatory drugs, naproxen and ibuprofen.**

Methods **18 325 patients age 50 years or older with osteoarthritis were randomised to lumiracoxib 400 mg once daily (n=9156), naproxen 500 mg twice daily (4754), or ibuprofen 800 mg three times daily (4415) in two substudies of identical design. Randomisation was stratified for low-dose aspirin use and age. The primary cardiovascular endpoint was the Antiplatelet Trialists' Collaboration endpoint of non-fatal and silent myocardial infarction, stroke, or cardiovascular death. Analysis was by intention to treat.**

Findings **81 (0·44%) patients did not start treatment and 7120 (39%) did not complete the study. At 1-year follow-up, incidence of the primary endpoint was low, both with lumiracoxib (59 events [0·65%]) and the non-steroidal anti-inflammatory drugs (50 events [0·55%]; hazard ratio 1·14 [95% CI 0·78–1·66], p=0·5074). Incidence of myocardial infarction (clinical and silent) in the overall population in the individual substudies was 0·38% with lumiracoxib (18 events) versus 0·21% with naproxen (ten) and 0·11% with lumiracoxib (five) versus 0·16% with ibuprofen (seven). In the naproxen substudy, rates of myocardial infarction (clinical and silent) did not differ significantly compared with lumiracoxib in the population not taking low-dose aspirin (hazard ratio 2·37 [95% CI 0·74–7·55], p=0·1454), overall (1·77 [0·82–3·84], p=0·1471), and in patients taking aspirin (1·36 [0·47–3·93], p=0·5658). In the ibuprofen substudy, these rates did not differ between lumiracoxib and ibuprofen in the population not taking low-dose aspirin (0·75 [0·20–2·79], p=0·6669), overall (0·66 [0·21–2·09], p=0·4833), and in patients taking aspirin (0·47 [0·04–5·14], p=0·5328).**

Interpretation **The primary endpoint, including incidence of myocardial infarction, did not differ between lumiracoxib and either ibuprofen or naproxen, irrespective of aspirin use. This finding suggests that lumiracoxib is an appropriate treatment for patients with osteoarthritis, who are often at high cardiovascular risk and taking low-dose aspirin.**

Introduction

The potential increased risk of cardiovascular adverse events with cyclo-oxygenase 2 (COX2)-selective inhibitors is controversial.[1–6] The Vioxx GI Outcomes Research (VIGOR) study[7] compared the COX2-selective inhibitor rofecoxib with the non-selective, non-steroidal anti-inflammatory drug naproxen in 8000 patients with rheumatoid arthritis. These investigators recorded a difference in the rate of a composite endpoint of non-fatal myocardial infarction, non-fatal stroke, and sudden death between the treatment groups favouring naproxen (0·8% for rofecoxib *vs* 0·4% for naproxen, p<0·05), which was largely attributable to the difference in the incidence of myocardial infarction (0·4% *vs* 0·1%, p<0·01).

Data from three, large case-control studies suggest a possible antithrombotic effect of naproxen.[8–10] One hypothesis is that this benefit arises mainly from the ability of naproxen to inhibit platelet aggregation[11] to a level comparable with that recorded with aspirin. Since, to our knowledge, no placebo or aspirin-controlled trials of naproxen have been done in patients with known cardiovascular disease, definitive data are scarce about naproxen's possible clinical antithrombotic effects. Conversely, two large observational studies did not show any clinically meaningful reduction in myocardial infarction rates in users of naproxen compared with those taking non-steroidal anti-inflammatory drugs.[4,12] Additionally, researchers are unsure whether or not cardioprotection can be provided while maintaining adequate gastric protection in patients taking COX2-selective inhibitors with concomitant low-dose aspirin.[13]

Since COX2-selective inhibition has no effect on platelet thromboxane production, it might reduce vascular prostacyclin synthesis, thereby possibly altering the balance between thromboxane and prostacyclin, promoting a prothrombotic state.[14,15] However, clinical data to support this hypothesis are absent.

Besides the concern about an increase in myocardial infarction and thrombotic events, some evidence from an observational study[6] has questioned whether the different pharmacokinetic and pharmacodynamic profiles of COX2-selective inhibitors confer in them differing cardiovascular adverse effects. Patients taking rofecoxib had a higher incidence of congestive heart failure and use of antihypertensive drugs than did those taking celecoxib or non-steroidal anti-inflammatory drugs versus controls.[6]

Osteoarthritis affects a large proportion of the population (18% women and 10% men worldwide),[16] and coronary heart disease and cardiovascular risk factors are frequent in these people. Clinicians need evidence balancing any possible increased risk of myocardial infarction with potentially favourable gastrointestinal outcomes to make rational decisions about whom to treat with a COX2-selective inhibitor. A survey by the US National Center for Health Statistics reported that 40% of patients with osteoarthritis have hypertension compared with 25% in the general population without arthritis.[17] Additionally, 20% of patients with osteoarthritis smoked, 11% had diabetes, and 32% had high total cholesterol (≥6·2 mmol/L). These statistics highlight the need to determine whether COX2-selective inhibitors differ in their adverse cardiovascular effects and whether this difference can alter their overall individual risk-benefit profiles.

Lumiracoxib is a novel COX2-selective inhibitor that has a different structure from others in the class, which are typically sulfonamides (celecoxib and valdecoxib) or sulfones (rofecoxib and etoricoxib).[18,19] It has a low lipophilicity, high selectivity, and a fairly short plasma half-life (3–6 h)[20] compared with other COX2-selective inhibitors.[18] These properties lead to less systemic drug exposure.

The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) was designed to assess the gastrointestinal and cardiovascular safety of lumiracoxib compared with naproxen and ibuprofen.

Patients and methods

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Details of the methodology and implementation of the TARGET study have been published elsewhere[21] and are reported here briefly and elsewhere in this issue.[22]

Study design

TARGET was an international double-blind study of more than 18 000 patients with osteoarthritis who received treatment with lumiracoxib 400 mg once daily (two or four times the recommended chronic dose for osteoarthritis), naproxen 500 mg twice daily (maximum therapeutic dose), or ibuprofen 800 mg three times daily (maximum therapeutic dose) for 52 weeks. Patients age 50 years or older were divided into one of six strata before randomisation by low-dose aspirin use (75–100 mg daily) and by age (50–64, 65–74, ≥75 years) and were followed up for 52 weeks, with clinic visits at 4, 13, 20, 26, 39, and 52 weeks. The study was undertaken in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The TARGET study was approved by the ethics committees of all participating institutions and all patients gave their informed consent at the time of enrolment.

For logistical and masking reasons, TARGET was divided into two substudies, one with naproxen as the comparator and the other with ibuprofen. Within each substudy randomisation was stratified by age and low-dose aspirin use. The sponsor prepared a computer-generated randomisation list with appropriate blocks. The study was centrally randomised according to strata with an interactive voice response system in all countries to ensure age and low-dose aspirin stratification. Allocation of treatment was done via the interactive system and all information was verified by this system before allocation of the patient to a treatment and assignment of the drug packs. To ensure allocation concealment all treatment packs were identically designed and all study drugs were supplied as tablets with matching placebo. We prespecified that data from the two substudies would be pooled for analysis.

The primary objective was to test the hypothesis that lumiracoxib reduces the risk of developing upper gastrointestinal ulcer complications compared with the non-steroidal anti-inflammatory drugs naproxen and ibuprofen. A key secondary objective was to measure and compare a composite endpoint of cardiovascular morbidity and mortality across the randomised treatment groups.

By design, TARGET included patients at high cardiovascular risk who were taking low-dose aspirin (75–100 mg daily) for primary or secondary prevention of coronary heart disease. We intended to include about 24% of patients in the overall study population who were taking low-dose aspirin, based on projections from other trials. Low-dose aspirin use was assessed at baseline with the interactive voice response system and stratification was done accordingly. The low-dose aspirin strata information in this system was cross-checked for a matching entry on the concomitant medication case report form; any discrepancies were queried and the information corrected in the appropriate database. The decision for administration of aspirin was ultimately left to the discretion of the individual investigator.

Patients

We enrolled patients age 50 years or older with primary osteoarthritis. We excluded those with a history of myocardial infarction, stroke, coronary-artery bypass graft

surgery, percutaneous coronary intervention, or new-onset angina within the 6 months before screening; patients with electrocardiogram evidence of silent myocardial ischaemia; those with congestive heart failure with symptoms at rest or minimal activity (New York Heart Association class III–IV); or patients who were receiving anticoagulation therapy (apart from low-dose aspirin).

Patients at increased risk for coronary heart disease were eligible for study entry provided that they had been receiving low-dose aspirin (75–100 mg daily) for primary or secondary cardiovascular prevention for a minimum of 3 months before randomisation. The definition of high cardiovascular risk was based on major independent cardiovascular risk factors assessed with Framingham risk assessment equations (for primary prevention)[23] or a previous history of cardiovascular or cerebrovascular events (for secondary prevention). Patients not at high cardiovascular risk by these criteria but who were taking low-dose aspirin were also enrolled.

Procedures

We obtained electrocardiograms at the screening visit and at the end of study or early termination visit and analysed them centrally. To assess any cardiac ischaemic events arising during the study, serial electrocardiograms were also obtained and analysed locally.

Predefined clinical events of myocardial infarction, unstable angina, cardiovascular death, cardiac arrest, stroke (ischaemic and haemorrhagic), transient ischaemic attack, deep vein thrombosis, and pulmonary embolism were independently adjudicated by a cardiovascular and cerebrovascular safety committee who were unaware of treatment allocation. We defined myocardial infarction as either established or acute. Established myocardial infarction was defined as development of new pathological Q waves on serial electrocardiograms. Acute or recent myocardial infarction was defined as a rise and gradual fall (troponin) or more rapid increase and decline (muscle-brain fraction of creatine kinase) of biochemical markers of myocardial necrosis with at least one of the following: ischaemic symptoms; development of pathological Q waves on electrocardiogram; changes on electrocardiogram indicative of ischaemia (ST segment elevation or depression); coronary artery intervention (eg, coronary angioplasty); or pathological findings of acute myocardial infarction. Events were assigned to one of the following categories: confirmed, probable, possible, not enough information for adjudication, or no event.

In addition to clinical events, the safety committee reviewed cases of electrocardiogram-detected myocardial infarctions—reported as a new finding on the end-of-study or post-baseline electrocardiogram by the central electrocardiogram reading laboratory. These events were categorised as either confirmed silent (electrocardiogram-detected) myocardial infarction or no silent myocardial infarction.

Other adverse events of interest included blood pressure measurements and congestive heart failure. Blood pressure was measured at every study visit after study drug was taken. The protocol stated that measurement should be taken after 5 min of rest using the same arm, the same device, and whenever possible at the same time of day (preferably between 0800 h and 1100 h). Blood-pressure changes were calculated for every patient as the average of their post-baseline values at every study visit and compared between treatment groups. Congestive heart failure data were obtained with case report forms as part of the monitoring and recording of all adverse events and serious adverse events. Congestive heart failure data were not adjudicated and analyses were done post hoc.

Statistical analysis

All cardiovascular and cerebrovascular events, as adjudicated by the safety committee, were summarised in frequency tables by type and adjudication category. The primary endpoint for analysis of cardiovascular adverse events was a composite cardiovascular endpoint, as defined by the Antiplatelet Trialists' Collaboration.[24] This

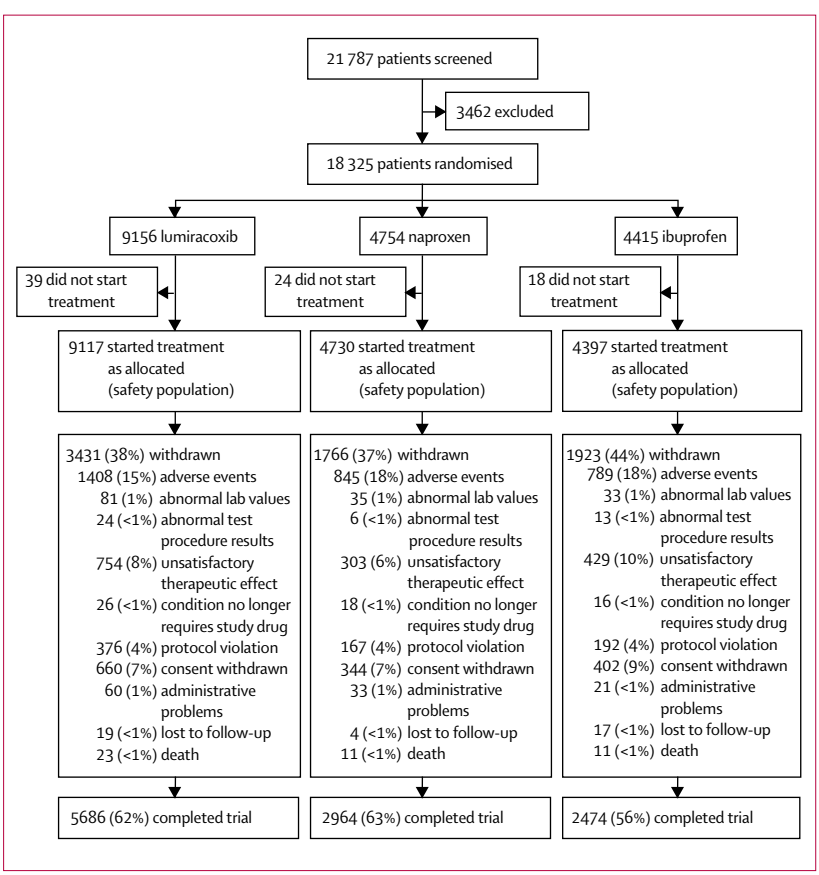

Figure 1: **Trial profile**
Percentages refer to safety population.

endpoint included confirmed silent (electrocardiogram-detected) myocardial infarctions, confirmed or probable clinical myocardial infarction, stroke (ischaemic and haemorrhagic), and cardiovascular death. Other cardiovascular events reported and adjudicated included cardiac arrest, transient ischaemic attack, unstable angina, deep vein thrombosis, and pulmonary embolism. Differences between treatment groups were measured with the Cox proportional-hazards regression model (with substudy, age, and low-dose aspirin as covariates), including estimation of hazard ratios and their associated 95% CIs. The Kaplan-Meier approach was used to generate estimates of the cumulative probability of events arising up to a particular timepoint. Analysis was by intention to treat. Analysis of blood pressure data used ANCOVA on average blood pressure changes across all post-baseline assessments, with baseline values and substudy as covariates.

The study was powered for the primary endpoint of confirmed or probable upper gastrointestinal ulcer complications, and these results are presented elsewhere in this issue.[22]

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Role of the funding source

The study was designed interactively between an advisory board and the sponsor. The sponsor managed the data and did all final analyses. Authors had full access to all data and were involved in data interpretation and wrote the first draft of the report, which was further developed in collaboration with the sponsor.

Results

Figure 1 shows the disposition of patients included in the study, and table 1 shows the baseline characteristics of randomised patients who received at least one dose of study medication (safety population). Compliance (defined as patients consuming full daily dose of study drug on at least 75% of days) was similar between lumiracoxib (6965, 76%) and non-steroidal anti-inflammatory drugs (6915, 76%) and within substudies (3189 [73%] ibuprofen *vs* 3213 [73%] lumiracoxib and 3726 [79%] naproxen *vs* 3752 [79%] lumiracoxib).

Overall, treatment groups were balanced in terms of baseline characteristics and major independent risk factors for cardiovascular disease (hypertension, diabetes, dyslipidaemia), with one notable exception. The substudy that compared naproxen with lumiracoxib included on average a higher number of patients with a previous history of vascular risk (1147, 12%) than the lumiracoxib versus ibuprofen substudy (733, 8%). 45% (n=8280) of patients in the overall population were hypertensive, 8% (1419) had diabetes mellitus, and

	Both substudies		Lumiracoxib *vs* ibuprofen substudy		Lumiracoxib *vs* naproxen substudy	
	Lumiracoxib (n=9117)	NSAIDs (n=9127)	Lumiracoxib (n=4376)	Ibuprofen (n=4397)	Lumiracoxib (n=4741)	Naproxen (n=4730)
Demographics						
Age (years)	63·5 (8·37)	63·4 (8·35)	63·4 (8·45)	63·3 (8·38)	63·6 (8·29)	63·6 (8·31)
Women	6963 (76%)	6970 (76%)	3298 (75%)	3345 (76%)	3665 (77%)	3625 (77%)
Body-mass index (kg/m²)	29·6 (5·70)	29·5 (5·64)	30·0 (5·91)	29·7 (5·88)	29·3 (5·48)	29·2 (5·39)
Cardiovascular characteristics						
Use of low-dose aspirin	2167 (24%)	2159 (24%)	975 (22%)	966 (22%)	1192 (25%)	1193 (25%)
High cardiovascular risk (Framingham)*	160 (2%)	167 (2%)	91 (2%)	83 (2%)	69 (1%)	84 (2%)
History of vascular disease*	981 (11%)	899 (10%)	393 (9%)	340 (8%)	588 (12%)	559 (12%)
Myocardial infarction	150 (2%)	138 (2%)	57 (1%)	65 (1%)	93 (2%)	73 (2%)
Cardiac revascularisation procedures†	65 (1%)	69 (1%)	33 (1%)	37 (1%)	32 (1%)	32 (1%)
Cardiac catheterisation	12 (<1%)	11 (<1%)	7 (<1%)	5 (<1%)	5 (<1%)	6 (<1%)
Cerebrovascular disease	177 (2%)	172 (2%)	69 (2%)	65 (1%)	108 (2%)	107 (2%)
Current smoker	929 (10%)	886 (10%)	464 (11%)	433 (10%)	465 (10%)	453 (10%)
Diabetes mellitus	744 (8%)	675 (7%)	392 (9%)	333 (8%)	352 (7%)	342 (7%)
Angina pectoris‡	248 (3%)	205 (2%)	79 (2%)	56 (1%)	169 (4%)	149 (3%)
Hypertension§	4219 (46%)	4061 (44%)	2025 (46%)	1965 (45%)	2194 (46%)	2096 (44%)
Dyslipidaemia§	1829 (20%)	1834 (20%)	1030 (24%)	1025 (23%)	799 (17%)	809 (17%)
Concurrent drugs¶						
β blocker, selective	949 (10%)	893 (10%)	474 (11%)	427 (10%)	475 (10%)	466 (10%)
β blocker, non-selective	201 (2%)	215 (2%)	88 (2%)	107 (2%)	113 (2%)	108 (2%)
ACE inhibitor, plain	1554 (17%)	1469 (16%)	774 (18%)	708 (16%)	780 (16%)	761 (16%)
ACE inhibitor and diuretic	231 (3%)	203 (2%)	107 (2%)	107 (2%)	124 (3%)	96 (2%)
Angiotensin II receptor blocker, plain	334 (4%)	347 (4%)	154 (4%)	206 (5%)	180 (4%)	141 (3%)
Angiotensin II receptor blocker and diuretic	167 (2%)	150 (2%)	102 (2%)	91 (2%)	65 (1%)	59 (1%)
Nitrates	286 (3%)	244 (3%)	105 (2%)	79 (2%)	181 (4%)	165 (3%)

Data are number of patients (%) or mean (SD). NSAIDs=non-steroidal anti-inflammatory drugs. ACE=angiotensin-converting enzyme. *The combination of these two mutually exclusive subgroups is called high cardiovascular risk in the text. †Includes medical history preferred terms "coronary artery surgery", "coronary angioplasty", "coronary arterial stent insertion", quadruple vessel bypass graft", "triple vessel bypass graft", double vessel bypass graft" as coded by MedDRA (medical dictionary for drug regulatory affairs). ‡Includes medical history preferred terms "angina pectoris" and "angina unstable" as coded by MedDRA. §Defined by medical history. ¶Drugs taken before randomisation.

Table 1: **Baseline characteristics**

	Both substudies		Lumiracoxib *vs* ibuprofen substudy		Lumiracoxib *vs* naproxen substudy	
	Lumiracoxib (n=9117)	NSAIDs (n=9127)	Lumiracoxib (n=4376)	Ibuprofen (n=4397)	Lumiracoxib (n=4741)	Naproxen (n=4730)
Patients with confirmed or probable cardiovascular or cerebrovascular events	85 (0·93%)	75 (0·82%)	33 (0·75%)	32 (0·73%)	52 (1·10%)	43 (0·91%)
Patients with confirmed or probable clinical myocardial infarction, silent myocardial infarction, stroke or cardiovascular death (primary endpoint)	59 (0·65%)	50 (0·55%)	19 (0·43%)	23 (0·52%)	40 (0·84%)	27 (0·57%)
Patients with confirmed or probable:						
Cardiovascular death	19 (0·21%)	18 (0·20%)	8 (0·18%)	10 (0·23%)	11 (0·23%)	8 (0·17%)
All myocardial infarctions	23 (0·25%)	17 (0·19%)	5 (0·11%)	7 (0·16%)	18 (0·38%)	10 (0·21%)
Silent	3 (0·03%)	5 (0·05%)	0	2 (0·05%)	3 (0·06%)	3 (0·06%)
Clinical	20 (0·22%)	12 (0·13%)	5 (0·11%)	5 (0·11%)	15 (0·32%)	7 (0·15%)
Fatal	2 (0·02%)	3 (0·03%)	0	2 (0·05%)	2 (0·04%)	1 (0·02%)
Non-fatal	18 (0·20%)	9 (0·10%)	5 (0·11%)	3 (0·07%)	13 (0·27%)	6 (0·13%)
Stroke	24 (0·26%)	21 (0·23%)	8 (0·18%)	9 (0·20%)	16 (0·34%)	12 (0·25%)
Fatal	5 (0·05%)	2 (0·02%)	2 (0·04%)	1 (0·02%)	3 (0·06%)	1 (0·02%)
Non-fatal	19 (0·21%)	19 (0·21%)	6 (0·14%)	8 (0·18%)	13 (0·27%)	11 (0·23%)
Ischaemic stroke	23 (0·25%)	17 (0·19%)	8 (0·18%)	6 (0·14%)	15 (0·32%)	11 (0·23%)
Fatal	4 (0·04%)	0	2 (0·04%)	0	2 (0·04%)	0
Non-fatal	19 (0·21%)	17 (0·19%)	6 (0·14%)	6 (0·14%)	13 (0·27%)	11 (0·23%)
Haemorrhagic stroke	1 (0·01%)	4 (0·04%)	0	3 (0·07%)	1 (0·02%)	1 (0·02%)
Fatal	1 (0·01%)	2 (0·02%)	0	1 (0·02%)	1 (0·02%)	1 (0·02%)
Non-fatal	0	2 (0·02%)	0	2 (0·05%)	0	0
Cardiac arrest	0	0	0	0	0	0
Transient ischaemic attack	7 (0·07%)	6 (0·07%)	5 (0·11%)	1 (0·02%)	2 (0·04%)	5 (0·11%)
Unstable angina	10 (0·11%)	11 (0·12%)	4 (0·09%)	7 (0·16%)	6 (0·13%)	4 (0·08%)
Deep vein thrombosis	6 (0·07%)	7 (0·08%)	4 (0·09%)	3 (0·07%)	2 (0·04%)	4 (0·08%)
Pulmonary embolism	4 (0·04%)	4 (0·04%)	2 (0·04%)	0	2 (0·04%)	4 (0·08%)

Data are number of patients with event (%). NSAIDs=non-steroidal anti-inflammatory drugs.

Table 2: **Incidence of confirmed or probable cardiovascular and cerebrovascular events**

20% (3663) had dyslipidaemia. As planned, about 24% (4326) of patients were taking low-dose aspirin. These data accord with the findings of the National Center for Health Statistics report.[17]

As expected, patients receiving low-dose aspirin were slightly older. About 5% (n=646) of patients did not receive low-dose aspirin during the study, despite being classified as either high cardiovascular risk or having had a previous cardiac event. Only slightly more than a third of patients (1561; 36%) who received low-dose aspirin were classified as high cardiovascular risk on post-hoc analysis (data not shown).

Table 2 provides a breakdown of all confirmed or probable vascular events into the different cardiovascular event categories. The primary endpoint did not differ between lumiracoxib and non-steroidal anti-inflammatory drugs in the overall population (figure 2, table 3). More primary endpoint events were recorded in the lumiracoxib versus naproxen substudy (n=67) compared with the lumiracoxib versus ibuprofen substudy (42), although this difference was not significant (p=0·1145, treatment by substudy interaction). As expected, incidence of the primary endpoint was higher in patients receiving low-dose aspirin in all treatment groups (table 3). The primary endpoint did not differ significantly in either substudy. None of the between-treatment group comparisons was significant. Tests for heterogeneity done post hoc were not significant (data not shown).

Table 4 and figure 3 show the results of all confirmed or probable myocardial infarctions (clinical and silent). Overall, no significant difference was recorded in rates of myocardial infarction between the lumiracoxib and the combined non-steroidal anti-inflammatory treatment groups. In the ibuprofen substudy, these rates did not differ significantly between lumiracoxib and

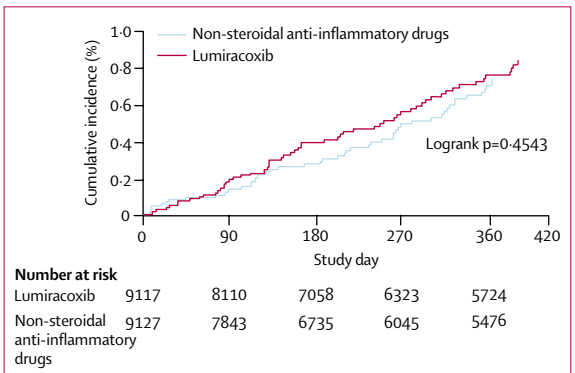

Figure 2: **Incidence of composite primary endpoint (confirmed or probable events)**

Treatment group		Number of patients with event (rate per 100 patient-years)	Hazard ratio (95% CI)	p*
Both substudies				
Overall population†	Lumiracoxib	59 (0·86)	1·14 (0·78–1·66)	0·5074
	NSAIDs	50 (0·75)		
Non-aspirin population‡	Lumiracoxib	35 (0·66)	1·22 (0·74–2·02)	0·4343
	NSAIDs	27 (0·53)		
Aspirin population‡	Lumiracoxib	24 (1·51)	1·04 (0·59–1·84)	0·8918
	NSAIDs	23 (1·46)		
Lumiracoxib versus ibuprofen substudy				
Overall population§	Lumiracoxib	19 (0·59)	0·76 (0·41–1·40)	0·3775
	Ibuprofen	23 (0·74)		
Non-aspirin population¶	Lumiracoxib	13 (0·51)	0·94 (0·44–2·04)	0·8842
	Ibuprofen	13 (0·54)		
Aspirin population¶	Lumiracoxib	6 (0·85)	0·56 (0·20–1·54)	0·2603
	Ibuprofen	10 (1·48)		
Lumiracoxib versus naproxen substudy				
Overall population§	Lumiracoxib	40 (1·10)	1·46 (0·89–2·37)	0·1313
	Naproxen	27 (0·76)		
Non-aspirin population¶	Lumiracoxib	22 (0·80)	1·49 (0·76–2·92)	0·2417
	Naproxen	14 (0·53)		
Aspirin population¶	Lumiracoxib	18 (2·04)	1·42 (0·70–2·90)	0·3368
	Naproxen	13 (1·45)		

NSAIDs=non-steroidal anti-inflammatory drugs. *Based on Wald χ^2 statistic for treatment group comparison. Cox proportional-hazards models include, in addition to treatment group, the factors: †substudy, low-dose aspirin, and age; ‡substudy and age; §low-dose aspirin and age; and ¶age.

Table 3: **Incidence of composite primary endpoint events (confirmed or probable), by substudy and aspirin use**

ibuprofen in the population not taking low-dose aspirin, patients taking aspirin, and overall (table 4). In the naproxen substudy, fewer patients had myocardial infarctions in the naproxen group (four events, 0·11%) than the lumiracoxib group (ten events, 0·28%) in patients not taking low-dose aspirin (p=0·1454). Incidence of myocardial infarction was similar overall and in patients taking low-dose aspirin.

About 89% of randomised patients had an electrocardiogram at and after baseline (8225 patients taking lumiracoxib and 8193 patients allocated non-steroidal anti-inflammatory drugs). Fewer silent (electrocardiogram-detected) myocardial infarctions took place in the lumiracoxib group (n=3) than in the non-steroidal anti-inflammatory drug group (n=5) in the overall population (table 2; p=0·7265, Fisher's exact test).[25]

	Treatment group	Number of patients with event (rate per 100 patient-years)	Hazard ratio (95% CI)	p*
Both substudies				
Overall population†				
	Lumiracoxib	23 (0·33)	1·31 (0·70–2·45)	0·4012
	NSAIDs	17 (0·26)		
Non-aspirin population‡	Lumiracoxib	14 (0·26)	1·47 (0·63–3·39)	0·3706
	NSAIDs	9 (0·18)		
Aspirin population‡	Lumiracoxib	9 (0·57)	1·14 (0·44–2·95)	0·7899
	NSAIDs	8 (0·51)		
Lumiracoxib versus ibuprofen substudy				
Overall population§	Lumiracoxib	5 (0·15)	0·66 (0·21–2·09)	0·4833
	Ibuprofen	7 (0·23)		
Non-aspirin population¶	Lumiracoxib	4 (0·16)	0·75 (0·20–2·79)	0·6669
	Ibuprofen	5 (0·21)		
Aspirin population¶	Lumiracoxib	1 (0·14)	0·47 (0·04–5·14)	0·5328
	Ibuprofen	2 (0·30)		
Lumiracoxib versus naproxen substudy				
Overall population§	Lumiracoxib	18 (0·49)	1·77 (0·82–3·84)	0·1471
	Naproxen	10 (0·28)		
Non-aspirin population¶	Lumiracoxib	10 (0·36)	2·37 (0·74–7·55)	0·1454
	Naproxen	4 (0·15)		
Aspirin population¶	Lumiracoxib	8 (0·91)	1·36 (0·47–3·93)	0·5658
	Naproxen	6 (0·67)		

NSAIDs=non-steroidal anti-inflammatory drugs. *Based on Wald χ^2 statistic for treatment group comparison. Cox proportional-hazards models include, in addition to treatment group, the factors: †substudy, low-dose aspirin, and age; ‡substudy and age; §low-dose aspirin and age; and ¶age.

Table 4: **Incidence of confirmed or probable myocardial infarction (clinical and silent), by substudy and aspirin use**

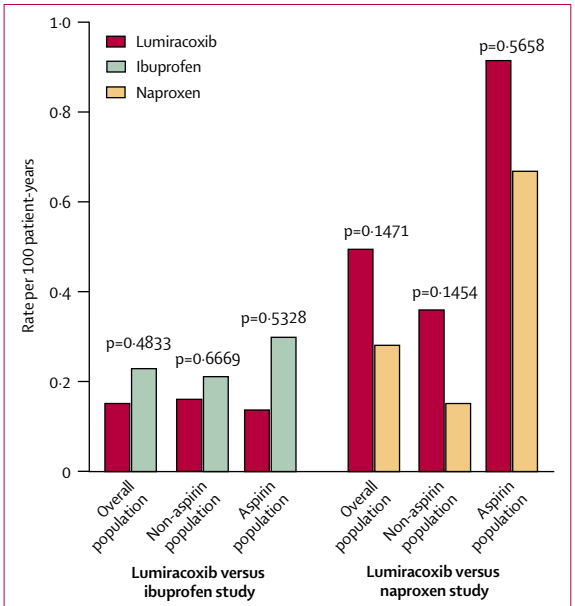

Figure 3: **Incidence of confirmed or probable myocardial infarctions (clinical and silent), by substudy and aspirin use**

Incidence of confirmed or probable stroke (ischaemic or haemorrhagic) was comparable across treatments, with an incidence of 0·26% (24 events) with lumiracoxib and 0·23% (21 events) with non-steroidal anti-inflammatory drugs (hazard ratio 1·11 [95% CI 0·62–1·99], p=0·7372). Of the 45 strokes, 40 (85%) were ischaemic (table 5). The number of confirmed or probable cardiovascular deaths overall was not different between the lumiracoxib and non-steroidal anti-inflammatory drug groups (19 *vs* 18 events; hazard ratio 1·00 [95% CI 0·52–1·91], p=0·9966). Occurrence of any reported cardiovascular and cerebrovascular events submitted for adjudication was low and comparable between the treatment groups (1·75% in the lumiracoxib group *vs* 1·59% in the non-steroidal anti-inflammatory drug group). As expected, incidence of these events was highest in the population taking low-dose aspirin.

Post-hoc analysis of vascular events of ischaemic origin (later referred to as ischaemic events) was done to assess the incidence of the combined endpoint of confirmed or probable myocardial infarction, ischaemic stroke, unstable angina, and transient ischaemic attack. No significant difference in ischaemic events was noted in the lumiracoxib versus naproxen substudy (hazard ratio 1·35 [95% CI 0·84–2·16], p=0·2147), in the lumiracoxib versus ibuprofen substudy (0·98 [0·54–1·79], p=0·9529), or in the populations taking and not taking low-dose aspirin (table 5).

Incidence of deep vein thrombosis and pulmonary embolism did not differ significantly between lumiracoxib and non-steroidal anti-inflammatory drugs and the individual comparators (table 2). Congestive heart failure (including cardiac failure, congestive cardiac failure, and chronic cardiac failure) happened less frequently in the lumiracoxib group (22 events, 0·24%) than with non-steroidal anti-inflammatory drugs (31 events, 0·34%; odds ratio 0·7098 [95% CI 0·3912–1·267], p=0·2727).[25]

Blood-pressure measurements were made at every study visit. At study end, 4678 patients taking lumiracoxib versus 4661 given naproxen and 4312

	Both substudies		Lumiracoxib *vs* ibuprofen substudy		Lumiracoxib *vs* naproxen substudy	
	Lumiracoxib	NSAIDs	Lumiracoxib	Ibuprofen	Lumiracoxib	Naproxen
Number of patients in non-aspirin population	6950	6968	3401	3431	3549	3537
Patients with confirmed or probable ischaemic events	34 (0·49%)	27 (0·39%)	13 (0·38%)	12 (0·35%)	21 (0·59%)	15 (0·42%)
All myocardial infarctions	14 (0·20%)	9 (0·13%)	4 (0·12%)	5 (0·15%)	10 (0·28%)	4 (0·11%)
Clinical	14 (0·20%)	5 (0·07%)	4 (0·12%)	3 (0·09%)	10 (0·28%)	2 (0·06%)
Silent	0	4 (0·06%)	0	2 (0·06%)	0	2 (0·06%)
Ischaemic stroke	12 (0·17%)	8 (0·11%)	6 (0·18%)	2 (0·06%)	6 (0·17%)	6 (0·17%)
Unstable angina	5 (0·07%)	5 (0·07%)	1 (0·03%)	4 (0·12%)	4 (0·11%)	1 (0·03%)
Transient ischaemic attack	3 (0·04%)	5 (0·07%)	2 (0·06%)	1 (0·03%)	1 (0·03%)	4 (0·11%)
Number of patients in aspirin population	2167	2159	975	966	1192	1193
Patients with confirmed or probable ischaemic events	29 (1·34%)	24 (1·11%)	9 (0·92%)	9 (0·93%)	20 (1·68%)	15 (1·25%)
All myocardial infarctions	9 (0·42%)	8 (0·37%)	1 (0·10%)	2 (0·21%)	8 (0·67%)	6 (0·50%)
Clinical	6 (0·28%)	7 (0·32%)	1 (0·10%)	2 (0·21%)	5 (0·42%)	5 (0·42%)
Silent	3 (0·14%)	1 (0·05%)	0	0	3 (0·25%)	1 (0·08%)
Ischaemic stroke	11 (0·51%)	9 (0·42%)	2 (0·21%)	4 (0·41%)	9 (0·76%)	5 (0·42%)
Unstable angina	5 (0·23%)	6 (0·28%)	3 (0·31%)	3 (0·31%)	2 (0·17%)	3 (0·25%)
Transient ischaemic attack	4 (0·18%)	1 (0·05%)	3 (0·31%)	0	1 (0·08%)	1 (0·08%)

Data are number of patients with event (%). NSAIDs=non-steroidal anti-inflammatory drugs.

Table 5: **Incidence of ischaemic events (confirmed or probable), by substudy and aspirin use**

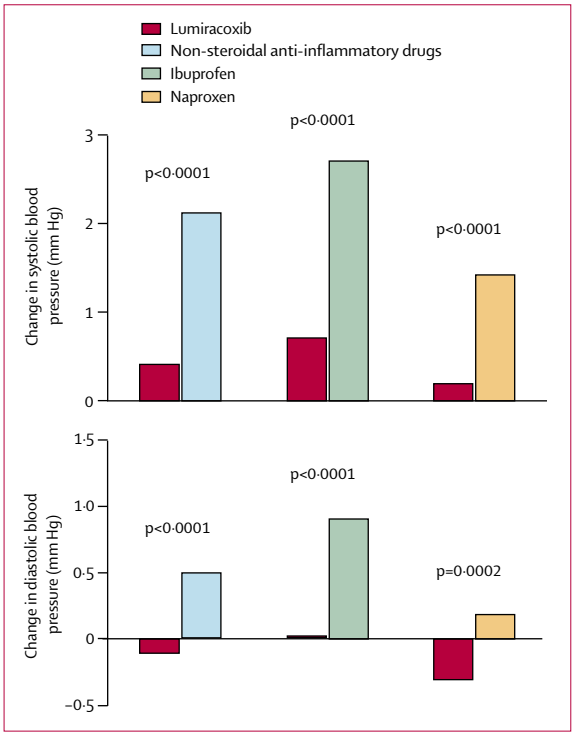

Figure 4: **Change from baseline in systolic and diastolic blood pressure (least square means) for lumiracoxib and non-steroidal anti-inflammatory drugs, pooled and by substudy**

p for treatment comparisons are based on ANCOVA models with baseline values and substudy as covariates for both substudies combined and baseline values only for each substudy.

allocated lumiracoxib versus 4331 taking ibuprofen had been measured. For systolic blood pressure, least squares mean change from baseline was +0·4 mm Hg for lumiracoxib and +2·1 mm Hg for non-steroidal anti-inflammatory drugs (p<0·0001). For diastolic blood pressure, mean change from baseline was –0·1 mm Hg for lumiracoxib and +0·5 mm Hg for non-steroidal anti-inflammatory drugs (p<0·0001). Figure 4 shows the substudy results.

Discussion

We have shown that the incidence of non-fatal and silent myocardial infarction, stroke, or cardiovascular death, which was low in our population, did not differ between treatment groups (lumiracoxib 0·65% *vs* non-steroidal anti-inflammatory drugs 0·55%) or when analysed by aspirin use, age, sex, high cardiovascular risk, or cerebrovascular history. More events arose in the lumiracoxib versus naproxen substudy than in the lumiracoxib versus ibuprofen substudy, which could represent the difference in baseline vascular risk between the two substudies.

The individual components of the primary endpoint did not differ between lumiracoxib and both non-steroidal anti-inflammatory drugs. However, in the naproxen substudy, incidence of myocardial infarctions differed between lumiracoxib (0·28%) and naproxen (0·11%) in the non-aspirin population. Although this difference was not significant, it could be accounted for by a play of chance or, possibly, that naproxen at this dose and dosing interval has antithrombotic effects via its COX1 activity. The absence of a placebo arm means we cannot definitively ascertain the real risk, if any, of myocardial infarction for lumiracoxib alone. However, alternative hypotheses are plausible. Capone and colleagues[26] showed that naproxen 500 mg twice daily suppresses thromboxane B2 production, a marker of platelet COX1 activity, to a similar level as low-dose aspirin 100 mg daily. If this hypothesis is correct, the relative difference in the incidence of myocardial infarction between lumiracoxib and naproxen should be reduced in the aspirin population, which indeed was shown in TARGET (rate of myocardial infarction was 0·67% for lumiracoxib and 0·50% for naproxen in the low-dose aspirin population). This premise is further lent support by data showing no difference in incidence of myocardial infarction between lumiracoxib and ibuprofen in all study populations. Additional data for the rates of ischaemic events, deep vein thromboses, and pulmonary embolisms suggest that lumiracoxib does not seem to be prothrombotic.

Ibuprofen can block the inhibition of platelet COX1 activity by aspirin.[27] In an observational study of a small number of patients, MacDonald and colleagues[28] showed that cardiovascular patients discharged from hospital taking both aspirin and ibuprofen had a two-fold increase in all-cause mortality compared with those taking aspirin alone. However in the CLASS study,[29] the incidence of cardiovascular adverse events with ibuprofen 800 mg three times a day did not differ when compared with celecoxib or diclofenac. In TARGET, the few myocardial infarctions in patients taking ibuprofen (two events) and lumiracoxib (one event) in the low-dose aspirin population render any meaningful interpretation purely speculative.

We investigated the apparent differences in the rates of myocardial infarctions in the two substudies. Although the number of events in the ibuprofen versus lumiracoxib substudy (n=12) was lower than in the naproxen versus lumiracoxib substudy (n=28), treatment by substudy interaction was not significant (p=0·1832). This finding could be accounted for by noting that the naproxen versus lumiracoxib substudy included on average a higher number of patients with a previous history of vascular risk (12%) compared with the lumiracoxib versus ibuprofen substudy (8%).

As far as we know, no double-blind randomised controlled trials have been done to compare naproxen with placebo or with low-dose aspirin for primary or secondary prevention of cardiovascular morbidity and mortality. Therefore, naproxen should not be regarded as an alternative to low-dose aspirin in patients with osteoarthritis at high cardiovascular risk. In TARGET, individuals at high cardiovascular risk and who were

taking low-dose aspirin and lumiracoxib had a similar number of cardiovascular events as did those on the individual non-steroidal anti-inflammatory drugs and low-dose aspirin. This finding implies that the beneficial effects of low-dose aspirin are maintained in patients taking lumiracoxib for osteoarthritis pain.

Findings of a large, population-based, observational cohort study showed that users of rofecoxib had a higher risk of admission for congestive heart failure than did people not using non-steroidal anti-inflammatory drugs.[6] Researchers on that study also investigated the introduction of antihypertensive and congestive heart failure treatment and reported that admission for heart failure was significantly more likely in patients on rofecoxib than celecoxib or non-steroidal anti-inflammatory drugs. The physicochemical and pharmacokinetic properties of the different COX2-selective inhibitors were proposed as being important factors in this differentiation. These drugs differ in their saturation kinetics, dose accumulation, and plasma half-lifes. Lumiracoxib has a short half-life (3–6 h) and no dose-accumulation kinetics. In a post-hoc analysis of the TARGET study, lumiracoxib was not associated with any increased risk of developing congestive heart failure when compared with non-selective non-steroidal anti-inflammatory drugs.

Findings of two large randomised trials showed an increase in systolic hypertension and worsening of oedema when rofecoxib was compared with celecoxib in elderly hypertensive patients with osteoarthritis[30] and in those with systemic hypertension and osteoarthritis.[31] In the TARGET study, blood pressure measurements were recorded during all study visits, after drug intake in the morning—ie, when plasma concentrations of lumiracoxib would be expected to be high. Patients taking lumiracoxib had a significantly smaller mean change from baseline for systolic blood pressure compared with non-steroidal anti-inflammatory drugs; the difference was also seen for diastolic blood pressure. These differences were maintained when lumiracoxib was compared with ibuprofen and naproxen in the substudies. In addition to the physicochemical and pharmacokinetic characteristics of lumiracoxib, this effect might indicate less sodium retention in patients taking lumiracoxib compared with non-steroidal anti-inflammatory drugs. Data from the Hypertension Optimal Treatment (HOT) study[32] showed that diastolic blood pressure differences of +4 mm Hg can lead to a 28% increase in myocardial infarctions, and MacMahon and colleagues[33] concluded that a prolonged difference in diastolic blood pressure of 5 mm Hg was associated with a 34% difference in risk of stroke and 21% difference in risk of coronary heart disease. Although the TARGET study was only done over 1 year, our findings could translate into a greater clinical cardiovascular benefit over a longer treatment period. This possibility is important in this population since patients with osteoarthritis taking rofecoxib, celecoxib, or non-steroidal anti-inflammatory drugs are more likely to start antihypertensive and congestive heart failure treatment.[6]

Patients with osteoarthritis at high cardiovascular risk should be provided with low-dose aspirin for primary or secondary prophylaxis, and the increased risk of complicated gastrointestinal ulcers associated with non-steroidal anti-inflammatory drugs should be considered. Understanding the cardiovascular risk associated with non-steroidal anti-inflammatory drugs, including COX2-selective inhibitors, is essential, since many patients prescribed these drugs are older than 60 years (at which age the incidence of hypertension is $\geqslant$50%) and have either had a previous vascular event or are at risk for a major cardiovascular event. Therefore, the TARGET results have useful clinical practice implications in that patients taking lumiracoxib did not have a significant increase compared with non-steroidal anti-inflammatory drugs in myocardial infarctions, stroke, cardiovascular death, or other thrombotic cardiovascular adverse events, and had a significantly reduced increase in diastolic and systolic blood pressure.

Contributors

The paper has been read and approved by all authors. Every author contributed to the drafting and reviewing of the paper. Further, M E Farkouh, C J Hawkey, X Gitton, A Gimona, and E Ehrsam contributed to development of the study protocol. T J Schnitzer was lead investigator. B Mellein was trial statistician. G Krammer was clinical trial leader. M E Farkouh (Chairman), J H Chesebro, H Kirshner, S Ruland, and F W A Verheugt were members of the independent cardiovascular and cerebrovascular safety committee and C J Hawkey was Chairman of the gastrointestinal safety committee. R A Harrington acted as a consultant on the TARGET data and safety monitoring board.

Conflict of interest statement

MEF has received clinical trial research support from Arginox and Berlex and has acted as a consultant for Novartis. HK has acted as a consultant for Novartis, Wyeth, Sanofi-Synthelabo, Bristol Myers Squibb, and AstraZeneca; as a study investigator for Pfizer, Bristol Myers Squibb, Sanofi-Synthelabo, Boehringer Ingelheim, ONO, Fujisawa, and AstraZeneca; and is a member of the speakers' bureau for Pfizer, Novartis, Janssen, Forest, Boehringer Ingelheim, Sanofi Synthelabo, Bristol Myers Squibb, AstraZeneca, and Wyeth. RAH has received research funding and consultant honoraria from Novartis. SR has received consultancy fees or honoraria from Novartis, Boehringer Ingelheim, Bristol Myers Squibb, Solvay, and ESP Pharma. FWAV has received educational and research grants from Bayer AG, Roche, Eli Lilly, and Boehringer Ingelheim; and has received honoraria for consultancies from Pharmacia Upjohn, Eli Lilly, Merck, and Bayer (Netherlands). TJS has acted as a consultant for AAI Pharma, GlaxoSmithKline, McNeil Consumer Healthcare, Merck, Novartis, Pfizer, and Winston; has received clinical research support from AAI Pharma, Merck, Novartis, Pfizer, and Winston; and is a member of the speakers' bureau for Merck and Ortho-McNeil. GRB has done clinical trials, acted as a scientific consultant, and is member of the speakers' bureau for Novartis, Pfizer, Merck Sharp and Dohme, and Merckle. EM has received consultancy fees from Novartis. MCH has acted as a consultant for Amgen, Arakis, AstraZeneca, Aventis Pharmaceutical, Bristol Myers Squibb, Genzyme, GlaxoSmithKline, Laboratories NEGMA, Merck, Novartis, Proctor and Gamble Pharmaceutical, Purdue Pharma, Roche, Scios, and Takeda Pharmaceuticals North America; and has received clinical research support from Merck and GlaxoSmithKline. MD has received genetic research funding from GlaxoSmithKline and AstraZeneca and has received honoraria for attending advisory boards related to osteoarthritis products from Novartis, Aventis, Genzyme, Bristol Myers Squibb, Johnson and

Johnson, and Merck. CJH has received research funding or honoraria from AstraZeneca, GlaxoSmithKline, Merck, Nitromed, Novartis, Pfizer, Takeda, and Wyeth. EE, XG, GK, BM, and PM are employees of Novartis, manufacturer of lumiracoxib. AG was an employee of Novartis until March, 2004. JHC has acted as a consultant for Novartis, Berlex, Sanofi-Synthelabo, and Bristol Myers Squibb; and has received research grants from Berlex.

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