

Risk of myocardial infarction associated with selective COX-2 inhibitors: Meta-analysis of randomised controlled trials[†]

Li-Chia Chen PhD[‡] and Darren M Ashcroft PhD^{*,§}

School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Oxford Road, Manchester, UK

SUMMARY

Purpose To evaluate the risk of myocardial infarction (MI) associated with the use of selective cyclooxygenase-2 (COX-2) inhibitors (coxibs).

Methods Systematic review and meta-analysis of randomised controlled trials (RCTs) using a fixed-effect model to estimate the odds ratios (ORs) for risk of MI associated with coxibs compared against placebo, non-steroidal anti-inflammatory drugs (NSAIDs) and other coxibs.

Results Fifty-five trials (99 087 patients) were included in the meta-analysis. The overall pooled OR for MI risk for any coxib compared against placebo was 1.46 (95%CI: 1.02, 2.09). We found celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib were associated with higher MI risks compared against placebo. The pooled OR for any coxib compared against other NSAIDs was 1.45 (95%CI: 1.09, 1.93). Rofecoxib had a significantly higher risk of MI than naproxen (OR: 5.39; 95%: 2.08, 14.02) and valdecoxib had lower MI risk than diclofenac (OR: 0.14, 95%CI: 0.03, 0.73). There were no significant differences identified in the risk of MI from the available head-to-head comparisons of coxibs.

Conclusions Coxibs were associated with increased risks of MI when compared against placebo or non-selective NSAIDs. Differences in MI risk were also apparent between comparisons of individual NSAIDs. Future work should consider using individual patient data (IPD) meta-analysis to explore differences in MI risk between different subgroups of patients. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS — COX-2 inhibitor; systematic review; meta-analysis; myocardial infarction

Received 12 March 2007; Accepted 14 March 2007

INTRODUCTION

The recent withdrawal of rofecoxib (Vioxx) has been described as a 'regulatory' failure in monitoring the safety of licensed medicines.^{1,2} By 2003, sales of

rofecoxib had reached US\$2.5 billion and it has been estimated that approximately 80 million people had used the drug by the time it was withdrawn.³ More recently, valdecoxib, a second selective cyclooxygenase-2 (COX-2) inhibitor (coxib) has also been withdrawn. These drug withdrawals have raised concerns about a potential class effect of coxibs as well as raising speculation about the safety of all non-steroidal anti-inflammatory drugs (NSAIDs).⁴

It has been proposed that the thrombotic risk associated with coxibs results from an imbalance in the prostacyclin to thromboxane ratio in favour of

* Correspondence to: Dr D. M. Ashcroft, School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Oxford Road, Manchester, M13 9PL, UK.

E-mail: darren.ashcroft@manchester.ac.uk

[†]No conflict of interest was declared.

[‡]Research Associate.

[§]Senior Clinical Lecturer.

thromboxane, therefore leading to thrombi formation.⁵ Several systematic reviews and meta-analyses have been conducted on randomised controlled trials (RCTs) to assess the cardiovascular risk associated with coxibs.^{6–12} These studies have either focused on individual coxibs, used composite cardiovascular end points as outcome measures or compared coxibs against control groups in which both placebo and non-selective NSAID groups have been combined.

The aim of this meta-analysis was to assess the risk of MI for all coxibs compared against placebo, non-selective NSAIDs and other coxibs in head-to-head comparisons.

METHODS

Search strategy

Trials were identified by searching the following computerised databases—MEDLINE (1966 to June 2006), EMBASE (1980 to June 2006), the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (2006, Issue 2)—using a structured electronic search strategy which included the name of any of the “coxibs” that had been licensed in the UK or US (celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib and lumiracoxib). This was supplemented by searching the reference lists of all retrieved studies, review articles, conference reports and proceedings of the relevant Food and Drug Administration (FDA) advisory panels and the online Pharmaceutical Research and Manufacturers of American Clinical Study Result Database.¹³ There were no language restrictions.

Inclusion criteria

Double-blind RCTs of at least 4-weeks duration were included if they compared any individual coxib against placebo or another active treatment (such as other NSAIDs), and reported on the proportion of patients experiencing MI. The methodological quality of included trials had to score a minimum of two points (for randomisation and double blinding) using the Jadad scale.¹⁴

Outcome measures and data extraction

Both investigators extracted outcome data independently from the included trials. The primary outcome measure was MI, including fatal and non-fatal events. For each trial, we extracted the number of patients

experiencing MI and the total number randomised to each study arm. If the number of patients experiencing MI reported in the published studies were different to the figures reported in the FDA files, we used the data reported by the FDA. Other trial characteristics (including condition treated, treatment regimen and duration) were also extracted.

Statistical analysis

Pooled odds ratios (ORs) for the proportion of patients experiencing MI and their corresponding 95% confidence intervals (95%CI) were calculated by using the Mantel–Haenszel method within a fixed-effect meta-analysis.¹⁵ Trials in which there were no MI events reported in any of the treatment groups were excluded. In cases where there were no MI events in one of the treatment groups, we used a continuity correction by adding 0.5 to each cell.⁶ Comparisons were undertaken for each individual coxib against their corresponding reference groups, that is placebo, NSAID group (or individual NSAIDs) or other coxibs.

Heterogeneity statistics were calculated to test the agreement of the individual trial results with the combined meta-analytical summary.^{16,17} For the placebo-controlled comparisons, fixed-effect meta-regression models were used to examine whether estimates of risk were affected by the dose of the coxibs, trial duration or the patients' treated disease state (such as rheumatoid arthritis, osteoarthritis, chronic lower back pain, colorectal adenomas or mild cognitive impairment). We also used subgrouping of RCTs to explore differences in MI risk between individual coxibs and naproxen and other NSAIDs. All statistical analyses were undertaken using STATA version 9.0 (Stata, College Station, TX, USA).

RESULTS

Characteristics of the included trials

Figure 1 outlines the results of the trial selection process. We identified 187 studies, of which 117 RCTs met the inclusion criteria. Of these, 62 trials reported no MI events in any of the treatment groups and the remaining 55 RCTs were included in the meta-analysis (Table 1). In all, the 55 trials included 99 087 patients with osteoarthritis (27 trials), rheumatoid arthritis (14 trials), osteoarthritis or rheumatoid arthritis (4 trials), ankylosing spondylitis (1 trial), chronic low back pain (2 trials), colorectal adenomas (3 trials) and mild cognitive impairment or early Alzheimer's disease (4 trials).

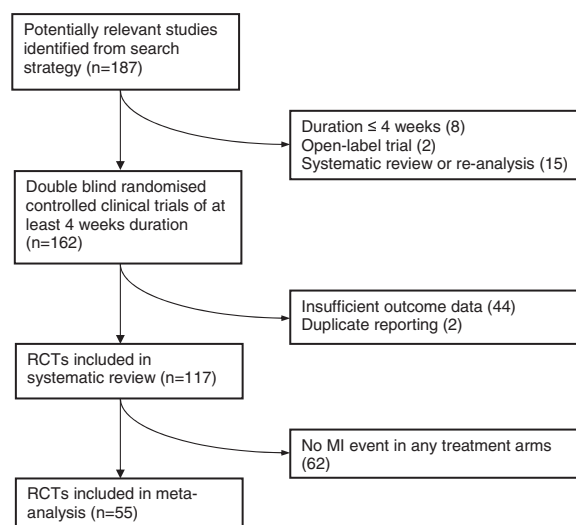


Figure 1. Process of identifying eligible studies in systematic review

Thirty-nine trials included at least one NSAID as an active comparator, 14 trials only included placebo as control, 16 trials included both active and placebo controls and two trials only compared coxibs directly.^{18,19} Treatment durations ranged from 4 weeks to 4 years; for 17 RCTs, the duration lasted for more than 6 months and 7 out of the 17 RCTs lasted for more than 1 year. Only one of the RCTs was not sponsored by the pharmaceutical industry.²⁰ Seven RCTs compared different coxibs directly. Of these, two RCTs compared celecoxib against rofecoxib^{18,19} and five trials compared celecoxib against lumiracoxib.^{21–25}

Comparison of coxibs against placebo

The analysis of MI risk comparing all coxibs against placebo was based on data from 26 082 patients included in 28 RCTs (one trial²⁶ also compared rofecoxib against lumiracoxib). Overall, the proportions of patients experiencing MI in each of the trials were low, as shown in Figure 2. The pooled analysis across all 28 RCTs showed that coxibs were associated with a significantly increased risk of MI compared against placebo; the corresponding pooled OR was 1.46 (95%CI: 1.02, 2.09). There was no evidence of heterogeneity between any of the pooled comparisons ($I^2 = 0.00\%$, p -value for heterogeneity = 0.62–0.96). Celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib were all associated with higher rates of patients experiencing MI

compared against placebo but none of these subgroup comparisons reached conventional significance levels ($p < 0.05$).

Meta-regression analyses examining MI risk in relation to the duration of treatment (less than 26 weeks, 27 to 52 weeks, more than 52 weeks) and the nature of the treated disease state found that there were no significant differences between any of the individual coxibs and placebo. We also compared recommended daily doses of coxibs (celecoxib 200 mg, etoricoxib 60 mg, valdecoxib 20 mg, rofecoxib 12.5 mg and lumiracoxib 200 mg for chronic arthritis) with higher daily doses, and found that celecoxib at a dose of more than 200 mg daily was associated with a significantly higher MI risk than placebo (OR: 2.25; 95%CI: 1.06, 4.77). Both rofecoxib 12.5 mg daily (OR: 2.04, 95%CI: 0.34, 12.38) and 25 mg daily (OR: 1.38, 95%CI: 0.84, 2.19) were found to have a higher odds of patients experiencing MI compared against placebo, but there were no significant differences detected.

Comparison of coxibs against traditional NSAIDs

Coxibs and traditional non-selective NSAIDs were compared in 37 out of the 55 RCTs. Naproxen (18 trials), diclofenac (12 trials) and ibuprofen (6 trials) were the most commonly used NSAIDs; there were also four trials that compared two NSAIDs concurrently against coxibs.^{27–30} Data from 81 105 patients included in the 37 trials comparing coxibs against NSAIDs showed a significantly increased MI risk associated with coxibs across all 37 RCTs; the corresponding pooled OR was 1.45 (95%CI: 1.09, 1.93) (Figure 3). There was no evidence of significant heterogeneity in any of the pooled comparisons ($I^2 = 0.00–33.5\%$, p -value for heterogeneity = 0.16–1.00).

Subgroup analysis comparing coxibs against naproxen and other NSAIDs

Eighteen RCTs including 48 322 patients compared coxibs against naproxen. The pooled OR across the 18 trials indicated a significantly higher risk of MI associated with coxibs than naproxen (OR: 1.93; 95%CI: 1.22, 3.05). Table 2 presents the results of the pooled comparisons of individual coxibs against NSAIDs. Rofecoxib was associated with a five-fold higher rate of patients experiencing MI compared with naproxen (pooled OR: 5.39; 95%CI: 2.08, 14.02) but there were no significant differences in MI risk between any of the other coxibs compared against

Table 1. Summary characteristics of included trials

Name (year)	Disease	Duration (weeks)	Coxibs		Pla no.	NSAIDs	
			No.	Drug/dose		No.	Drugs
Pfizer, N49-96-02-023 (1998) ⁵⁰	RA	12	663	cel/200, 400, 800	221	218	nap
Pfizer, N49-97-02-071 (1998) ²⁹	OA or RA	12	366	cel/400	—	732	dic, ibu
Pfizer, N49-96-02-060 (1998) ⁵¹	OA	6	464	cel/100, 200	231	—	—
Bensen <i>et al.</i> (1999) ⁵²	OA	12	602	cel/100, 200, 400	203	198	nap
Emery <i>et al.</i> (1999) ⁵³	RA	24	326	cel/400	—	329	dic
Simon <i>et al.</i> (1999) ⁵⁴	RA	12	693	cel/200, 400, 800	231	225	nap
Goldstein <i>et al.</i> (2001) ⁵⁵	OA or RA	12	270	cel/400	—	267	nap
Kivitz <i>et al.</i> (2001) ⁵⁶	OA	12	636	cel/100, 200, 400	218	207	nap
Pfizer, SUCCESS-1 (2001) ³⁰	OA	12	8850	cel/100, 200	—	4424	dic, nap
Chan <i>et al.</i> (2002) ²⁰	OA	24	144	cel/400	—	143	dic
White <i>et al.</i> (2002) ²⁸	OA or RA	24	3987	cel/800	—	3981	dic, ibu
Pfizer, IQ5-97-02-001 (2004) ⁵⁷	MCI	52	285	cel/400	140	—	—
Pfizer, I49-01-02-217 (2004) ⁵⁸	CLBP	4	425	cel/200	—	421	lexo
Pfizer, A3191006 (2005) ⁵⁹	OA	52	458	cel/400, 800	—	485	dic
Levin B (2005) ³⁶	CA	156	933	cel/400	628	—	—
Solomon <i>et al.</i> (2005) ³⁷	CA	161	1356	cel/400, 800	679	—	—
Sheldon <i>et al.</i> (2005) ²²	CA	13	1169	cel/200; lum/100	382	—	—
Whelton <i>et al.</i> SUCCESS VII (2002) ¹⁹	OA	6	1092	cel/200; rof/25	—	—	—
Fleischmann <i>et al.</i> (2003) ²⁵	OA	13	1369	cel/200; lum/200, 400	231	—	—
Hawkey <i>et al.</i> (2004) ²³	OA	13	782	cel/200; lum/200, 400	—	260	ibu
Kivitz <i>et al.</i> Novartis 0110 (2004) ²¹	RA	13	677	cel/200; lum/400, 800	—	216	ibu
Tannenbaum <i>et al.</i> (2004) ²⁴	OA	13	1459	cel/200; lum/200, 400	243	—	—
Whelton <i>et al.</i> SUCCESS VI (2001) ¹⁸	OA	6	810	cel/200; rof/25	—	—	—
Matsumoto <i>et al.</i> (2002) ⁶⁰	RA	12	323	eto/90	323	170	nap
Merck, EDGE (2005) ⁶¹	OA	48	3593	eto/90	—	3518	dic
van der Heijde <i>et al.</i> stage 2 (2005) ⁶²	AS	46	249	eto/90, 120	—	125	nap
Scott <i>et al.</i> (2003) ⁶³	RA	4	79	lum/800, 1200	—	41	nap
Farkouh <i>et al.</i> (PN 0117) (2004) ⁴²	OA	52	4741	lum/400	—	4730	nap
Farkouh <i>et al.</i> (PN 2332) (2004) ⁴²	OA	52	4376	lum/400	—	4397	ibu
Geusens <i>et al.</i> (2004) ⁶⁴	RA	26	561	lum/200, 400	284	279	nap
Pavelka <i>et al.</i> (2004) ⁶⁵	RA	13	458	lum/200	465	228	nap
Beaulieu <i>et al.</i> (2005) ⁶⁶	RA	39	376	lum/200	—	271	nap
Villalba ML, Merck 034-10 (1998) ⁶⁷	OA	86	442	rof/12.5, 25	—	215	dic
Laine <i>et al.</i> (1999) ⁶⁸	OA	24	381	rof/25, 50	177	184	ibu
Villalba ML, VIGOR (2001) ⁶⁹	RA	48	4047	rof/50	—	4029	nap
Cannon <i>et al.</i> (2000) ⁷⁰	OA	48	516	rof/12.5, 50	—	268	dic
Hawkey <i>et al.</i> (2000) ⁷¹	OA	24	388	rof/25, 50	194	193	ibu
Saag <i>et al.</i> stage2 (2000) ⁷²	OA	52	463	rof/12.5, 25	—	230	dic
Villalba ML, Merck, 091 (2001) ⁶⁹	MCI	60	346	rof/25	346	—	—
Ehrlich <i>et al.</i> (2001) ⁷³	OA	6	527	rof/5, 12.5, 25	145	—	—
Geba <i>et al.</i> (2001) ⁷⁴	OA	6	390	rof/12.5	196	392	nab
Villalba ML, Merck, 126 (2001) ⁶⁹	MCI	60	381	rof/25	376	—	—
Truitt <i>et al.</i> (2001) ⁷⁵	OA	6	174	rof/12.5, 25	52	115	nab

Table 1. Summary characteristics of included trials

Name (year)	Disease	Duration (weeks)	Coxibs		NSAIDs	
			No.	Drug/dose	No.	Drugs
Katz <i>et al.</i> (2004) ⁷⁶	CLBP	4	462	rof/25, 50	228	—
Lisse <i>et al.</i> (2003) ⁷⁷	OA	12	2785	rof/25	—	nap
Kivitz <i>et al.</i> (2004) ⁷⁸	OA	6	424	rof/12.5	208	para
Bresalier <i>et al.</i> (2005) ⁴³	CA	156	1287	rof/25	1299	—
Thal <i>et al.</i> (2005) ⁷⁹	MCI	208	725	rof/25	732	—
Berenbaum <i>et al.</i> (2005) ²⁶	OA	13	307	rof/25; lum/400	204	—
Pfizer, I91-99-02-063 (2002) ⁸⁰	OA	26	520	val/10, 20	—	dic
Pfizer, N91-97-02-016 (2000) ⁸¹	RA	6	504	val/0.5, 1, 5, 10, 20	87	nap
Weaver <i>et al.</i> (2001) ⁸²	RA	12	654	val/10, 20, 40	220	nap
Bensen <i>et al.</i> (2002) ⁸³	RA	12	642	val/10, 20, 40	222	nap
Sikes <i>et al.</i> (2002) ²⁷	OA	12	423	val/10, 20	210	dic, ibu
Pavelka <i>et al.</i> (2003) ⁸⁴	RA	26	483	val/20, 40	—	dic

Note: No., number of patients; OA, osteoarthritis; RA, rheumatoid arthritis; AS, ankylosing spondylitis; CLBP, chronic lower back pain; MCI, mild cognitive impairment or Alzheimer's disease; CA, colon adenoma; coxib, selective COX-2 inhibitors; cel, celecoxib; rof, rofecoxib; eto, etoricoxib; val, valdecoxib; lum, lumiracoxib; Pla, placebo; NSAIDs, non-steroidal anti-inflammatory drugs; dic, diclofenac; ibu, ibuprofen; nap, naproxen; nab, nabumetone; para, paracetamol; lexo, lexaprofen; EDGE, Etoricoxib Diclofenac Gastrointestinal (Evaluation) study; SUCCESS, Successive Celecoxib Efficacy and Safety Study; VIGOR, Vioxx Gastrointestinal Outcomes Research Study.

naproxen. There was also no evidence of heterogeneity in any of the coxib subgroups analyses ($I^2 = 0.00\%$, p -value for heterogeneity = 0.69–0.99).

No significant differences in risk of MI were identified when we compared celecoxib, rofecoxib and etoricoxib against diclofenac based on data from nine RCTs, whereas valdecoxib (three RCTs, 2558 patients) was associated with a significantly lower risk of MI than diclofenac (pooled OR: 0.14, 95%CI: 0.03, 0.73). In the comparisons of celecoxib and lumiracoxib against ibuprofen, there was no significant difference of MI risk identified.

Direct comparisons between different coxibs

Two trials including 1902 patients compared the risk of MI between celecoxib and rofecoxib.^{18,19} We found no significant difference in the risk of MI between the two coxibs; the corresponding pooled OR was 0.97 (95%CI: 0.10, 9.35). Fixed-effect meta-analysis of five trials (5456 patients) that compared celecoxib against lumiracoxib found that there was also no significant difference in the risk of MI between these two coxibs,^{21–25} although lower rates of experiencing MI were associated with celecoxib (pooled OR: 0.90, 95%CI: 0.25, 3.27). For both pooled comparisons, there was no evidence of heterogeneity ($I^2 = 0\%$, $p = 0.35–1.00$).

DISCUSSION

Principal findings

This meta-analysis has found an increased risk of MI when comparing coxibs against placebo and non-selective NSAIDs based on evidence from available RCTs. Differences in the risk of MI were apparent when we compared individual coxibs against different NSAIDs; for example rofecoxib was found to have a significantly higher MI risk than naproxen, whilst valdecoxib had a significantly lower risk than diclofenac. No significant differences in MI risk were identified between individual coxibs, but these comparisons were based on limited data.

Myocardial infarction (MI) associated with coxibs

Previous epidemiological studies have also suggested that coxibs³¹ and certain non-selective NSAIDs³² are associated with increased risks of MI, and the risks with coxibs were dose-related^{31–33} rather than duration-related.^{33–35} Similarly, we found the MI risk associated with celecoxib significantly increased with

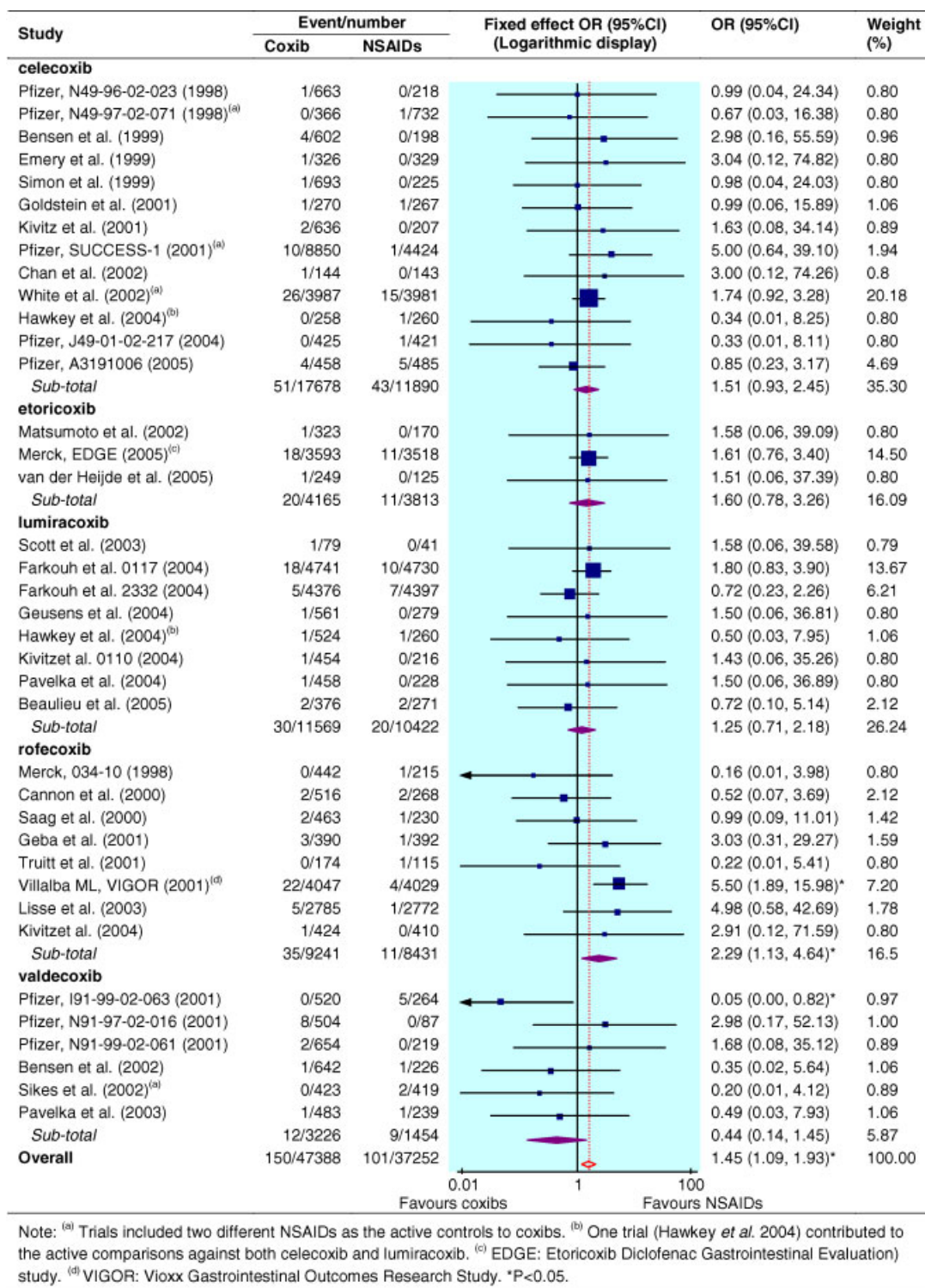


Figure 3. OR (95%CI) for risk of MI comparing coxibs against any NSAID

Table 2. Risk of myocardial infarction comparing coxibs against individual NSAIDs

Comparison	No. of trials	Pooled OR (95%CI)	Crude rate		Heterogeneity test	
			Coxib	NSAIDs	<i>p</i> -value	<i>I</i> ² (%)
Coxibs versus naproxen						
Celecoxib versus naproxen	6	1.26 (0.41, 3.90)	19/11714	2/2029	0.99	0.00
Etoricoxib versus naproxen	2	1.55 (0.16, 14.94)	2/572	0/295	0.98	0.00
Lumiracoxib versus naproxen	5	1.58 (0.81, 3.10)	23/6215	12/5549	0.95	0.00
Rofecoxib versus naproxen	2	5.39 (2.08, 14.02)*	27/6832	5/6801	0.94	0.00
Valdecoxib versus naproxen	3	0.99 (0.23, 4.28)	11/1800	2/532	0.69	0.00
<i>Overall</i>	18	1.93 (1.22, 3.05)*	82/27133	21/15206	0.96	0.00
Coxibs versus non-naproxen NSAIDs						
Celecoxib versus non-naproxen NSAIDs	8	1.50 (0.89, 2.54)	42/15037	23/10077	0.70	0.00
Etoricoxib versus non-naproxen NSAIDs	1	1.61 (0.76, 3.40)	18/3593	11/3518	—	—
Lumiracoxib versus non-naproxen NSAIDs	3	0.73 (0.27, 2.00)	7/5354	8/4873	0.89	0.00
Rofecoxib versus non-naproxen NSAIDs	5	0.71 (0.24, 2.14)	7/1985	6/1220	0.54	0.00
Valdecoxib versus non-naproxen NSAIDs	3	0.17 (0.03, 0.90)*	1/1426	8/922	0.50	0.00
<i>Overall</i>	20	1.16 (0.80, 1.66)	75/27395	56/20610	0.54	0.00
Coxibs versus diclofenac						
Celecoxib versus diclofenac	5	1.28 (0.71, 2.31)	42/13765	16/6463	0.62	0.00
Etoricoxib versus diclofenac	1	1.61 (0.76, 3.40)	18/3593	11/3518	—	—
Rofecoxib versus diclofenac	3	0.42 (0.11, 1.54)	4/1421	5/713	0.64	0.00
Valdecoxib versus diclofenac	3	0.14 (0.03, 0.73)*	1/1426	8/715	0.49	0.00
<i>Overall</i>	12	1.06 (0.70, 1.62)	65/20205	40/11409	0.22	22.70
Coxibs versus ibuprofen						
Celecoxib versus ibuprofen	3	2.16 (0.83, 5.61)	26/4611	6/2590	0.20	39.90
Lumiracoxib versus ibuprofen	3	0.73 (0.27, 2.00)	7/5354	8/4873	0.89	0.00
<i>Overall</i>	6	1.29 (0.65, 2.59)	33/9965	14/7463	0.32	14.50
Rofecoxib versus nabumetone	2	1.26 (0.20, 8.04)	3/564	2/507	0.19	0.00
Rofecoxib versus paracetamol	1	2.91 (0.12, 71.59)	1/424	0/410	—	—
Rofecoxib versus lexoprofen	1	0.33 (0.01, 8.11)	0/425	1/421	—	—

**p* < 0.05.

addition, other factors such as the individual patient's cardiovascular risk profile are also likely to influence differences in MI risk between different population groups.^{34,38,39}

Individual patient data (IPD) meta-analyses can provide the most comprehensive and reliable assessment of safety of licensed drugs based on existing RCTs.⁴⁰ Specific benefits of IPD meta-analysis include the ability to undertake survival and other time-to-event analyses and the possibility for examining hypotheses about differences in effects between different patient groups.⁴¹ Future research should explore the use of IPD meta-analyses in order to evaluate emerging safety concerns and the influences of other potential risk factors.

Strengths and limitations of this study

This meta-analysis builds on earlier reviews and includes updated data from several large-scale trials which were reported after the withdrawal of rofecoxib in September 2004.^{36,37,42–44} To avoid the risk of

publication bias, we comprehensively searched for RCTs across a wide range of databases. The heterogeneity test results also suggested that there was no evidence of heterogeneity between trials for any of the pooled comparisons undertaken.

The main challenges associated with this study were the relatively small number of events available for analysis and a lack of standardised reporting of adverse events in some of the retrieved RCTs. Problems in reporting of safety data in RCTs have previously been identified in other studies.^{45,46} Ioannidis⁴⁷ (2001) has suggested that the reporting of safety information in RCTs is largely neglected and inadequate. In our study, we found that the definitions of the composite outcome measures varied across studies, and hence we focused our analysis to investigate a specific outcome—the risk of MI. Of particular interest, reports concerning inconsistent reporting of serious cardiovascular events associated with coxibs in RCTs have been highlighted recently.^{7,48,49} In the future, efforts should be made to improve the reporting of adverse events in RCTs in order to facilitate the use of such data in proactively

monitoring the safety of new drugs through meta-analysis following licensing.

CONCLUSIONS

Coxibs are associated with increased pooled risks of MI compared against placebo and NSAIDs, however, it is important to take account of differences in MI risk between different NSAID comparisons. The increased risk of MI associated with celecoxib was found to be dose-related, but other patient-related risk factors are also likely to be important when considering the risk of MI associated with coxibs.

REFERENCES

- Breckenridge A, Woods K, Raine J. Monitoring the safety of licensed medicines. *Nat Rev Drug Discov* 2005; **4**(7): 541–543. DOI: 10.1038/nrd1778.
- Eisenberg RS. Learning the value of drugs—is rofecoxib a regulatory success story? *N Engl J Med* 2005; **352**(13): 1285–1287.
- Topol EJ. Failing the public health—rofecoxib, Merck, and the FDA. *N Engl J Med* 2004; **351**(17): 1707–1709.
- Velentgas P, West W, Cannuscio CC, Watson DJ, Walker AM. Cardiovascular risk of selective cyclooxygenase-2 inhibitors and other non-aspirin non-steroidal anti-inflammatory medications. *Pharmacoepidemiol Drug Saf* 2006; **15**(5): 360. DOI: 10.1002/pds.1192.
- Jones SC. Relative thromboembolic risks associated with COX-2 inhibitors. *Ann Pharmacother* 2005; **39**(7,8): 1249–1259. DOI: 10.1345/aph.1E654.
- Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *The Lancet* 2004; **364**(9450): 2021–2029. DOI: 10.1016/S0140-6736(04)17514-4.
- Caldwell B, Aldington S, Weatherall M, Shirlcliffe P, Beasley R. Risk of cardiovascular events and celecoxib: a systematic review and meta-analysis. *J R Soc Med* 2006; **99**(3): 132–140.
- White WB, Strand V, Roberts R, Whelton A. Effects of the cyclooxygenase-2 specific inhibitor valdecoxib versus nonsteroidal antiinflammatory agents and placebo on cardiovascular thrombotic events in patients with arthritis. *Am J Ther* 2004; **11**(4): 244–250.
- Matchaba P, Gitton X, Krammer G, *et al.* Cardiovascular safety of lumiracoxib: a meta-analysis of all randomized controlled trials \geq 1 week and up to 1 year in duration of patients with osteoarthritis and rheumatoid arthritis. *Clin Ther* 2005; **27**(8): 1196–1214.
- Aldington S, Shirlcliffe P, Weatherall M, Beasley R. Systematic review and meta-analysis of the risk of major cardiovascular events with etoricoxib therapy. *N Z Med J* 2005; **118**(1223): U1684.
- Aldington S, Shirlcliffe P, Weatherall M, Beasley R. Increased risk of cardiovascular events with parecoxib/valdecoxib: a systematic review and meta-analysis. *N Z Med J* 2005; **118**(1226): U1755.
- Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *Br Med J* 2006; **332**(7553): 1302–1308. DOI:10.1136.
- Pharmaceutical Research and Manufacturers of America. Clinical Study Results Database. 2002; <http://www.clinicalstudyresults.org>
- Jadad AR, Moore RA, Carroll D, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**(1): 1–12.
- Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *Br Med J* 1997; **315**(7121): 1533–1537.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**(11): 1539–1558. DOI: 10.1002/sim.1186.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J* 2003; **327**(7414): 557–560. DOI: 10.1136/bmj.327.7414.557.
- Whelton A, Fort JG, Puma JA, Normandin D, Bello AE, Verburg KM. Cyclooxygenase-2-specific inhibitors and cardiovascular function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. *Am J Ther* 2001; **8**(2): 85–95.
- Whelton A, White WB, Bello AE, Puma JA, Fort JG. Effects of celecoxib and rofecoxib on blood pressure and edema in patients $>$ or $=$ 65 years of age with systemic hypertension and osteoarthritis. *Am J Cardiol* 2002; **90**(9): 959–963.
- Chan FK, Hung LC, Suen BY, *et al.* Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. *N Engl J Med* 2002; **347**(26): 2104–2110.
- Kivitz AJ, Nayiager S, Schimansky T, Gimona A, Thurston HJ, Hawkey C. Reduced incidence of gastroduodenal ulcers associated with lumiracoxib compared with ibuprofen in patients with rheumatoid arthritis. *Aliment Pharmacol Ther* 2004; **19**(11): 1189–1198. DOI:10.1111/j.1365-2036.2004.01956.x.
- Sheldon E, Beaulieu A, Paster Z, Dutta D, Yu S, Sloan VS. Efficacy and tolerability of lumiracoxib in the treatment of osteoarthritis of the knee: a 13-week, randomized, double-blind comparison with celecoxib and placebo. *Clin Ther* 2005; **27**(1): 64–77.
- Hawkey CC, Svoboda P, Fiedorowicz-Fabrycy IF, *et al.* Gastro-duodenal safety and tolerability of lumiracoxib compared with Ibuprofen and celecoxib in patients with osteoarthritis. *J Rheumatol* 2004; **31**(9): 1804–1810.
- Tannenbaum H, Berenbaum F, Reginster JY, *et al.* Lumiracoxib is effective in the treatment of osteoarthritis of the knee: a 13 week, randomised, double blind study versus placebo and celecoxib. *Ann Rheum Dis* 2004; **63**(11): 1419–1426. DOI: 10.1136/ard.2003.015974.
- Fleischmann R, Sheldon E, Maldonado Cocco J. A prospective randomized 13-week study evaluating the efficacy of lumiracoxib in patients with osteoarthritis of the knee. *Ann Rheum Dis* 2003; **62**(Suppl 1): 266.
- Berenbaum F, Grifka J, Brown JP, *et al.* Efficacy of lumiracoxib in osteoarthritis: a review of nine studies. *J Int Med Res* 2005; **33**(1): 21–41.
- Sikes DH, Agrawal NM, Zhao WW, Kent JD, Recker DP, Verburg KM. Incidence of gastroduodenal ulcers associated with valdecoxib compared with that of ibuprofen and diclofenac in patients with osteoarthritis. *Eur J Gastroenterol Hepatol* 2002; **14**(10): 1101–1111.
- White WB, Faich G, Whelton A, *et al.* Comparison of thromboembolic events in patients treated with celecoxib, a cyclooxygenase-2 specific inhibitor, versus ibuprofen or diclofenac. *Am J Cardiol* 2002; **89**(4): 425–430.

29. Pfizer, Inc. Protocol N49-97-02-071: A multicenter, double-blind, parallel group study comparing the incidence of gastroduodenal ulcer associated with SC-58635 200 mg BID with that of diclofenac 75 mg BID and ibuprofen 800 mg TID, taken for 12 weeks in patients with osteoarthritis or rheumatoid arthritis. 1998; http://www.clinicalstudyresults.org/documents/company-study_79_4.pdf (Accessed December 2005).
30. Pfizer, Inc. Protocol I49-98-02-96: Successive Celecoxib Efficacy and Safety Studies in osteoarthritis (SUCCESS-1). 2001; http://www.clinicalstudyresults.org/documents/company-study_79_5.pdf (Accessed December 2005).
31. Andersohn F, Suissa S, Garbe E. Use of first- and second-generation Cyclooxygenase-2-selective nonsteroidal anti-inflammatory drugs and risk of acute myocardial infarction. *Circulation* 2006; **113**(16): 1950–1957. DOI: 10.1161/CIRCULATIONAHA.105.602425.
32. Hernandez-Diaz S, Varas-Lorenzo C, Garcia Rodriguez LA. Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction. *Basic Clin Pharmacol Toxicol* 2006; **98**(3): 266–274. DOI: 10.1111/j.1742-7843.2006.pto_302.x.
33. Helin-Salmivaara A, Virtanen A, Vesalainen R, et al. NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case-control study from Finland. *Eur Heart J* 2006; **27**(14): 1657–1663. DOI: 10.1093/eurheartj/ehl053.
34. Brophy JM. Celecoxib and cardiovascular risks. *Expert Opin Drug Saf* 2005; **4**(6): 1005–1015. DOI: 10.1517/14740338.4.6.1005.
35. Andersohn F, Schade R, Suissa S, Garbe E. Cyclooxygenase-2 selective nonsteroidal anti-inflammatory drugs and the risk of ischemic stroke. A nested case-control study. *Stroke* 2006; **37**(7): 1725–1730. DOI: 10.1161/01.STR.0000226642.55207.94.
36. Levin B. *Celecoxib in Adenoma Prevention - The PreSAP Trial*. FDA Advisory Committee on COX-2 Inhibitors and NSAIDs, February 16-18: 2005; http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4090S1_09_FDA-Levin_files/frame.htm#slide0714.htm (Accessed April 2005).
37. Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005; **352**(11): 1071–1080.
38. Gislason GH, Jacobsen S, Rasmussen JN, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. *Circulation* 2006; **113**(29): 1132906–1132913. DOI: 10.1161/CIRCULATIONAHA.106.616219.
39. Maillard M, Burnier M. Comparative cardiovascular safety of traditional nonsteroidal anti-inflammatory drugs. *Expert Opin Drug Saf* 2006; **5**(1): 83–94. DOI: 10.1517/14740338.5.1.83.
40. Simmonds MC, Higgins JP, Stewart LA, Tierney JF, Clarke MJ, Thompson SG. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. *Clin Trials* 2005; **2**(3): 209–217.
41. Clarke MJ, Stewart LA. Obtaining individual patient data from randomised controlled trials. In *Systematic Reviews in Health Care: Meta-Analysis in Context* (2nd edn), Egger M, Smith GD, Altman GD (eds). BMJ Publishing Group: London, 2001; 109–121.
42. Farkouh ME, Kirshner H, Harrington RA, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. *The Lancet* 2004; **364**(9435): 675–684. DOI: 10.1016/S0140-6736(04)16894-3.
43. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005; **352**(11): 1092–1102.
44. Merck Research Laboratories. FDA Advisory Committee Meeting background document on Etoricoxib. 2005; http://origin.www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B2_01_Merck-Etoricoxib.pdf (Accessed April 2005).
45. Ioannidis JP, Contopoulos-Ioannidis DG. Reporting of safety data from randomised trials. *The Lancet* 1998; **352**(9142): 1752–1753. DOI: 10.1016/S0140-6736(05)79825-1.
46. Mucklow JC. Reporting drug safety in clinical trials: getting the emphasis right. *The Lancet* 2001; **357**(9266): 1384.
47. Ioannidis JP, Lau J. Improving safety reporting from randomised trials. *Drug Saf* 2002; **25**(2): 77–84.
48. Tanne JH. Journal criticises Vioxx study for omitting three heart attacks. *Br Med J* 2005; **331**(7530): 1423. DOI: 10.1136/bmj.331.7530.1423.
49. Tanne JH. NEJM stands by its criticism of Vioxx study. *Br Med J* 2006; **332**(7540): 505-a. DOI: 10.1136/bmj.332.7540.505-a.
50. Pfizer, Inc. Protocol N49-96-02-023: A double-blind, placebo controlled, randomized comparison study of the efficacy and safety of SC-58635 100mg, 200 mg and 400 mg BID and naproxen 500 mg BID in treating the signs and symptoms of rheumatoid arthritis. 1998; http://www.clinicalstudyresults.org/documents/company-study_79_19.pdf (Accessed December 2005).
51. Pfizer, Inc. Protocol N49-96-02-060: A multicenter, double-blind, placebo controlled comparison study of the efficacy of SC-58635 200 mg QD versus SC-58635 100 mg BID in treating the signs and symptoms of osteoarthritis of the knee. 1998; http://www.clinicalstudyresults.org/documents/company-study_79_14.pdf (Accessed December 2005).
52. Bensen WG, Fiechtner JJ, McMillen JJ, et al. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. *Mayo Clin Proc* 1999; **74**(11): 1095–1105.
53. Emery P, Zeidler H, Kvien TK, et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. *The Lancet* 1999; **354**(9196): 2106–2111. DOI: 10.1016/S0140-6736(99)02332-6.
54. Simon LS, Weaver AL, Graham DY, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *J Am Med Assoc* 1999; **282**(20): 1921–1928.
55. Goldstein JL, Correa P, Zhao WW, et al. Reduced incidence of gastroduodenal ulcers with celecoxib, a novel cyclooxygenase-2 inhibitor, compared to naproxen in patients with arthritis. *Am J Gastroenterol* 2001; **96**(4): 1019–1027.
56. Kivitz AJ, Moskowitz RW, Woods E, et al. Comparative efficacy and safety of celecoxib and naproxen in the treatment of osteoarthritis of the hip. *J Int Med Res* 2001; **29**(6): 467–479.
57. Pfizer, Inc. Protocol IQ5-97-02-001: A double-blind, randomized, placebo-controlled, comparative study of celecoxib (SC-58635) for the inhibition of progression of Alzheimer's disease. 2004; http://www.clinicalstudyresults.org/documents/company-study_76_0.pdf (Accessed December 2005).
58. Pfizer, Inc. Protocol J49-01-02-217: A randomized, double-blind, multicenter, active controlled parallel group study to evaluate the efficacy and safety of celecoxib (YM177) 100 MG X2/D compared to loxoprofen 60 MG X3/D in patients with

- low back pain. 2004; http://www.clinicalstudyresults.org/documents/company-study_80_3.pdf (Accessed December 2005).
59. Pfizer, Inc. Protocol A3191006: A one-year, double blind, parallel group study to compare the tolerability of celecoxib 200 mg once daily versus diclofenac 50 mg twice daily in elderly patients with osteoarthritis of the hip or knees (coxarthrosis/gonarthrosis). 2005; http://www.clinicalstudyresults.org/documents/company-study_79_21.pdf (Accessed December 2005).
 60. Matsumoto AK, Melian A, Mandel DR, *et al.* A randomized, controlled, clinical trial of etoricoxib in the treatment of rheumatoid arthritis. *J Rheumatol* 2002; **29**(8): 1623–1630.
 61. Merck Research Laboratories. FDA Advisory Committee Meeting background information, ARCOXIA™ (Etoricoxib Tablets). 2005; http://origin.www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B2_01_Merck-Etoricoxib.pdf (Accessed May 2005).
 62. van der HD, Baraf HS, Ramos-Remus C, *et al.* Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study. *Arthritis Rheum* 2005; **52**(4): 1205–1215. DOI: 10.1002/art.20985.
 63. Scott G, Rordorf C, Milosavljev S. Multiple-dose lumiracoxib shows rapid absorption and COX-2 selectivity without accumulation in patients with rheumatoid arthritis. Springer, Berlin, Germany: *European Collaboration: Towards Drug Development and Rational Drug Therapy*; 2003; p. 124.
 64. Geusens P, Alten R, Rovensky J, *et al.* Efficacy, safety and tolerability of lumiracoxib in patients with rheumatoid arthritis. *Int J Clin Pract* 2004; **58**(11): 1033–1041. DOI: 10.1111/j.1368-5031.2004.00398.x.
 65. Pavelka K, Nayaiger S, Kivitz A. Efficacy and tolerability of lumiracoxib in the treatment of rheumatoid arthritis: a 13-week, randomized, double-blind study. *Ann Rheum Dis* 2004; **63**(Suppl 1): 280.
 66. Beaulieu A, Rovensky J, Philipp T. Lumiracoxib is effective in the long-term management of pain associated with rheumatoid arthritis. *Ann Rheum Dis* 2005; **64**(Suppl 3): 426.
 67. Villalba ML. NDA executive summary: Vioxx, excerpts from primary review of NDA 21-042- osteoarthritis. Food and Drug Administration; 1998; http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1_05_F-FDA-Tab-D-1.pdf (Accessed May 2005).
 68. Laine L, Harper S, Simon T, *et al.* A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. Rofecoxib Osteoarthritis Endoscopy Study Group. *Gastroenterology* 1999; **117**(4): 776–783.
 69. Villalba ML. Medical Officer Review: NDA 21-042 and NDA 21-052 (rofecoxib tablets and rofecoxib oral Solution). Food and Drug Administration; 2001; http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1_09_J-FDA-Tab-F-1.pdf (Accessed May 2005).
 70. Cannon GW, Caldwell JR, Holt P, *et al.* Rofecoxib, a specific inhibitor of cyclooxygenase 2, with clinical efficacy comparable with that of diclofenac sodium: results of a one-year, randomized, clinical trial in patients with osteoarthritis of the knee and hip. Rofecoxib Phase III Protocol 035 Study Group. *Arthritis Rheum* 2000; **43**(5): 978–987.
 71. Hawkey C, Laine L, Simon T, *et al.* Comparison of the effect of rofecoxib (a cyclooxygenase 2 inhibitor), ibuprofen, and placebo on the gastroduodenal mucosa of patients with osteoarthritis: a randomized, double-blind, placebo-controlled trial. The Rofecoxib Osteoarthritis Endoscopy Multinational Study Group. *Arthritis Rheum* 2000; **43**(2): 370–377.
 72. Saag K, van der HD, Fisher C, *et al.* Rofecoxib, a new cyclooxygenase 2 inhibitor, shows sustained efficacy, comparable with other nonsteroidal anti-inflammatory drugs: a 6-week and a 1-year trial in patients with osteoarthritis. Osteoarthritis Studies Group. *Arch Fam Med* 2000; **9**(10): 1124–1134.
 73. Ehrlich EW, Bolognese JA, Watson DJ, Kong SX. Effect of rofecoxib therapy on measures of health-related quality of life in patients with osteoarthritis. *Am J Manag Care* 2001; **7**(6): 609–616.
 74. Geba GP, Polis AB, Najarian DK, Dixon ME, Storms WW, Weaver AL. Onset of efficacy and patient assessment of clinical response in osteoarthritis (OA): comparison of rofecoxib to nubumetone. *J Am Geriatr Soc* 2001; **49**(4): S126.
 75. Truitt KE, Sperling RS, Ettinger WH, Jr, *et al.* A multicenter, randomized, controlled trial to evaluate the safety profile, tolerability, and efficacy of rofecoxib in advanced elderly patients with osteoarthritis. *Aging Clin Exp Res* 2001; **13**(2): 112–121.
 76. Katz N, Rodgers DB, Krupa D, Reicin A. Onset of pain relief with rofecoxib in chronic low back pain: results of two four-week, randomized, placebo-controlled trials. *Curr Med Res Opin* 2004; **20**(5): 651–658. DOI: 10.1185/030079904125003160.
 77. Lisse JR, Perlman M, Johansson G, *et al.* Gastrointestinal tolerability and effectiveness of rofecoxib versus naproxen in the treatment of osteoarthritis: a randomized, controlled trial. *Ann Intern Med* 2003; **139**(7): 539–546.
 78. Kivitz AJ, Greenwald MW, Cohen SB, *et al.* Efficacy and safety of rofecoxib 12.5 mg versus nabumetone 1,000 mg in patients with osteoarthritis of the knee: a randomized controlled trial. *J Am Geriatr Soc* 2004; **52**(5): 666–674.
 79. Thal LJ, Ferris SH, Kirby L, *et al.* A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. *Neuropsychopharmacology* 2005; **30**(6): 1204–1215. DOI: 10.1038/sj.npp.1300690.
 80. Pfizer, Inc. Protocol I91-99-02-063: A multicenter, double-blind, randomized parallel group comparison study of the efficacy and safety over 6 months of therapy, and joint X-ray changes over 12 months of therapy of valdecoxib 10 mg and 20 mg once daily and diclofenac 75 mg SR twice daily in treating the signs and symptoms of osteoarthritis of the knee and/or hip. 2002; http://www.clinicalstudyresults.org/documents/company-study_83_0.pdf (Accessed December 2005).
 81. Pfizer, Inc. Protocol No. N91-97-02-016: A Double-Blind, Placebo-Controlled, Randomized, Dose Ranging and Pilot Efficacy Study of SC-65872 in Treating the Signs and Symptoms of Rheumatoid Arthritis. 2000; http://www.clinicalstudyresults.org/documents/company-study_82_1.pdf (Accessed December 2005).
 82. Weaver A, Bensen W, Espinoza L, Riley W, Recker DP. Valdecoxib provides improved efficacy in patients with rheumatoid arthritis (RA) even when administered concomitantly to patients already taking DMARDs or low dose corticosteroids. *Arthritis Rheum* 2002; **46**(Suppl): S336.
 83. Bensen W, Weaver A, Espinoza L, *et al.* Efficacy and safety of valdecoxib in treating the signs and symptoms of rheumatoid arthritis: a randomized, controlled comparison with placebo and naproxen. *Rheumatology* 2002; **41**(9): 1008–1016.
 84. Pavelka K, Recker DP, Verburg KM. Valdecoxib is as effective as diclofenac in the management of rheumatoid arthritis with a lower incidence of gastroduodenal ulcers: results of a 26-week trial. *Rheumatology* 2003; **42**(10): 1207–1215.