Non-steroidal anti-inflammatory drugs and myocardial infarctions: comparative systematic review of evidence from observational studies and randomised controlled trials

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Objective: The comparative risk of myocardial infarction (MI) with cyclo-oxygenase-2-specific drugs and traditional non-steroidal anti-inflammatory drugs (NSAIDs) was determined.

Methods: The results of studies of a suitable size in colonic adenoma and arthritis—that had been published in English and from which crude data about MIs could be extracted—were evaluated. Medline, Embase and Cinahl (2000–2006) databases, as well as published bibliographies, were used as data sources. Systematic reviews examined MI risks in case-control and cohort studies, as well as in randomised controlled trials (RCTs).

Results: 14 case-control studies (74 673 MI patients, 368 968 controls) showed no significant association of NSAIDs with MI in a random-effects model (OR 1.17; 95% CI 0.99 to 1.37) and a small risk of MI in a fixed-effects model (OR 1.32; 95% CI 1.29 to 1.35). Sensitivity analyses showed higher risks of MI in large European studies involving matched controls. Six cohort studies (387 983 patient years, 1 120 812 control years) showed no significant risk of MI with NSAIDs (RR 1.03; 95% CI 1.00 to 1.07); the risk was higher with rofecoxib (RR 1.25; 95% CI 1.17 to 1.34) but not with any other NSAIDs. Four RCTs of NSAIDs in colonic adenoma (6000 patients) showed an increased risk of MI (RR 2.68; 95% CI 1.43 to 5.01). Fourteen RCTs in arthritis (45 425 patients) showed more MIs with cyclo-oxygenase-2-specific drugs (Peto OR 1.6; 95% CI 1.1 to 2.4), but fewer serious upper gastrointestinal events (Peto OR 0.40; 95% CI 0.31 to 0.53).

Conclusion: The overall risk of MI with NSAIDs and cyclo-oxygenase-2-specific drugs was small; rofecoxib showed the highest risk. There was an increased MI risk with cyclo-oxygenase-2-specific drugs compared with NSAIDs, but less serious upper gastrointestinal toxicity.

Emphasis on the adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs) has moved from their upper gastrointestinal (GI) to their cardiovascular toxicity.¹ This reflects widespread concern that cyclo-oxygenase-2-specific drugs in general, and rofecoxib in particular, increase the risk of myocardial infarction (MI) compared with traditional NSAIDs.² Like other cyclo-oxygenase-2-specific drugs, rofecoxib minimises serious GI toxicity whilst retaining anti-inflammatory efficacy. Although these benefits have been established experimentally in randomised controlled trials (RCTs), a large trial by Bombardier *et al*³ (the Vigor trial) showed an excess of MIs with rofecoxib. When a second RCT in colonic adenoma also reported an excess of MIs, rofecoxib was withdrawn worldwide.⁴ Since then, there has been substantial debate about the risk of MI with cyclo-oxygenase-2-specific drugs in particular and with NSAIDs in general.

In addition to the debate amongst clinicians and patients on the cardiovascular toxicity of NSAIDs, regulators have also taken different views. The US Food and Drug Administration (FDA)⁵ has concluded that there are significant cardiovascular risks with all NSAIDs, while the European Medicines Agency has concluded that cyclo-oxygenase-2-specific drugs present only specific risks.^{6,7} Any potential risk of MI needs to be placed in the context of the overall risks of serious events with NSAIDs, including upper GI events. The authors have therefore evaluated the available published evidence by undertaking systematic reviews of the risk of MI with cyclo-oxygenase-2-specific drugs and traditional NSAIDs in observational studies, and with cyclo-oxygenase-2-specific drugs in RCTs in a non-rheumatic disease (colonic adenoma) and in arthritis. Other published systematic reviews of MI in RCTs of cyclo-oxygenase-2-specific drugs were also examined, to ensure consistency in interpretation. Finally, the

risks of MI and serious upper GI events in RCTs of cyclo-oxygenase-2-specific drugs in arthritis were compared.

METHODS

Search strategies

Medline, Embase and Cinahl databases (January 2000 to June 2006) were searched to find both primary references and published systematic reviews. The authors also searched published bibliographies and the Cochrane Library. The following search terms were used: non-steroidal anti-inflammatory drugs, Cox-2 inhibitors, rofecoxib, celecoxib, lumiracoxib, valdecoxib, etoricoxib, ibuprofen, diclofenac, naproxen, myocardial infarction, ischaemic heart disease, colonic adenoma and colonic neoplasm. Both generic and proprietary drug names were used as search terms. The authors only considered studies published in English. Studies that contained insufficient information about cardiac adverse events to enable the assessment of the presence or absence of MIs, or from which raw numerical data about MIs could not be extracted, were excluded. Studies of meloxicam were also excluded due to the debate on its degree of cyclo-oxygenase-2 selectivity.^{8,9}

Types of study

Four relevant categories of peer-reviewed paper were identified:

- case-control and cohort studies that examined the association between the occurrence of MI and NSAIDs, and that had enrolled at least 100 patients;

Abbreviations: GI, gastrointestinal; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; RCT, randomised controlled trial; RR, relative risk

- RCTs of NSAIDs in patients with colonic adenoma, where at least 100 patients had been enrolled;
- RCTs comparing cyclo-oxygenase-2-specific drugs with traditional NSAIDs in arthritis, where at least 100 patients had been enrolled; these studies were also evaluated to assess the development of complicated upper GI ulcers, defined by Silverstein *et al*¹⁰ as perforation, obstruction or upper GI bleeding;
- published systematic reviews of RCTs of cyclo-oxygenase-2-specific drugs focusing on the occurrence of MIs.

Details of the case-control studies, cohort studies and RCTs evaluated are summarised in table 1.

Data extraction

Two researchers independently assessed studies for eligibility and extracted data on year of publication, population source, study design, study size, study setting, case definition, exposure definition, reference group, funding source, study period and outcomes. Where their initial conclusions did not agree (in the case of two studies), the researchers reviewed these studies together and reached a joint conclusion.

Statistics

The results from observational studies and RCTs were analysed using Review Manager V.4.2 (Nordic Cochrane Centre, Denmark). The relative risk (RR) of MI in RCTs and cohort studies, and the random- and fixed-effects odds ratios (ORs) in case-control studies were evaluated. In studies with few or no events the Peto OR was used.

To assess for heterogeneity in the observational studies, separate subgroup meta-analyses were carried out. Stratification was by sample size, country of study, source of funding, study design (matched versus unmatched) and definition of exposure for the case-control studies, and by type of study design for the cohort studies. In addition, a funnel plot was produced to look for publication bias in the case-control studies.

Quality

The quality of the RCTs was judged using the Jadad scoring instrument.¹¹ Non-RCT studies were judged using factors recommended by the Standards for the Reporting of Observational Studies in Epidemiology Group¹²; the authors scored six items (items 6–11) from the second version of the STROBE statement (STrengthening the Reporting of OBservational studies in Epidemiology) checklist.¹³

RESULTS

Systematic review of MI in observational studies of NSAID use

Out of a total of 806 studies found, 705 were retrieved that were in English and involved human subjects, and 24 potentially relevant studies were identified. Four of these were excluded because they evaluated only one or two drugs or did not have suitable comparable groups.^{14–17} Fourteen studies had case-control designs (including one retrospective cohort study analysed using a case-control approach) and six had cohort designs (tables 2 and 3).^{18–37}

The 14 case-control studies enrolled 74 673 MI patients who were either taking NSAIDs or had recent exposure to NSAIDs and 368 968 comparable controls.^{18–31} Twelve of these studies evaluated NSAID use from prescription data and two used telephone interviews. Overall, there was no significant association between NSAID use and MI (fig 1) using a random-effects model (OR 1.17; 95% CI 0.99 to 1.37), but there was a small risk of MI using a fixed-effects model (OR 1.32; 95% CI 1.29 to 1.35). Sensitivity analysis (tables 2 and 3) showed that a

number of factors influenced potential risk. ORs (fixed and random) were larger in studies that involved substantial numbers of patients, only enrolled European patients, had matched controls and did not involve industrial sponsorship. Evaluating the risks of individual commonly used drugs showed that the highest risks were with rofecoxib (OR 1.19 and 1.14, respectively, in random-effects and fixed-effects models). Other NSAIDs—celecoxib, diclofenac, ibuprofen and naproxen—showed either no increased or minimally increased risks in these models (tables 2 and 3). Two studies evaluated the effects of different rofecoxib doses using the random-effects model; high doses (>25 mg daily) showed a greater risk of MI (OR 2.9; 95% CI 1.2 to 7.0) than lower doses (OR 1.3; 95% CI 1.1 to 1.5).^{25 29}

The six cohort studies enrolled 529 090 patients (387 983 years of follow-up) currently taking NSAIDs and 604 871 controls (1 120 812 years of follow-up).^{32–37} They identified NSAID use from prescription data. There was no overall risk (fig 1) of developing MI whilst receiving NSAIDs (RR 1.03; 95% CI 1.00 to 1.07). Rofecoxib, but none of the other commonly used NSAIDs (tables 2 and 3), showed an increased risk of MI (RR 1.25; 95% CI 1.17 to 1.34). One study evaluated the effects of different rofecoxib doses³³; the relative risk of MI with high doses (>25 mg daily) was 1.6 (95% CI 0.9 to 2.8) and with lower doses was 1.1 (95% CI 0.8 to 1.4), but neither difference was significant.

Both meta-analyses showed significant heterogeneity (case-control studies, χ^2 622, df 13, $p < 0.001$; cohort studies, χ^2 63, df 5, $p < 0.001$). In the case-control studies, subgroup analysis suggested that country of study, sample size and definition of NSAID exposure (prescription data versus telephone interview) all contributed to the heterogeneity, while funding source did not. A funnel plot showed some evidence of publication bias, and there is evidence for an over-reporting of small negative studies (fig 2). In the cohort studies, removing one study whose design was significantly different (case-control study analysed as a cohort study) reduced the heterogeneity considerably (χ^2 27, df 4, $p < 0.001$).³⁵ However, with both types of study, despite subgroup stratification, there was still significant unexplained residual heterogeneity.

Systematic review of MI in RCTs of NSAIDs in colonic adenoma

Out of a total of 220 studies found in colonic adenoma, 167 that were published in English and involved human subjects were retrieved, and 26 were identified as potentially relevant. Only four of these were large placebo-controlled RCTs of NSAIDs in colonic adenoma^{4 38–40}; we specifically omitted the low-dose aspirin group (82 mg) used in one of these trials from our review, as this dose is never used for its anti-inflammatory effects.³⁸ The RCTs in these studies involved aspirin, rofecoxib and celecoxib, with half the celecoxib-treated patients taking a dose higher than that recommended in routine practice (800 mg daily). These studies enrolled 3332 cases and 2668 controls; 44 cases and 13 controls experienced an MI. As fig 3 shows, the risk of MI was increased for all three NSAIDs studied (RR 2.68; 95% CI 1.43 to 5.01).

Systematic review of MI in RCTs of NSAIDs in arthritis

Seven relevant published systematic reviews in arthritis reporting cardiovascular adverse reactions with celecoxib (three reviews), rofecoxib (two reviews), lumiracoxib (one review), and all cyclo-oxygenase-2-specific drugs and traditional NSAIDs (one review) were identified.^{1 41–46} We excluded four systematic reviews that did not focus on MIs.^{47–50}

The four most recently published systematic reviews^{1 43–45} that focused on MI summarised 138 trials involving 145 373

Table 1 Details of the studies included in the systematic reviews

Study (year)	Patient source	Subject age (years)	Design	Number of subjects	Country	Funding	Entry period	Quality*
<i>Case-control studies</i>								
Garcia Rodriguez <i>et al</i> (2000) ¹⁸	GP database	50–74	Case-control	1013 cases, 5000 controls	UK	Novartis	1991–5	5
Rahme <i>et al</i> (2002) ¹⁹	Two healthcare systems	≥65	Matched case-control	4163 cases, 14 160 controls	Canada	Merck	1988–94	5
Schlienger <i>et al</i> (2002) ²⁰	GP database	≥75	Matched case-control	3319 cases, 13 139 controls	UK	Unstated	1992–7	5
Solomon <i>et al</i> (2002) ²¹	Drug benefits programmes	–	Case-control	4425 cases, 17 700 controls	USA	NIA	1991–5	5
Garcia Rodriguez <i>et al</i> (2004) ²²	GP database	50–84	Cohort as case-control	4975 cases, 20 000 controls	UK	Pharmacia	1997–2000	5
Kimmel <i>et al</i> (2004) ²³	Hospital admissions	40–75	Case-control	1055 cases, 4153 controls	USA	NIH, Pharmacia	1998–2001	5
Fischer <i>et al</i> (2005) ²⁴	GP database	≤89	Matched case-control	8688 cases, 33 923 controls	UK	Swiss National Science Foundation	1995–2001	4
Graham <i>et al</i> (2005) ²⁵	Care organisation registrants	18–84	Matched case-control	8143 cases, 31 496 controls	USA	Kaiser Permanente/FDA	1999–2001	6
Hippisley-Cox <i>et al</i> (2005) ²⁶	GP database	–	Matched case-control	9218 cases, 86 349 controls	UK	Not specified	2000–4	6
Johnsen <i>et al</i> (2005) ²⁷	Hospital databases	≥20	Matched case-control	10 280 cases, 102 797 controls	Denmark	WDRFHS, IEI	2000–3	5
Kimmel <i>et al</i> (2005) ²⁸	Attending hospitals	40–75	Case-control	1718 cases, 6800 controls	USA	NIH, Searle, Merck	1998–2002	6
Levesque <i>et al</i> (2005) ²⁹	Healthcare databases	≥66	Cohort as case-control	2844 cases, 56 880 controls	Canada	CIHR	1999–2002	5
Andersohn <i>et al</i> (2006) ³⁰	GP database	≥40	Cohort as case-control	3643 cases, 13 918 controls	UK	CFI, CIHR, Schering AG	2000–4	5
Helin-Salmivaara <i>et al</i> (2006) ³¹	Healthcare database	–	Case-control	33 309 cases, 138 949 controls	Finland	–	2000–3	5
<i>Cohort studies</i>								
Ray <i>et al</i> (2002) ³²	Registered with Medicaid programme	50–84	Retrospective cohort	181 441 users, 181 441 non-users	USA	AHRQ, FDA	1987–98	4
Ray <i>et al</i> (2002) ³³	Registered with Medicaid programme	50–84	Retrospective cohort	175 860 users, 202 916 non-users	USA	AHRQ, USPHS, FDA	1999–2001	4
Mamdani <i>et al</i> (2003) ³⁴	Healthcare database	≥65	Retrospective cohort	66 964 users, 100 000 non-users	Canada	CIHR	1998–2001	4
Patel and Goldberg (2004) ³⁵	Medical centre database	–	Case-control as cohort	3859 users, 52 139 non-users	USA	Not specified	1990–2000	4
Chan <i>et al</i> (2006) ³⁶	Nurses' Health Study	44–69	Prospective cohort	26 128 users, 44 843 controls	USA	NIH	1990–2002	5
Solomon <i>et al</i> (2006) ³⁷	Registered with Medicaid/drug benefit programmes	–	Retrospective cohort	74 838 users, 23 532 controls	USA	Pfizer, NIH, AF, EAOI	1999–2003	5
<i>RCTs in colonic adenoma</i>								
Baron <i>et al</i> (2003) ³⁸	Previous colorectal adenoma	21–80	RCT	749 aspirin (372 on 325 mg once daily), 372 placebo	USA	NIH	1994–8	4
Sandler <i>et al</i> (2003) ⁴⁰	Previous colorectal cancer	30–80	RCT	317 aspirin (325 mg once daily), 318 placebo	USA	NIH, NCI	1993–2000	4
Solomon <i>et al</i> (2005) ³⁹	Previous colorectal adenoma	32–88	RCT	1356 celecoxib (200/400 mg twice daily), 679 placebo	Multinational	NCI, Pfizer	1999–2002	4
Bresalier <i>et al</i> (2005) ⁴	Previous colorectal adenoma	≥40	RCT	1287 rofecoxib (25 mg once daily), 1299 placebo	Multinational	Merck	2000–1	5
<i>RCTs in arthritis</i>								
Bombardier <i>et al</i> (2000) ³	Patients with rheumatoid arthritis	≥40	RCT	4047 rofecoxib (50 mg once daily), 4029 naproxen (500 mg twice daily)	Multinational	Merck	1999	3
Cannon <i>et al</i> (2000) ⁸⁷	Patients with osteoarthritis	≥40	RCT	516 rofecoxib (12.5/25 mg once daily), 268 diclofenac (150 mg once daily)	USA	Merck	1996–7	4
Collantes <i>et al</i> (2002) ⁸⁸	Patients with rheumatoid arthritis	–	RCT	353 etoricoxib (90 mg/day), 181 naproxen (1000 mg/day), 357 placebo	Multinational	Merck	1999–2000	3
Dougados <i>et al</i> (2001) ⁸⁹	Patients with ankylosing spondylitis	–	RCT	80 celecoxib (100 mg twice daily), 90 ketoprofen (100 mg twice daily), 76 placebo	France	Searle	Not stated	3
Farkouh <i>et al</i> (2004) ⁹⁰	Patients with osteoarthritis	≥50	RCT	9156 lumiracoxib (400 mg once daily), 4415 ibuprofen (800 mg three times daily), 4754 naproxen (500 mg twice daily)	Multinational	Novartis	Not stated	5
Geusens <i>et al</i> (2002) ⁹¹	Patients with rheumatoid arthritis	–	RCT	592 rofecoxib (25/50 mg once daily), 142 naproxen (100 mg once daily), 289 placebo	Multinational	Merck	Not stated	3
Kivitz <i>et al</i> (2004) ⁹²	Patients with rheumatoid arthritis	≥40	RCT	424 rofecoxib (12.5 mg once daily), 410 nabumetone (1000 mg once daily), 208 placebo	USA	Merck	Not stated	5
Lisse <i>et al</i> (2003) ⁹³	Patients with osteoarthritis	≥40	RCT	2785 rofecoxib (25 mg once daily), 2772 naproxen (500 mg twice daily)	USA	Merck	Not stated	5
Matsumoto <i>et al</i> (2002) ⁹⁴	Patients with rheumatoid arthritis	–	RCT	323 etoricoxib (90 mg once daily), 170 naproxen (500 mg twice daily), 323 placebo	USA	Merck	Not stated	3
McKenna <i>et al</i> (2001) ⁹⁵	Patients with osteoarthritis	–	RCT	201 celecoxib (100 mg twice daily), 199 diclofenac (50 mg three times daily), 200 placebo	USA	Pharmacia	Not stated	2
Saag <i>et al</i> (2000) ⁹⁶	Patients with osteoarthritis	≥40	RCT	463 rofecoxib (12.5/25 mg once daily), 230 diclofenac (150 mg once daily)	USA	Merck	Not stated	5

Table 1 Continued

Study (year)	Patient source	Subject age (years)	Design	Number of subjects	Country	Funding	Entry period	Quality*
Silverstein <i>et al</i> (2000) ¹⁰	Patients with osteoarthritis or rheumatoid arthritis	–	RCT	3987 celecoxib, 1985 ibuprofen, 1996 diclofenac	USA	Searle	1998–2000	5
Weisenhutter <i>et al</i> (2005) ¹⁷	Patients with osteoarthritis	40–89	RCT	214 etoricoxib (30 mg once daily), 210 ibuprofen (2400 mg once daily), 104 placebo	USA	Merck	2003	3
Zacher <i>et al</i> (2003) ⁷⁸	Patients with osteoarthritis	≥40	RCT	256 etoricoxib (60 mg once daily), 260 diclofenac	Multinational	Merck	Not stated	4

*The quality of a study was judged out of 6 for epidemiological studies using the STROBE Statement (STrengthening the Reporting of OBservational studies in Epidemiology) checklist and out of 5 for RCTs using Jadad scores.
AHRQ, Agency For Healthcare Research and Quality; AF, Arthritis Foundation; CFI, Canadian Foundation for Innovation; CIHR, Canadian Institutes of Health Research; EAOI, Engalitcheff Arthritis Outcomes Initiative; FDA, Food and Drug Administration; IEI, International Epidemiology Institute; NCI, National Cancer Institute; NIA, National Institute on Ageing; NIH, National Institutes of Health; USPHS, United States Public Health Service; WDRFHS, Western Danish Research Forum For Health Sciences.

patients (table 4). All reported small increases in the risk of MI with cyclo-oxygenase-2-specific drugs. The highest risk was with rofecoxib (RR 2.2; 95% CI 1.2 to 4.0) and this risk was most marked at high doses (RR 2.8; 95% CI 1.2 to 6.4). An additional systematic review specifically compared celecoxib with placebo and other comparators in six RCTs enrolling 12 780 patients; it found an increased risk of MI with celecoxib (OR 1.88; 95% CI 1.15 to 3.08). These systematic reviews did not specifically compare the risk of MI with the risk of serious upper GI events.

Comparison of MI with serious upper GI events in RCTs of cyclo-oxygenase-2-specific drugs

Out of a total of 452 studies found, 188 were retrieved that were in English and involved human subjects; of these, 50 RCTs were identified that reported comparisons of cyclo-oxygenase-2-specific drugs with traditional NSAIDs. Thirty-six RCTs were excluded as they gave insufficient information about the

occurrence of MIs.^{51–86} The remaining 14 RCTs allowed comparisons of MI with serious upper GI adverse events.^{3 10 87–98} These trials enrolled 45 425 patients into active treatment groups receiving either a cyclo-oxygenase-2-specific drug or a traditional NSAID; they reported 97 MIs. Three trials used double the highest-recommended long-term doses of cyclo-oxygenase-2-specific drugs.^{3 10 90} We also took into account recently published additional data about the number of MIs in the Vigor trial.⁹⁹ There was a significant increase in the number of MIs with cyclo-oxygenase-2-specific drugs (Peto OR 1.6; 95% CI 1.1 to 2.4), as shown in table 5. This increase was mainly due to the results from a single trial, the Vigor trial that compared rofecoxib with naproxen.³

These trials also resulted in 216 serious upper GI events and cyclo-oxygenase-2-specific drugs decreased the risk of serious upper GI events (Peto OR 0.40; 95% CI 0.31 to 0.53). Complicated upper GI events occurred in 61 patients given cyclo-oxygenase-2-specific drugs and 155 patients given tradi-

Table 2 Case-control studies of myocardial infarction in patients receiving non-steroidal anti-inflammatory drugs (NSAIDs)

Exposure		Number of studies	Number of participants	Random-effects OR (95% CI)	Fixed-effects OR (95% CI)
All NSAIDs	All studies	14	443 641	1.17 (0.99 to 1.37)	1.32 (1.29 to 1.35)
	Large studies (>10 000 controls)	11	426 232	1.34 (1.18 to 1.51)	1.40 (1.37 to 1.43)
	Small studies (<10 000 controls)	3	17 409	0.70 (0.39 to 1.27)	0.61 (0.56 to 0.67)
	European	8	326 471	1.41 (1.25 to 1.59)	1.50 (1.46 to 1.55)
	North American	6	117 170	0.91 (0.66 to 1.24)	1.02 (0.98 to 1.06)
	Matched controls	6	231 922	1.40 (1.17 to 1.68)	1.38 (1.33 to 1.42)
	Unmatched controls	8	211 719	1.01 (0.73 to 1.36)	1.26 (1.22 to 1.30)
	Industrial support	6	64 512	0.98 (0.66 to 1.43)	1.05 (1.00 to 1.10)
	No industrial support	8	379 129	1.33 (1.14 to 1.55)	1.41 (1.37 to 1.45)
	Specific NSAIDs	11	384 324	1.03 (0.83 to 1.29)	1.06 (1.00 to 1.13)
Specific NSAIDs	Naproxen	8	286 089	1.08 (0.80 to 1.46)	1.14 (1.09 to 1.19)
	Ibuprofen	7	260 791	1.12 (0.68 to 1.87)	1.07 (1.01 to 1.12)
	Celecoxib	7	319 841	1.01 (0.73 to 1.39)	1.02 (0.94 to 1.10)
	Rofecoxib	7	203 487	1.19 (0.70 to 2.01)	1.14 (1.05 to 1.24)

Table 3 Cohort studies of myocardial infarction (MI) in patients receiving non-steroidal anti-inflammatory drugs (NSAIDs)

Exposure		Number of studies	Patient years	Number of MI events	RR (95% CI)
All NSAIDs	All studies	6	1 508 795	15 966	1.03 (1.00 to 1.07)
	Large studies (>10 000 users)	5	1 491 415	15 144	1.06 (1.02 to 1.10)
Specific NSAIDs	Ibuprofen	3	552 150	8969	0.90 (0.82 to 0.97)
	Naproxen	4	571 679	9483	0.96 (0.90 to 1.03)
	Celecoxib	3	330 651	6842	1.06 (1.00 to 1.13)
	Rofecoxib	3	322 443	6389	1.25 (1.17 to 1.34)

Figure 1 Analysis of 14 case-control and six cohort studies of myocardial infarction in users and non-users of non-steroidal anti-inflammatory drugs. n, events; N, subjects.

tional NSAIDs. In contrast, MIs occurred in 61 patients given cyclo-oxygenase-2-specific drugs and 36 patients given traditional NSAIDs. Consequently, reductions in complicated upper GI events with cyclo-oxygenase-2-specific drugs occurred at the same time as an increase in MIs.

DISCUSSION

The overall risk of MI does not appear to be substantially increased with standard doses of most traditional NSAIDs and most cyclo-oxygenase-2-specific drugs. Rofecoxib consistently showed a significant increase in the risk of MI in all types of study. Some other cyclo-oxygenase-2-specific drugs and some

Figure 2 Funnel plot for 14 case-control studies, plotting standard errors against odds ratios (ORs) (fixed). SE, standard error.

Table 4 Summary of systematic reviews of myocardial infarction (MI) with cyclo-oxygenase-2-specific drugs

	Number of trials	Number of subjects	RR versus traditional NSAIDs (95% CI)	RR versus placebo (95% CI)
Celecoxib ⁴³	30	38 499	1.4 (0.9 to 2.2)	N/A*
Rofecoxib ¹	18	21 432	2.2 (1.2 to 4.0)	1.0 (0.3 to 3.1)
Lumiracoxib ⁴⁴	22	34 668	1.3 (0.8 to 2.1)	1.3 (0.3 to 6.6)
All cyclo-oxygenase-2-specific drugs ⁴⁵	138	145 373	1.5 (1.2 to 2.0)	1.9 (1.3 to 2.6)

*Actual event rates small (eight events) and therefore result did not reach statistical significance.

Table 5 Comparison of the risks of myocardial infarction (MI) and complicated ulcers in RCTs of cyclo-oxygenase-2-specific drugs					
Trial	Number of subjects	Number of MIs	Number of complicated upper GI events	MIs: Peto OR (95% CI)	Serious GI events (complicated ulcers): Peto OR (95% CI)
All cyclo-oxygenase-2-specific drugs	45 425	97	216	1.62 (1.09 to 2.42)	0.40 (0.31 to 0.53)
Rofecoxib	16 678	36	69	2.81 (1.46 to 5.44)	0.36 (0.22 to 0.58)
Celecoxib	8536	21	35	0.91 (0.39 to 2.14)	0.60 (0.31 to 1.16)
Lumiracoxib	18 244	40	112	1.35 (0.73 to 2.51)	0.38 (0.26 to 0.55)

GI, gastrointestinal.

traditional NSAIDs showed small increases in the risk of an MI in certain types of study, particularly in case-control studies analysed using a fixed-effects OR model. This analysis includes all types of peer-reviewed evidence, ranging from observational studies of NSAID use in MI patients to RCTs in colonic adenoma and an overview of NSAID RCTs in arthritis. It compares MI and GI risks in RCTs of NSAIDs. It is also independent of pharmaceutical companies and government agencies.

The most definitive evidence that NSAIDs increase the risk of MI comes from RCTs in patients with colonic adenoma who, in comparison with patients with rheumatoid arthritis, do not have a specific pre-existing cardiovascular risk. However, as the number of these trials is small, caution is required in generalising their findings. One RCT involved a supratherapeutic dose of celecoxib (800 mg daily) and may not be relevant to patients using standard doses. The apparent risk with aspirin is based on limited evidence; one RCT on aspirin that was evaluated showed a high RR of 5.0 (95% CI 0.6 to 43.5) for MI, but the study's small size means that this risk is not significant.³⁸ However, in support of the view that anti-inflammatory doses of aspirin may increase serious vascular side-effects, the combined frequency of MI and stroke with 323 mg aspirin was significantly increased in this trial (10 events with aspirin, one event with placebo; RR 10.0 (95% CI 1.3 to 77.7)). These findings must be set against the negative effects of low-dose aspirin in the same study (omitted from the formal systematic review), which suggests that dosing may be of critical importance.

Although RCTs in arthritis comparing cyclo-oxygenase-2-specific drugs with traditional NSAIDs show an excess of MIs, this finding is heavily influenced by a single RCT of rofecoxib: the Vigor trial.³ Not only did this trial exclusively enrol patients with rheumatoid arthritis, who have an underlying increased frequency of MI, but it also compared double the recommended dose of rofecoxib with traditional doses of naproxen.¹⁰⁰ Its relevance to routine practice is therefore uncertain. The data about MI risks from traditional NSAIDs are weak. RCTs

performed before 2000 did not routinely report MIs and almost all these studies were of a relatively small size and short duration. Even a 5-year RCT of traditional NSAIDs that enrolled 802 patients with osteoarthritis did not specifically report MIs, although there were more cardiovascular adverse events with indomethacin (12/202 (6%) cases) than with placebo (8/303 (3%) cases).¹⁰¹ The dearth of data on MI before 2000 makes it impractical to assess cardiac risks in these earlier RCTs.

We found that some case-control studies showed a small overall increase in the risk of MI, particularly with rofecoxib; however, cohort studies indicated no overall added risk. A number of factors—including small study size, selection of potentially inappropriate controls and the population studied—influenced the assessment of risk. A number of confounding factors may also affect the results in these observational studies. Patients given different NSAIDs may have different underlying MI risks; for example, cyclo-oxygenase-2-specific drugs were recommended for patients over 65 years of age, who often have underlying MI risks, and case-control studies could therefore overestimate their MI risks. We did not correct for variations in risk factors because individual studies require different types of correction; however, the counter-arguments in favour of such correction are acknowledged.¹⁰²

Another confounding factor, confounding by indication, seems more important and cannot be overcome by corrections. It is exemplified by a Danish mortality study with paracetamol, which reported a standardised mortality rate for MI of 1.6 in 50 000 patients prescribed paracetamol.¹⁰³ The most likely explanation for this relationship is that patients who are unwell with conditions such as ischaemic heart disease often take a readily available symptomatic remedy such as paracetamol. This is an example of confounding by indication, and such confounding may explain some or all of the association of NSAIDs with MIs in observational studies.

Furthermore, many reviews use not only published data but also material provided by pharmaceutical companies or obtained from regulatory bodies, such as the FDA, for the sake

Figure 3 Analysis of myocardial infarction in randomised controlled trials of non-steroidal anti-inflammatory drugs in colonic adenoma. n, events; N, subjects.

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of completeness. However, we only evaluated data published in peer-reviewed journals because we believe that such papers meet a guaranteed standard of reporting that is less prone to idiosyncratic variability and maintains independence.

Given the importance of cardiovascular safety with NSAIDs, it is unsurprising that several groups have reported systematic analyses of RCTs^{41–45} and observational studies.¹⁰⁴ These studies have evaluated different data based on varying search and selection strategies. However, their main conclusions mirror our own: a definite risk with rofecoxib, a possible risk with diclofenac, and small or nonexistent risks with other cyclo-oxygenase-2-specific drugs and traditional NSAIDs. The interpretation of the findings varies between reviews, reflecting the different values of individual authors when faced with complex data. Interestingly, although it was published after the search period of our review, the Medal trial—which compared etoricoxib with diclofenac in over 34 000 patients—found no difference in the risk of MI between these two drugs.¹⁰⁵ The interpretation of this result depends on the assessment of risk with diclofenac, which the results of our review suggest is above that with some other traditional NSAIDs.

Cyclo-oxygenase-2-specific drugs were developed to meet the need for effective NSAIDs with improved GI safety. In retrospect, this aim was incomplete; the key need is improved overall safety. Falling GI risks with NSAIDs, reflecting the use of reduced doses of traditional NSAIDs and the co-prescribing of proton-pump inhibitors, emphasise the need to evaluate overall safety.¹⁰⁶ Rofecoxib reduced serious GI toxicity but increased the risk of MI, giving it a different side-effect profile to traditional NSAIDs. The increased risks of MIs with rofecoxib together with its improved GI safety ensured that overall it was neither more nor less safe than conventional NSAIDs. Part of the concern about rofecoxib^{107–108} reflects the representation of its relative safety.^{109–110} In this context, although reports of cardiac risks with cyclo-oxygenase-2-specific drugs imply that naproxen is a safe NSAID, a study of 18 424 deaths in individuals who were prescribed NSAIDs found that mortality was highest with naproxen (2.7 times the mortality with nabumetone) and that it was the least safe of four traditional NSAIDs.¹¹¹

Taken as a whole, the available evidence suggests that the risks of MI with NSAIDs other than rofecoxib are not large, especially when compared with preventable MI risk factors such as smoking.¹¹² The risks of most side-effects of NSAIDs are greatest when high doses are given for prolonged periods to elderly patients and such an approach should be avoided. The multiplicity of cardiovascular side-effects with NSAIDs—particularly hypertension and fluid retention—mean that caution should also be exercised when considering the prescription of NSAIDs for patients with high cardiovascular risk. However, for some patients with severe arthritis there may be no realistic alternative and they will need access to effective treatment with information about its risks and benefits. Giving patients informed choice about risks and being involved in taking decisions about therapy is supported by recent regulatory guidance.¹¹³ Finally, economic and decision analyses do not favour cyclo-oxygenase-2-specific drugs in the majority of cases, although they recognise that some patients benefit from these drugs.^{114–115}

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