

Cardiovascular Risk and Inhibition of Cyclooxygenase

A Systematic Review of the Observational Studies of Selective and Nonselective Inhibitors of Cyclooxygenase 2

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IN THE LAST 5 YEARS, INTEREST IN THE cardiovascular effects of the relatively selective inhibitors of cyclooxygenase 2 (COX-2) has been intense. In October 2004, rofecoxib was withdrawn from world markets after a randomized placebo-controlled trial found that in doses of 25 mg/d, it increased rates of cardiovascular events in patients with colorectal polyps.¹ The results were confirmed by several large pharmacoepidemiological studies.²⁻⁴ Celecoxib continues to be widely used, despite meta-analyses of randomized controlled trials showing an increased risk of myocardial infarction.^{5,6}

Attention has turned to the cardiovascular safety of the older nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). These agents are used extensively and some are available in many countries without prescription. NSAIDs reversibly block both isoforms of cyclooxygenase but vary in their degree of selectivity.⁷ In one trial, it was suggested that the apparent excess cardiovascular risk with rofecoxib may be explained by a "cardioprotective" effect of the comparator drug, naproxen.⁸ However, the results of another trial suggested that naproxen may increase the

Context Evidence that rofecoxib increases the risk of myocardial infarction has led to scrutiny of other nonsteroidal anti-inflammatory drugs (NSAIDs). Regulatory agencies have provided variable advice regarding the cardiovascular risks with older nonselective NSAIDs.

Objective To undertake a systematic review and meta-analysis of controlled observational studies to compare the risks of serious cardiovascular events with individual NSAIDs and cyclooxygenase 2 inhibitors.

Data Sources Searches were conducted of electronic databases (1985-2006), scientific meeting proceedings, epidemiological research Web sites, and bibliographies of eligible studies.

Study Selection Eligible studies were of case-control or cohort design, reported on cardiovascular events (predominantly myocardial infarction) with cyclooxygenase 2 inhibitor, NSAID use, or both with nonuse/remote use of the drugs as the reference exposure. Of 7086 potentially eligible titles, 17 case-control and 6 cohort studies were included. Thirteen studies reported on cyclooxygenase 2 inhibitors, 23 on NSAIDs, and 13 on both groups of drugs.

Data Extraction Two people independently extracted data and assessed study quality with disagreements resolved by consensus.

Data Synthesis Data were combined using a random-effects model. A dose-related risk was evident with rofecoxib, summary relative risk with 25 mg/d or less, 1.33 (95% confidence interval [CI], 1.00-1.79) and 2.19 (95% CI, 1.64-2.91) with more than 25 mg/d. The risk was elevated during the first month of treatment. Celecoxib was not associated with an elevated risk of vascular occlusion, summary relative risk 1.06 (95% CI, 0.91-1.23). Among older nonselective drugs, diclofenac had the highest risk with a summary relative risk of 1.40 (95% CI, 1.16-1.70). The other drugs had summary relative risks close to 1: naproxen, 0.97 (95% CI, 0.87-1.07); piroxicam, 1.06 (95% CI, 0.70-1.59); and ibuprofen, 1.07 (95% CI, 0.97-1.18).

Conclusions This review confirms the findings from randomized trials regarding the risk of cardiovascular events with rofecoxib and suggests that celecoxib in commonly used doses may not increase the risk, contradicts claims of a protective effect of naproxen, and raises serious questions about the safety of diclofenac, an older drug.

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risk of myocardial infarction,⁹ and a recently published meta-analysis of randomized trials has implicated high doses of ibuprofen and diclofenac.⁶

Regulatory authorities have provided variable advice regarding the

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safety of NSAIDs. In the United States, the US Food and Drug Administration (FDA) requires that both selective COX-2 inhibitors and NSAIDs carry a warning highlighting the potential for increased risk of cardiovascular events.¹⁰ In contrast, the European Medicines Agency has required labeling of selective COX-2 inhibitors, but made no recommendation about the cardiovascular safety of the older NSAIDs.^{11,12}

Meta-analyses of randomized placebo-controlled trials have provided information about cardiovascular risks with selective COX-2 inhibitors but in total, these have captured only 340 cardiovascular events in users of the drugs.⁶ A full evaluation of data on cardiovascular risks with these drugs requires an examination of controlled pharmaco-epidemiological studies.

METHODS

Studies were eligible for inclusion if they were controlled (case-control or cohort design), and reported on cardiovascular risks associated with the use in population settings of selective COX-2 inhibitors, reported on cardiovascular risks associated with the use in population settings of conventional NSAIDs, with nonuse/remote exposure as the reference exposure for calculation of the relative risk (RR).

We searched electronic databases from 1985 until January 2006. These included MEDLINE, EMBASE, Cochrane Library, Google Scholar, epidemiological research Web sites, abstracts of scientific meetings, and bibliographies of relevant studies. The search terms were compiled from the names of individual drugs, the therapeutic class, mode of activity, cardiovascular and cerebrovascular outcome terms, and study design terms. We also searched on authors' names. Titles and abstracts of articles identified by the searches were reviewed by the authors. Searches were repeated using additional search terms identified from articles considered relevant to the review.

Quality assessment and data extraction were performed in duplicate with resolution of any discrepancies by

consensus. Methodologic quality was assessed using an established instrument.¹³ The instrument assessed case-control studies in terms of methods of selection of cases and controls, comparability of cases and controls, and ascertainment of exposure to the agent of interest. Cohort studies were assessed in terms of selection of the exposed and nonexposed cohorts, comparability of the cohorts, and outcomes ascertainment.

All but 3 of the studies were conducted using linkage of large electronic databases or electronic medical records.¹⁴⁻¹⁶ Such studies use prescribing or dispensing as a proxy for drug consumption. All eligible cases occurring within the time frame were available for inclusion, and controls were selected randomly from the source populations; drug exposure and outcomes were recorded in real time, meaning these studies should have been free of the selection and recall biases that affect ad hoc case-control studies. Misclassification of clinical outcomes and comorbid states, and incomplete information regarding consumption of nonprescription drugs, alcohol, and tobacco are potential problems with database studies, but are equally likely whether data are analyzed prospectively or retrospectively. For these reasons we felt it appropriate to combine data from case-control and cohort analyses in order to increase the precision of our estimates and improve our ability to discriminate between individual drugs. The outcome under study is relatively uncommon, meaning the odds ratio is an accurate estimate of the RR. Many studies controlled for cohort enrollment date and applied the same index day to cases and controls. As this provides a control for calendar time, we felt it was justified to summarize odds ratios derived from the case-control analyses and hazard or rate ratios extracted from the cohort analyses. Point estimates and standard errors were extracted from each study and were combined by the random-effects model of DerSimonian and Laird using Cochrane Review Manager software (The Cochrane Collaboration, Oxford, England).

RESULTS

The searches returned 7086 potentially relevant articles. After review of the titles and removal of duplicates, 745 abstracts were read and 233 articles were selected for further evaluation (FIGURE 1). After application of inclusion criteria, 23 studies were eligible for inclusion (TABLE 1, TABLE 2).

Seventeen case-control analyses included 86 193 cases with cardiovascular events^{2-4,14-16,23-33} (almost exclusively myocardial infarction or sudden cardiovascular death, Table 1), and at least 528 000 controls (1 study did not report the number of controls²⁴). All case-control analyses reported risks with nonselective NSAIDs and 9 also reported risks with selective COX-2 inhibitors. Two studies by Kimmel et al^{15,16} used the same population and had overlapping time frames, reporting on NSAIDs in the early study,¹⁵ and NSAIDs and COX-2 inhibitors in the later analysis.¹⁶ The risk estimates from the latter were used in the data summaries except for ibuprofen, which was reported only in the earlier study.¹⁵ Studies reporting on selective COX-2 inhibitors focused on celecoxib, rofecoxib, or meloxicam. Studies that provided data on individual NSAIDs reported mainly on ibuprofen, diclofenac, naproxen, indomethacin, and piroxicam.

Six studies were based on cohort analyses and included 75 520 users of selective COX-2 inhibitors,¹⁷⁻²² 375 619 users of nonselective NSAIDs, and 594 720 unexposed participants (Table 2). The main outcomes reported were acute myocardial infarction and sudden cardiovascular death.

Excluded Studies

Most exclusions were because reports did not provide information on the study outcomes or the drugs of interest (Figure 1). Four studies were reported more than once and the most comprehensive analysis was used as the data source.^{18,26-28} As a consequence, 4 reports were excluded from the analyses but where these provided additional information relevant to the re-

view, were included.³⁴⁻³⁷ Two additional studies were excluded; 1 compared parenteral ketorolac with opioids in acutely ill hospitalized patients³⁸; the second was the subject of allegations of scientific misconduct that remained unresolved at the time of compiling this report.³⁹

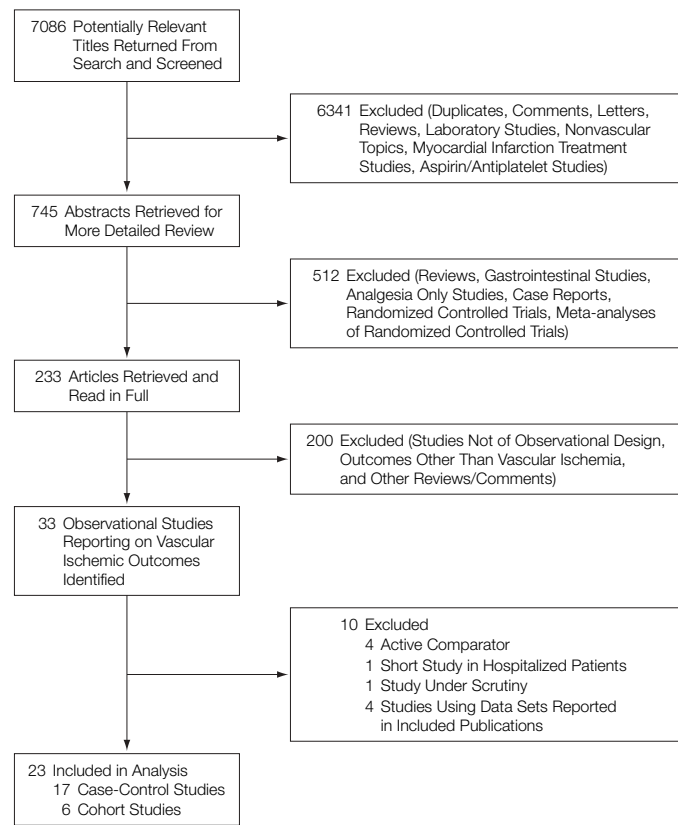
Characteristics of Included Studies

Eleven studies reported on first cardiovascular events^{2,15,16,25-27,29-33} (Table 1, Table 2), 9 included both first and recurrent events (any event),^{3,4,14,20-24,28} 2 reported only on death following an event,^{18,19} and 1 on death or recurrent myocardial infarction following an event.¹⁷ Thirteen studies indicated that both fatal and nonfatal cardiovascular events were included,* 3 reported non-fatal events only¹⁴⁻¹⁶; the remaining studies did not specify whether both fatal and nonfatal events were included.

Study populations varied in their age and sex distributions (Table 1, Table 2). In all but 3 studies, information on the drugs of interest, hospitalization diagnoses, cardiovascular risk factors, and the presence of comorbid states was determined from linked health care databases or electronic medical records that included hospital discharge diagnoses, general practice encounters, and dispensing of prescriptions. The remaining studies collected information through face-to-face¹⁴ or telephone-based structured interviews.^{15,16}

All studies reported adjusted estimates of risk for cardiovascular events. Factors adjusted for included age, sex, cardiovascular risk factors, and use of cardiac medications. Many studies also adjusted for comorbidity (Table 1, Table 2). Fifteen studies adjusted for prescribed aspirin use,† 2 did not report on aspirin adjustment,^{3,4} 5 excluded users of prescribed aspirin or reported on a subgroup of non-users,^{15,16,26,30,32} 7 could report on a subgroup of aspirin users or investigated only users of prescribed aspirin,^{15,16,18,19,26-28} and 1 study assumed all

Figure 1. Results of Searches and Screening of Potentially Relevant Studies



participants were aspirin users.¹⁷ Adjustments for smoking, alcohol intake, and body mass index (calculated as weight in kilograms divided by height in meters squared) were undertaken variably across the studies. Studies that relied on an interview included information on over-the-counter drug use, including NSAIDs and aspirin, smoking, and alcohol intake.¹⁴⁻¹⁶

Five case-control studies used the General Practice Research Database in Great Britain.^{27,28,31-33} Two large studies spanned the period 1992 to 2000 and apparently overlapped by 10 months.^{28,31} The 3 remaining studies overlapped variably in the time periods studied.^{27,32,33} Two studies evaluated risk in specific patient groups (patients with rheumatoid arthritis,³² women³³). To allow for the effects of double counting, data summaries were made omitting studies in which the exposure periods overlapped with those of the 2 largest studies.

We selected studies that had non-use or remote use of the drugs of interest as the reference exposure category. Seven studies also reported RRs of cardiovascular events estimated from between-drug agent comparisons.^{3,4,16,23,24,27,32} Where possible, we also extracted and summarized data from these analyses.

Quality of the Studies

Using the quality assessment instrument, case-control studies could score a maximum of 4 points in the selection and exposure categories and 2 points in the comparability category. Studies scored consistently well across categories (7-8 points in total from a possible 9), the exceptions being those reported only in abstract form^{23,24} (scoring 4/9 and 5/9, respectively). Cohort studies could score a maximum of 4 points in the selection and outcomes assessment categories and 2 for cohort

*References 2-4, 17, 21-24, 26, 28, 30, 32, 33.
†References 2, 14-16, 20-23, 25-29, 31, 33.

Table 1. Details of the Case-Control Studies Included in the Meta-analysis

Source	Outcomes Evaluated	Nested	No.		Drugs Studied	Data Source	Exposure Period	Factors Reported as Being Adjusted For	Factors Reported as Not Being Adjusted For	Population Details
			Cases	Controls						
Hippisley-Cox and Coupland, ² 2005	First AMI, fatal and nonfatal	Yes	9218	86349	COX-2 inhibitors, NSAIDs	Great Britain, QRESEARCH database	Aug 2000-Jul 2004	Age, sex, vascular risks, other comorbidities, aspirin, medicines, general practice, smoking, BMI, social deprivation	OTC aspirin/NSAID use, alcohol	Inception cohort, participants registered with general practice; cases, more than 68% older than age 55 y; 63% men
Graham et al, ³ 2005	Any AMI; sudden cardiac death	Yes	8143	31469	COX-2 inhibitors, NSAIDs	Kaiser Permanente database	Jan 1999-Dec 2001	Age, sex, vascular risks, other comorbidities, medicines, alcohol dependence	Prescribed aspirin, OTC aspirin/NSAID use, smoking, BMI	Inception cohort, participants aged 18-84 y dispensed a COX inhibitor/NSAID; cases, age 66 y (mean); 62% men
Solomon et al, ⁴ 2004	Any AMI, fatal and nonfatal	No	10895	49044	COX-2 inhibitors, NSAIDs	Pennsylvania/New Jersey, dispensing databases for Medicare patients	Jan 1999-Dec 2000	Age, sex, vascular risks, medicines, other comorbidities	Prescribed aspirin, OTC aspirin/NSAID use, alcohol, smoking, BMI	Total population, aged 80 y (mean); ≈ 20% men
McGettigan et al, ¹⁴ 2006	Any nonfatal AMI or validated episode of unstable angina pectoris	No	328	478	COX-2 inhibitors, NSAIDs	New South Wales, Australia, face-to-face interview	Aug 2003-Oct 2004	Age, sex, vascular risks, other comorbidities, aspirin, medicines, smoking, alcohol, OTC aspirin/NSAIDs	BMI	Cases, age 63 y (mean); range, 55-78 y; 64% men
Kimmel et al, ¹⁵ 2004	First nonfatal AMI	No	*	*	NSAIDs	Pennsylvania, telephone interview	May 1998-Dec 2002	Age, sex, vascular risks, other comorbidities, aspirin, medicines, smoking, BMI, physical activity, insurance, OTC aspirin/NSAIDs	Alcohol	Cases, age 60 y (mean); % men not reported
Kimmel et al, ¹⁶ 2005	First nonfatal AMI	No	1718*	6800*	COX-2 inhibitors, NSAIDs	Pennsylvania, telephone interview	May 1998-Dec 2002	Age, sex, vascular risks, other comorbidities, aspirin, medicines, smoking, BMI, physical activity, insurance, OTC aspirin/NSAIDs	Alcohol	Cases, age 60 y (mean); % men not reported
Singh et al, ²³ 2005†	Any AMI, fatal and nonfatal	Yes	15343	61372	COX-2 inhibitors, NSAIDs	California, Medicaid database	Jan 1999-Jun 2004	38 risk factors (not specified further), aspirin (abstract only)	Not reported	Inception cohort, age >18 y with arthritis treated with NSAID; no case details
Sturkenboom et al, ²⁴ 2005†	Any fatal or nonfatal thromboembolic cardiovascular event	Yes	1482	Not reported	COX-2 inhibitors, NSAIDs	the Netherlands, integrated primary care database	1999-2004	Adjusted, but factors not reported (abstract only)	Not reported	Inception cohort, NSAID/COX inhibitor users, age >45 y; no case details
Johnsen et al, ²⁵ 2005	First AMI‡	No	10280	102797	COX-2 inhibitors, NSAIDs	Danish health care databases	Jan 2000-Dec 2003	Age, sex, vascular risks, aspirin, medicines, comorbidities, alcoholism	OTC aspirin/NSAID use, smoking, BMI	Cases, age 70 y (mean); range, 20-100 y; 60% men

(continued)

Table 1. Details of the Case-Control Studies Included in the Meta-analysis (cont)

Source	Outcomes Evaluated	Nested	No.		Drugs Studied	Data Source	Exposure Period	Factors Reported as Being Adjusted For	Factors Reported as Not Being Adjusted For	Population Details
			Cases	Controls						
Levesque et al, ²⁶ 2005	First AMI, fatal and nonfatal	Yes	2844	56 880	COX-2 inhibitors, NSAIDs	Quebec, health care databases	Jan 1999-Jun 2002	Age, sex, vascular risks, other comorbidities, aspirin, medicines, health care utilization	OTC aspirin/NSAID use, alcohol, smoking, BMI	Inception cohort, age ≥66 y dispensed an NSAID; cases, age 78 y (mean); 46% men
Fischer et al, ²⁷ 2005	First AMI‡	No	8688	33 923	NSAIDs	Great Britain, General Practice Research Database	Jan 1995-Apr 2001	Age, sex, vascular risks, other comorbidities, aspirin, medicines, BMI, smoking	OTC aspirin/NSAID use, alcohol	50% of cases aged ≥70 y; 63% men
Garcia Rodriguez et al, ²⁸ 2004	Any AMI, death from coronary heart disease	Yes	4975	20 000	NSAIDs	Great Britain, General Practice Research Database	Jan 1997-Dec 2000	Age, sex, vascular risks, other comorbidities, aspirin, medicines, alcohol, BMI, smoking	OTC aspirin/NSAID use	Inception cohort, participants aged 50-84 y registered with general practice; 55 cases aged ≥70 y; 65% men
Bak et al, ²⁹ 2003	First (ischemic) stroke†	Yes	2717	40 000	NSAIDs	Danish health care databases	Jan 1994-Dec 1999	Age, sex, aspirin, other medicines as proxy for vascular risks and other comorbidities	OTC aspirin/NSAID use, alcohol, smoking, BMI	Inception cohort, participants listed on population registries; cases, 63% aged ≥65 y; 51% men
Solomon et al, ³⁰ 2002	First AMI, fatal and nonfatal	No	4425	17 700	NSAIDs	New Jersey, Medicare/Medicaid databases	Jan 1991-Dec 1995	Age, sex, vascular risks, medicines, comorbidity index, deprivation. Users of prescribed aspirin excluded	OTC aspirin/NSAID use, alcohol, smoking, BMI	Cases, 84% aged ≥65 y; 31% men
Schlienger et al, ³¹ 2002	First AMI‡	No	3315	13 139	NSAIDs	Great Britain, General Practice Research Database	Jan 1992-Oct 1997	Age, sex, aspirin, hormone therapy, smoking, BMI. Excluded those with vascular risk factors	Nonvascular comorbidities, medicines other than aspirin & hormone therapy, OTC aspirin/NSAID use, alcohol	Cases, 60% aged 60-75 y; 26% men
Watson et al, ³² 2002	First nonfatal AMI in patients with rheumatoid arthritis	No	809	2285	NSAIDs	Great Britain, General Practice Research Database	1988-1999	Age, sex, vascular risks, medicines, smoking, comorbidities. Users of prescribed aspirin excluded	OTC aspirin/NSAID use, alcohol, BMI	Cases, all with rheumatoid arthritis; 57% aged ≥65 y; 36% men
Garcia Rodriguez et al, ³³ 2000	First AMI in women, fatal and nonfatal	Yes	1013	5000	NSAIDs	Great Britain, General Practice Research Database	Jan 1991-Dec 1995	Age, sex, vascular risks, other comorbidities, aspirin, medicines, obesity	OTC aspirin/NSAID use	Inception cohort, women aged 50-74 y registered in general practice database; case, 40% aged ≥65 y
Total			86 193	527 236						

Abbreviations: AMI, acute myocardial infarction; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug; OTC, over-the-counter.

*Kimmel et al,¹⁹ used the same approximate overlapping study population as Kimmel et al.¹⁵ Case and control numbers are for the later largest study.

†Abstract details only.

‡Not reported if fatal and nonfatal events were included.

comparability. All studies scored well (7-8 points).

Summary Estimates of Relative Risk

The individual study values and summary estimates of RRs for the comparisons of COX-2 inhibitors and NSAIDs with remote or nonuse of anti-inflammatory drugs are presented in TABLE 3 and TABLE 4. The summary RR estimates from the case-control and co-

hort analyses were similar (Table 3, Table 4). Between-study heterogeneity in RR estimates was statistically significant, but quantitatively modest (FIGURE 2, FIGURE 3).

Rofecoxib was included in 9 case-control and 2 cohort studies (Table 3). The summary RRs for cardiovascular events were 1.31 (95% confidence interval [CI], 1.18-1.46) for the case-control studies and 1.53 (95% CI, 0.68-3.44) for the cohort

studies. Combining across all studies, the summary RR was 1.35 (95% CI, 1.15-1.59) (Figure 2). A dose effect was apparent: the summary RR with doses in excess of 25 mg/d was 2.19 (95% CI, 1.64-2.91) compared with 1.33 (95% CI, 1.00-1.79) with 25 mg/d or less (Table 3).

Eight case-control and 3 cohort studies reported on celecoxib (Table 3). Celecoxib exposure did not lead to an elevation of the risk of cardiovascular

Table 2. Details of the Cohort Studies Included in the Meta-analysis

Source	Outcomes Evaluated	No.			Data Source	Exposure Period	Factors Reported as Being Adjusted For	Factors Reported as Not Being Adjusted For	Population Details
		COX-2 Inhibitor Users	NSAID Users	Non-Users					
Gíslason et al, ¹⁷ 2005	Death or AMI after first AMI	5511	23 851	37 339	Danish health care databases	1995-2002	Age, sex, year of infarction, comorbidities, medicines, socioeconomic status (assumed aspirin use in all)	OTC aspirin/NSAID use, alcohol, smoking, BMI	Participants with history of a first ever AMI; age 68 y (mean); 63% men
Curtis et al, ¹⁸ 2003	Death within 1 year of AMI	0	3577	66 739	All US states, Cooperative Cardiovascular Project, Medicare databases	1994-1996	Demographics, comorbidities, admission diagnosis, hospital course, discharge care	OTC NSAID use, alcohol, smoking, BMI	Participants with prior AMI prescribed aspirin on discharge; 54% aged ≥75 y; 52% men
MacDonald and Wei, ¹⁹ 2003	Cardiovascular death following hospitalization for cardiovascular disease	0	822	6285	Scotland, MEMO database	Jan 1989-Dec 1997	Age, sex, vascular risks, other comorbidities, medicines, deprivation, duration of aspirin/NSAID exposure	OTC NSAID use, alcohol, smoking, BMI	Participants with cardiovascular disease; age 27-100 y (range), mean age not reported; % men not reported
Mamdani et al, ²⁰ 2003	AMI*	27 427	39 537	100 000	Ontario, health care databases	Apr 1998-Mar 2001	Age, sex, vascular risks, aspirin, medicines as measure of comorbidity, hospitalizations, income status, long-term care	OTC aspirin/NSAID use, alcohol, smoking, BMI	Ontario residents aged ≥66 y at inception; age 75 y (mean); 44% men
Ray et al, ²¹ 2002	Any AMI, death from coronary heart disease	42 582	126 391	202 916	United States, TennCare database	Jan 1999-Jun 2001	Age, sex, vascular risk score, comorbidities, aspirin, medicines, insurance status	OTC aspirin/NSAID use, alcohol, smoking, BMI	Participants aged 50-84 y eligible for TennCare benefits; aged 61 y (mean); 31% men
Ray et al, ²² 2002	Any AMI, death from coronary heart disease	0	181 441	181 441	United States, TennCare database	Jan 1997-Dec 1998	Age, sex, vascular risk score, comorbidities, aspirin, other medicines, residence, insurance status	OTC aspirin/NSAID use, alcohol, smoking, BMI	Participants aged 50-84 y eligible for TennCare benefits; aged 64 y (mean); 30% men
Total		75 520	375 619	594 720					

Abbreviations: AMI, acute myocardial infarction; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug; OTC, over-the-counter.
 *Not reported if fatal and nonfatal events included.

events: summary RR 1.01 (95% CI, 0.90-1.13) for the case-control studies and 1.22 (95% CI, 0.69-2.16) for the cohort studies. Combining across all studies, the summary RR was 1.06 (95% CI, 0.91-1.23). Three studies provided dose-stratified RR estimates for celecoxib.^{17,21,26} There were insufficient data to enable stable estimates of the effects of different doses of celecoxib.

Only 3 case-control studies provided data on meloxicam, of which 1 reported an elevation in vascular risk (Table 3). The summary RR was 1.25 (95% CI, 1.00-1.55).

Sixteen studies reported on ibuprofen and/or naproxen individually, 9 on diclofenac, 6 on indomethacin, and 4 provided data on piroxicam (Table 4). The summary RR with naproxen was close to 1 at 0.97 (95% CI, 0.87-1.07). There was no significant elevation in risk with use of ibuprofen or piroxicam at summary RRs of 1.07 (95% CI, 0.97-1.18) and 1.06 (95% CI, 0.70-1.59), respectively. Diclofenac and indomethacin were associated

with increased risks of cardiovascular events. The summary RR for diclofenac from 9 studies was 1.40 (95% CI, 1.16-1.70). In all but 1 of the studies,¹⁹ the point estimate for the risk with diclofenac exceeded the risks simultaneously measured for ibuprofen and naproxen. Indomethacin was included in 6 studies and the summary RR was 1.30 (95% CI, 1.07-1.60).

Within-Study Comparisons of Risk

To minimize the effects of between-study heterogeneity, we undertook a series of “pairwise” comparisons, summarizing only data from studies that simultaneously evaluated both a selective COX-2 inhibitor and a nonselective NSAID, with nonuse or remote use as the reference exposure. The RRs were as follows: rofecoxib, 1.37 (95% CI, 1.04-1.79) and ibuprofen, 1.05 (95% CI, 0.88-1.25) in 6 studies; rofecoxib, 1.32 (95% CI, 1.18-1.48) and naproxen, 1.11 (95% CI, 0.96-1.28) in 7 studies; celecoxib, 1.07 (95% CI, 0.82-1.38) and ibuprofen,

1.03 (95% CI, 0.88-1.21) in 7 studies; celecoxib, 1.00 (95% CI, 0.89-1.12) and naproxen, 1.07 (95% CI, 0.93-1.22) in 7 studies. Three studies provided data on celecoxib, rofecoxib, and diclofenac; the summary RRs were: celecoxib, 1.28 (95% CI, 0.74-2.22); rofecoxib, 1.61 (95% CI, 1.07-2.43); and diclofenac, 1.80 (95% CI, 1.34-2.40). Two studies evaluated celecoxib, rofecoxib, and indomethacin; the summary RRs were: celecoxib, 0.98 (95% CI, 0.76-1.26); rofecoxib, 1.32 (95% CI, 1.23-1.42); indomethacin, 1.48 (95% CI, 1.13-1.94).

Direct Comparisons Between Drugs

A number of studies provided analyses of risk where the reference exposure was another drug rather than nonuse. Compared with any nonselective NSAID, the summary RR for rofecoxib was 1.21 (95% CI, 1.13-1.29) and for celecoxib it was 0.95 (95% CI, 0.85-1.05). With naproxen as the reference, the summary RR for rofecoxib was 1.68 (95% CI, 1.22-2.32) and with celecoxib it was 0.94

Table 3. Results of Case-Control and Cohort Studies Reporting on Cardiovascular Risks With Cyclooxygenase 2 Inhibitors

Source	Relative Risk (95% Confidence Interval)				
	All Celecoxib	All Rofecoxib	Rofecoxib ≤25 mg/d	Rofecoxib >25 mg/d	Meloxicam
Case-control studies that reported on COX-2 inhibitors					
Hippisley-Cox and Coupland, ² 2005	1.21 (0.96-1.54)	1.32 (1.09-1.61)	NR	NR	NR
Graham et al, ³ 2005	0.84 (0.67-1.04)	1.34 (0.98-1.82)	1.23 (0.98-1.71)	3.00 (1.09-8.31)	NR
Solomon et al, ⁴ 2004	0.93 (0.84-1.02)	1.14 (1.00-1.31)	1.21 (1.01-1.44)*	1.70 (1.07-2.71)†	NR
McGettigan et al, ¹⁴ 2006	1.11 (0.59-2.11)	0.63 (0.31-1.28)	NR	NR	NR
Kimmel et al, ^{15,16} 2004/5	0.43 (0.23-0.79)	1.16 (0.70-1.93)	NR	NR	NR
Singh et al, ²³ 2005‡	1.09 (1.02-1.15)	1.32 (1.22-1.42)	NR	NR	1.37 (1.05-1.78)
Sturkenboom et al, ²⁴ 2005‡	NR	1.52 (1.08-2.15)	NR	2.32 (1.2-4.4)§	NR
Johansen et al, ²⁵ 2005	1.25 (0.97-1.62)	1.80 (1.47-2.21)	NR	NR	NR
Levesque et al, ²⁶ 2005	0.99 (0.85-1.16)	1.24 (1.05-1.46)	1.2 (1.02-1.43)	1.73 (1.09-2.76)	1.06 (0.49-2.30)
Garcia Rodriguez et al, ²⁸ 2004	NR	NR	NR	NR	0.97 (0.60-1.56)
Summary relative risk	1.01 (0.90-1.13)	1.31 (1.18-1.46)	1.21 (1.08-1.36)	1.89 (1.43-2.51)	1.25 (1.00-1.55)
Cohort studies that reported on COX-2 inhibitors					
Gislason et al, ¹⁷ 2006	2.06 (1.73-2.45)	2.29 (1.99-2.65)	2.17 (1.86-2.54)	3.31 (2.37-4.61)	NR
Mamdani et al, ²⁰ 2003	0.90 (0.70-1.20)	1.0 (0.80-1.40)	NR	NR	NR
Ray et al, ²¹ 2002	0.96 (0.76-1.21)	NR	1.03 (0.78-1.35)	1.70 (0.98-2.95)	NR
Summary relative risk	1.22 (0.69-2.16)	1.53 (0.68-3.44)	1.51 (0.73-3.13)	2.46 (1.29-4.71)	NR
Case-control and cohort studies combined risk estimates	1.06 (0.91-1.23)	1.35 (1.15-1.59)	1.33 (1.00-1.79)	2.19 (1.64-2.91)	1.25 (1.00-1.55)

Abbreviations: COX, cyclooxygenase; NR, not reported.

*vs Celecoxib ≤ 200 mg/d; author's reported risk was similar compared with no current nonsteroidal anti-inflammatory drug.

†vs Celecoxib > 200 mg/d; author's reported risk was similar compared with no current nonsteroidal anti-inflammatory drug.

‡Published abstract only.

§“Twice the recommended dose”; odds ratio reported only for cerebrovascular ischemia; no elevation in risk for cardiovascular ischemia but odds ratio not reported.

||Data for combined end point of death/recurrent acute myocardial infarction provided by study author.

(95% CI, 0.74-1.18). An elevation in risk was evident with rofecoxib when it was compared directly with celecoxib: summary RR, 1.34 (95% CI, 1.14-1.56). When compared directly with other NSAIDs (including diclofenac, indomethacin, or both) naproxen was associated with a lower risk of cardiovascular complications: summary RR, 0.75 (95% CI, 0.63-0.88).

Risk With Early Use of Selective COX-2 Inhibitors

Three studies evaluated vascular risk among new users of COX-2 inhibitors, with remote or nonuse as the reference^{21,25,26} and 1 study compared new users of rofecoxib directly with new users of celecoxib.⁴ The exposure category was the first 30 days of treatment. An early risk was evident with rofecoxib (summary RR, 1.66; 95%

CI, 1.09-2.51) but not with celecoxib, 1.32 (95% CI, 0.80-2.19). The data from the cohort study by Ray et al²¹ suggest an early risk with rofecoxib 25 mg/d or more. Comparing first-time users of celecoxib and rofecoxib, Solomon et al⁴ reported that relative to celecoxib, the odds ratio for acute myocardial infarction associated with first-time use of rofecoxib was 1.43 (95% CI, 1.12-1.83) for use in the first 30 days.

Effects of Aspirin Use

In an attempt to explore whether cardiovascular risk might vary with aspirin use, we attempted to extract data from studies of COX-2 inhibitors and NSAIDs in groups defined by aspirin exposure. Unfortunately, there were insufficient data to provide stable estimates of whether aspirin protects

against the cardiovascular risk with rofecoxib or other risk-inducing drugs. In the case of ibuprofen, the summary RR in the absence of aspirin was 0.82 (95% CI, 0.50-1.32) in 3 studies, compared with 0.99 (95% CI, 0.75-1.31) in aspirin users in 5 studies.

Adjustment for Possible Double Counting

Of the 5 studies that used the General Practice Research Database, all reported on NSAIDs^{27,28,31-33} and 1 also evaluated COX-2 inhibitors²⁸ (Table 1). Including in the pooled analyses only the data from the 2 least overlapping studies,^{28,31} the summary RRs were little different from the overall estimates (Table 4) for naproxen, 0.98 (95% CI, 0.89-1.08); diclofenac, 1.35 (95% CI, 1.08-1.69), or ibuprofen, 1.08 (95% CI, 0.97-1.19).

Table 4. Results of Case-Control and Cohort Studies Reporting on Cardiovascular Risks With Nonselective NSAIDs

Source	Naproxen	Diclofenac	Ibuprofen	Indomethacin	Any/Other NSAIDs	Piroxicam
Hippisley-Cox and Coupland, ² 2005	1.27 (1.01-1.60)	1.55 (1.39-1.72)	1.24 (1.11-1.39)	NR	1.21 (1.20-1.44)*	NR
Graham et al, ³ 2005	1.14 (1.00-1.30)	1.60 (0.92-2.79)	1.06 (0.96-1.17)	1.30 (1.06-1.59)	1.13 (1.01-1.27)*	NR
McGettigan et al, ¹⁴ 2006	NR	NR	0.98 (0.53-1.81)	NR	0.57 (0.41-1.09)†	NR
Kimmel et al, ^{15,16} 2004/5	0.48 (0.28-0.82)‡	NR	0.52 (0.39-0.69)	NR	0.61 (0.52-0.71)†	NR
Singh et al, ²³ 2005§	1.08 (0.95-1.22)	NR	1.11 (1.01-1.22)	1.71 (1.36-2.17)	1.12 (1.06-1.19)¶	NR
Johnsen et al, ²⁵ 2005	1.50 (0.99-2.29)	NR	NR	NR	1.68 (1.52-1.85)*	NR
Levesque et al, ²⁶ 2005	1.17 (0.75-1.84)	NR	NR	NR	1.00 (0.73-1.37)†	NR
Fischer et al, ²⁷ 2005	0.96 (0.66-1.38)	1.23 (1.00-1.51)	1.16 (0.92-1.46)	1.36 (0.82-2.25)	1.07 (0.96-1.19)†	0.95 (0.53-1.69)
Garcia Rodriguez et al, ²⁸ 2004	0.89 (0.64-1.24)	1.18 (0.99-1.40)	1.06 (0.87-1.29)	0.86 (0.87-1.32)	0.95 (0.77-1.18)*	1.25 (0.69-2.2)
Bak et al, ²⁹ 2003	0.7 (0.4-1.1)	1.1 (0.7-1.17)	1.3 (1.0-1.6)	1.40 (0.80-2.40)	1.2 (1.1-1.4)†	NR
Solomon et al, ³⁰ 2002	0.84 (0.72-0.98)	NR	1.02 (0.88-1.18)	NR	1.00 (0.92-1.08)†	0.5 (0.2-1.3)
Schlienger et al, ³¹ 2002	0.68 (0.42-1.13)	1.38 (1.08-1.77)	1.17 (0.87-1.58)	1.03 (0.58-1.85)	1.17 (0.99-1.37)†	1.65 (0.78-3.49)
Watson et al, ³² 2002	0.57 (0.31-1.06)	1.68 (1.14-2.49)	0.74 (0.35-1.55)	NR	1.47 (1.00-2.16)*	NR
Garcia Rodriguez et al, ³³ 2004	NR	NR	NR	NR	1.45 (1.18-1.79)†	NR
Summary relative risk	0.96 (0.84-1.10)	1.36 (1.21-1.54)	1.06 (0.95-1.18)	1.30 (1.07-1.60)	1.10 (0.98-1.24)	1.06 (0.70-1.59)
Adjusted date cohort studies that reported on NSAIDs						
Gislason et al, ¹⁷ 2006	NR	2.19 (1.93-2.49)	1.39 (1.27-1.53)	NR	1.33 (1.21-1.46)*	NR
Curtis et al, ¹⁸ 2003	NR	NR	0.84 (0.70-1.01)	NR	0.96 (0.86-1.06)*	NR
MacDonald and Wei, ¹⁹ 2003	NR	0.80 (0.49-1.31)	1.73 (1.05-2.84)	NR	1.03 (0.77-1.37)*	NR
Mamdani et al, ²⁰ 2003	1.0 (0.6-1.7)	NR	NR	NR	1.2 (0.9-1.4)*	NR
Ray et al, ²¹ 2002	0.93 (0.82-1.06)	NR	0.91 (0.78-1.06)	NR	NR	NR
Ray et al, ²² 2002	0.95 (0.82-1.09)	NR	1.15 (1.02-1.28)	NR	1.03 (0.92-1.16)	NR
Summary relative risk	0.94 (0.85-1.04)	1.36 (0.51-3.65)	1.12 (0.90-1.38)		1.10 (0.95-1.29)	
Case-control and cohort studies combined risk estimates	0.97 (0.87-1.07)	1.40 (1.16-1.70)	1.07 (0.97-1.18)	1.30 (1.07-1.60)	1.10 (1.00-1.21)	1.06 (0.70-1.59)

Abbreviations: NR, not reported; NSAID, nonsteroidal anti-inflammatory drug.
 *NSAIDs other than those reported on individually.
 †All NSAIDs.
 ‡vs Celecoxib ≤ 200 mg/d.
 §Published abstract only.
 ||Data for combined end point of death/recurrent acute myocardial infarction provided by study author.

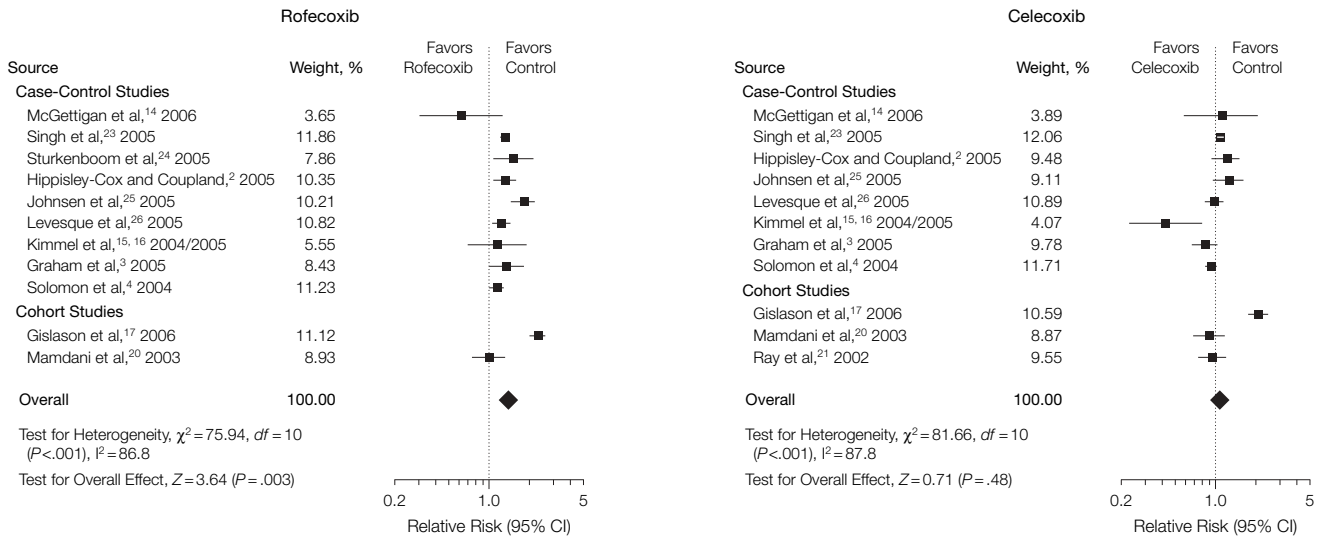
COMMENT

The results of this systematic review of controlled observational studies allow conclusions to be drawn about the risks of cardiovascular events during treatment with selective and nonselective NSAIDs. The data confirm the elevated

risk with rofecoxib and indicate that it is dose-related. In doses of around 200 mg/d, celecoxib was not associated with an increased risk, but the data did not exclude an increased risk with higher doses. Use of naproxen was not associated with any reduction in risk, as was

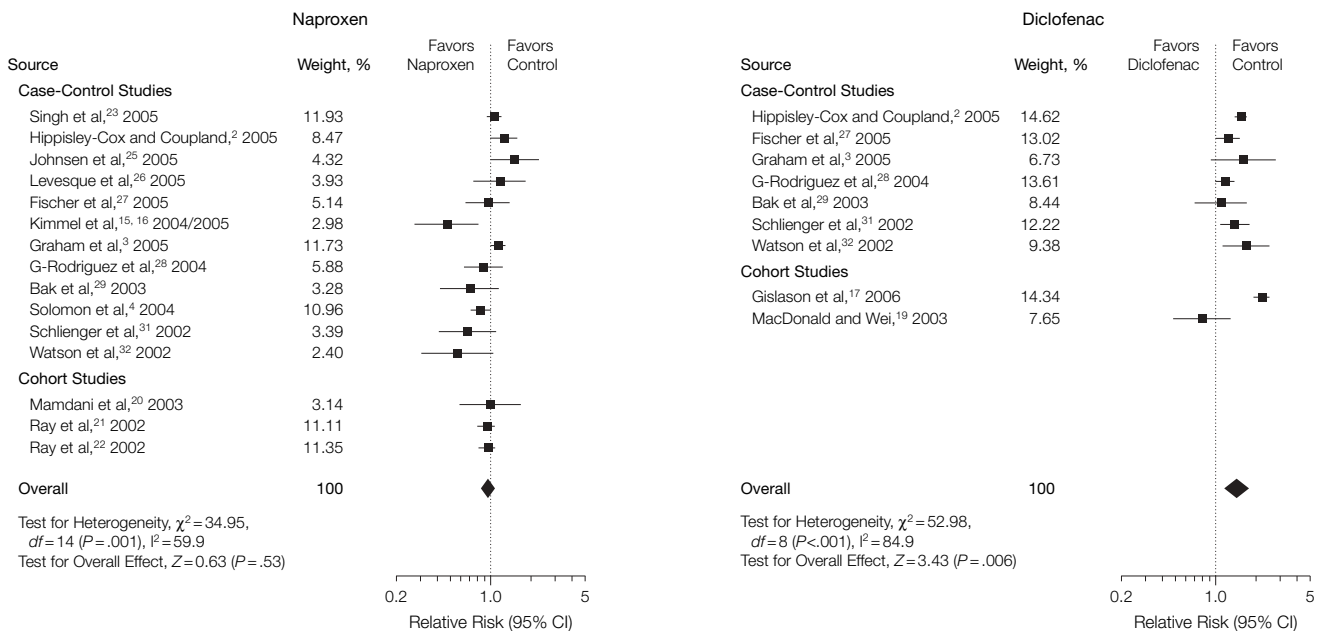
suggested by the authors of a report of a large trial comparing it with rofecoxib.⁸ Of the other nonselective NSAIDs, the highest risk was seen with diclofenac. The increased cardiovascular risk with rofecoxib could be observed during the first 30 days of treat-

Figure 2. Point Estimates and Summary Relative Risks for Cardiovascular Events With Rofecoxib and Celecoxib



Reference exposure, nonuse or remote use of anti-inflammatory drugs (random effects model). CI indicates confidence interval.

Figure 3. Point Estimates and Summary Relative Risks for Cardiovascular Events With Naproxen and Diclofenac



Reference exposure, nonuse or remote use of anti-inflammatory drugs (random effects model). CI indicates confidence interval.

ment. This conclusion is consistent with a recent re-analysis of the APPROVe trial of rofecoxib, which contradicts the original suggestion that the vascular risk was only seen after 18 months of treatment.⁴⁰ The data on meloxicam did not allow any definite conclusions and the elevated summary RR was largely due to the results of a single study.

It is instructive to compare these data with the results of a recently published meta-analysis of randomized controlled clinical trials.⁶ Between them, these systematic reviews include most of the clinical epidemiological evidence on cardiovascular risk with anti-inflammatory drugs. In reviewing data from 138 randomized trials, Kearney et al⁶ estimated a summary RR for COX-2 inhibitors of 1.42 (95% CI, 1.13-1.78), close to the estimate we made for rofecoxib, 1.31 (95% CI, 1.18-1.46). The observational data gave a summary RR of 2.19 (95% CI, 1.64-2.91) with rofecoxib doses above 25 mg/d; but there were insufficient data from the randomized trials to make this calculation.^{6,41} In contrast to the evidence from the randomized trials, we found no increase in risk with commonly used doses of celecoxib. However, the randomized data only showed an increased risk with daily celecoxib doses of 400 mg and above.^{5,6} There is agreement between the randomized and non-randomized data that naproxen did not alter the risk of cardiovascular events.⁶ Of more concern is the evidence from both randomized and nonrandomized studies that diclofenac increases the risk of cardiovascular events: summary RR, 1.63 (95% CI, 1.12-2.37) in the case of randomized trials,⁶ and 1.40 (95% CI, 1.16-1.70) with the observational studies. We did not find an elevated RR with ibuprofen and the summary estimate from the randomized trials was not significantly different from 1.⁶ It has been suggested that ibuprofen may interact with low-dose aspirin,^{19,42} but we found the RRs to be close to 1 in users and nonusers of aspirin. We found inconsistent effects of aspirin on the risks with other drugs. Significantly, Kearney et al⁶ found no evidence from the ran-

domized trials that aspirin modifies the risk of cardiovascular events with COX-2 inhibitors.

The differences between rofecoxib and celecoxib appear important from both a clinical and regulatory standpoint. The data do not point to a safe dose level with rofecoxib, which justifies the decision taken to withdraw the drug from sale. At doses of 200 mg or less there is no convincing evidence of an increased risk of cardiovascular events with celecoxib, which remains on international markets. However, based on the randomized data celecoxib appears unsafe in doses of 400 mg or more.^{5,6} These results seem to point to different dose-effect gradients in the vascular compartment across the ranges of doses of celecoxib and rofecoxib that were used in clinical practice. This review does not allow a judgment about whether any claimed advantages of celecoxib outweigh the elevated cardiovascular risk seen with high doses.

Diclofenac is another relatively COX-2 selective drug that has been much less studied than either rofecoxib or celecoxib. Both the randomized and observational data point to an RR that is similar to what was seen with rofecoxib. Diclofenac is reported to have a similar degree of COX-2 selectivity to celecoxib.⁴³ The increased cardiovascular risk may indicate that diclofenac is commonly ingested in relatively high doses in relation to the drug's effects on COX-2 in the vascular compartment.

We found very few data on cardiovascular risk with meloxicam. This is significant because in some markets (eg, Australia), it has replaced rofecoxib and celecoxib following the publicity given to their adverse effects. The summary RR was 1.25 (upper 95% confidence limit 1.56), meaning that it may be no different from other relatively COX-2-selective drugs. Finally, we found an elevated risk of cardiovascular events with indomethacin. This is not easily explained from its pharmacology as it is not a selective COX-2 inhibitor.^{7,43} The data reviewed here were sparse and indomethacin is seldom recommended because of gastrointestinal and central

nervous system toxicity. This review provides an additional reason not to use indomethacin.

As with any systematic review, the limitations reflect those of the individual studies. Most relied on information from databases. While minimizing selection and recall biases, the definition of exposure relies on the recording of a drug being prescribed or dispensed rather than actually consumed, so misclassification is possible. An additional weakness was the inability in many studies to measure directly consumption of nonprescription aspirin and NSAIDs. Several authors acknowledged the latter but pointed out that the generally elderly populations studied would have had access to subsidized medicines and therefore, little incentive to purchase their own. Notwithstanding, it remains a concern that self-prescription with agents that might confound the results cannot be quantified. It is possible that unrecorded exposure to aspirin or anti-inflammatory drugs might account for some of the observed heterogeneity. Because of the reliance on stored data, which were not collected primarily for research, information on other potential confounders such as smoking, hypertension, and elevated cholesterol was incomplete. Use of relevant drugs will have acted as a proxy for these risk factors but it is possible that adjustments for confounding were inadequate. Other possible causes of between-study heterogeneity include the different ages and baseline risks of the study populations and varying ingested doses of drugs. From a statistical standpoint, the degree of heterogeneity was impressive mandating the use of a random-effects meta-analysis. But inspection of Figure 2 and Figure 3 shows that the range of individual study estimates of RRs was not massive. The large size of many of the studies led to precise RR estimates, meaning that relatively small differences between them were statistically highly significant.

In our view, the other problem with this review lies in the interpretation of pooled RR estimates that are precise but

in many cases close to the null. Typically, in pharmacoepidemiological studies there is a reluctance to accept as causal RR estimates much below 2. These studies are subject to a range of biases including confounding by indication and by disease severity. Channeling of certain drugs to patients with high levels of morbidity may lead to serious adverse events being wrongly attributed to the drug rather than a condition from which the patient was already experiencing. This has been noted in the case of selective COX-2 inhibitors.⁴⁴

However, in the face of this and the heterogeneity noted above, a number of factors lead us to believe that the associations are real. The first is that while selection factors may bias estimates of cardiovascular risk made for the class of drugs, they are less likely to affect between-drug comparisons (eg, celecoxib vs rofecoxib or diclofenac vs naproxen). To account for potential confounding at study level, we performed sensitivity analyses where we used only within-study comparisons of drug risks, and our conclusions were unaffected. Additional factors supporting the validity of our observations are the concordance between the results of the randomized and nonrandomized studies and the biological plausibility of the proposed mechanisms.

In conclusion, controlled data from observational and randomized studies confirm a dose-related risk of cardiovascular events with selective COX-2 inhibitors. The observational data indicate that the risk increases early in treatment. An older NSAID, diclofenac, seems to share this risk and, unlike celecoxib, it appears to be harmful at commonly used doses. We believe that there are grounds for reviewing its regulatory status.

ADDENDUM

Since this article was submitted, Helin-Salmivaara and colleagues in Finland have published a population-based study of the risks of hospitalization with myocardial infarction and use of nonsteroidal anti-inflammatory drugs (*Eur Heart J* 2006;27:1657-1663; doi

10.1093/eurheartj/ehl053). We have not updated our systematic review but in view of the size of this study we believed it was important to determine if inclusion of the new data would change the results or conclusions of our study. Accordingly, we reran the analyses with inclusion of the new data. The revised summary RR estimates (95% CI) using a random-effects model are as follows: rofecoxib, 1.36 (1.18-1.58; 12 studies); celecoxib, 1.06 (0.92-1.22; 12 studies); diclofenac, 1.40 (1.19-1.65; 10 studies); meloxicam, 1.24 (1.06-1.45; 4 studies); naproxen, 0.99 (0.89-1.09; 16 studies); ibuprofen, 1.09 (0.99-1.20; 17 studies); piroxicam, 1.16 (0.86-1.56; 5 studies); indomethacin, 1.36 (1.15-1.61; 7 studies). Our conclusions are unchanged: there appear to be clinically significant differences in summary RR estimates between individual drugs in the doses that are used in the community.

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Author Contributions: Dr Henry had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: McGettigan, Henry.

Acquisition of data: McGettigan.

Analysis and interpretation of data: McGettigan, Henry.

Drafting of the manuscript: McGettigan, Henry.

Critical revision of the manuscript for important intellectual content: McGettigan, Henry.

Statistical analysis: McGettigan, Henry.

Obtained funding: McGettigan, Henry.

Administrative, technical, or material support: McGettigan.

Study supervision: Henry.

Financial Disclosures: Drs McGettigan and Henry report that they are separately conducting a case-control study to examine the clinical and genetic determinants of risk of cardiovascular events with use of NSAIDs and COX-2 inhibitors. The study is funded by the National Health and Medical Research Council and Heart Foundation of Australia. The genetic component of the study looks at polymorphisms of the COX-2 gene and also at aspirin resistance polymorphisms. They also report that the laboratory that is working with this effort plans to enter a contract with Pfizer to support the laboratory work. There is currently no contract and the money will not come into Dr McGettigan or Dr Henry's department or the University of Newcastle. The staff in the genetics laboratory are not involved in the systematic review.

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