Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study

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Summary

Background Controversy has surrounded the question about whether high-dose rofecoxib increases or naproxen decreases the risk of serious coronary heart disease. We sought to establish if risk was enhanced with rofecoxib at either high or standard doses compared with remote non-steroidal anti-inflammatory drug (NSAID) use or celecoxib use, because celecoxib was the most common alternative to rofecoxib.

Methods We used data from Kaiser Permanente in California to assemble a cohort of all patients age 18–84 years treated with a NSAID between Jan 1, 1999, and Dec 31, 2001, within which we did a nested case-control study. Cases of serious coronary heart disease (acute myocardial infarction and sudden cardiac death) were risk-set matched with four controls for age, sex, and health plan region. Current exposure to cyclo-oxygenase 2 selective and non-selective NSAIDs was compared with remote exposure to any NSAID, and rofecoxib was compared with celecoxib.

Findings During 2 302 029 person-years of follow-up, 8143 cases of serious coronary heart disease occurred, of which 2210 (27·1%) were fatal. Multivariate adjusted odds ratios versus celecoxib were: for rofecoxib (all doses), 1·59 (95% CI 1·10–2·32, p=0·015); for rofecoxib 25 mg/day or less, 1·47 (0·99–2·17, p=0·054); and for rofecoxib greater than 25 mg/day, 3·58 (1·27–10·11, p=0·016). For naproxen versus remote NSAID use the adjusted odds ratio was 1·14 (1·00–1·30, p=0·05).

Interpretation Rofecoxib use increases the risk of serious coronary heart disease compared with celecoxib use. Naproxen use does not protect against serious coronary heart disease.

Introduction

Cyclo-oxygenase 2 (COX2) selective non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed for the treatment of arthritis and other musculoskeletal complaints because of the reduced occurrence of gastrointestinal toxic effects compared with non-selective NSAIDs.[1,2] Questions about cardiovascular risk with these COX2-selective drugs were raised by the finding of a five-fold difference in incidence of acute myocardial infarction between patients treated with rofecoxib 50 mg/day and naproxen 1000 mg/day in a large randomised clinical trial (Vioxx Gastrointestinal Outcomes Research; VIGOR),[2] and by a meta-analysis of clinical trials of celecoxib and rofecoxib.[3] Because the VIGOR trial did not have a placebo group, its findings could have suggested either an adverse effect of rofecoxib, an adverse effect of coxibs in general, or a hitherto unrecognised protective effect of naproxen.[4,5] In view of the high use of COX2 drugs in the USA, even a small increase in adverse cardiovascular events would have substantial public-health effects.

Several observational studies have sought to clarify the findings of the VIGOR trial. High-dose rofecoxib (>25 mg/day) has been reported to enhance the risk of adverse cardiovascular events relative to non-users of any NSAID[6] or users of celexoxib.[7] In one study, no increased risk was noted with rofecoxib compared with other NSAIDs, but high-dose rofecoxib was not assessed separately.[8] Studies investigating the effect of naproxen on cardiovascular risk have yielded conflicting results. In three cohort studies, no reduction in risk was reported with naproxen use,[6,7,9] whereas a cardioprotective effect was noted in three other studies.[10–12] We sought to address these important questions about the cardiovascular effects of NSAIDs.

Methods

Kaiser Permanente is a national integrated managed care organisation providing comprehensive health care to more than 6 million residents in the state of California.[13] The enrolled population varies with respect to age, educational attainment, family income, and ethnic origin. The organisation maintains computer files of eligibility for care, outpatient visits, admissions, medical procedures, emergency room visits, laboratory testing, and outpatient drug prescriptions for all its members. Mortality status, including underlying cause of death as recorded on death certificates, is periodically updated with data obtained from the California Department of Health, Center for Health Statistics. This study was approved by the institutional review boards of both the northern and southern divisions of Kaiser Permanente in California.

We assembled a cohort of NSAID-treated patients to undertake a nested case-control study. From Jan 1, 1999, to Dec 31, 2001, we identified all individuals age 18–84 years who filled at least one prescription for a COX2 selective (celecoxib or rofecoxib) or non-selective (all other) NSAID. Those with at least 12 months of health plan coverage before the date of that first NSAID prescription were entered into the cohort if they had no diagnoses of cancer, renal failure, liver failure, severe respiratory disease, organ transplantation, or HIV/AIDS during the screening interval. We followed up cohort members from this entry date until the end of the study period (December, 2001) or until occurrence of an acute myocardial infarction or death, whichever came first.

The study outcome was incident serious coronary heart disease, defined as acute myocardial infarction requiring admission or sudden cardiac death. We identified acute myocardial infarction requiring admission with the international classification of diseases, 9th revision, clinical modification (ICD-9-CM) code 410 (acute myocardial infarction) or 411·1 (intermediate coronary syndrome, as long as laboratory documentation was available of acute myocardial infarction—ie, raised creatine kinase MB fraction or troponin I). We classified outpatient deaths as sudden cardiac death if the underlying cause of death listed hypertensive heart disease, ischaemic heart disease, conduction disorders, dysrhythmias, heart failure, atherosclerotic heart disease, sudden death, or death from an unknown cause.[6,9] In validation studies of computerised hospital data, a principal diagnosis code for acute myocardial infarction has a positive predictive value between 92%[14] and 95%[15] and a sensitivity of 94%.[14] Furthermore, we used computerised laboratory data, from which we noted that 87·4% of patients admitted with acute myocardial infarction had cardiac enzyme concentrations that confirmed diagnosis. Although there is probably more misclassification of the out-of-hospital sudden cardiac deaths, their inclusion is important (and routine in clinical trials), because coronary artery disease frequently manifests as sudden death outside of the hospital.[16]

For every case, we randomly selected four controls from individuals under observation in the study cohort on the date of the case event (index date), and matched them for age (year of birth), sex, and health plan region (north or south).[17] A given cohort member selected as a control for a case on one date could become a control for another case occurring on a later index date, as long as he or she remained in the study cohort and was therefore also at risk of becoming a case. Thus, a control could subsequently become a case. We excluded potential cases and controls if they were not enrolled on the index date and for at least 11 of the 12 preceding months. During the study period, pharmacy benefits persisted for enrolment lapses of up to 1 calendar month.

We established the NSAID exposure status of cases and controls at the case index date. We based exposure classification on the duration, or days of drug supply, dispensed in the NSAID prescription. Patients were current users if the duration of the NSAID prescription closest to and preceding the index date overlapped with the index date. Remote users were those whose drug supply ended more than 60 days before the index date. We judged these patients unlikely to be taking the prescription NSAID on the index data and thus they were the reference category in several analyses. Recent users were individuals whose NSAID prescriptions ended between 1 and 60 days before the index date. We classified these patients separately for several reasons. The effects of NSAIDs on cardiovascular risk might persist a short time after the last dose. Because of dosing as required or incomplete compliance, some recent users might have been taking the drug after the nominal end of the dispensed supply. Thus, we created a separate category to avoid the misclassification that would arise by regarding these patients as either current or remote users.

We initially classified rofecoxib exposure as either standard (≤25 mg/day) or high (>25 mg/day) dose on the basis of the dispensed tablet strength. However, review of computerised patients' prescription histories showed inconsistencies between the instructions for use, days supply, and frequency of refills. For example, some patients dispensed the 25 mg strength were taking two tablets per day, whereas others who were dispensed the 50 mg strength were taking a half tablet per day. To address this potential misclassification, computerised printouts of all NSAID prescriptions for all rofecoxib-treated patients, covering the entire study period, were reviewed by a panel masked to case or control status (DC, RH, MS, CC). We reclassified patients with respect to rofecoxib dose status only if there was unanimous consensus among panel members.

For the 365-day period before the index date, we obtained data for potential risk factors for the occurrence of serious coronary heart disease. These included: cardiovascular admissions, as defined by diagnosis-related group coding (acute myocardial infarction, coronary revascularisation, angina, congestive heart failure, other ischaemic heart disease, cardiac arrhythmias, cerebrovascular accidents, peripheral vascular disease); emergency room visits for cardiovascular reasons and outpatient diagnoses for tobacco use, as defined by ICD 9-CM coding; and cardiovascular prescription drug use (thiazide diuretics, loop diuretics, angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers, calcium-channel blockers, β blockers, digoxin, nitrates, antiarrhythmics, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors, fibrates, nicotinic acid, antiplatelet drugs [ticlopidine, clopidogrel], anticoagulants [warfarin, low molecular weight heparin], insulin, oral hypoglycaemics). We also obtained data for non-cardiovascular admissions and emergency room visits, same-day admissions for medical procedures, outpatient diagnoses of alcohol dependence, rheumatoid arthritis,

and prescription use of hormone replacement therapy, oral prednisone (>1000 mg in the past year) or disease-modifying antirheumatic drugs.

To control for potential differences in cardiovascular disease between study exposure groups, we calculated a cardiovascular risk score for cases and controls.[6,9,18–20] The score was estimated from a logistic regression analysis of the effects of the above factors on the odds of serious coronary heart disease for unexposed (remote or recent use) patients. We used the coefficients from this regression to calculate every participant's predicted probability of serious coronary heart disease—the risk score. This score then was categorised into ten values, with the lowest value representing patients with no diagnosed or treated cardiovascular disease and the remaining nine representing approximate quantiles of the controls. A 12·1-fold difference in risk was present between the lowest (0) and highest (9) value of the score, with a progressive increase in risk with every increasing score value. The results thus obtained were virtually identical to those from more complex models that included the individual components of the risk score. For example, the odds ratio for recent users, the largest exposure group in our study, was 1·140 (95% CI 1·062–1·223) with the complex model and 1·109 (1·034–1·190) with the cardiovascular risk score, a difference of 0·031. Similarly, for ibuprofen users, the largest currently exposed drug group in our study, the odds ratio with the complex models was 1·074 (0·969–1·191) and with the score-based model it was 1·059 (0·956–1·174), a difference of 0·015, less than 2%. Of note, the risk score produced slightly more conservative point estimates and lower bounds for the CIs than did the complex models.

We used conditional logistic regression to compare current exposure to a specific NSAID with remote exposure to any NSAID. We obtained estimates of the odds ratio and 95% CIs from the regression. An a-priori aim of the study was to compare current exposure to either standard-dose or high-dose rofecoxib with current exposure to celecoxib. The same regression model was rerun with celecoxib as the reference to obtain odds ratio estimates for standard-dose and high-dose rofecoxib. We did analyses with Stata version 7.0 (College Station, TX, USA).

To assess the potential for confounding from low-dose aspirin use, over-the-counter NSAID use, smoking history, and family history of acute myocardial infarction, we undertook a standardised telephone survey of a random sample of controls currently exposed to celecoxib, ibuprofen, naproxen, or rofecoxib, or controls with remote exposure to a NSAID.

Role of the funding source

A document describing portions of this study was prepared for the US Food and Drug Administration (FDA) by the lead author (DG), and the FDA posted this on its website on Nov 2, 2004.[21] This document was preliminary,

	Cases (n=8143)	Controls (n=31 496)
Age (years)	66·8 (11·6)	67·0 (11·5)
Men	5031 (62%)	19 399 (62%)
Cardiovascular admission in past year*	1153 (14%)	962 (3%)
Myocardial infarction or revascularisation	202 (2%)	133 (<1%)
Angina	230 (3%)	271 (1%)
Heart failure	287 (4%)	106 (<1%)
Other ischaemic heart disease	354 (4%)	192 (1%)
Cardiac arrhythmia	186 (2%)	204 (1%)
Peripheral vascular disease	45 (1%)	35 (<1%)
Stroke	123 (2%)	143 (<1%)
Cardiovascular drug use in past year*	6526 (80%)	18 274 (58%)
Angiotensin-converting-enzyme inhibitor	2839 (35%)	6287 (20%)
Angiotensin-receptor blocker	372 (5%)	596 (2%)
Antiarrhythmic drug	219 (3%)	345 (1%)
Anticoagulant drug	494 (6%)	1014 (3%)
β blocker	3162 (39%)	6929 (22%)
Calcium-channel blocker	2196 (27%)	4483 (14%)
Digitalis glycoside	808 (10%)	1126 (4%)
Hypoglycaemic drug	2196 (27%)	3735 (12%)
Lipid-lowering drug	2800 (34%)	6069 (19%)
Loop diuretic	1714 (21%)	2214 (7%)
Nitrate	2382 (29%)	2658 (8%)
Platelet inhibitor	432 (5%)	434 (1%)
Thiazide diuretic	2038 (25%)	6752 (21%)
Other medical care in past year		
Non-cardiovascular admission	1368 (17%)	2514 (8%)
Cardiovascular emergency room visit*	337 (4%)	276 (1%)
Non-cardiovascular emergency room visit†	2778 (34%)	6931 (22%)
Oestrogen use by women	1167 (14%)	5125 (16%)
Smoking-related diagnosis	552 (7%)	1013 (3%)
Alcohol dependence	63 (1%)	161 (1%)
Treated by rheumatologist	166 (2%)	524 (2%)
Diagnosis of rheumatoid arthritis	55 (1%)	139 (<1%)
Disease-modifying antirheumatic drug use	191 (2%)	536 (2%)
Prednisone use (>1000 mg)	378 (5%)	691 (2%)

Data are mean (SD) or number of participants (%). *Totals lower than the sum of the contributing subcategories because patients could contribute to more than one subcategory. †Visits not resulting in admission.

Table 1: **Characteristics of cases and matched controls from a base population of 1 394 764 users of COX2 selective and non-selective NSAIDs, 1999–2001**

and has been a source of controversy within the FDA. With respect to the study described here, which has been revised from that previously posted to correctly apply enrolment criteria for cases and controls, Kaiser Permanente and FDA management had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 1 394 764 people contributed 2 302 029 person-years of observation time to the study cohort of NSAID users. Patients received various NSAIDs, including celecoxib (n=40 405), ibuprofen (991 261), naproxen (435 492), and rofecoxib (26 748). From this cohort, we identified 8199 cases of serious coronary heart disease and 32 796 matched controls. Of these, we excluded 56 cases and 1300 controls who did not meet the enrolment criteria, resulting in 8143 cases and 31 496 controls.

	Celecoxib (n=491)	Ibuprofen (n=2573)	Naproxen (n=1409)	Rofecoxib (n=196)	Remote use (n=18 720)
Age (years)	73·4 (8·5)	66·9 (11·3)	68·4 (10·9)	72·1 (9·9)	66·4 (11·7)
Men	245 (50%)	1591 (62%)	801 (57%)	91 (46%)	11 807 (63%)
Cardiovascular risk score	4·21 (3·24)	3·11 (3·14)	3·22 (3·15)	3·14 (3·16)	2·91 (3·16)
Cardiovascular admissions in past year	31 (6%)	59 (2%)	51 (4%)	5 (3%)	581 (3%)
Cardiovascular drug use in past year	373 (76%)	1535 (60%)	876 (62%)	129 (66%)	10 388 (55%)
Angiotensin-converting-enzyme inhibitor	140 (29%)	512 (20%)	301 (21%)	43 (22%)	3555 (19%)
Angiotensin-receptor blocker	29 (6%)	33 (1%)	28 (2%)	2 (1%)	348 (2%)
Antiarrhythmic drug	11 (2%)	29 (1%)	19 (1%)	2 (1%)	214 (1%)
Anticoagulant drug	46 (9%)	38 (1%)	27 (2%)	15 (8%)	674 (4%)
β blocker	159 (32%)	589 (23%)	318 (23%)	50 (26%)	3974 (21%)
Calcium-channel blocker	111 (23%)	351 (14%)	231 (16%)	31 (16%)	2532 (14%)
Digitalis glycoside	40 (8%)	74 (3%)	44 (3%)	9 (5%)	679 (4%)
Hypoglycaemic drug	78 (16%)	324 (13%)	182 (13%)	18 (9%)	2192 (12%)
Lipid-lowering drug	130 (26%)	489 (19%)	287 (20%)	48 (24%)	3505 (19%)
Loop diuretic	82 (17%)	165 (6%)	122 (9%)	19 (10%)	1239 (7%)
Nitrate	64 (13%)	243 (9%)	128 (9%)	23 (12%)	1463 (8%)
Platelet inhibitor	9 (2%)	27 (1%)	19 (1%)	1 (1%)	278 (1%)
Thiazide diuretic	127 (26%)	605 (24%)	352 (25%)	56 (29%)	3658 (20%)
Other medical care in past year					
Non-cardiovascular admission	49 (10%)	176 (7%)	97 (7%)	15 (8%)	1524 (8%)
Non-cardiovascular emergency room visit*	100 (20%)	532 (21%)	248 (18%)	36 (18%)	4162 (22%)
Oestrogen use by women	107 (22%)	434 (17%)	322 (23%)	52 (27%)	2779 (15%)
Smoking-related diagnoses	8 (2%)	88 (3%)	40 (3%)	2 (1%)	610 (3%)
Treated by rheumatologist	18 (4%)	39 (2%)	39 (3%)	17 (9%)	239 (1%)
Disease-modifying antirheumatic drug use	28 (6%)	60 (2%)	46 (3%)	9 (5%)	218 (1%)
Prednisone use (>1000 mg)	22 (4%)	56 (2%)	39 (3%)	12 (6%)	368 (2%)

Data are mean (SD) or number of controls (%). *Visits not resulting in admission.

Table 2: **Characteristics of controls currently exposed to celecoxib, ibuprofen, naproxen or rofecoxib, or remotely exposed to an NSAID.**

Of the 8143 cases of serious coronary heart disease, 6635 were admitted with acute myocardial infarction and 1508 had sudden cardiac death. Laboratory

	Cases	Controls	Unadjusted odds ratio (95% CI)	Adjusted* odds ratio (95% CI)	p
Compared with remote use					
Remote use	4658	18 720	1·00	1·00	
Recent use	1720	6258	1·12 (1·05–1·20)	1·11 (1·03–1·19)	0·004
Current use					
Celecoxib	126	491	1·05 (0·86–1·28)	0·84 (0·67–1·04)	0·12
Ibuprofen	670	2573	1·07 (0·98–1·18)	1·06 (0·96–1·17)	0·27
Naproxen	367	1409	1·07 (0·95–1·21)	1·14 (1·00–1·30)	0·05
Rofecoxib (all doses)	68	196	1·39 (1·05–1·83)	1·34 (0·98–1·82)	0·066
Rofecoxib ≤25 mg/day	58	188	1·23 (0·92–1·66)	1·23 (0·89–1·71)	0·21
Rofecoxib >25 mg/day	10	8	5·03 (1·98–12·76)	3·00 (1·09–8·31)	0·03
Other NSAIDs	534	1849	1·19 (1·07–1·32)	1·13 (1·01–1·27)	0·03
Compared with celecoxib use					
Celecoxib use	126	491	1·00	1·00	
Remote use	4658	18 720	0·95 (0·78–1·16)	1·11 (0·96–1·48)	0·12
Recent use	1720	6258	1·07 (0·87–1·31)	1·32 (1·06–1·65)	0·015
Current use					
Ibuprofen	670	2573	1·02 (0·82–1·27)	1·26 (1·00–1·60)	0·054
Naproxen	367	1409	1·02 (0·81–1·28)	1·36 (1·06–1·75)	0·016
Rofecoxib (all doses)	68	196	1·32 (0·94–1·85)	1·59 (1·10–2·32)	0·015
Rofecoxib ≤25 mg/day	58	188	1·17 (0·82–1·67)	1·47 (0·99–2·17)	0·054
Rofecoxib >25 mg/day	10	8	4·78 (1·85–12·38)	3·58 (1·27–10·11)	0·016
Other NSAIDs	534	1849	1·13 (0·91–1·41)	1·35 (1·06–1·72)	0·015

*Adjusted for age, sex, and health plan region, cardiovascular risk score, admission for non-cardiac-related disorders and same-day procedures, emergency room visits for non-cardiac reasons, hormone replacement therapy, and high-dose prednisone.

Table 3: **Risk of acute myocardial infarction with use of selected NSAIDs compared with remote use of a NSAID or with current use of celecoxib**

confirmation (raised creatine kinase MB fraction or troponin I) was present in 5799 (87%) patients admitted with acute myocardial infarction. Of all admitted cases, 702 (11%) died. As expected, the prevalence of previous cardiovascular admission, emergency room visits, and drug use was uniformly increased in cases (table 1).

To establish if risk factors for cardiovascular disease varied by NSAID use, we investigated the distribution of these factors in controls (table 2). Controls exposed to ibuprofen or naproxen, and those with remote exposure to any NSAID, were similar with respect to age, sex, and most covariates, although anticoagulant drug use was more common in the remotely exposed group than in the other groups. Rofecoxib-exposed controls were older, more likely to be women and to be treated by a rheumatologist, and more likely to have used anticoagulants or oral prednisone than controls exposed to ibuprofen, naproxen, or a remote NSAID. Celecoxib-treated controls had more cardiovascular admissions in the preceding year and had a higher frequency of use for various cardiovascular drugs than those exposed to rofecoxib. Cardiovascular risk scores were significantly greater for controls treated with celecoxib than for those from all other groups including rofecoxib (p=0·0001, rofecoxib vs celecoxib).

When all current users of rofecoxib were compared with remote users of NSAIDs, the risk of serious coronary heart disease was enhanced 1·34-fold (p=0·066; table 3). Risk fell slightly with celecoxib (odds ratio 0·84) and rose a little with standard-dose rofecoxib

	Celecoxib use (n=169)	Ibuprofen use (n=190)	Naproxen use (n=192)	Rofecoxib use (n=81)	Remote use (n=185)	Total (n=817)	p
Aspirin use	32 (19%)	43 (23%)	53 (28%)	19 (23%)	44 (24%)	191 (23%)	0·43
Over-the-counter NSAID use (≥2 days a week for ≥1 year)	26 (15%)	18 (9%)	23 (12%)	11 (14%)	24 (13%)	102 (12%)	0·55
Smoking history							
Current	15 (9%)	17 (9%)	22 (11%)	6 (7%)	20 (11%)	80 (10%)	0·80
Past	72 (43%)	100 (53%)	78 (41%)	35 (43%)	89 (48%)	374 (46%)	0·14
Family history of acute myocardial infarction							
First-degree relative	65 (38%)	90 (47%)	89 (46%)	34 (42%)	84 (45%)	362 (44%)	0·45
First-degree at early age*	27 (16%)	34 (18%)	34 (18%)	13 (16%)	29 (16%)	137 (17%)	0·97

Data are number of controls (%). *Men age ≤55 years, women age ≤60 years.

Table 4: Aspirin use, over-the-counter NSAID use, smoking history, and family history of acute myocardial infarction in 817 randomly selected controls with remote NSAID exposure or current exposure to celecoxib, ibuprofen, naproxen, or rofecoxib

(1·23). When all current users of rofecoxib were compared with current users of celecoxib, risk was increased 1·59-fold (p=0·015, table 3). For high-dose rofecoxib, the odds ratio was 3·58 (p=0·016) and for standard-dose rofecoxib it was 1·47 (p=0·054). Compared with remote use, risk of serious coronary heart disease was amplified with recent use of any NSAID, current use of naproxen, and current use of other NSAIDs. The increased odds ratio for other NSAIDs was attributable to the effects of diclofenac (odds ratio 1·60 [95% CI 0·92–2·79]; p=0·09) and indometacin (1·30 [1·06–1·59]; p=0·01).

A random sample of 1015 controls with current exposure to celecoxib, ibuprofen, naproxen, or rofecoxib or with remote exposure to a NSAID was contacted by telephone to complete a brief questionnaire; 817 (80%) participated. Controls were generally comparable with respect to cardiovascular disease risk factors, although low-dose aspirin use was somewhat lower in celecoxib-exposed controls than in the other groups (table 4).

Discussion

The data from the present study provide further evidence that rofecoxib increases the risk of serious coronary heart disease.

Our study has several limitations. NSAID exposure was established from records of filled prescriptions and thus would not include data for drugs obtained over the counter. A telephone survey of a random sample of controls established that use of over-the-counter NSAIDs did not differ by prescription NSAID use status. Therefore, any misclassification of exposure should be non-differential and would not account for the study findings.

Although we adjusted for a wide range of recognised and potential cardiovascular risk factors, we did not have information on important factors such as smoking, family history of myocardial infarction, and use of low-dose aspirin. However, the findings of the telephone survey showed these factors were not differentially distributed with respect to NSAID exposure and thus such confounding is unlikely to account for study findings. These survey results accord with those of other studies, in which low-dose aspirin use[22–24] or smoking behaviour[22,24] did not differ by specific NSAID. In an analysis of data from a nationwide in-home survey of US Medicare beneficiaries, patients treated with celecoxib, rofecoxib, or non-selective NSAIDs did not differ with respect to body-mass index, smoking behaviour, aspirin use, or educational level.[7]

Although we studied serious coronary heart disease in a population of 6 million people, sample size was limited for some comparisons. Relatively few people in the study base were exposed to high-dose rofecoxib. Nevertheless, the sample size was sufficient to show a substantially higher risk for high-dose use than for either remote NSAID use or celecoxib use. Our findings accord with those of the two other published epidemiological studies that have analysed use of rofecoxib in doses greater than 25 mg.[6,7]

Because of limited power, we were unable to fully address whether the cardiovascular risk associated with rofecoxib varied by duration of use. This issue arose after interpretation of data for a study of 2586 patients randomly allocated either rofecoxib 25 mg/day or placebo, who were followed up for 3 years for the development of colon polyps (Adenomatous Polyp Prevention on Vioxx; APPROVe).[25] 25 cardiovascular events arose in the placebo group and 45 in the rofecoxib group, and the difference in incidence became significant only after 18 months on the drug.[25] An entirely plausible explanation for these results is insufficient statistical power before 18 months of study time. Indeed, inadequate sample size and low power of tests of interaction make it unlikely that true differences could be found when assessing the subgroup of events occurring early in the study.[26]

In our study, the mean duration of use before occurrence of a study event was 113 days (range 4–688) with standard-dose rofecoxib and 112 days (8–262) with high-dose use (p=0·96), consistent with the idea that risk begins early in treatment. Furthermore, analysis by the FDA of data from the VIGOR trial showed that the survival curve for acute myocardial infarction risk with high-dose rofecoxib began to diverge from the naproxen curve after 1 month of rofecoxib use.[27] The absence of divergence during the first month could be attributable to the few events in either study group, leading to inadequate

statistical power.[26] Thus, these results cannot be viewed as evidence that the first month is free of risk. Indeed, in this same FDA review, analysis of a Merck-sponsored postapproval randomised clinical trial (study 090) of very short-term use of the 12·5 mg rofecoxib dose showed substantial differences in cardiovascular risk between rofecoxib and nabumetone or placebo.[27] Moreover, findings of three reports—two large nested case-control studies[7,28] and a cumulative meta-analysis of rofecoxib clinical trials[29]—strongly suggest that cardiovascular risk begins early with both standard-dose and high-dose rofecoxib treatment.

The present study provides data relevant to several other active controversies about the cardiovascular safety of NSAIDs. In current users of celecoxib, a slightly reduced risk of serious coronary heart disease was noted; in other studies, a similar diminished risk with celecoxib was seen.[6–8] Indeed, in several studies,[30,31] potentially beneficial effects of celecoxib on endothelial function and coronary-artery blood flow have been reported, and findings of a case-control study published online in December, 2004,[28] showed that celecoxib protected against the occurrence of non-fatal myocardial infarction compared with non-use of NSAIDs or rofecoxib use. However, the US National Cancer Institute halted its Adenoma Prevention with Celebrex (APC) trial[32] after the data safety monitoring board reported a 2·5-fold greater risk of acute myocardial infarction and stroke in patients treated with celecoxib 400 mg/day and a 3·4-fold increase in risk with 800 mg/day.

Findings of other studies raise concerns about a COX2 class effect. Higher rates of acute myocardial infarction, stroke, and death have been recorded in patients treated with valdecoxib after coronary-artery bypass surgery than in those given opioid treatment for postoperative pain.[33] These increases were not significant but the study was small. The manufacturer of valdecoxib announced the results of a second study,[34] in which an increased risk of serious coronary heart disease was again noted in patients treated with the drug after bypass surgery. In a large clinical trial,[35] the rate of acute myocardial infarction was increased in individuals treated with another COX2-selective drug, lumiracoxib, compared with naproxen, especially in those not taking low-dose aspirin. This difference was not significant and was not present when compared with ibuprofen use. Additional data from clinical trials in patients with baseline cardiovascular disease would be useful.[36]

After publication of the VIGOR trial findings, considerable speculation arose that naproxen reduced the risk of coronary heart disease.[2] However, our findings, like those of some[7–9] but not all[10–12] others, suggest this drug does not have cardioprotective effects. Indeed, the present data show the possibility of a small increased risk of serious coronary heart disease, and a US National Institutes of Health trial was stopped after preliminary analysis suggested a 50% increase in risk of acute myocardial infarction and stroke in patients treated with naproxen.[37] The lack of a protective effect of naproxen is important, because the drug frequently is a comparator in clinical trials of new coxibs.[2,35] Thus, findings from such studies showing that the new drug has an increased risk of cardiovascular disease relative to naproxen should alert doctors and patients to potential cardiotoxic effects.

While this report was in preparation, rofecoxib was withdrawn from the market by the manufacturer.[38] Many would argue that, in view of the findings of the VIGOR trial[2] and subsequent observational studies,[6,7] withdrawal or restriction of rofecoxib should have happened much earlier.[29,36]

We should assess the potential public-health effects of failure to take earlier action. From 1999 to September, 2004, an estimated 106·7 million rofecoxib prescriptions were dispensed in the USA, of which 17·6% were high-dose.[39] In two Merck-sponsored randomised clinical trials,[2,25] relative risks for acute myocardial infarction of 5 for high-dose rofecoxib and 2 for the standard dose were recorded. The background rate for acute myocardial infarction among control groups from studies of cardio-vascular risk in NSAID users varied from 7·9 per 1000 person-years in CLASS[1] to 12·4 per 1000 person-years in TennCare.[6] Using the relative risks from the above-mentioned randomised clinical trials and the background rates seen in NSAID risk studies, an estimated 88000–140000 excess cases of serious coronary heart disease probably occurred in the USA over the market-life of rofecoxib.[40] The US national estimate of the case-fatality rate (fatal acute myocardial infarction plus sudden cardiac death) was 44%,[41] which suggests that many of the excess cases attributable to rofecoxib use were fatal.

In the future, when trials such as VIGOR show that a new treatment confers a greater risk of a serious adverse effect than a standard treatment, we must be much more careful about allowing its unrestrained use.

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