

Memorandum from David J. Graham, MD, MPH, Associate Director for Science, Office of Drug Safety to Paul Seligman, MD, MPH, Acting Director, Office of Drug Safety entitled, "Risk of Acute Myocardial Infarction and Sudden Cardiac Death in Patients Treated with COX-2 Selective and Non-Selective NSAIDs," September 30, 2004

The attached report was prepared for internal FDA use by an FDA staff person who was the principal FDA investigator on a study performed to investigate the cardiovascular risk of the COX-2 selective NSAIDs, rofecoxib and celecoxib, and a variety of non-selective, traditional NSAIDs. This report may differ from any subsequent manuscript publication of the study results. As of the date of posting (November 2), the report has not been fully evaluated by the FDA and may not reflect the official views of the agency. However, in light of the recent market withdrawal of Vioxx, FDA has decided to publicly release the document at this time. An error has been identified on page 6 of the report. The National Disease and Therapeutic Index collects detailed information from a representative panel of 3,500 physicians, not 2,000 physicians.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 30, 2004

FROM: David J. Graham, MD, MPH
Associate Director for Science, Office of Drug Safety

TO: Paul Seligman, MD, MPH
Acting Director, Office of Drug Safety

SUBJECT: Risk of acute myocardial infarction and sudden cardiac death in patients treated with COX-2 selective and non-selective NSAIDs

The following report describes the study we performed to investigate the cardiovascular risk of the COX-2 selective NSAIDs rofecoxib and celecoxib, and a variety of non-selective, traditional NSAIDs.

The study team included the following:

FDA, CDER: David J. Graham, MD, MPH (Principal investigator)

Kaiser Permanente, California: David Campen, MD, Craig Cheetham, PharmD, Rita Hui, PhD, Michel Spence, PhD, Gerald Levy, MD, Stanford Shoor, MD

Vanderbilt University School of Medicine: Wayne A. Ray, PhD

Background

Cyclooxygenase-2 (COX-2) selective nonsteroidal antiinflammatory drugs (NSAIDs) are prescribed for the treatment of arthritis and other musculoskeletal complaints because of their reduced gastrointestinal toxicity compared with traditional, non-selective NSAIDs.^{1,2} Questions about cardiovascular risk with these newer agents were raised by the finding of a 4-fold difference in incidence of acute myocardial infarction (AMI) between patients treated with rofecoxib 50 mg/day compared to naproxen 1000 mg/day in a large randomized clinical trial.² Given the high utilization of COX-2 agents in the US, even a small difference in cardiovascular risk between members of this class would have substantial public health impact.

A series of observational studies have examined the questions of cardiovascular risk with rofecoxib and potential cardioprotection with naproxen. A cohort study found nearly a 2-fold increased risk of serious coronary heart disease (AMI and sudden cardiac death (SCD)) among users of high-dose rofecoxib (>25 mg/day) compared to non-users.³ Another cohort study found no increase in risk but did not look at high-dose rofecoxib separately.⁴ A case-control study found an increased risk of hospitalized AMI in patients treated with rofecoxib compared with celecoxib use or no current use of other NSAIDs at both high- and standard-doses of rofecoxib.⁵ Studies examining the effect of naproxen on cardiovascular risk have also yielded conflicting results. Three cohort studies reported no reduction in risk with naproxen use.^{3,4,6} Three other studies, two funded by the manufacturer of rofecoxib, reported a protective cardiovascular effect with naproxen.⁷⁻⁹

The purpose of this study was to examine whether the risk of serious coronary heart disease was increased among patients treated with rofecoxib and whether naproxen use was protective against this outcome.

Methods

Study setting. Kaiser Permanente is an integrated managed care organization providing comprehensive health care to over 6 million residents in the state of California.¹⁰ The plan maintains automated files of eligibility, outpatient visits, hospitalizations, medical procedures, emergency room visits, laboratory testing and outpatient drug prescriptions for all its members. Mortality status, with underlying cause of death from death certificates, is periodically updated for the system's membership using mortality data obtained from the California Department of Health, Center for Health Statistics.

Base cohort. From January 1, 1999 through December 31, 2001, all patients from age 18 to 84 years who filled at least one prescription for a COX-2 selective or non-selective NSAID were identified. Patients with at least 365 days of health plan coverage prior to the date of that first NSAID prescription were entered into the study cohort if they had no diagnoses of cancer, renal failure, liver failure, severe respiratory disease, organ transplantation, or HIV/AIDS during the screening interval. Cohort members were followed from this entry date until the end of the study period, occurrence of an AMI or death, whichever came first.

Study design. Within this NSAID-treated cohort, a nested case-control study was performed. The primary study questions were 1) is the risk of AMI and SCD increased in patients taking rofecoxib at standard (≤ 25 mg/day)- or high (>25 mg/day)-doses compared with a) remote use of any NSAID or b) current use of celecoxib; and 2) is the risk of AMI and SCD decreased in patients taking naproxen compared with remote use of any NSAID.

Study outcome. The study outcome of interest was a serious cardiac event, defined as hospitalized AMI or out-of-hospital SCD. Hospitalized AMI was defined using the ICD 9-CM code 410 (acute myocardial infarction), or 411.1 (intermediate coronary syndrome) provided there was laboratory documentation of acute myocardial infarction (elevated creatine kinase MB fraction or troponin I). Outpatient deaths were classified as SCD if the underlying cause of death listed conditions previously associated with this outcome including hypertensive heart disease, ischemic heart disease, conduction disorders, dysrhythmias, heart failure, atherosclerotic heart disease, sudden death, or death from an unknown cause.^{3,6}

Control selection. For each case, four controls were randomly selected from among those patients under observation in the study cohort on the date of the case event (index date), and matched on age (year of birth), gender and health plan region (north or south). This type of control selection is sometimes referred to as risk-set or incidence density matching and models the approach used in survival analysis, by sampling from the pool of patients (and their time at risk of becoming a case) that gave rise to the case on the index date.¹¹ A given patient, selected as a control for a case on one date could be selected to serve as a control for another case occurring on a later index date, provided he or she remained in the study cohort and was therefore also at risk of becoming a case. Likewise, a patient serving as a control could subsequently become a case.

Exposure classification. The NSAID exposure status of cases and controls was determined as of the case index date. Patients were considered currently exposed if the duration of the NSAID prescription closest to, and preceding, the index date overlapped with the index date itself. Those with NSAID prescriptions ending between 1 and 60 days before the index date were classified as recently exposed, and those for whom exposure ended more than 60 days before the index date were classified as remotely exposed. Rofecoxib exposure was classified as either

standard dose (≤ 25 mg/d) or high dose (> 25 mg/d) based on tablet strength, number of tablets dispensed, instructions for use, the days-supply and the refill pattern of drug use. For rofecoxib-treated patients with inconsistencies between the instructions for use, days-supply and frequency of refills, computerized print-outs of all NSAID prescriptions covering the entire study period were reviewed by a panel blinded to case or control status (DC, CC, RH, MS). Patients were classified as exposed to high dose rofecoxib only if there was unanimous consensus among panel members.

Covariates. For the 365-day period prior to the index date, data were collected on potential risk factors for the occurrence of AMI or sudden cardiac death. These included cardiovascular hospitalizations as determined by diagnosis-related-group coding (AMI, coronary revascularization, angina, congestive heart failure, other ischemic heart disease, cardiac arrhythmias, cerebrovascular accidents, peripheral vascular disease); emergency room visits for cardiovascular reasons and outpatient diagnoses for tobacco use as determined by ICD 9 coding; and cardiovascular prescription drug use (thiazide diuretics, loop diuretics, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, calcium channel blockers, beta-blockers, digoxin, nitrates, anti-arrhythmics, 3-hydroxy-3-methyl-glutaryl co-enzyme A reductase inhibitors, fibrates, niacin, antiplatelet agents (ticlopidine, clopidogrel), anticoagulants (warfarin, low molecular weight heparin), insulin, oral hypoglycemics). Data were also collected on non-cardiovascular hospitalizations and emergency room visits, same-day hospitalizations for medical procedures, outpatient diagnoses of alcohol dependence and rheumatoid arthritis, and prescription use of hormone replacement therapy, oral prednisone ($>1,000$ mg in the past year) or disease modifying anti-rheumatic drugs (DMARDs).

Cardiovascular risk score. To control for potential differences in cardiovascular risk between patients treated with different NSAIDs, a summary cardiovascular risk score was created from regression models of the effects of the cardiovascular factors shown in table 1 on the odds of an acute cardiac event, in which the regression coefficients determined the weight given to each factor.^{3,6,12-14} As with propensity scores, an advantage of this method is that it conserves degrees of freedom and improves the precision of risk estimates, especially in situations where the number of events for a particular exposure or covariate are small.¹⁵

Table 1. List of variables contributing to the generation of the cardiovascular risk score.

Cardiovascular hospitalizations	Cardiovascular medications
Acute myocardial infarction/revascularization	ACE inhibitors/ARBs
Angina	β-blockers
Congestive heart failure	Calcium channel blockers
Other ischemic heart disease	Digoxin
Arrhythmias	Loop diuretics
Other (includes CVA & PVD)	Nitrates
	Thiazide diuretics
Cardiovascular ER visits	Statins
	Fibrates
Smoking diagnosis	Niacin
	Insulin
	Oral hypoglycemics
	Anticoagulants
	Anti-platelet agents (clopidogrel/ticlopidine)
	Anti-arrhythmics

There was a 12.5-fold difference in risk of AMI or SCD between the lowest (0) and highest (9) value of the score, with a progressive increase in risk with each increasing score value.

To evaluate the quality and reliability of the cardiovascular risk score, we examined its performance in situations where there was no concern about degrees of freedom and found that regression analyses performed using the score or all 23 covariates summarized by the score yielded nearly identical results (table 2).

Table 2. Comparison of two approaches for estimating the odds ratio of AMI and SCD.

	Ibuprofen	All other NSAIDs
Full model	1.106	1.155
Model with CVS	1.094	1.137
Difference	.012	.018

Analysis. Conditional logistic regression was performed to evaluate the independent effects of current exposure to COX-2 selective- and non-selective-NSAIDs, adjusted for the covariates described above. A single regression model was used in which current exposure to all NSAIDs, recent exposure to any NSAID and remote exposure to any NSAID were included as a single variable (drug exposure) that was handled as a series of

categorical (dummy) variables. In this way, all data from all patients was incorporated in the estimation of coefficients, odds ratios and 95% confidence intervals.

The primary analysis compared current exposure to a specific NSAID with remote exposure to any NSAID as reference. An a priori purpose of the study was to compare current exposure to either standard- or high-dose rofecoxib against current exposure to celecoxib. The Wald test was used to compare the coefficients for these drugs derived from the above regression. The same regression model was rerun using celecoxib as the reference to obtain estimates of the odds ratio and 95% confidence intervals for standard- and high-dose rofecoxib. Secondary analyses examined the risk of AMI and SCD with other NSAIDs, compared to remote NSAID use or celecoxib use.

Survey of controls. To determine if confounding of an association between selected NSAIDs and a serious cardiac event was occurring because of low-dose aspirin use, over-the-counter NSAID use, smoking history and family history of AMI, a standardized telephone survey was administered by a contract research organization specializing in patient surveys. The survey was conducted on a random sample of controls currently exposed to celecoxib, ibuprofen, naproxen or rofecoxib, or controls with remote exposure to any NSAID and asked a series of questions related to these potential confounding factors.

Number needed to harm and population impact. The impact of using rofecoxib rather than celecoxib was examined by estimating the number of excess cases of AMI or SCD that occurred among rofecoxib users within the study cohort. This was done by calculating the number needed to treat for one year to generate one excess case of a AMI or SCD (number needed to harm (NNH)) and dividing the cumulative person-time of exposure to rofecoxib at standard- and high-doses by their respective NNH.

The NNH was obtained using the formula: $NNH = [PEER(OR-1)+1]/[PEER(OR-1)(1-PEER)]$, where OR was the odds ratios obtained from the regression analysis that compared rofecoxib to celecoxib and PEER was the population expected event rate, calculated as the incidence rate of serious cardiac events within the study cohort during NSAID-exposed time.¹⁶

To examine the potential national impact of using rofecoxib rather than celecoxib within the US, data on rofecoxib use (total prescriptions, mean prescription length in days, tablet strength and physician instructions for use) was obtained from two audits maintained by IMS Health, a national health information company.¹⁷ The National Prescription Audit-Plus® collects data on all prescriptions filled at 20,000 computerized pharmacies throughout the US. It is used by IMS to generate national estimates of prescription use. The National Disease and Therapeutic Index® collects detailed information from a representative panel of 2,000 physicians across the US on a number of drug-related items including instructions about how to take medications. For the years 1999-2003, the total person-years of rofecoxib use at standard- and high-doses within the US was estimated using the above data, and divided by the NNH to derive estimates of the number of excess cases of serious cardiac events.

Analyses were performed using Stata version 7.0 (College Station, TX). This study was approved by the institutional review boards of both the northern and southern divisions of Kaiser Permanente in California.

Results

A total of 1,394,764 patients contributed 2,295,168 person-years of observation time to the study cohort of NSAID users. At different times during this period, most patients were exposed to a variety of different NSAIDs including celecoxib (n=40,405), ibuprofen (n=991,261), naproxen (n=435,492) and rofecoxib (n=26,748) (table 3).

Table 3. Exposure to Specific NSAIDs within the Study Cohort of 1,394,764 Patients

Drug	Number
Celecoxib	40,405
Diclofenac	6,293
Etodolac	34,115
Ibuprofen	991,261
Indomethacin	118,261
Nabumetone	93,976
Naproxen	435,492
Piroxicam	35,893
Rofecoxib	26,748
Sulindac	78,481
Other NSAIDs	22,891

There were 8,199 incident cardiac events (6,675 hospitalized AMI, 1,524 SCD). Laboratory confirmation (elevated creatine kinase-MB fraction or troponin I) was present in 5,836 (87.4%) hospitalized cases and of these, 706 (10.6%) died. With 350,071 person-years of exposure to any NSAID within the study cohort and 1,772 incident cases during current exposure to any of these drugs, the incidence rate was 5.06 per 1,000 person-years. Matching resulted in balance of age and gender between cases and controls. As expected, the prevalence of prior cardiovascular hospitalizations, emergency room visits and drug use was uniformly increased among cases (table 4, at end of report).

Controls exposed to ibuprofen or naproxen, or those with remote exposure to any NSAID were similar with respect to age, gender and most covariates, though anticoagulant use and emergency department visits for cardiovascular reasons were more common among the remotely exposed group (table 5, at end of report). Rofecoxib exposed controls were older and more likely to be women than controls exposed to ibuprofen, naproxen or a remote NSAID. However, the rofecoxib group was similar to these other control groups for most other covariates, except for an increased prevalence of anticoagulant and oral prednisone use and of having been treated by a rheumatologist. Celecoxib treated controls tended to have a higher prevalence of use for a variety of cardiovascular drugs compared with those exposed to rofecoxib, including angiotensin converting enzyme inhibitors, β -blockers, calcium channel blockers, digoxin, loop diuretics and hypoglycemic agents. The greater prevalence of cardiovascular disease in celecoxib users is shown by their higher cardiovascular risk score.(table 6).

The cardiovascular risk score of patients treated with standard-dose rofecoxib (3.69 (3.35)) is much lower than for celecoxib ($p=0.002$) but the score for high-dose patients (5.61 (3.52)) is not statistically different ($p=0.16$).

Table 6. Cardiovascular risk scores for celecoxib, rofecoxib and remote NSAID users.

	Celecoxib	Rofecoxib	Remote
N	623	266	24,575
CVS, mean (SD)	4.48 (3.33)	3.82 (3.39)	3.28 (3.36)
p-value vs. remote	<0.0001	0.01	Ref
p-value vs. celecoxib	Ref	0.007	<0.0001

The risk of serious coronary heart disease with rofecoxib (all doses) was increased 1.40-fold (95% CI 1.03-1.90, $p=0.03$) compared to remote NSAID use and 1.63-fold (95% CI 1.12-2.36, $p=0.01$) compared to celecoxib use. The risk of hospitalized AMI and SCD with high-dose rofecoxib was increased 3.15-fold (95% CI 1.14-8.75) compared to remote use of an NSAID (table 7).

Table 7. Risk of acute myocardial infarction with current use of celecoxib, ibuprofen, naproxen, rofecoxib or other NSAID compared with remote use of a nonsteroidal agent.

NSAID use	Cases	Adjusted ¹ OR (95% CI)
Remote use	4699	1.00
Recent use	1728	1.14 (1.06-1.22)
Current use		
Celecoxib	126	0.86 (0.69-1.07)
Ibuprofen	674	1.09 (0.99-1.21)
Naproxen	369	1.18 (1.04-1.35)
Rofecoxib \leq 25 mg	58	1.29 (0.93-1.79)
Rofecoxib $>$ 25 mg	10	3.15 (1.14-8.75)
Other NSAIDs	535	1.16 (1.04-1.30)

¹ Adjusted for age, gender and health plan region; hospitalization for AMI, coronary artery revascularization, angina, heart failure, other ischemic heart disease, peripheral vascular disease, cerebrovascular accident, non-cardiac-related disorders and same-day procedures; emergency room visits for cardiac and non-cardiac reasons; smoking-related diagnoses; and use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, anti-arrhythmics, anticoagulants, β -blockers, calcium channel blockers, digoxin, insulin, loop diuretics, nitrates, oral hypoglycemic agents, thiazide diuretics, HMG-CoA reductase inhibitors, fibrates, niacin, clopidogrel, ticlopidine, hormone replacement therapy, and high-dose prednisone.

Risk was decreased with celecoxib and increased with standard-dose rofecoxib, but neither significantly so when compared to remote exposure. Of note, the lower bound of the 95% CI for standard-dose rofecoxib excluded the point estimate of the odds ratio for celecoxib and the upper bound of the 95% CI for celecoxib excluded the point estimate for the odds ratio with standard-dose rofecoxib. The Wald test for the difference in coefficients between celecoxib and standard-dose rofecoxib was $p=0.04$. Compared to celecoxib, the odds ratio for a serious cardiac event with high-dose rofecoxib was 3.69 (95% CI 1.30-10.45, $p=0.01$) and with standard-dose rofecoxib, 1.50 (95% CI 1.02-2.21, $p=0.04$).

For the non-coxib NSAIDs, compared to remote use, risk was increased with naproxen (1.18; 95% CI 1.04-1.35) and with "other NSAIDs" (1.16; 95% CI 1.04-1.30). The increased odds ratio here was due to the effects of diclofenac (1.69; 95% CI 0.97-2.93, $p=0.06$) and indomethacin (1.33; 95% CI 1.09-1.63, $p=0.005$).

A random sample of 1,028 controls with current exposure to celecoxib, ibuprofen, naproxen or rofecoxib, or with remote exposure to any NSAID, were contacted by telephone to complete a brief questionnaire, of which 831 (80.8%) agreed to participate. The control groups were generally comparable with respect to each of these risk factors although low dose aspirin use was somewhat less among celecoxib users (table 8, at end of report). The extent of OTC NSAID use was high in all groups.

The mean length of rofecoxib use prior to occurrence of AMI or SCD was 112 days (range 8-262) in the high-dose group and 113 days (range 4-688) in the standard-dose group ($p=0.96$). Six of 8 patients (75%) with a non-fatal AMI in the high-dose group filled no additional rofecoxib prescriptions after their event compared to 21 of 41 patients (51.2%) in the standard-dose group ($p=0.27$).

There were 350,071 person-years of exposure to any NSAID within the base cohort and 1,772 serious cardiac events during current exposure to one of these drugs, for an incidence rate of 5.06 per 1,000 person-years. Using this as the population expected event rate (PEER), the NNH for high-dose rofecoxib was 75 (95% CI 22-661) and for standard-dose rofecoxib 397 (95% CI 165-9894) compared to celecoxib use. For the period of this study, the number of excess cases of AMI and SCD within the rofecoxib cohort at Kaiser was 21 of 58 cases at the standard-dose and 9.7 of 10 cases at the high-dose.

Over the years 1999-2003, an estimated 92,791,000 rofecoxib prescriptions were dispensed in the US, of which 17.6% were for greater than 25 mg/day. The estimated number of excess cases of AMI and SCD attributable to rofecoxib use was 14,845 at the standard-dose and 12,940 at the high-dose. (table 9). The excess number was nearly equal for the periods 1999-2001 and 2002-2003.

Table 9. Rofecoxib use in the US, 1999-2003, and number of excess cases of AMI and SCD resulting from the use of rofecoxib rather than celecoxib.

	Rxs	Person-years	NNH	Excess AMI and SCD
Rofecoxib \leq 25 mg/day	76,406,000	5,893,650	397	14,845
Rofecoxib $>$ 25 mg/day	16,385,000	970,453	75	12,940
Total	92,791,000	7,005,626		27,785

Discussion

Our data suggest that risk of serious coronary heart disease is increased in patients treated with rofecoxib compared with celecoxib use. High-dose rofecoxib conferred a 3.7-fold increase in risk and standard-dose a 1.5-fold increase compared with celecoxib, the most frequently prescribed COX-2 selective agent. To put this in perspective, we used our data to calculate the number needed to harm per year of treatment with rofecoxib and obtained estimates of 75 per year and 397 per year for high- and standard-dose respectively. From 1999 to 2003, there were an estimated 92,791,000 prescriptions for rofecoxib, of which 17.6% were high-dose.¹⁷ Combining this with data on mean prescription length, we estimate that the increased rofecoxib risk observed in this study would yield an excess of 27,785 cases of AMI and SCD in the US over the years 1999-2003, with 53.4% due to standard-dose use. These cases would have been avoided had celecoxib been used instead of rofecoxib.

The observation of an increased cardiovascular risk with rofecoxib compared to celecoxib should be considered in the context of potential benefits conferred by one over the other and by the magnitude and clinical importance of that benefit. Serious coronary heart disease carried a 27% mortality rate in our study. In the only published head-to-head comparison of drug benefit, rofecoxib had a 90% greater incidence rate of hospitalization for gastrointestinal bleeding compared to celecoxib, which itself, was indistinguishable from no NSAID use.¹⁸

In addition to an increased risk compared with celecoxib, we found an increased risk with high-dose use compared with remote use of any NSAID. Although the odds ratio was also increased with standard-dose use, this difference did not achieve statistical significance. A number of other observational studies have examined the question of cardiovascular risk with rofecoxib use. A cohort study comparing the incidence of serious coronary heart disease among users of rofecoxib and other NSAIDs found nearly a 2-fold increase in risk with high-dose rofecoxib compared to non-users.³ In another cohort study, the risk of hospitalized AMI was similar in rofecoxib users compared with non-users, but the effect of high-dose rofecoxib use was not examined separately.⁴ A population-based case-control study found an increased risk of hospitalized AMI in patients treated with rofecoxib compared with either celecoxib use or no current use of other NSAIDs.⁵ Risk was elevated with both high- and standard-dose rofecoxib but was greater with high-dose use.

The second important finding from this study was that naproxen was not protective against serious coronary heart disease, but may actually confer an increase in risk. This issue has been intensively investigated since a protective effect with naproxen was proposed as an explanation for a 4-fold greater risk of AMI in high-dose rofecoxib treated patients compared to naproxen use in the VIGOR trial.² Three cohort studies reported that naproxen use had no effect on cardiovascular risk compared to non-users of NSAIDs.^{3,4,6}

Three case-control studies, two funded by the manufacturer of rofecoxib, reported a protective effect against AMI with naproxen use.⁷⁻⁹ The first study found a 16% reduction in risk of hospitalized AMI among patients with any exposure to naproxen in the preceding 6 months compared with no exposure to NSAIDs during the same interval.⁷ The same degree of risk reduction was present for patients with current naproxen exposure, naproxen exposure ending 1-60 days before the index date, and naproxen exposure ending 61-180 days before the index date. This finding appears more consistent with selection bias than with a protective effect for naproxen.

Another study used a composite outcome of AMI, cerebrovascular event (including stroke, subarachnoid hemorrhage and subdural hematoma) and sudden death, and reported a 39% reduction in risk with current naproxen use compared to no use of naproxen in the past year.⁸ Of note, the regression model yielding this result did not adjust for most cardiovascular risk factors and those models that did include more complete adjustment did not show a protective effect. The use of a composite outcome, where 46% of cases were cerebrovascular events, further calls into question the interpretation of these results.

A third study reported a 21% reduction in risk of hospitalized AMI with current naproxen use compared to current use of other NSAIDs.⁹ Use of this reference group resulted in a mixing of the effects of naproxen with those of other NSAIDs such as ibuprofen, which has been shown to antagonize the protective effect of aspirin.¹⁵ Reanalysis of these data show that if former naproxen users were chosen as the reference, the unadjusted odds ratio would be 1.01 and if no NSAID use was selected as reference, the unadjusted odds ratio would be 1.28 (95% CI 1.06-1.55, $p=0.009$), a result similar to that in our study. These observations suggest that naproxen was not protective against AMI in this study. One final case-control study, which compared rofecoxib with celecoxib, did not report about naproxen risk.⁵ Using the data provided in that paper, the unadjusted odds ratio for hospitalized AMI with naproxen compared to no current NSAID use was 0.94 (95% CI 0.70-1.25, $p=0.73$).

Although we adjusted for a wide range of recognized and potential cardiovascular risk factors, there were some that could not be adjusted for directly because that information is not captured by the data systems we used. To address this, we performed a telephone survey of a random sample of exposed controls and established that use of low-dose aspirin and OTC NSAIDs, history of smoking and family history of AMI were not differentially distributed with respect to type of NSAID used within the study. Therefore, these could not function as confounders of the association between rofecoxib use and serious coronary heart disease. These survey results are consistent with the experience of others. In a number of studies, low-dose aspirin use was found not to differ by specific NSAID.¹⁹⁻²¹ Likewise, smoking behavior was not differentially distributed with respect to the NSAID a patient was treated with.^{19,21} Recently, an analysis of data from a nationwide in-home survey of US Medicare beneficiaries found that patients treated with celecoxib, rofecoxib or COX-2 non-selective NSAIDs did not differ with respect to body mass index, smoking behavior, aspirin use or educational level.⁵

There were several other limitations to this study, the most important possibly being that the use of high-dose rofecoxib was low within the population we studied, resulting in a relatively small number of exposed cases. High-dose use accounted for about 7.4% of all rofecoxib use in our study, compared with 16.1% in Tennessee Medicaid³ and 17.4% nationally in the US.¹⁷ Despite this, there was sufficient statistical power to show an increased risk for high-dose rofecoxib use compared to either celecoxib or remote NSAID use. For all other exposure categories, our study had among the largest numbers of exposed cases reported in the literature. This study and one other⁵ found an increased risk of cardiovascular disease among patients treated with standard-dose rofecoxib compared with celecoxib use. Perhaps not coincidentally, these two studies also had the largest numbers of cases exposed to these two drugs, that is, they had the most statistical power.

Medical record review and case validation was not performed in this study. However, validation studies of computerized hospital data have reported that a principle diagnosis code for AMI has a positive predictive value

between 92%²² and 95%²³ and a sensitivity of 94%.²² Furthermore, we utilized computerized laboratory data from which we observed that 87.4% of hospitalized AMI cases had confirmatory cardiac enzyme levels. Although there is probably more misclassification of the out-of-hospital SCDs, their inclusion is important (and routine in clinical trials), because coronary artery disease frequently is manifested as sudden death outside of the hospital.

Conclusions

Rofecoxib increases the risk of serious coronary heart disease defined as acute myocardial infarction and sudden cardiac death. High-dose rofecoxib increased risk by 3.7-fold and standard-dose rofecoxib increased risk by 1.5-fold compared to celecoxib use. The observation of an increased risk was first noted with the VIGOR trial, where a 5-fold difference in risk was found between high-dose rofecoxib and naproxen. The manufacturer attributed this difference to a never before recognized protective effect of naproxen. To explain a 5-fold difference, naproxen would have had to be one of the most potent and effective cardio-protectants known. Three cohort studies and the present nested case-control study found no evidence of cardio-protection with naproxen. The three case-control studies that reported a protective effect were misleading. When analyzed in a manner comparable to the present study, no protective effect is shown.

The population impact of rofecoxib's increased risk is great because of the widespread exposure to the drug. This illustrates the effect that even a relatively small increase in risk can have if you're dealing with a serious outcome that is not rare in the general population, such as is the case with AMI and SCD.

Disturbingly, while evidence of increased cardiovascular risk with rofecoxib continued to accrue following VIGOR in 2000, the only study to examine the gastrointestinal benefits of rofecoxib compared to celecoxib found that the risk of hospitalization for gastrointestinal bleeding was significantly increased in patients treated with rofecoxib. Additionally, this reviewer was unable to identify articles demonstrating a substantial benefit with the high-dose strength of rofecoxib that would counter-balance the level of cardiovascular risk shown in VIGOR or any subsequent observational study, including this one.

Prior to today, my conclusions regarding rofecoxib were that high-dose use of the drug should be ended and that lower-dose rofecoxib should not be used by physicians or patients. If lower-dose rofecoxib remained on the market, physicians and patients needed to understand that risk of AMI and SCD was substantially increased and that there were safer alternatives.

References

1. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled study. *JAMA* 2000; **284**: 1247-55.
2. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000; **343**: 1520-28.
3. Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet* 2002; **360**:1071-73.
4. Mamdani M, Rochon P, Juurlink DN, et al. Effect of selective cyclooxygenase 2 inhibitors and naproxen on short term risk of acute myocardial infarction in the elderly. *Arch Intern Med* 2003; **163**: 481-86.
5. Solomon DH, Schneeweiss S, Glynn RJ, et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. *Circulation* 2004; **109**: 2068-73.
6. Ray WA, Stein CM, Hall K, Daugherty JR, Griffin MR. Non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease: an observational study. *Lancet* 2002; **359**: 118-23.
7. Solomon DH, Glynn RJ, Levin R, Avorn J. Nonsteroidal anti-inflammatory drug use and acute myocardial infarction. *Arch Intern Med* 2002; **162**: 1099-104.
8. Watson DJ, Rhodes T, Cai B, Guess HA. Lower risk of thromboembolic cardiovascular events with naproxen among patients with rheumatoid arthritis. *Arch Intern Med* 2002; **162**: 1105-10.
9. Rahme E, Pilote L, LeLorier J. Association between naproxen use and protection against acute myocardial infarction. *Arch Intern Med*; **162**: 1111-15.
10. Sidney S, Petitti DB, Soff GA, Cundiff DL, Tolan KK, Quesenberry CP. Venous thromboembolic disease in users of low-estrogen combined estrogen-progestin oral contraceptives. *Contraception* 2004; **70**: 3-10.
11. Rothman KJ, Greenland S. Case-control studies. In: *Modern epidemiology*, 2nd ed. Rothman KJ, Greenland S, eds. Lippincott-Raven Publishers, Philadelphia, 1998:93-114.
12. Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry* 2001; **58**:1161-67.
13. Ray WA, Meredith S, Thapa PB, Hall K, Murray KT. Cyclic antidepressants and risk of sudden cardiac death. *Clin Pharmacol Ther* 2004; **75**:234-41.
14. Ray WA, Murry KT, Meridith S, Narasimhulu SS, Hall K, Stein CM. Oral erythromycin and risk of sudden death from cardiac causes. *N Engl J Med* 2004; **351**: 1089-96
15. D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998; **17**: 2265-81.
16. McAlister FA, Straus SE, Guyatt GH, Haynes RB, for the Evidence-Based Medicine Working Group. Users' guide to the medical literature: XX. Integrating research evidence with the care of the individual patient. *JAMA* 2000; **283**:2829-36.
17. IMS Health. Plymouth Meeting, PA.

18. Mamdani M, Rochon PA, Juurlink DN, et al. Observational study of upper gastrointestinal haemorrhage in elderly patients given selective cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs. *BMJ* 2002; **325**: 624-29.
19. Griffin MR, Piper JM, Daugherty JR, Snowden M, Ray WA. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. *Ann Intern Med* 1991; **114**: 257-63.
20. Smalley WE, Ray WA, Daugherty J, Griffin MR. Nonsteroidal anti-inflammatory drug use and colorectal cancer incidence: a population-based study. *Arch Intern Med* 1999; **159**: 161-66.
21. Griffin MR, Yared A, Ray WA. Nonsteroidal anti-inflammatory drugs and acute renal failure in elderly persons. *Am J Epidemiol* 2000; **151**: 488-96.
22. Fisher ES, Whaley FS, Krushat WM, et al. The accuracy of Medicare's hospital claims data: progress has been made, but problems remain. *Am J Public Health* 1992; **82**: 243-48.
23. Rawson NSB, Malcolm E. Validity of the recording of ischaemic heart disease and chronic obstructive pulmonary disease in the Saskatchewan health care datafiles. *Stat Med* 1995; **14**: 2627-43.

Table 4. Characteristics of cases (new-onset acute myocardial infarction or sudden cardiac death) and matched controls from a base population of 1,394,764 users of COX-2 selective and non-selective NSAIDs, 1999-2001.

Characteristic	Cases (n=8199)	Controls (n=32796)
Age (years, mean±SD)	66.8±11.6	66.8±11.6
Men	5067 (61.8%)	20268 (61.8%)
Cardiovascular hospitalization in past year	1241 (15.14%)	1088 (3.32%)
Myocardial infarction or revascularization	204 (2.5%)	133 (0.4%)
Angina	232 (2.8%)	275 (0.8%)
Heart failure	287 (3.5%)	111 (0.3%)
Other ischemic heart disease	356 (4.3%)	193 (0.6%)
Cardiac arrhythmia	186 (2.3%)	209 (0.6%)
Peripheral vascular disease	45 (0.6%)	37 (0.1%)
Stroke	123 (1.5%)	147 (0.5%)
Cardiovascular drug use in past year	6566 (80.1%)	18751 (57.2%)
Angiotensin-converting enzyme inhibitor	2854 (34.8%)	6456 (19.7%)
Angiotensin receptor blocker	373 (4.6%)	606 (1.9%)
Anti-arrhythmic	219 (2.7%)	351 (1.1%)
Anticoagulant	496 (6.1%)	1035 (3.2%)
β-blocker	3182 (38.8%)	7109 (21.7%)
Calcium-channel blocker	2209 (26.9%)	4588 (14%)
Digitalis glycoside	810 (9.9%)	1160 (3.5%)
Hypoglycemic agent	2214 (27%)	3841 (11.7%)
Lipid-lowering drug	2817 (34.4%)	6225 (19%)
Loop diuretic	1720 (21%)	2265 (6.9%)
Nitrate	2394 (29.2%)	2713 (8.3%)
Platelet inhibitor	435 (5.3%)	442 (1.4%)
Thiazide diuretic	2046 (25%)	6911 (21.1%)
Other medical care in past year		
Non-cardiovascular hospitalization	1372 (16.7%)	2585 (7.7%)
Cardiovascular emergency room visit ¹	338 (4.1%)	283 (0.9%)
Non-cardiovascular emergency room visit ¹	2797 (34.1%)	7147 (21.8%)
Estrogen use by women	1173 (14.3%)	5277 (16.1%)
Smoking-related diagnosis	558 (6.81%)	1038 (3.17%)
Alcohol dependence	63 (0.77%)	168 (0.51%)
Treated by rheumatologist	166 (2%)	533 (1.6%)
Diagnosis of rheumatoid arthritis	65 (0.8%)	180 (0.6%)

DMARD use	192 (2.3%)	551 (1.7%)
Prednisone use (>1gm)	379 (4.6%)	707 (2.2%)
¹ Visits not resulting in hospitalization		

Table 5. Characteristics of controls currently exposed to celecoxib, ibuprofen, naproxen or rofecoxib, or remotely exposed to an NSAID.

Characteristic	Celecoxib (n=497)	Ibuprofen (n=2606)	Naproxen (n=1416)	Rofecoxib (n=198)	Other NSAIDs (n=1864)	Remote use (n=19876)
Age (years, mean±SD)	73.3±8.5	66.8±11.3	68.4±10.6	72.0±10.1	69.9±10.6	66.1±11.8
Men	248 (49.9%)	1613 (61.9%)	805 (56.6%)	91 (46.0%)	1051 (56.4%)	12579 (63.3%)
Cardiovascular hospitalizations in past year	31 (6.2%)	64 (2.5%)	55 (3.9%)	5 (2.5%)	50 (2.7%)	675 (3.4%)
Myocardial infarction or revascularization	4 (0.8%)	68 (0.3%)	7 (0.5%)	1 (1.0%)	10 (0.5%)	72 (0.4%)
Angina	10 (2.0%)	20 (0.8%)	16 (1.1%)	0 (0%)	7 (0.4%)	159 (0.8%)
Heart failure	3 (0.6%)	6 (0.2%)	7 (0.5%)	0 (0%)	11 (0.6%)	61 (0.3%)
Other ischemic heart disease	10 (2.0%)	11 (0.4%)	10 (0.7%)	2 (1.0%)	12 (0.6%)	121 (0.6%)
Cardiac arrhythmia	3 (0.6%)	13 (0.5%)	12 (0.9%)	2 (1.0%)	6 (0.3%)	136 (0.7%)
Peripheral vascular disease	0 (0%)	3 (0.1%)	0 (0)	0 (0%)	3 (0.2%)	26 (0.1%)
Stroke	3 (0.6%)	6 (0.2%)	3 (0.2%)	0 (0%)	8 (0.4%)	95 (0.5%)
Cardiovascular drug use in past year	376 (75.7%)	1551 (59.5%)	879 (62.1%)	130 (65.7%)	1237 (66.4%)	10786 (54.3%)
Angiotensin-converting enzyme inhibitor	141 (28.4%)	517 (19.8%)	302 (21.3%)	43 (21.7%)	458 (24.6%)	3694 (18.6%)
Angiotensin receptor blocker	29 (5.9%)	39 (1.5%)	28 (2.0%)	2 (1.0%)	40 (2.2%)	356 (1.8%)
Anti-arrhythmic	11 (2.2%)	29 (1.1%)	19 (1.3%)	2 (1.0%)	20 (1.1%)	300 (1.1%)
Anticoagulant	46 (9.3%)	40 (1.5%)	27 (1.9%)	15 (7.6%)	55 (3.0%)	693 (3.5%)
β-blocker	161 (32.5%)	596 (22.9%)	319 (22.5%)	51 (25.8%)	454 (24.4%)	4120 (20.7%)
Calcium-channel blocker	111 (22.4%)	353 (13.6%)	232 (16.4%)	31 (15.7%)	325 (17.4%)	2623 (13.2%)
Digitalis glycoside	40 (8.1%)	76 (2.9%)	44 (3.1%)	9 (4.6%)	73 (3.9%)	711 (3.6%)
Hypoglycemic agent	80 (16.1%)	330 (12.7%)	182 (12.9%)	18 (9.1%)	237 (12.7%)	2277 (11.5%)
Lipid-lowering drug	130 (26.2%)	496 (19.0%)	290 (20.5%)	48 (24.2%)	389 (20.9%)	3635 (18.3%)
Loop diuretic	82 (16.5%)	167 (6.4%)	122 (8.6%)	19 (9.6%)	185 (9.9%)	1283 (6.5%)
Nitrate	64 (12.9%)	246 (9.4%)	128 (9.0%)	23 (11.6%)	182 (9.7%)	1509 (7.6%)
Platelet inhibitor	9 (1.8%)	27 (1.0%)	19 (1.3%)	1 (0.5%)	20 (1.1%)	286 (1.4%)

Thiazide diuretic	130 (26.2%)	612 (23.5%)	352 (24.9%)	57 (28.8%)	516 (27.7%)	3783 (19.0%)
Other medical care in past year						
Non-cardiovascular hospitalization	49 (9.9%)	176 (6.8%)	97 (6.9%)	15 (7.6%)	187 (10.0%)	1591 (8.0%)
Cardiovascular emergency room visit ¹	2 (0.4%)	14 (0.5%)	6 (0.4%)	0 (0%)	24 (1.3%)	343 (1.7%)
Non-cardiovascular emergency room visit ¹	100 (20.1%)	538 (20.6%)	248 (17.5%)	37 (18.7%)	369 (19.8%)	4346 (21.9%)
Estrogen use by women	107 (21.6%)	438 (16.8%)	324 (22.9%)	53 (26.8%)	411 (22.1%)	2913 (14.7%)
Smoking-related diagnoses	8 (1.61%)	89 (3.42%)	40 (2.82%)	2 (1.0%)	55 (2.95%)	631 (3.17%)
Alcohol dependence	0 (0%)	15 (0.58%)	2 (0.14%)	0 (0%)	8 (0.43%)	112 (0.56%)
Treated by rheumatologist	18 (3.6%)	39 (1.5%)	39 (2.8%)	17 (8.6%)	78 (4.2%)	244 (1.2%)
Diagnosis of rheumatoid arthritis	2 (0.4%)	15 (0.6%)	2 (0.1%)	3 (1.5%)	20 (1.1%)	79 (0.4%)
DMARD use	28 (5.7%)	60 (2.3%)	46 (3.3%)	9 (4.6%)	86 (4.6%)	232 (1.2%)
Prednisone use (> 1gm)	23 (4.6%)	56 (2.2%)	39 (2.8%)	13 (6.6%)	75 (4.0%)	379 (1.9%)

¹ Visits not resulting in hospitalization

Table 8 Aspirin use (≤ 325 mg/day), over-the-counter NSAID use, smoking history and family history of acute myocardial infarction among 831 randomly selected controls with remote NSAID exposure or current exposure to celecoxib, ibuprofen, naproxen or rofecoxib.

	Celecoxib (n=172)	Ibuprofen (n=194)	Naproxen (n=194)	Rofecoxib (n=83)	Remote (n=188)	Total (n=831)	P-value
Aspirin use, %	18.6	22.2	27.3	24.1	23.9	23.2	0.39
OTC NSAID use, [†] %	84.9	90.2	88.1	86.8	87.2	87.6	0.64
Smoking history, %							
Current	8.7	8.8	11.3	7.2	11.2	9.8	0.73
Past	43.0	52.6	40.2	43.4	47.9	45.7	0.13
Family history AMI, %							
1 st degree relative	39.5	46.9	46.4	41.0	45.7	44.4	0.56
1 st degree at early age [‡]	16.9	17.5	17.5	15.7	15.4	16.7	0.98

[†] Use ≥ 2 d/wk for ≥ 1 year

[‡] Age at first AMI: males ≤ 55 , females ≤ 60 .

CELEBREX (celecoxib) Capsules
[June 7, 2002: G.D. Searle]

CLINICAL STUDIES -

Analgnesia, including primary dysmenorrhea: In acute analgesic models of post-oral surgery pain, post-orthopedic surgical pain, and primary dysmenorrhea, CELEBREX relieved pain that was rated by patients as moderate to severe. Single doses (see DOSAGE AND ADMINISTRATION) of CELEBREX provided pain relief within 60 minutes.

Use with Aspirin:

Information on the Celecoxib Long-Term Arthritis Safety Study (CLASS), a prospective long-term safety outcome study included. Contact the company for a copy of the label/package insert.

Platelets: In clinical trials, CELEBREX at single doses up to 800 mg and multiple doses of 600 mg BID for up to 7 days duration (higher than recommended therapeutic doses) had no effect on platelet aggregation and bleeding time. Comparators (naproxen 500 mg BID, ibuprofen 800 mg TID, diclofenac 75 mg BID) significantly reduced platelet aggregation and prolonged bleeding time.

Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis.

WARNINGS

CLASS Study: The estimated cumulative rates at 9 months of *complicated and symptomatic ulcers* (an adverse event similar but not identical to the "upper GI ulcers, gross bleeding or perforation" described in the preceding paragraphs) for patients treated with CELEBREX 400 mg BID (see Special Studies - Use with Aspirin) are described in Table 5. Table 5 also displays results for patients less than or greater than or equal to the age of 65 years. The differences in rates between the CELEBREX alone and CELEBREX with ASA groups may be due to the higher risk for GI events in ASA users.

Table 5
Complicated and Symptomatic Ulcer Rates in Patients Taking CELEBREX 400 mg BID (Kaplan-Meier Rates at 9 months [%]) Based on Risk Factors

	<i>Complicated and Symptomatic Ulcer Rates</i>
All Patients	0.78
Celebrex alone (n=3105)	2.19
Celebrex with ASA (n=882)	
Patients < 65 Years	0.47
Celebrex alone (n=2025)	1.26
Celebrex with ASA (n=403)	
Patients ≥65 Years	1.40
Celebrex alone (n=1080)	3.06
Celebrex with ASA (n=479)	

In a small number of patients with a history of ulcer disease, the *complicated and symptomatic ulcer rates* in patients taking CELEBREX alone or CELEBREX with ASA were, respectively, 2.56% (n=243) and 6.85% (n=91) at 48 weeks. These results are to be expected in patients with a prior history of ulcer disease (see WARNINGS- Gastrointestinal (GI) Effects- Risk of GI Ulceration, Bleeding, and Perforation).

PRECAUTIONS

Fluid Retention, Edema, and Hypertension: Fluid retention and edema have been observed in some patients taking CELEBREX (see ADVERSE REACTIONS). In the CLASS study (see Special Studies-Use with Aspirin), the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on CELEBREX 400 mg BID (4-fold and 2-fold the recommended OA and RA doses, respectively, and the approved dose for FAP), ibuprofen 800 mg TID and diclofenac 75 mg BID were 4.5%, 6.9% and 4.7%, respectively. The rates of hypertension in the CELEBREX, ibuprofen and diclofenac treated patients were 2.4%, 4.2% and 2.5%, respectively. As with other NSAIDs, CELEBREX should be used with caution in patients with fluid retention, hypertension, or heart failure.

Drug Interactions

Aspirin: CELEBREX can be used with low-dose aspirin. However, concomitant administration of aspirin with CELEBREX increases the may result in an increased rate of GI ulceration or other complications, compared to use of CELEBREX alone (see CLINICAL STUDIES - Special Studies – Gastrointestinal Use