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# Cardiovascular Risks of Nonsteroidal Antiinflammatory Drugs in Patients After Hospitalization for Serious Coronary Heart Disease

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**Background**—The cardiovascular safety of individual nonsteroidal antiinflammatory drugs (NSAIDs) is highly controversial, particularly in persons with serious coronary heart disease.

**Methods and Results**—We conducted a multisite retrospective cohort study of commonly used individual NSAIDs in Tennessee Medicaid, Saskatchewan Health, and United Kingdom General Practice Research databases. The cohort included 48 566 patients recently hospitalized for myocardial infarction, revascularization, or unstable angina pectoris with more than 111 000 person-years of follow-up. Naproxen users had the lowest adjusted rates of serious coronary heart disease (myocardial infarction, coronary heart disease death) and serious cardiovascular disease (myocardial infarction, stroke)/death from any cause, with respective incidence rate ratios (relative to NSAID nonusers) of 0.88 (95% CI, 0.66 to 1.17) and 0.91 (0.78 to 1.06). Risk did not increase with doses  $\geq 1000$  mg. Relative to NSAID nonusers, serious coronary heart disease risk increased with short term ( $< 90$  days) use for ibuprofen (1.67 [1.09 to 2.57]), diclofenac (1.86 [1.18 to 2.92]), celecoxib (1.37 [0.96 to 1.94]), and rofecoxib (1.46 [1.03 to 2.07]), but not for naproxen (0.88 [0.50 to 1.55]). Relative to naproxen, current users of diclofenac had increased risk of serious coronary heart disease (1.44 [0.96 to 2.15],  $P=0.076$ ) and serious cardiovascular disease/death (1.52 [1.22 to 1.89],  $P=0.0002$ ), and those of ibuprofen had increased risk of the latter end point (1.25 [1.02 to 1.53],  $P=0.032$ ). Compared to naproxen in doses  $\geq 1000$  mg, serious coronary heart disease incidence rate ratios were increased for rofecoxib  $> 25$  mg (2.29 [1.24 to 4.22],  $P=0.008$ ) and celecoxib  $> 200$  mg (1.61 [1.01 to 2.57],  $P=0.046$ ).

**Conclusions**—In patients recently hospitalized for serious coronary heart disease, naproxen had better cardiovascular safety than did diclofenac, ibuprofen, and higher doses of celecoxib and rofecoxib. (*Circ Cardiovasc Qual Outcomes*. 2009;2:155-163.)

**Key Words:** antiinflammatory agents, nonsteroidal ■ coxib ■ rofecoxib ■ celecoxib ■ naproxen ■ diclofenac ■ coronary disease ■ myocardial infarction

The cardiovascular safety of the nonsteroidal antiinflammatory drugs (NSAIDs) is highly controversial. For several of the newer drugs in this class that are selective inhibitors of cyclooxygenase 2 (coxibs), randomized placebo-controlled clinical trials have demonstrated an increased risk of serious cardiovascular disease.<sup>1-4</sup> However, there is considerable uncertainty with regard to the cardiovascular safety of the older traditional NSAIDs.<sup>5</sup> Meta-analyses of observational studies<sup>6,7</sup> suggest that cardiovascular risk varies for individual drugs in this class, with diclofenac associated with greater risk than naproxen, and a meta-analysis of clinical

trials<sup>5</sup> reported both diclofenac and ibuprofen had greater risk than naproxen.

## Editorial see p 146

This question is particularly important for patients with existing serious coronary heart disease, whose baseline risk of adverse cardiovascular events is increased. However, with the exception of 2 short duration studies of parecoxib/valdecoxib,<sup>3</sup> the placebo-controlled clinical trials have included limited numbers of patients with a recent history of cardiovascular disease. Thus, the relative cardiovascular safety of

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both the traditional NSAIDs and coxibs in this high-risk population is unclear, even though a substantial proportion of these patients will have musculoskeletal symptoms that often are treated with these drugs. We thus assessed the cardiovascular safety of NSAIDs in patients recently hospitalized for serious coronary heart disease in a large multi-site retrospective cohort study.

### WHAT IS KNOWN

- There is limited information on the cardiovascular safety of individual NSAIDs and coxibs in patients with serious coronary heart disease.

### WHAT THE STUDY ADDS

- We examined a large cohort of patients recently discharged from the hospital with coronary heart disease, tabulating the rates of subsequent serious coronary heart and serious cardiovascular disease.
- Five individual drugs were examined: naproxen, ibuprofen, diclofenac, celecoxib, and rofecoxib.
- In patients recently hospitalized for serious coronary heart disease, naproxen had better cardiovascular safety than did diclofenac, ibuprofen, and higher doses of celecoxib and rofecoxib.

## Methods

### Cohort and Follow-Up

The study was conducted for the period January 1, 1999 through December 31, 2004 in 3 large automated databases: Tennessee's expanded Medicaid program,<sup>8,9</sup> Saskatchewan Health databases in Canada,<sup>10</sup> and the United Kingdoms General Practice Research Database (GPRD).<sup>11,12</sup> These databases were selected because each had had key data elements validated in prior studies and study investigators had experience with their use. The Tennessee and Saskatchewan databases consist of medical care encounters for persons covered by the corresponding health plans and include an enrollment file (linked with death certificates) as well as files recording prescriptions filled at the pharmacy, hospital admissions, outpatient visits, and long-term care residence. The GPRD database, derived from computerized physician medical records, is organized in 4 files: a registration (enrollment) file, a prescribed medications file, an event file with all clinically relevant diagnoses as well as the event dates and care location, and a patient history file that includes height, weight, and smoking status.

The cohort included community-dwelling persons 40 to 89 years of age hospitalized with serious coronary heart disease, defined as an acute myocardial infarction, coronary artery revascularization, or unstable angina pectoris. In Tennessee and Saskatchewan, myocardial infarctions were identified from the primary discharge diagnosis of hospitalizations with  $\geq 48$ -hour stay (to exclude diagnostic evaluations), a definition with a positive predictive value between 92%<sup>13</sup> and 95%<sup>14</sup> and a sensitivity of 94%.<sup>13</sup> In GPRD, the computerized medical records (profiles) of patients with a possible myocardial infarction were manually reviewed to identify those satisfying the adapted international standardized diagnostic criteria for acute myocardial infarction,<sup>15,16</sup> a procedure with a positive predictive value of 96%.<sup>12</sup> Coronary revascularization (angioplasty with/without stent and coronary artery bypass graft surgery) was identified from codes for procedures, excluding those only associated with aortic valve replacement. Other admissions for unstable angina were identified from hospital discharge diagnoses in Tennessee and Saskatchewan, using the definition of Shahi et al.<sup>17</sup> In GPRD, a similar definition

was applied by manually reviewing the profiles for potentially qualifying episodes.

Other cohort eligibility criteria sought to assure the availability of necessary study data and to exclude patients likely to have events of noncoronary etiology. During the 365 days preceding the qualifying hospital admission, cohort members had to have: enrollment in a plan with full medication information, at least one prescription or outpatient visit, and no evidence of serious coronary heart disease, serious cerebrovascular disease, cocaine use, or potentially life-threatening noncardiovascular exclusion illness (cancer excluding nonmelanoma skin cancers, HIV, renal, hepatic or respiratory failure, organ transplant).

To assure that study data accurately reflected medication changes in the hospital, follow-up began on day 45 ( $t_0$ ) after the qualifying admission. Thus, cohort members had to survive until  $t_0$ , and, for the period between the qualifying admission and  $t_0$ , they had to continue to meet study baseline eligibility criteria (except for respiratory failure, occasionally coded with myocardial infarctions), to have at least 1 prescription, and to be out of the hospital at least 15 consecutive days before  $t_0$ . Follow-up continued until the first of the following dates: the end of the study, failure to satisfy the baseline eligibility criteria (with the exception of the prescription/outpatient visit criteria and renal or respiratory failure, associated with postinfarction left ventricular dysfunction), or a study end point.

### Medication Exposure

Medications given outside the hospital were identified from pharmacy (Tennessee and Saskatchewan) and physician (GPRD) records, which included the prescription date, drug, quantity, dose, and days of supply (except in Saskatchewan). For NSAIDs and coxibs, these data were checked to ensure that days of supply, from which we calculated prescription duration, were consistent with drug quantity. Computerized pharmacy and physician records are an excellent source of medication data because they are not subject to information bias<sup>8</sup> and have high concordance with patient self-report of medication use.<sup>18–20</sup> During the study period, Tennessee had a relatively open formulary and there was no deductible or copay for prescriptions. Past experience suggests that the misclassification attributable to nonprescription NSAIDs was limited.<sup>21–24</sup> Saskatchewan had patient cost-sharing arrangements throughout the study period, and there were restrictions on coxib use for persons  $< 65$  years of age (35% of the site cohort); an internal study reported an estimated 30% of prescriptions for celecoxib in this age group were not included in the Drug Plan database. In the United Kingdom, many patients  $< 60$  years of age had an £6.85 copay.

Each person-day of follow-up was classified according to current use of individual NSAIDs. Current use was defined as the period between the prescription date and the end of the days of supply, indeterminate use (a separate category to reduce misclassification) as that from the end of the days of supply through the subsequent 90 days, and former use the remainder of the 365 days after the end of current use. Current use of multiple NSAIDs was placed in a separate category. Duration was defined as total days of supply prescribed from the 365 days before the qualifying admission through the current follow-up day. New use was defined as that which began during study follow-up with no prior use (365 days before the qualifying admission through  $t_0$  to 1).

Preplanned analyses were conducted for the following individual NSAIDs (low/medium dose cut point): naproxen ( $< 1000$  mg), ibuprofen ( $\leq 1600$  mg), diclofenac ( $< 150$  mg), celecoxib ( $\leq 200$  mg), and rofecoxib ( $\leq 25$  mg), which were those most frequently prescribed in the study populations. In some analyses, data also are presented for indomethacin and valdecoxib and for other NSAIDs, considered as a group. Prescribed aspirin was not considered as an NSAID because it was most commonly prescribed in low doses for cardioprotection.

### Study End Points

The primary study end point was serious coronary heart disease, defined as acute myocardial infarction or out-of-hospital death from coronary heart disease. Acute myocardial infarction was defined as

**Table 1. Study Cohort, by Site**

	All Sites	Tennessee	Saskatchewan	United Kingdom
No. of patients	48 566	23 332	12 187	13 047
Mean age, years	64.6	61.2	68.2	67.5
Male, %	57.8	50.6	63.0	65.9
Qualifying event AMI, %	40.0	30.2	39.2	58.1
Qualifying event coronary revascularization, %	40.3	53.3	31.3	25.4
Qualifying event unstable angina pectoris, %	19.7	16.5	29.5	16.5

AMI indicates acute myocardial infarction.

for cohort entry, except that for fatal infarctions there was no minimum length of stay requirement. Deaths from coronary heart disease were defined as sudden cardiac deaths or fatal myocardial infarctions in persons not hospitalized and were identified using previously developed procedures.<sup>12,25–27</sup>

A secondary end point was the composite of serious cardiovascular disease (nonfatal myocardial infarction or stroke) and death from any cause. Stroke was defined in Tennessee and Saskatchewan from hospitalizations with a primary diagnosis of hemorrhagic or ischemic stroke; this procedure had a reported 86% positive predictive value.<sup>28,29</sup> In GPRD, they were identified from manual review of profiles using a procedure that in a sample of 119 cases had a positive predictive value of 76% for ischemic strokes and 100% for hemorrhagic strokes.<sup>30</sup> The analysis for this end point extended the definition of current use to include indeterminate use, which reduces the potential bias that could occur when patients with deteriorating health stop taking NSAIDs.

### Statistical Analysis

The statistical analysis compared the adjusted incidence of end points between groups defined by NSAID use status. The relative risk was estimated with the incidence rate ratio (IRR), as calculated from Poisson regression models. This technique is efficient for large cohort studies with time-dependent covariates having many categories. In addition to NSAID use status, the models included study site, demographic characteristics (age, gender, calendar year of cohort entry) and variables reflecting comorbidity at baseline (ascertained from medical care in the 365 days preceding the qualifying hospital admission and the 45 subsequent days preceding  $t_0$ ) and subsequent changes during follow-up.

Baseline comorbidity included the qualifying hospital admission type, revascularization status (angioplasty/stent, coronary artery bypass grafting, none), and a cardiovascular risk score, which combined information from a large number of potential baseline risk factors (Table 1). These included prescribed medications and diagnosed disease, medical care use (frequency of inpatient admissions, emergency department visits, and outpatient encounters), a measure of compliance with drugs such as statins that are prescribed for long-term use, and other risk factors available only at individual sites.

The cardiovascular risk score was calculated by performing a Poisson regression analysis among noncurrent users of NSAIDs with all of the potential risk factors in the model. The score was then defined for the entire cohort as the end point probability predicted by this model (separate scores calculated for each end point), conditional on no current NSAID exposure, and then expressed as 20 quantiles. The risk score was then entered into the model used to estimate NSAID IRRs. This technique yields findings similar to traditional methods, and, like propensity scores, permits more parsimonious models when there are numerous covariates.<sup>31</sup> The risk score also facilitates description of how baseline cardiovascular risk differed among the study groups. After controlling for study site, age, sex, calendar year, qualifying admission type, and revascularization status, there was more than a 14-fold difference in the rate of

serious coronary heart disease between the highest and lowest quantiles of the risk score.

Time-dependent covariates were updated annually. These included time since  $t_0$ , coronary revascularization procedures, hospitalization for unstable angina pectoris, and indicators of new or worsening heart failure (new diagnosis or new prescription for digoxin or a loop diuretic), which was a strong and consistent predictor of end point occurrence.

The primary reference group for calculation of the IRRs for NSAID use was nonusers of any NSAID. In most analyses, IRRs also were calculated relative to current users of naproxen because the available data suggest naproxen has the best cardiovascular safety.<sup>5–7</sup> This analysis also should reduce bias attributable to unmeasured factors that differed between users and nonusers of NSAIDs. One analysis of NSAID dose was conducted with a reference group of naproxen in doses of 1000 mg or greater (the most commonly used dose in the cohort [ $>75\%$ ]) and that studied in large pivotal trials of coxibs<sup>32,33</sup>.

The study was designed to include at least 3000 person-years for celecoxib use, 1000 person-years of current use for the other 4 drugs of primary interest, and at least 20 000 person-years of nonuse. Given an anticipated end point occurrence of between 3% and 6% per year would provide detectable ( $\alpha=.05$ ,  $\beta=.20$ ) rate-ratios of between 1.25 to 1.35 for celecoxib and 1.4 to 1.6 for the other drugs of primary interest. All analyses were done with SAS version 9.1. All probability values are 2-sided.

The study was approved by each site's human subjects/research ethics committee. Dr Ray 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.

### Results

The cohort included 48 566 patients with a mean age of 65 years, of whom 58% were male (Table 1). The qualifying hospitalization for 40% of patients was for an acute myocardial infarction, 40% had a coronary revascularization procedure, and the remaining 20% had unstable angina only. Nearly one half of the patients were from Tennessee; these patients had lower mean age and were more likely to be female or to enter the cohort because of a revascularization procedure than were those from other sites.

When cohort members were classified according to baseline use of NSAIDs (Table 2), those receiving naproxen and ibuprofen were approximately 5 years younger than were nonusers and users of the other NSAIDs. There was some variability in the gender distribution of individual NSAID users, with the proportion of males ranging from 61% for diclofenac to 45% for celecoxib. After adjusting for age and site, differences in baseline cardiovascular risk status between the groups were minor. Nonusers had a mean cardiovascular risk score of 9.5 (the population median), and the mean score varied between 9 and 10 for individual study NSAIDs. The proportions of the cohort members from the study sites varied according to baseline NSAID: 87% of naproxen users were from Tennessee, as were 70% or more of users of ibuprofen, celecoxib, and rofecoxib, whereas 53% of diclofenac users were from the United Kingdom.

There were 111 162 person-years of follow-up for the serious coronary heart disease end point and 3600 events (2484 acute myocardial infarctions and 1116 sudden deaths), a rate of 3.2 per 100 person-years. The rates of serious coronary heart disease for the 3 sites were: 3.6 per 100 for Tennessee, 2.7 per 100 for Saskatchewan, and 3.1 per 100 for the United Kingdom. For the broader composite end point of

**Table 2. Baseline Characteristics According to NSAID Use Status at the Start of Follow-Up, Adjusted for Age and Study Site\***

	Baseline NSAID Use					
	Nonuser	Naproxen	Ibuprofen	Diclofenac	Celecoxib	Rofecoxib
No. of patients	29 313	1188	1228	804	1288	1050
Calendar year of cohort entry, mean	2002	2001	2001	2002	2002	2002
Study site, %						
Tennessee	37.9	87.3	75.7	19.5	70.0	72.7
Saskatchewan	30.5	6.1	3.6	25.9	21.8	18.4
United Kingdom	31.6	6.6	20.7	54.6	8.2	9.0
Mean age, years	65.5	60.2	61.0	65.5	66.8	64.7
Male, %	61.5	53.4	51.3	61.3	44.8	47.6
Qualifying hospital stay days, mean	6.3	6.2	5.8	6.0	5.6	5.4
Reason for qualifying hospitalization, %						
AMI	42.9	38.5	38.0	36.8	34.0	38.6
Coronary revascularization only	37.5	40.2	35.7	40.7	43.8	37.1
Unstable angina pectoris only	19.6	21.2	26.3	22.4	22.2	24.3
Coronary revascularization status, %						
CABG	19.4	19.8	19.8	21.6	18.5	14.5
Angioplasty/stent	32.5	34.6	31.0	30.9	38.0	35.7
None	48.1	45.6	49.3	47.4	43.5	49.8
Indicators of cardiovascular and other comorbidity at start of follow-up						
Cardiovascular risk score, mean	9.5	8.9	10.0	9.0	9.9	9.7
Medications, %†						
Loop diuretic	32.7	32.3	33.4	34.0	34.8	36.1
Other diuretic	24.3	25.6	31.4	28.4	31.6	33.2
Insulin	10.2	10.1	13.0	11.1	10.3	10.8
Prescribed low-dose aspirin	53.7	56.6	66.2	60.2	59.7	58.4
Other platelet inhibitor	33.0	31.4	33.5	32.0	43.7	42.1
Anticoagulant	13.5	5.6	8.5	8.8	11.3	10.1
Nitrate	70.4	72.9	75.7	73.0	69.3	74.0
ACE inhibitor/ARB	64.2	55.2	63.0	65.2	70.6	67.9
$\beta$ -blocker	69.3	73.6	70.1	69.7	66.8	67.0
Statin	65.0	59.6	65.8	64.6	69.0	69.9
Diagnoses, %†						
Heart failure	21.9	19.1	18.6	20.3	21.5	23.1
Diabetes	28.7	34.3	32.3	29.4	30.6	31.9
Cerebrovascular disease	11.4	10.2	9.4	9.6	12.1	10.7
Rheumatoid arthritis	1.3	4.9	5.2	6.6	7.7	5.3
Gout	4.1	8.7	5.5	8.6	7.1	6.5

AMI indicates acute myocardial infarction; CABG, coronary artery bypass grafting; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

\*Baseline use of NSAID defined as any current use in the first 30 days of follow-up; nonuse as those with none in the past 365 days. Data not shown for 416 users of indomethacin, 233 users of valdecoxib, 1522 users of other individual drugs or multiple drugs, and 11 524 who had past use of NSAIDs but no current use in the first 30 days of follow-up.

†Any time from the year preceding the qualifying hospital admission through the day preceding  $t_0$ .

myocardial infarction, stroke, or death from any cause, there were 111 103 person-years of follow-up and 6488 events (3525 myocardial infarction or coronary heart disease deaths, 1002 strokes, 693 other cardiovascular deaths, and 1268 noncardiovascular deaths), or 5.9 events per 100 person-years. The incidence was 6.4 per 100 for Tennessee, 4.9 per 100 for Saskatchewan, and 5.9 per 100 for GPRD.

Current users of naproxen (Table 3) had the lowest adjusted rates of both serious coronary heart disease and serious cardiovascular disease/death from any cause. Relative to nonusers of any NSAID, the respective IRRs (95% CI) were 0.88 (0.66 to 1.17) and 0.91(0.78 to 1.06). When compared with current users of naproxen, current users of diclofenac had increased risk of serious coronary heart

**Table 3. Occurrence of Serious Coronary Heart Disease (Myocardial Infarction or Coronary Heart Disease Death) and Serious Cardiovascular Disease (Myocardial Infarction or Stroke)/Death From any Cause According to NSAID Current Use**

	Person-years	Events	Reference Nonusers			Reference Naproxen		
			IRR	95% CI	<i>P</i>	IRR	95% CI	<i>P</i>
Serious coronary heart disease*								
Nonuser	69 966	2231	1	Reference				
Former	15 604	489	0.95	0.86–1.05	0.3242			
Naproxen	1908	49	0.88	0.66–1.17	0.3940	1	Reference	
Ibuprofen	1613	60	1.18	0.92–1.53	0.1978	1.34	0.92–1.96	0.1280
Diclofenac	1311	47	1.27	0.95–1.70	0.1037	1.44	0.96–2.15	0.0761
Celecoxib	3140	108	1.03	0.85–1.25	0.7795	1.16	0.83–1.63	0.3798
Rofecoxib	2482	94	1.19	0.97–1.47	0.0948	1.35	0.96–1.91	0.0886
Serious cardiovascular disease/death†								
Nonuser	69 297	4061	1	Reference				
Former	15 424	887	0.96	0.89–1.03	0.2423			
Naproxen	3404	163	0.91	0.78–1.06	0.2346	1	Reference	
Ibuprofen	3322	214	1.14	0.99–1.30	0.0726	1.25	1.02–1.53	0.0322
Diclofenac	2436	170	1.38	1.18–1.61	<0.0001	1.52	1.22–1.89	0.0002
Celecoxib	4245	274	0.99	0.87–1.12	0.8341	1.09	0.89–1.32	0.4047
Rofecoxib	3641	238	1.07	0.94–1.22	0.2996	1.18	0.97–1.44	0.1046

\*Data not presented for indeterminate use (410 end points/11 447 person-years), indomethacin (23/500, adjusted IRR, 1.38 [0.91–2.08]), valdecoxib (20/692, adjusted IRR, 0.98 [0.63–1.52]), other single drugs (57/1954), or concurrent use multiple drugs (12/545).

†The analysis for this end point extended the definition of current use to include indeterminate use (up to 90 days after the end of the prescription days of supply), which reduces the potential bias that could occur when patients with deteriorating health stop taking NSAIDs. Data not presented for indomethacin (75 end points/1155 person-years), valdecoxib (42/861), other single drugs (165/2986), or concurrent use multiple drugs (199/3353).

disease (1.44 [0.96 to 2.15],  $P=0.076$ ) and serious cardiovascular disease/death (1.52 [1.22 to 1.89],  $P=0.0002$ ) and those of ibuprofen had increased risk of the latter end point (1.25 [1.02 to 1.53],  $P=0.032$ ).

The most commonly prescribed dose of naproxen was 1000 mg or greater, accounting for 77% of current use (Table 4). Relative to nonusers of any NSAID, current users of this naproxen dose had no increased risk of either serious coronary heart disease (IRR=0.78 [0.55 to 1.10]) or serious cardiovascular disease/death (IRR=0.85 [0.71 to 1.03]). Relative to high-dose naproxen, current users of high dose celecoxib (>200 mg) and rofecoxib (>25 mg) had increased risk of serious coronary heart disease (IRRs of 1.61 [1.01 to 2.57] and 2.29 [1.24 to 4.22], respectively). For diclofenac, the risk of serious cardiovascular disease/death was increased for both low/moderate and high doses (reference high-dose naproxen).

We assessed the incidence of serious coronary heart disease according to duration of NSAID therapy (Figure). For current users of naproxen, the adjusted rates did not vary with duration. However, the adjusted rates for the other study drugs were increased with durations of use <90 days (Figure). The IRRs (reference nonusers of any NSAID) were 1.67 (1.09 to 2.57) for ibuprofen, 1.86 (1.18 to 2.92) for diclofenac, 1.37 (0.96 to 1.94) for celecoxib, and 1.46 (1.03 to 2.07) for rofecoxib. In contrast, there was no significantly increased risk for use of longer duration of any study drug.

Inclusion of persons with NSAID use before the start of follow-up (prevalent users) may underestimate risk if there is a period of increased risk early in therapy.<sup>34</sup> We thus

performed a new-user analysis that excluded prevalent users of individual NSAIDs (Table 2). When new users of naproxen were compared to nonusers of any NSAID, the IRR for serious coronary heart disease was 0.68 (0.38 to 1.20) whereas those for the other NSAIDs were all greater than 1, with that for rofecoxib statistically significant (IRR=1.32 [1.01 to 1.72]).

When the cohort was divided into subgroups according to important baseline cardiovascular characteristics (Table 5), the adjusted rate of serious coronary heart disease among current users of naproxen was lower than that for nonusers of any NSAID and generally lower than that for the other study drugs. There was more variability across the study sites which was statistically significant for rofecoxib ( $P=0.0275$ ) but not for the other study drugs ( $P>0.30$ ).

## Discussion

There is growing evidence that the relationship between nonaspirin NSAIDs and cardiovascular disease is more complex than initially thought. Some of the early studies analyzed the NSAIDs as a single group,<sup>35</sup> tacitly assuming that a class effect was an important factor in determining their cardiovascular safety. This perspective changed with the introduction of the coxibs. However, even within groups of NSAIDs defined by relative COX2 selectivity, studies of both mechanisms<sup>36</sup> and clinical outcomes<sup>5–7</sup> are inconsistent with a uniform class effect. Both individual drug and dose are likely to be important factors in defining cardiovascular safety.

The question of which NSAID has the best cardiovascular safety profile is particularly important for patients with

**Table 4. Occurrence of Serious Coronary Heart Disease (Myocardial Infarction or Coronary Heart Disease Death) and Serious Cardiovascular Disease (Myocardial Infarction or Stroke)/Death From any Cause According to NSAID Dose**

	Person-years	Events	Reference Nonusers			Reference Naproxen, $\geq 1000$ mg		
			IRR	95% CI	<i>P</i>	IRR	95% CI	<i>P</i>
Serious coronary heart disease								
Naproxen, <1000 mg	434	16	1.22	0.74–1.99	0.4325			
Naproxen, $\geq 1000$ mg	1474	33	0.78	0.55–1.10	0.1601	1	Reference	
Ibuprofen, $\leq 1600$ mg	706	23	0.99	0.66–1.50	0.9723	1.27	0.75–2.17	0.3771
Ibuprofen, >1600 mg	907	37	1.35	0.97–1.87	0.0742	1.73	1.08–2.76	0.0227
Diclofenac, <150 mg	571	27	1.65	1.13–2.42	0.0094	2.12	1.27–3.53	0.0040
Diclofenac, $\geq 150$ mg	741	20	0.97	0.62–1.50	0.8861	1.24	0.71–2.17	0.4481
Celecoxib, $\leq 200$ mg	2194	70	0.94	0.74–1.19	0.5913	1.20	0.79–1.82	0.3896
Celecoxib, >200 mg	946	38	1.26	0.91–1.73	0.1639	1.61	1.01–2.57	0.0457
Rofecoxib, $\leq 25$ mg	2210	79	1.12	0.90–1.41	0.3111	1.44	0.96–2.16	0.0797
Rofecoxib, >25 mg	272	15	1.79	1.07–2.97	0.0253	2.29	1.24–4.22	0.0079
Serious cardiovascular disease/death*								
Naproxen, <1000 mg	821	49	1.06	0.80–1.40	0.6709			
Naproxen, $\geq 1000$ mg	2582	114	0.85	0.71–1.03	0.1000	1	Reference	
Ibuprofen, $\leq 1600$ mg	1531	102	1.13	0.92–1.37	0.2384	1.32	1.01–1.72	0.0441
Ibuprofen, >1600 mg	1792	112	1.14	0.95–1.38	0.1669	1.34	1.03–1.74	0.0286
Diclofenac, <150 mg	1084	81	1.43	1.14–1.78	0.0016	1.67	1.25–2.23	0.0005
Diclofenac, $\geq 150$ mg	1352	89	1.34	1.09–1.65	0.0065	1.57	1.19–2.07	0.0016
Celecoxib, $\leq 200$ mg	2985	194	0.97	0.84–1.12	0.6517	1.13	0.90–1.43	0.2964
Celecoxib, >200 mg	1261	80	1.04	0.83–1.30	0.7402	1.22	0.91–1.62	0.1826
Rofecoxib, $\leq 25$ mg	3232	211	1.06	0.92–1.22	0.4233	1.24	0.99–1.56	0.0667
Rofecoxib, >25 mg	410	27	1.19	0.82–1.74	0.3639	1.40	0.92–2.12	0.1201

\*The analysis for this end point extended the definition of current use to include indeterminate use (up to 90 days after the end of the prescription days of supply), which reduces the potential bias that could occur when patients with deteriorating health stop taking NSAIDs.

existing cardiovascular disease, for whom data from lower risk populations cannot necessarily be extrapolated. First, these patients have a greater baseline absolute risk and thus small differences in relative risk may be important. Second, approximately 90% of such patients take low dose aspirin,<sup>37,38</sup> which may interact with the NSAID. Third, either recent episodes of acute disease (eg, myocardial infarction) or disease treatment (eg, percutaneous interventions) may alter the cardiac safety of NSAIDs.

We thus studied the cardiovascular safety of individual NSAIDs in nearly 50 000 patients with a recent hospitalization for serious coronary heart disease. Cardiovascular safety was best for naproxen. Relative to nonusers of any NSAIDs, current users of naproxen had IRRs of 0.88 (0.66 to 1.17) for serious coronary heart disease and 0.91 (0.78 to 1.06) for the composite end point of myocardial infarction, stroke, or death from any cause. There was no evidence of increased risk for naproxen in higher doses ( $\geq 1000$  mg/d), with use of short duration, after the exclusion of prevalent users or among patients in the upper tertile for baseline cardiovascular risk.

In contrast, there was evidence that cardiovascular risk was increased for users of the other study NSAIDs. Relative to naproxen users, those of diclofenac, which is widely used outside of the United States and has been the reference drug in several coxib outcome trials,<sup>39,40</sup> had 50% increased risk of the composite end point of myocardial infarction, stroke, or

death from any cause. The increased risk was present for low/moderate doses (<150 mg/d). Ibuprofen users had 25% increased risk for this end point. When compared to high-dose naproxen use, users of higher doses of celecoxib (>200 mg/d) and rofecoxib (>25 mg/d) had increased risk of serious coronary heart disease.

Current users of diclofenac, ibuprofen, celecoxib and rofecoxib with less than 90 days cumulative duration had increased rates of serious coronary heart disease. This is in contrast to a widely publicized posthoc analysis of the APPROVe trial data, interpreted by some as suggesting no risk for use of less than 18 months duration.<sup>1</sup> However, observational studies of rofecoxib have reported increased risk within the first month of therapy,<sup>7</sup> and in the VICTOR trial rofecoxib patients had increased risk after a mean duration of 7.4 months. Thus, our findings add to the evidence that at least one of the mechanisms for increased cardiovascular risk is acute.

These findings are generally consistent with previous studies, most of which were not restricted to patients with serious coronary heart disease. Placebo-controlled clinical trials have demonstrated increased risk of serious cardiovascular disease for rofecoxib<sup>1,7</sup> and celecoxib in daily doses 400 mg or greater.<sup>2,41</sup> Meta-analyses of both clinical trials<sup>5</sup> and observational studies<sup>6,7</sup> suggest that naproxen does not increase cardiovascular risk, whereas diclofenac is consistently

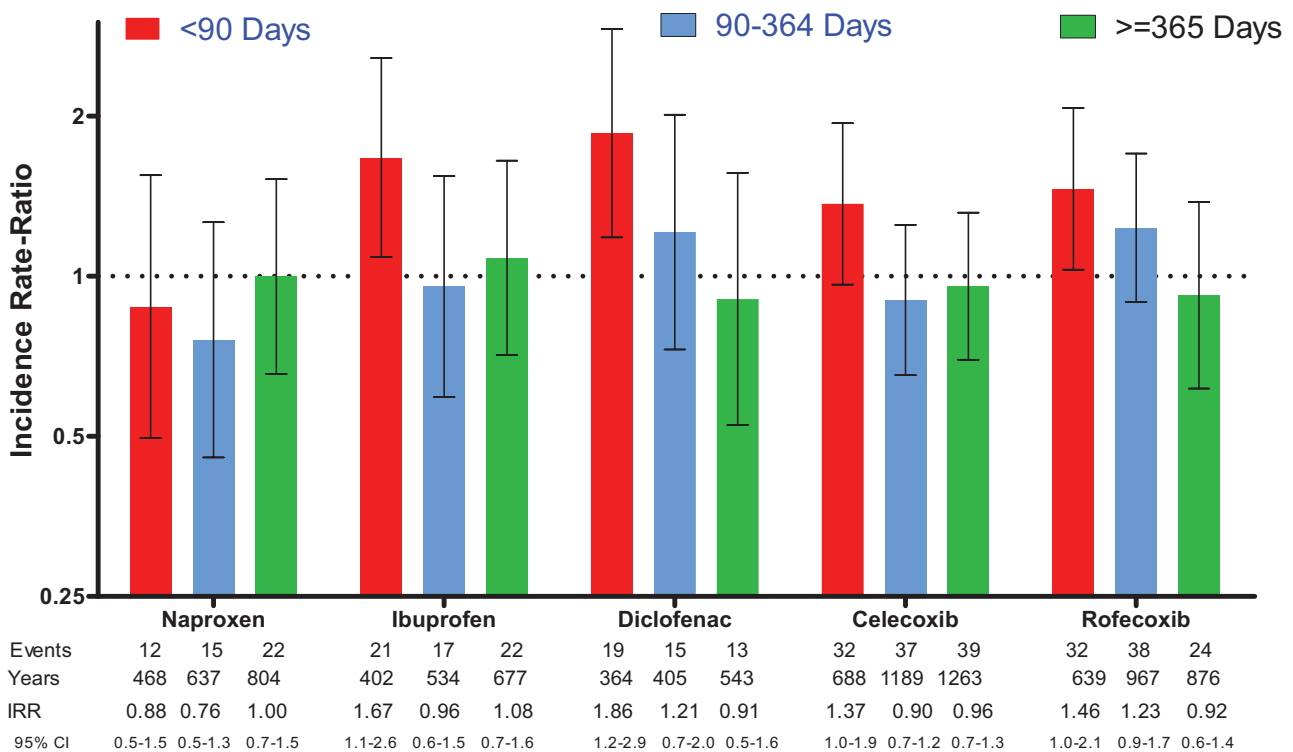


Figure. Occurrence of coronary heart disease by total duration of NSAID current use. Reference category is nonuse of any NSAID.

associated with increased risk in the observational studies. Ibuprofen has been associated with a trend of increased risk in the meta-analyses at doses above 1800 mg daily<sup>5-7</sup> and with increased risk of death in recently hospitalized cardiovascular patients taking low-dose aspirin.<sup>42</sup> In a case-crossover analysis of patients recently discharged with myocardial infarction, Gislason et al reported increased risk of reinfarction or death for diclofenac, rofecoxib, celecoxib, and ibuprofen in doses >1200 mg/d.<sup>43</sup>

A key study limitation was that follow-up began 45 days after the qualifying hospitalization admission for coronary heart disease. This was done because study databases identified medication use from filled outpatient prescriptions and lacked information on medications given in the hospital. For this reason, medication information was likely to be incomplete until patients filled/refilled prescriptions after hospital discharge (up to 34 days for the study sites). Thus, our findings cannot be generalized to the early postdis-

Table 5. Relative Risk of Serious Coronary Heart Disease (Myocardial Infarction or Coronary Heart Disease Death) According to Current Use of NSAIDs, Within Cohort Subgroups

	IRR 95% CI (Events/Years Follow-Up)									
	Naproxen		Ibuprofen		Diclofenac		Celecoxib		Rofecoxib	
Baseline cardiovascular characteristics										
AMI	0.98	0.65-1.48	1.23	0.86-1.75	1.26	0.86-1.84	0.97	0.72-1.31	1.11	0.81-1.53
(1954/43304)	(24/554)	(31/530)	(27/558)	(45/938)	(40/749)					
Angioplasty/stent	0.99	0.66-1.48	1.28	0.85-1.93	1.00	0.52-1.93	1.15	0.85-1.56	1.49	1.08-2.05
(1123/37769)	(25/857)	(24/632)	(9/378)	(45/1269)	(40/974)					
CV risk score upper tertile	0.82	0.53-1.27	1.17	0.82-1.67	1.41	0.98-2.04	1.05	0.81-1.35	1.12	0.84-1.49
(2067/35123)	(21/467)	(32/486)	(29/393)	(65/1088)	(50/812)					
Study site										
Tennessee	0.86	0.63-1.16	1.25	0.94-1.67	1.36	0.83-2.23	1.03	0.81-1.30	1.39	1.10-1.76
(1905/52714)	(43/1655)	(49/1228)	(16/343)	(75/2140)	(75/1702)					
Saskatchewan	0.34	0.05-2.44	1.54	0.49-4.80	0.95	0.49-1.83	1.04	0.69-1.59	1.03	0.64-1.67
(798/29838)	(1/135)	(3/68)	(9/357)	(23/732)	(17/523)					
United Kingdom	1.61	0.67-3.90	0.77	0.38-1.54	1.45	0.95-2.22	1.15	0.61-2.15	0.23	0.06-0.92
(897/28610)	(5/119)	(8/317)	(22/611)	(10/269)	(2/257)					

Reference category is nonusers of any NSAID. AMI indicates acute myocardial infarction; CV, cardiovascular.

charge period, during which NSAID use may be particularly hazardous.<sup>3</sup>

Another study limitation was potentially incomplete information for several relevant variables. Although an extensive set of prognostic factors was identified from records of medical care encounters in the study databases, some important covariates (eg, left ventricular ejection fraction) were not directly available (eg, available were diagnosed/treated heart failure). NSAID exposure would be misclassified for patients who self-paid for prescriptions not authorized by their health plan as well as for those with over-the-counter use. This type of misclassification would affect cohort members classified as nonusers of NSAIDs (which would include persons with self-pay/OTC NSAID use) and could thus bias to the null. For similar reasons, misclassification of low-dose aspirin use also is likely for the North American sites, although the practical effect of such misclassification should be limited given that an estimated 90% of the cohort will be using low-dose aspirin.<sup>37,38</sup> Hence, the comparisons with naproxen are important, as these misclassification effects should be reduced for between-NSAID comparisons.

Despite the use of data from 3 large health plans in 3 countries, sample size was limited for several comparisons. Thus, there was insufficient data for robust analysis of the less frequently used NSAIDs and power was reduced for subgroup analyses. There was substantial variation among the study sites in the patterns of use of individual NSAIDs. Naproxen and ibuprofen use came predominantly from a US low-income population and diclofenac use from Canada and the United Kingdom. Although there was no statistical evidence of effect heterogeneity across the sites (with the exception of rofecoxib), study of other populations, including more representative U.S. populations, is needed.

In conclusion, our study provides information on the cardiovascular safety of individual NSAIDs in patients recently hospitalized for serious coronary heart disease. The data suggest that in this population naproxen had better cardiovascular safety than diclofenac, ibuprofen, rofecoxib in doses >25 mg/d, and celecoxib in doses >200 mg/d.

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### References

- Bresalier RS, Sandler RS, Quan H. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med*. 2005;352:1–11.
- Solomon SD, McMurray JJV, Pfeffer MA. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med*. 2005;352:1–10.
- Nussmeier NA, Whelton AA, Brown MT. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med*. 2005;352:11.
- Kerr DJ, Dunn JA, Langman MJ. Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer. *N Engl J Med*. 2007; 357:360–369.
- Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ*. 2008;00:1–7.
- Hernandez-Diaz S, Varas-Lorenzo C, Garcia Rodriguez LA. Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction. *Basic Clin Pharmacol Toxicol*. 2006;98:266–274.
- McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase. *JAMA*. 2006;296:1633–1644.
- Ray WA, Griffin MR. Use of Medicaid data for pharmacoepidemiology. *Am J Epidemiol*. 1989;129:837–849.
- Ruther M, Pagan BA, Rinkle V, Yanck J. Program statistics: Medicare and Medicaid data book, 1984. *Health Care Financing Administration* 1986;June.
- Rawson NSB, D'Arcy C. Assessing the validity of diagnostic information in administrative health care utilization data: Experience in Saskatchewan. *Pharmaco Drug Safety*. 1998;7:389–398.
- Garcia Rodriguez LA, Perez-Guthann S, Jick S. The UK general practice research database. In: Strom B, editor. *Pharmacoepidemiology*. III ed. New York: John Wiley & Sons LTD; 2000:375–385.
- Garcia Rodriguez LA, Varas-Lorenzo C, Maguire A, Gonzalez-Perez A. Non-steroidal anti-inflammatory drugs and the risk of myocardial infarction in the general population. *Circulation*. 2004;109:3000–3006.
- Fisher ES, Whaley FS, Krushat WM. The accuracy of Medicare's hospital claims data: Progress has been made, but problems remain. *Am J Pub Health*. 1992;82:243–248.
- 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;14:2627–2643.
- Gillum RF, Fortmann SP, Prineas RJ, Kottke TE. International diagnostic criteria for acute myocardial infarction and acute stroke. *Am Heart J*. 1984;108:150–158.
- World Health Organization Regional Office for Europe Copenhagen. Myocardial infarction community registers. *WHO Public Health in Europe* 1976;5.
- Shahi CN, Rathore SS, Wang Y. Quality of care among elderly patients hospitalized with unstable angina. *Am Heart J*. 2001;142:263–270.
- Landry JA, Smyer MA, Tubman JG, Lago DJ, Roberts J, Simonson W. Validation of two methods of data collection of self-reported medicine use among the elderly. *Gerontologist*. 1988;28:672–676.
- West SL, Savitz DA, Koch G, Strom BL, Guess HA, Hartzema A. Recall accuracy for prescription medications: self-report compared with database information. *Am J Epidemiol*. 1995;142:1103–1110.
- Johnson RE, Vollmer WM. Comparing sources of drug data about the elderly. *J Am Geriatr Soc*. 1991;39:1079–1084.
- 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;114:257–263.
- Smalley WE, Ray WA, Daugherty J, Griffin MR. Use of nonsteroidal anti-inflammatory drugs and incidence of colorectal cancer. *Arch Intern Med*. 1999;159:161–166.
- Griffin MR, Yared A, Ray WA. Nonsteroidal anti-inflammatory drugs and acute renal failure in elderly persons. *Am J Epidemiol*. 2000;151: 488–496.

24. Graham DJ, Campen D, Hui R. 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. *Lancet*. 2005;365:475–481.
25. Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry*. 2001;58:1161–1167.
26. Fox CS, Evans JC, Larson MG. A comparison of death certificate out-of-hospital coronary heart disease death with physician-adjudicated sudden cardiac death. *Am J Cardiol*. 2005;95:856–859.
27. Sorlie PD, Coady S, Lin C, Arias E. Factors associated with out-of-hospital coronary heart disease death: The National Longitudinal Mortality Study. *Ann Epidemiol*. 2004;14:447–452.
28. Liu L, Reeder B, Shuaib A, Mazagri R. Validity of stroke diagnosis on hospital discharge records in Saskatchewan, Canada: Implications for stroke surveillance. *Cerebrovasc Dis*. 1999;9:224–230.
29. Roumie CL, Mitchel E, Gideon PS, Varas-Lorenzo C, Castellsague J, Griffin MR. Validation of ICD-9 codes with a high positive predictive value for incident strokes resulting in hospitalization using Medicaid health data. *Pharmaco Drug Safety*. 2008;17:20–26.
30. Arana A, Varas C, Gonzalez-Perez A, Gutierrez L, Bjerrum L, Garcia Rodriguez LA. Hormone therapy and cerebrovascular events: a population-based nested case-control study. *Menopause*. 2006;13:730–736.
31. Arbogast PG, Kaltenbach L, Ding H, Ray WA. Adjustment of multiple cardiovascular risk factors with a summary risk score. *Epidemiol*. 2007;19:30–37.
32. Bombardier C, Laine L, Reicin A. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med*. 2000;343:1520–1528.
33. Farkouh ME, Kirshner H, Harrington RA. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. *Lancet*. 2004;364:675–684.
34. Ray WA. Evaluating medication effects outside of clinical trials: New-user designs. *Am J Epidemiol*. 2003;158:915–920.
35. Ray WA, Stein CM, Hall K, Daugherty JR, Griffin MR. Non-steroidal anti-inflammatory drugs and the risk of serious coronary heart disease. *Lancet*. 2002;359:118–123.
36. Catella-Lawson F, Reilly MP, Kapoor SC. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med*. 2001;345:1809–1817.
37. Jencks SF, Huff ED, Cuerdon T. Change in the quality of care delivered to Medicare beneficiaries, 1998–1999 to 2000–2001. *JAMA*. 2003;289:305–312.
38. McLeod AL, Brooks L, Taylor V, Currie PF, Dewhurst NG. Secondary prevention for coronary artery disease. *Q J Med*. 2004;97:127–131.
39. Silverstein FE, Faich G, Goldstein JL, Simon LS. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: The CLASS Study: A randomized controlled trial. *JAMA*. 2000;284:1247–1255.
40. Cannon CP, Curtis SP, FitzGerald GA. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet*. 2006;368:1771–1781.
41. Solomon SD, Wittes J, Finn PV. Cardiovascular risk of celecoxib in 6 randomized placebo-controlled trials. The CORSS trial safety analysis. *Circulation*. 2008;117:1–10.
42. MacDonald TM, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet*. 2003;361:573–574.
43. Gislason GH, Jacobsen S, Rasmussen JN. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. *Circulation*. 2006;113:2906–2913.