Epidemiology

Risk of Death or Reinfarction Associated With the Use of Selective Cyclooxygenase-2 Inhibitors and Nonselective Nonsteroidal Antiinflammatory Drugs After Acute Myocardial Infarction

Gunnar H. Gislason, MD; Søren Jacobsen, MD, DMSc; Jeppe N. Rasmussen, MD;
Søren Rasmussen, MSc, PhD; Pernille Buch, MD; Jens Friberg, MD, PhD; Tina Ken Schramm, MD;
Steen Z. Abildstrom, MD, PhD; Lars Køber, MD, DMSc;
Mette Madsen, MSc; Christian Torp-Pedersen, MD, DMSc

Background—The selective cyclooxygenase-2 (COX-2) inhibitors and other nonselective nonsteroidal antiinflammatory drugs (NSAIDs) have been associated with increased cardiovascular risk, but the risk in patients with established cardiovascular disease is unknown. We analyzed the risk of rehospitalization for acute myocardial infarction (MI) and death related to the use of NSAIDs including selective COX-2 inhibitors in patients with prior MI.

Methods and Results—All patients with first-time MI between 1995 and 2002 as well as all prescription claims for NSAIDs after discharge were identified from nationwide Danish administrative registers. The risk of death and rehospitalization for MI associated with the use of selective COX-2 inhibitors and nonselective NSAIDs was studied with the use of multivariable proportional hazards models and case-crossover analysis. A total of 58 432 patients were discharged alive and included in the study; 9773 experienced rehospitalization for MI, and 16 573 died. A total of 5.2% of patients received rofecoxib, 4.3% celecoxib, 17.5% ibuprofen, 10.6% diclofenac, and 12.7% other NSAIDs. For any use of rofecoxib, celecoxib, ibuprofen, diclofenac, and other NSAIDs, the hazard ratios and 95% confidence intervals for death were 2.80 (2.41 to 3.25; for rofecoxib), 2.57 (2.15 to 3.08; for celecoxib), 1.50 (1.36 to 1.67; for ibuprofen), 2.40 (2.09 to 2.80; for diclofenac), and 1.29 (1.16 to 1.43; for other NSAIDS); there were dose-related increases in risk of death for all of the drugs. There were trends for increased risk of rehospitalization for MI associated with the use of both the selective COX-2 inhibitors and the nonselective NSAIDs.

Conclusions—Selective COX-2 inhibitors in all dosages and nonselective NSAIDs in high dosages increase mortality in patients with previous MI and should therefore be used with particular caution in these patients. (*Circulation*. 2006;113: 2906-2913.)

Key Words: cyclooxygenase-2 inhibitors ■ drugs ■ mortality ■ myocardial infarction
■ nonsteroidal antiinflammatory drugs

The selective cyclooxygenase-2 (COX-2) inhibitors have been used widely for the treatment of pain and rheumatic disease since they were introduced in the late 1990s. However, the use of the COX-2 inhibitors and the associated excess cardiovascular risk has caused increasing concern since the publication of the Vioxx Gastrointestinal Outcomes Research (VIGOR) study[1] in 2000. Although some studies have reported mixed results with regard to the cardiovascular risk,[2–4] several recently published randomized trials and population-based studies have established an increased risk of acute myocardial infarction (MI) and thromboembolic events related to the use of most COX-2 inhibitors.[5–14] This caused the pharmaceutical company Merck to withdraw their COX-2 inhibitor rofecoxib (Vioxx) from the market, and health authorities in several countries have issued a warning about the cardiovascular risk associated with the use of COX-2 inhibitors.

Editorial p 2868
Clinical Perspective p 2913

The more traditional nonselective nonsteroidal antiinflammatory drugs (NSAIDs) have long been used uncritically in the treatment of pain and rheumatic diseases, but knowledge

about the cardiovascular safety of the nonselective NSAIDs is sparse. Nevertheless, results from recently published population-based studies have also raised concern about the cardiovascular risk of NSAIDs in general.[9,15,16]

Patients with acute MI have an increased risk of recurrent MI and death. Little is known about the extent to which the cardiovascular risk of selective COX-2 inhibitors relates to this population and whether other nonselective NSAIDs are also associated with increased risk. Therefore, we used nationwide administrative registers of hospitalization and drug dispensing from pharmacies in Denmark to study the risk of recurrent MI and death related to the use of selective COX-2 inhibitors and nonselective NSAIDs in patients discharged after first-time acute MI between 1995 and 2002.

Methods
The Danish National Patient Registry has since 1978 registered all hospital admissions in Denmark. Each admission is registered by 1 primary diagnosis and 1 or more secondary diagnoses by the *International Classification of Diseases* (ICD), until 1994 the ICD-8 and from 1994 the ICD-10.

The Danish Registry of Medicinal Product Statistics (national prescription registry) has since 1995 kept records of every prescription dispensed from pharmacies in Denmark. Each medication is classified by the Anatomical Therapeutical Chemical system, and the registry also includes information about the date of dispensing, formulation, strength, and quantity dispensed. Information on patients' vital status (dead or alive) was obtained from the civil registration system through Statistics Denmark. In Denmark, every resident is provided with a permanent and unique civil registration number that enables linkage between these administrative registries.

Population
From the National Patient Registry we identified all patients, aged ≥30 years, hospitalized with acute MI (*ICD-10* code I21 to I22) for the first time between 1995 and 2002. The diagnosis of acute MI has been validated in the National Patient Registry, with a specificity of >90%.[17] A more detailed description of selection of patients has been published previously.[18] All patients who were alive at discharge were included in the present study and analyzed for the risk of death and rehospitalization for MI.

Drug Use
From the national prescription registry, all claimed prescriptions of NSAIDs (Anatomical Therapeutical Chemical code M01A) by the study cohort were identified. The 2 most frequently used COX-2 inhibitors, rofecoxib (M01AH02) and celecoxib (M01AH01), were analyzed separately because they represented >90% of all COX-2 inhibitors used. Similarly, the nonselective NSAIDs ibuprofen (M01AE01) and diclofenac (M01AB05) represented the majority of nonselective NSAIDs used and were therefore analyzed separately. All other NSAIDs were categorized as 1 group in the analyses.

Dosages
The national prescription registry does not include information on prescribed daily dosage of the medication. Therefore, by calculating average dosages from up to 3 consecutive prescriptions, the daily dosage was estimated at each new prescription dispensing. This method allowed for dosages to change at dispensing of a new prescription. The method has been described in detail previously.[19] To analyze whether there was a dose-related response in risk of death or rehospitalization for MI, the 2 COX-2 inhibitors (rofecoxib and celecoxib) and the 2 nonselective NSAIDs (ibuprofen and diclofenac) were divided into low or high dosages. The upper limit of low dosage was defined as the lower recommended daily dosage for the individual NSAIDs, ie, 25 for rofecoxib, 200 for celecoxib, 1200 for

ibuprofen, and 100 mg for diclofenac. NSAIDs other than the aforementioned ones were not divided into specific dosages.

Comorbidity and Socioeconomic Status
Comorbidity was defined from diagnoses at discharge from index MI as specified in the Ontario acute MI mortality prediction rule.[20] The comorbidity index was further enhanced by adding diagnoses from the year before the event, as done by Rasmussen et al.[21] Diagnoses used in the comorbidity index are shown in Table 1. Socioeconomic status was defined by the individual average yearly gross income during a 5-year period before the index MI (excluding the year of index MI). Patients were divided into tertiles according to income.

Statistical Analysis
To ensure the strength of our findings, we used 2 different statistical methods to estimate the risk of taking selective COX-2 inhibitors or nonselective NSAIDs after an MI. At first, Cox proportional hazards models were used when the exposure covariates (drug) were included as time-dependent variables, meaning that patients were only considered at risk when they were taking the drug. The Cox models were adjusted for age, gender, year of first MI, length of treatment, concomitant medical treatment (Table 1), socioeconomic status, and comorbidity. Model assumptions—the linearity of continuous variables, the proportional hazards assumption, and lack of interaction—were tested and found valid unless otherwise indicated. The other method was the case-crossover design with the use of conditional logistic regression.[22] The case-crossover design is based on the case-base paradigm, but instead of using matched controls, the case serves as its own control. Only patients experiencing an event of interest are included in the case-crossover analysis. Among these patients, the number having medication available in the case period (which is the period immediately before the event of interest) is compared with the number having medication available in the control period (which is a period further back in time than the case period but of the same length as the case period). The case-crossover design eliminates the effect of many potential confounders by keeping characteristics such as age, sex, socioeconomic status, and comorbidity fixed. We defined the case period as 0 to 30 days before the event (MI or death), and, to enhance the strength of the analyses, we selected 2 control periods as 60 to 90 and 90 to 120 days before the event. The numbers needed to harm (NNH) were calculated for each drug from unadjusted mortality ratios. All statistical calculations were performed with the SAS statistical software package version 8.2 for UNIX servers (SAS Institute Inc, Cary, NC).

Ethics
The Danish Data Protection Agency approved this study, and data at the individual level were made available to us such that specific individuals could not be identified. Retrospective register studies do not require ethical approval in Denmark.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results
The total of 71 515 patients were admitted with first-time MI during 1995–2002; 58 432 (81.7%) were alive at discharge and included in the study. After discharge, 21 093 patients (36.1%) claimed at least 1 prescription of 1 of the NSAIDs. A detailed description of baseline characteristics of the study population and distribution between treatment groups is shown in Table 1. Patients taking nonselective NSAIDs were younger and more were male than patients taking selective COX-2 inhibitors, but otherwise there were no major differences between the treatment groups.

The duration of treatment was similar with rofecoxib, celecoxib, and ibuprofen, at 37 to 40 days, but the duration of treatment was only 20 days for diclofenac and 83 days for

TABLE 1.   Baseline Characteristics of the Total Study Sample and Individual Treatment Groups

Characteristic	Total	Any Use of Rofecoxib	Any Use of Celecoxib	Any Use of Ibuprofen	Any Use of Diclofenac	Any Use of Other NSAIDs
Total patients	58 432	3022	2489	10 230	6172	7449
Age, mean±SD, y	68.0±12.9	69.2±12.1	69.2±11.9	64.7±13.0	64.5±12.5	66.7±12.6
Women	21 737 (37.2)	1511 (50.0)	1240 (49.8)	3506 (34.3)	2083 (33.7)	2932 (39.4)
Men	36 695 (62.8)	1511 (50.0)	1249 (50.2)	6724 (65.7)	4089 (66.3)	4517 (60.6)
Comorbidity						
Congestive heart failure	7525 (12.9)	331 (11.0)	284 (11.4)	851 (8.3)	506 (8.2)	720 (9.7)
Cardiac arrhythmias	5316 (9.1)	258 (8.5)	197 (7.9)	625 (6.1)	400 (6.5)	520 (7.0)
Peripheral vascular disease	1026 (1.8)	41 (1.4)	34 (1.4)	125 (1.2)	78 (1.3)	97 (1.3)
Cerebral vascular disease	2532 (4.3)	112 (3.7)	84 (3.4)	255 (2.5)	160 (2.6)	204 (2.7)
Diabetes with complications	2190 (3.8)	105 (3.5)	85 (3.4)	326 (3.2)	167 (2.7)	193 (2.6)
Acute renal failure	395 (0.7)	14 (0.5)	7 (0.3)	30 (0.3)	13 (0.2)	19 (0.3)
Chronic renal failure	546 (0.9)	20 (0.7)	14 (0.6)	54 (0.5)	24 (0.4)	25 (0.3)
Malignancy	1425 (2.4)	66 (2.2)	51 (2.1)	160 (1.6)	96 (1.6)	135 (1.8)
Shock	435 (0.7)	25 (0.8)	14 (0.6)	43 (0.4)	23 (0.4)	35 (0.5)
COPD	3272 (5.6)	171 (5.7)	147 (5.9)	457 (4.5)	271 (4.4)	331 (4.5)
Gastric ulcer	1106 (1.9)	79 (2.6)	50 (2.0)	97 (1.0)	64 (1.0)	117 (1.6)
Concomitant medical treatment						
β-Blockers	32 737 (56.7)	1739 (57.6)	1497 (60.2)	5842 (57.2)	3678 (59.7)	4140 (55.6)
Angiotensin-converting enzyme inhibitors	16 501 (28.6)	853 (28.3)	668 (26.9)	2585 (25.3)	1613 (26.2)	1987 (26.7)
Statins	16 795 (31.1)	936 (31.7)	751 (31.1)	3131 (31.0)	1909 (31.3)	1952 (26.5)
Loop diuretics	21 820 (37.3)	1180 (39.1)	989 (39.7)	3288 (32.2)	1877 (30.4)	2677 (36.0)
Antidiabetic drugs	5965 (10.2)	304 (10.1)	240 (9.6)	1002 (9.8)	583 (9.5)	672 (9.0)

Values are number (%). COPD indicates chronic obstructive pulmonary disease.

other NSAIDs (Table 2). There were 9773 rehospitalizations (18.6%) for MI and 16 561 deaths (28.3%) during the observation period. Higher death rates were associated with exposure to all of the NSAIDs compared with nonexposure, but the death rates were highest among those exposed to rofecoxib and celecoxib (Table 2). The NNH values were calculated from unadjusted mortality ratios and are shown as number of patients needed to treat with each drug for 1 year to cause 1 additional death (Table 2).

Cox Proportional Hazards Analysis

Results from the Cox proportional hazards analysis for hazard ratios for death and rehospitalization for MI are shown in Table 3 and illustrated in Figures 1 and 2. There was significantly increased risk of death associated with any use of both the nonselective NSAIDs and the selective COX-2 inhibitors. After the most commonly used nonselective NSAIDs, ibuprofen and diclofenac, and selective COX-2 inhibitors, rofecoxib and celecoxib, were divided into low

TABLE 2.   Average Dosages, Average Duration of Treatment, Number of Deaths, and Time Exposed to Drug and Death Rate Related to Treatment With Selective COX-2 Inhibitors or Nonselective NSAIDs After MI

	No. of Patients (%)	Average Dosage,* mg	Average Duration of Treatment,* d	Deaths, n	Time, Person-Years	Death Rate per 1000 Person-Years (95% CI)	NNH† (95% CI)
Rofecoxib	3022 (5.2)	25 (12.5–25)	39 (14–224)	152‡	896§	169 (144–198)	13 (10–20)
Celecoxib	2489 (4.3)	200 (200–200)	40 (20–181)	112‡	675§	165 (137–198)	14 (10–24)
Ibuprofen	10 230 (17.5)	1600 (1200–1800)	37 (10–463)	313‡	2669§	117 (105–131)	45 (29–102)
Diclofenac	6172 (10.6)	100 (100–150)	20 (10–272)	160‡	1167§	137 (117–160)	24 (16–45)
Other NSAIDs	7449 (12.7)	…	83 (20–461)	348‡	3402§	102 (92–113)	143 (58–315)
No NSAIDs	37 339 (63.9)	…	…	15 476	163 059	95 (94–97)	…
Total study cohort	58 432	…	…	16 561	171 868	96 (95–97)	…

*Median (interquartile range).
†Unadjusted for confounders.
‡Deaths while receiving treatment.
§Total person-years in treatment.

TABLE 3.   Hazard Ratios for Death and Rehospitalization for MI; Cox Proportional Hazards Analysis*

Drug	Death			Re-MI		
	No. of Events†	HR (95% CI)	P	No. of Events†	HR (95% CI)	P
Rofecoxib (n=3022)						
No use‡		1.00			1.00	
Any use	152	2.80 (2.41–3.25)	<0.0001	59	1.63 (1.27–2.10)	0.0001
Daily dose ≤25 mg	106	2.49 (2.11–2.94)	<0.0001	53	1.68 (1.30–2.17)	<0.0001
Daily dose >25 mg	46	5.26 (3.90–7.09)	<0.0001	6	1.27 (0.57–2.86)	0.56
Celecoxib (n=2489)						
No use‡		1.00			1.00	
Any use	112	2.57 (2.15–3.08)	<0.0001	42	1.50 (1.10–2.05)	0.01
Daily dose ≤200 mg	54	1.92 (1.52–2.43)	<0.0001	36	1.47 (1.03–2.09)	0.03
Daily dose >200 mg	58	4.69 (3.58–6.14)	<0.0001	6	1.64 (0.91–2.90)	0.10
Ibuprofen						
No use‡		1.00			1.00	
Any use	266	1.50 (1.36–1.67)	<0.0001	136	1.25 (1.07–1.46)	0.005
Daily dose ≤1200 mg	47	0.75 (0.61–0.92)	0.006	77	1.28 (1.03–1.60)	0.03
Daily dose >1200 mg	219	2.20 (1.95–2.48)	<0.0001	59	1.22 (0.99–1.51)	0.055
Diclofenac						
No use‡		1.00			1.00	
Any use	160	2.40 (2.09–2.80)	<0.0001	61	1.54 (1.23–1.93)	0.0002
Daily dose <100 mg	28	0.89 (0.66–1.20)	0.45	40	1.27 (0.92–1.76)	0.15
Daily dose ≥100 mg	132	4.44 (3.79–5.19)	<0.0001	21	1.89 (1.40–2.55)	<0.0001
Other NSAIDs						
No use‡		1.00			1.00	
Any use	348	1.29 (1.16–1.43)	<0.0001	14	1.27 (1.09–1.47)	0.002

Re-MI indicates rehospitalization for MI; HR, hazard ratio.

*Adjusted for age, gender, year of MI, concomitant medical treatment, socioeconomic status, and comorbidity.

†No. of events while having drug available for treatment.

‡Reference group.

and high dosages, the Cox proportional hazards analysis demonstrated a clear dose-related response in the increase in the risk of death for all drugs. There was a trend for increased risk of readmission for MI related to the use of both the selective COX-2 inhibitors and nonselective NSAIDs; however, the dose-related increase in risk was not as evident as that observed for death.

Case-Crossover Analyses

Odds ratios for death and readmission for MI from the conditional logistic regression analyses with the use of the case-crossover design are shown in Table 4. These analyses confirmed the results of the Cox proportional hazards analyses, with increased risk of death associated with any use of both the nonselective NSAIDs and the selective COX-2 inhibitors and higher risk with higher dosages. The trend for increased risk of readmission for MI was even more evident in the case-crossover analyses.

Supplementary Analyses

We tested for interactions for each of the COX-2 inhibitors and NSAIDs with available covariates, and the analyses were repeated in subgroups of sex and median age with similar results. There were no important interactions with available covariates.

Discussion

This study demonstrated dose-related excess mortality associated with the use of NSAIDs in patients with prior MI. There was a trend for increased risk of rehospitalization for MI, although the dose-related response in risk was not as clear as for death.

The VIGOR study was the first to report increased cardiovascular risk associated with the selective COX-2 inhibitors.[1] Since then, several studies,[5,6,8,12,23] although not all,[2,24–26] have confirmed the findings. Several recently published observational studies have also indicated an increased cardiovascular risk associated with the nonselective NSAIDs.[7–9,13]

The present study is the first to address the risk of all NSAIDs in a selected population of post-MI patients. These patients are elderly, are frequently treated with NSAIDs, and have a high risk of additional cardiovascular events. Many of the randomized trials have excluded these patients. The results of the present study indicate acute or subacute effects of both the selective COX-2 inhibitors and nonselective NSAIDs on the cardiovascular system because events were closely tied to the timing of taking the drugs, and most patients were receiving treatment for a short time. In the Adenomatous Polyp Prevention on Vioxx (APPROVe) study, increased risk of thrombotic events associated with use of
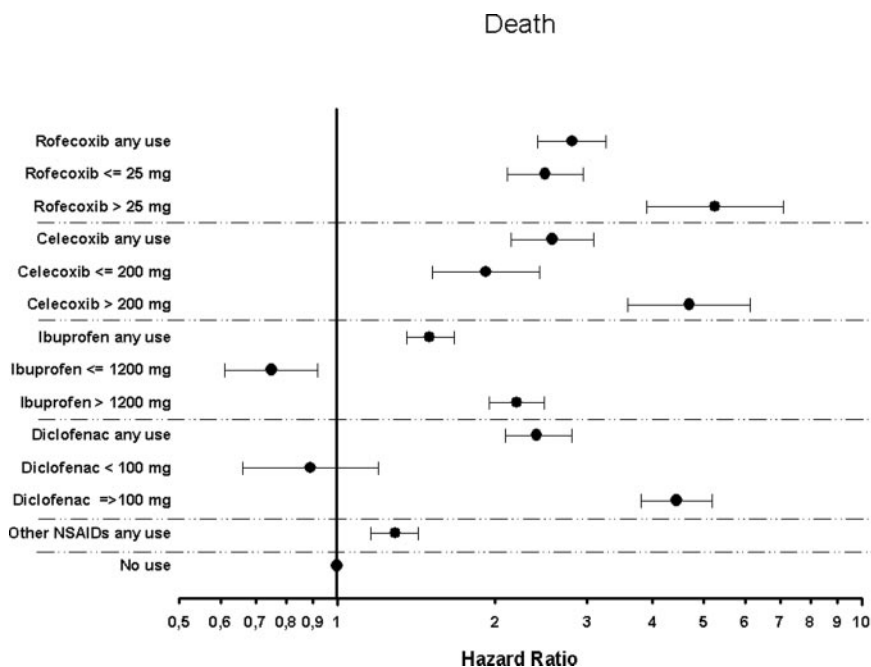
Death

Figure 1. Hazard ratios for the risk of death associated with the use of selective COX-2 inhibitors and nonselective NSAIDs after acute MI. Adjusted for age, sex, year of MI, concomitant medical treatment, socioeconomic status, and comorbidity. Reference group: no use of COX-2 inhibitors or NSAIDs. Error bars indicate 95% CIs.

rofecoxib only became apparent after 18 months of treatment, but there was an earlier separation between groups in the incidence of heart failure after 5 months of treatment.[5] The Adenoma Prevention with Celecoxib (APC) study was stopped because of excess cardiovascular events and deaths after 3 years, but the survival curves began to diverge after 12 months.[6] A study by Nussmeier et al[12] on patients after coronary artery bypass graft surgery found increased cardiovascular risk after only 10 days of treatment with selective COX-2 inhibitors. A meta-analysis by Juni et al[23] found no association between duration of treatment with rofecoxib and cardiovascular risk, and other observational studies have shown that recent use of NSAIDs increases risk, whereas risk

of remote use is less apparent.[7,9] Current data therefore suggest harmful effects after short-term as well as after long-term treatment. This may be influenced further by the baseline cardiovascular risk of the individual patient.

Prior observational studies have failed to show increased cardiovascular risk of the selective COX-2 inhibitor celecoxib.[7,8,10] In the present study the risks associated with celecoxib and rofecoxib could be compared directly and were similar. This increases the likelihood that the harmful effects can be attributed to the drug class rather than the peculiarities of one of the drugs. Because the population in the present study comprised post-MI patients, this might indicate more abrupt effects on a vulnerable cardiovascular system, and the
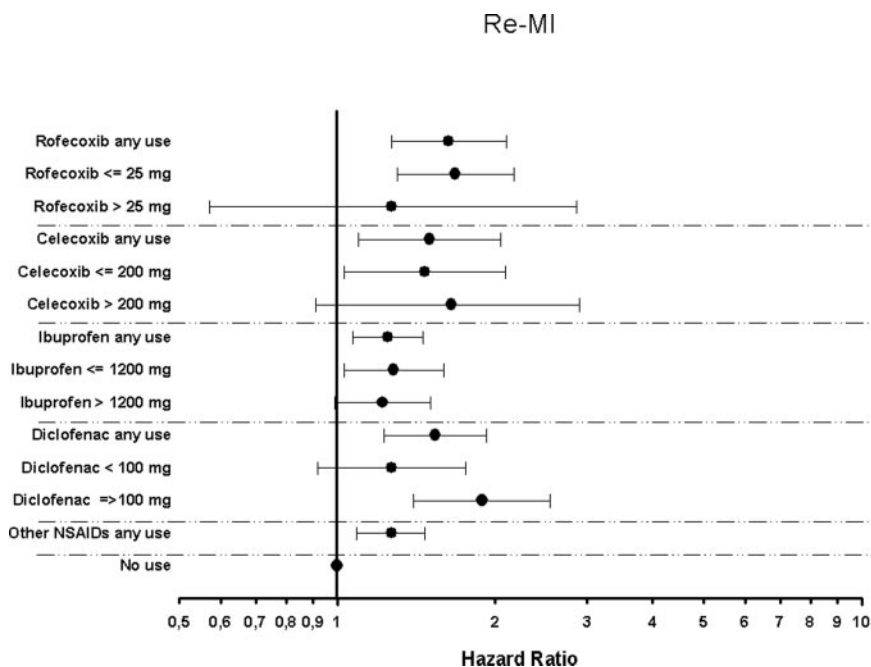
Re-MI

Figure 2. Hazard ratios for the risk of readmission for MI associated with the use of selective COX-2 inhibitors and nonselective NSAIDs after acute myocardial infarction. Adjusted for age, sex, year of MI, concomitant medical treatment, socioeconomic status, and comorbidity. Reference group: no use of COX-2 inhibitors or NSAIDs. Error bars indicate 95% CIs.

TABLE 4. Odds Ratios for Death and Rehospitalization for MI: Conditional Logistic Regression Analysis by the Case-Crossover Design*

Drug and Daily Dosage	Death			Re-MI		
	OR	95% CI	P	OR	95% CI	P
Rofecoxib						
No use	1.00			1.00		
Any use	2.36	1.75–3.19	<0.0001	2.46	1.42–4.24	0.001
Daily dose ≤25 mg	1.96	1.43–2.69	<0.0001	2.37	1.35–4.16	0.003
Daily dose >25 mg	8.65	3.71–20.1	<0.0001	3.73	0.67–20.6	0.13
Celecoxib						
No use	1.00			1.00		
Any use	2.37	1.68–3.35	<0.0001	1.36	0.73–2.53	0.34
Daily dose ≤200 mg	1.97	1.33–2.93	0.001	1.01	0.50–2.02	0.98
Daily dose >200 mg	3.88	2.04–7.36	<0.0001	5.27	1.07–25.9	0.04
Ibuprofen						
No use	1.00			1.00		
Any use	1.05	0.88–1.24	0.61	1.32	1.02–1.72	0.04
Daily dose ≤1200 mg	0.57	0.45–0.74	<0.0001	1.41	0.95–2.08	0.08
Daily dose >1200 mg	1.65	1.33–2.04	<0.0001	1.26	0.89–1.78	0.19
Diclofenac						
No use	1.00			1.00		
Any use	1.59	1.28–1.98	<0.0001	1.67	1.15–2.42	0.007
Daily dose <100 mg	0.86	0.63–1.17	0.34	1.66	1.04–2.63	0.03
Daily dose ≥100 mg	2.82	2.08–3.83	<0.0001	1.69	0.96–2.98	0.07
Other NSAIDs						
No use	1.00			1.00		
Any use	1.14	0.93–1.39	0.20	1.07	0.77–1.48	0.70

Re–MI indicates rehospitalization for MI; OR, odds ratio.

*Case period 0–30 days before event and control periods 60–90 and 90–120 days before event.

harmful effects of celecoxib may therefore become more apparent than in previous studies.

The dose relationship found in this study is overall in agreement with previous studies.[5,6,8] The upper limit of low dosage was in this study defined as the lower limit of recommended daily dosage for the individual NSAIDs studied, but there may be differences in pharmacological properties of the individual NSAIDs not accounted for in the current definition. Nevertheless, the increased risk associated with any use of the selective COX-2 inhibitors and high dosages of the 2 nonselective NSAIDs, demonstrated in the present study, needs to be acknowledged.

Most patients receive treatment with low-dose acetylsalicylic acid (aspirin) after MI to prevent recurrent cardiovascular events.[27] The effect of aspirin on the associated excess cardiovascular risk of COX-2 inhibitors has been the subject of debate, and some studies have excluded patients receiving aspirin. The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) involved treatment with lumiracoxib, stratified to the concomitant use of aspirin. There was an insignificant trend toward lower incidence of cardiovascular events in the lumiracoxib group receiving concomitant aspirin compared with those who did not receive aspirin.[28] Therefore, the relatively low risk of recurrent MI observed in the present study compared with the risk of death may be due to the protective role of aspirin. Another contributing factor may be that many patients died out of hospital, perhaps because of recurrent infarctions.

The prostanoids are generated from arachidonic acid by COX-1– and COX-2–mediated metabolism and have a wide range of biological actions. A detailed discussion of the potential mechanisms has been published previously.[29,30] In brief, COX-1 is involved in the generation of thromboxane A_2, which is a vasoconstrictor and platelet agonist and promotes smooth muscle proliferation. COX-2 mediates synthesis of prostaglandin I_2, which is a potent vasodilator, inhibits platelet function, and promotes renal sodium excretion. Platelets express only COX-1, but endothelial cells express both COX-1 and COX-2.

An unbalanced inhibition of only COX-2 therefore early caused some concern about cardiovascular side effects, but the theory of balanced versus unbalanced COX inhibition is now debatable because the nonselective NSAIDs are also associated with increased cardiovascular risk. However, other mechanisms may explain the harmful effects of NSAIDs on the cardiovascular system. Ibuprofen has been found to compete with low-dose aspirin in binding to the COX-1 pathway in the platelets, but, in contrast to low-dose aspirin, the block is not irreversible and therefore leaves the patient only partially protected against thrombosis.[31] Furthermore,

clinical and observational studies have demonstrated increased risk of heart failure, fluid retention, destabilization of blood pressure control, and development of hypertension associated with the use of selective COX-2 inhibitors and nonselective NSAIDs.[32–35] In addition, animal models indicate that imbalance in thromboxane A_2/prostaglandin I_2 homeostasis could promote cardiac fibrosis and cardiac hypertrophy as well as modulate response to endothelial injury.[30,36]

Previous studies have focused mainly on combined end points, whereas we are able to demonstrate an association with all-cause mortality. We find low NNH values (Table 2) for COX-2 inhibitors and high-dosage nonselective NSAIDs, whereas in the APC trial NNH for a combined end point is ≈70. This illustrates that the harmful effects of these drugs appear much more severe in patients with a previous MI.

Strengths and Limitations of the Study

The Danish National Patient Registry as well as the national prescription registry have been shown to be accurate.[17,37] In Denmark, ibuprofen is the only NSAID that is available over-the-counter without prescription and only in a low dosage and limited quantity at each dispensing. Therefore, it is unlikely that over-the-counter use of NSAIDs has a major impact on this study. We assumed that most of our patients used aspirin on a daily basis, as shown in epidemiological surveys of post-MI patients.[27] If aspirin use was lower in the group taking NSAIDs, a higher event rate would be expected in that group, but because aspirin is primarily dispensed over the counter, the effects of aspirin cannot be assessed properly. The Cox models used provide control of available confounders, but the control for confounding by indication—that the patients put on treatment are sicker than those not treated—may not be adequate. For this reason, we performed supplementary analyses using the case-crossover design. By using the case as its own control, the effects of chronic confounders are almost eliminated. Confounding is still possible, however. If the risk of death was increased by the pain-eliciting conditions only, the observed association between COX-2 and NSAID intake and increased risk of death would be due to confounding. Whereas such confounding cannot be excluded in an observational study, the dose-response effect, the different effect of different drugs used for similar indications, and the clear relation between degree of COX-2 inhibition and risk all indicate the importance of the drugs rather than the indications.

Conclusions and Clinical Implications of the Study

The present study demonstrates that treatment with 2 COX-2 inhibitors and high dosages of 2 nonselective NSAIDs are associated with a highly increased risk of death in patients with prior MI. The results add important information to the treatment of high-risk patients, notably those with prior MI, and must be viewed together with the rest of the evidence. Given the additional evidence from randomized trials and other observational studies of selective COX-2 inhibitors and nonselective NSAIDs, these drugs should be used with particular caution in patients with a prior MI. Post-MI patients with pain conditions relieved by these drugs should discuss carefully with their doctor the balance between benefits and risk of treatment.

Because studies in this field have revealed major safety concerns where none were thought present, the cardiovascular safety of not only the selective COX-2 inhibitors but of all NSAIDs needs to be addressed further.

Disclosures

The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication. Dr Jacobsen has served as an expert witness for the Danish Council for Patient Complaints. The remaining authors report no conflicts.

References

1. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ, for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med*. 2000;343:1520–1528.
2. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowith JB, Verburg KM, Geis GS. Gastrointestinal toxicity with celecoxib vs nonsteroidal antiinflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial: Celecoxib Long-term Arthritis Safety Study. *JAMA*. 2000;284:1247–1255.
3. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA*. 2001;286:954–959.
4. Lefkowith JB, Geis GS, Silverstein F. Safety of celecoxib vs other nonsteroidal antiinflammatory drugs. *JAMA*. 2000;284:3123–3124.
5. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, Lines C, Riddell R, Morton D, Lanas A, Konstam MA, Baron JA. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med*. 2005;352:1092–1102.
6. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med*. 2005;352:1071–1080.
7. Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal antiinflammatory drugs: population based nested case-control analysis. *BMJ*. 2005;330:1366.
8. Graham DJ, Campen D, Hui R, Spence M, Cheetham C, Levy G, Shoor S, Ray WA. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal antiinflammatory drugs: nested case-control study. *Lancet*. 2005;365:475–481.
9. Johnsen SP, Larsson H, Tarone RE, McLaughlin JK, Norgard B, Friis S, Sorensen HT. Risk of hospitalization for myocardial infarction among users of rofecoxib, celecoxib, and other NSAIDs: a population-based case-control study. *Arch Intern Med*. 2005;165:978–984.
10. Kimmel SE, Berlin JA, Reilly M, Jaskowiak J, Kishel L, Chittams J, Strom BL. Patients exposed to rofecoxib and celecoxib have different odds of nonfatal myocardial infarction. *Ann Intern Med*. 2005;142:157–164.
11. Levesque LE, Brophy JM, Zhang B. The risk for myocardial infarction with cyclooxygenase-2 inhibitors: a population study of elderly adults. *Ann Intern Med*. 2005;142:481–489.
12. Nussmeier NA, Whelton AA, Brown MT, Langford RM, Hoeft A, Parlow JL, Boyce SW, Verburg KM. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med*. 2005;352:1081–1091.
13. Shaya FT, Blume SW, Blanchette CM, Weir MR, Mullins CD. Selective cyclooxygenase-2 inhibition and cardiovascular effects: an observational study of a Medicaid population. *Arch Intern Med*. 2005;165:181–186.
14. Solomon DH, Schneeweiss S, Glynn RJ, Kiyota Y, Levin R, Mogun H, Avorn J. Relationship between selective cyclooxygenase-2 inhibitors and

acute myocardial infarction in older adults. *Circulation*. 2004;109: 2068–2073.

15. Fischer LM, Schlienger RG, Matter CM, Jick H, Meier CR. Discontinuation of nonsteroidal antiinflammatory drug therapy and risk of acute myocardial infarction. *Arch Intern Med*. 2004;164:2472–2476.

16. Reicin AS, Shapiro D, Sperling RS, Barr E, Yu Q. Comparison of cardiovascular thrombotic events in patients with osteoarthritis treated with rofecoxib versus nonselective nonsteroidal antiinflammatory drugs (ibuprofen, diclofenac, and nabumetone). *Am J Cardiol*. 2002;89: 204–209.

17. Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. *J Clin Epidemiol*. 2003;56:124–130.

18. Gislason GH, Abildstrom SZ, Rasmussen JN, Rasmussen S, Buch P, Gustafsson I, Friberg J, Gadsboll N, Kober L, Stender S, Madsen M, Torp-Pedersen C. Nationwide trends in the prescription of beta-blockers and angiotensin-converting enzyme inhibitors after myocardial infarction in Denmark, 1995–2002. *Scand Cardiovasc J*. 2005;39:42–49.

19. Gislason GH, Rasmussen JN, Abildstrom SZ, Gadsboll N, Buch P, Friberg J, Rasmussen S, Kober L, Stender S, Madsen M, Torp-Pedersen C. Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. *Eur Heart J*. 2006;27:1153–1158.

20. Tu JV, Austin PC, Walld R, Roos L, Agras J, McDonald KM. Development and validation of the Ontario acute myocardial infarction mortality prediction rules. *J Am Coll Cardiol*. 2001;37:992–997.

21. Rasmussen S, Zwisler AD, Abildstrom SZ, Madsen JK, Madsen M. Hospital variation in mortality after first acute myocardial infarction in Denmark from 1995 to 2002: lower short-term and 1-year mortality in high-volume and specialized hospitals. *Med Care*. 2005;43:970–978.

22. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol*. 1991;133:144–153.

23. Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet*. 2004;364:2021–2029.

24. 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;162:1105–1110.

25. Rahme E, Pilote L, LeLorier J. Association between naproxen use and protection against acute myocardial infarction. *Arch Intern Med*. 2002; 162:1111–1115.

26. Solomon DH, Glynn RJ, Levin R, Avorn J. Nonsteroidal antiinflammatory drug use and acute myocardial infarction. *Arch Intern Med*. 2002;162:1099–1104.

27. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries: principal results from EUROASPIRE II Euro Heart Survey Programme. *Eur Heart J*. 2001;22: 554–572.

28. Farkouh ME, Kirshner H, Harrington RA, Ruland S, Verheugt FW, Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehrsam E, Gitton X, Krammer G, Mellein B, Gimona A, Matchaba P, Hawkey CJ, Chesebro JH. 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.

29. Antman EM, DeMets D, Loscalzo J. Cyclooxygenase inhibition and cardiovascular risk. *Circulation*. 2005;112:759–770.

30. Spektor G, Fuster V. Drug insight: cyclo-oxygenase 2 inhibitors and cardiovascular risk: where are we now? *Nat Clin Pract Cardiovasc Med*. 2005;2:290–300.

31. Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, Vyas SN, FitzGerald GA. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med*. 2001;345:1809–1817.

32. Hudson M, Richard H, Pilote L. Differences in outcomes of patients with congestive heart failure prescribed celecoxib, rofecoxib, or non-steroidal antiinflammatory drugs: population based study. *BMJ*. 2005;330:1370.

33. Mamdani M, Juurlink DN, Lee DS, Rochon PA, Kopp A, Naglie G, Austin PC, Laupacis A, Stukel TA. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal antiinflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. *Lancet*. 2004;363:1751–1756.

34. Sowers JR, White WB, Pitt B, Whelton A, Simon LS, Winer N, Kivitz A, van Ingen H, Brabant T, Fort JG. The Effects of cyclooxygenase-2 inhibitors and nonsteroidal antiinflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and type 2 diabetes mellitus. *Arch Intern Med*. 2005;165:161–168.

35. Aw T-J, Haas SJ, Liew D, Krum H. Meta-analysis of cyclooxygenase-2 inhibitors and their effects on blood pressure. *Arch Intern Med*. 2005; 165:490–496.

36. Francois H, Athirakul K, Howell D, Dash R, Mao L, Kim HS, Rockman HA, Fitzgerald GA, Koller BH, Coffman TM. Prostacyclin protects against elevated blood pressure and cardiac fibrosis. *Cell Metab*. 2005; 2:201–207.

37. Gaist D, Andersen M, Aarup AL, Hallas J, Gram LF. Use of sumatriptan in Denmark in 1994–5: an epidemiological analysis of nationwide prescription data. *Br J Clin Pharmacol*. 1997;43:429–433.

CLINICAL PERSPECTIVE

Some nonsteroidal antiinflammatory drugs (NSAIDs) are associated with increased cardiovascular risk in patients without known cardiovascular disease. Because these drugs are used frequently in patients with cardiovascular disease, it is of particular importance to know the risk in these patients. We used nationwide Danish registers on hospital admissions, pharmacy prescriptions, and mortality to study the risk of selective cyclooxygenase-2 (COX-2) inhibitors and nonselective NSAIDs in patients with a myocardial infarction. The study shows an increased risk of death associated with any use of the COX-2 inhibitors rofecoxib and celecoxib and a dose-related increase in risk. Furthermore, there was an increased risk associated with high dosages of the nonselective NSAIDs ibuprofen and diclofenac, whereas low dosages of these drugs did not appear harmful. There was also increased risk of reinfarction, but the dose relation was less clear than for death. Therefore, in patients with prior myocardial infarction, high dosages of NSAIDs or any dosages of COX-2 inhibitors should, if at all possible, be avoided and only used with caution, balancing benefit with a substantial increase in risk of death and reinfarction.

Circulation

American Heart Association®

Risk of Death or Reinfarction Associated With the Use of Selective Cyclooxygenase-2 Inhibitors and Nonselective Nonsteroidal Antiinflammatory Drugs After Acute Myocardial Infarction

Gunnar H. Gislason, Søren Jacobsen, Jeppe N. Rasmussen, Søren Rasmussen, Pernille Buch, Jens Friberg, Tina Ken Schramm, Steen Z. Abildstrom, Lars Køber, Mette Madsen and Christian Torp-Pedersen

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circ.ahajournals.org/content/113/25/2906