Increased Mortality and Cardiovascular Morbidity Associated With Use of Nonsteroidal Anti-inflammatory Drugs in Chronic Heart Failure

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Background: Accumulating evidence indicates increased cardiovascular risk associated with nonsteroidal anti-inflammatory drug (NSAID) use, in particular in patients with established cardiovascular disease. We studied the risk of death and hospitalization because of acute myocardial infarction and heart failure (HF) associated with use of NSAIDs in an unselected cohort of patients with HF.

Methods: We identified 107 092 patients surviving their first hospitalization because of HF between January 1, 1995, and December 31, 2004, and their subsequent use of NSAIDs from individual-level linkage of nationwide registries of hospitalization and drug dispensing by pharmacies in Denmark. Data analysis was performed using Cox proportional hazard models adjusted for age, sex, calendar year, comorbidity, medical treatment, and severity of disease, and propensity-based risk-stratified models and case-crossover models.

Results: A total of 36 354 patients (33.9%) claimed at least 1 prescription of an NSAID after discharge; 60 974 (56.9%) died, and 8970 (8.4%) and 39 984 (37.5%) were hospitalized with myocardial infarction or HF, respectively. The hazard ratio (95% confidence interval) for death was 1.70 (1.58-1.82), 1.75 (1.63-1.88), 1.31 (1.25-1.37), 2.08 (1.95-2.21), 1.22 (1.07-1.39), and 1.28 (1.21-1.35) for rofecoxib, celecoxib, ibuprofen, diclofenac, naproxen, and other NSAIDs, respectively. Furthermore, there was a dose-dependent increase in risk of death and increased risk of hospitalization because of myocardial infarction and HF. Propensity-based risk-stratified analysis and case-crossover models yielded similar results.

Conclusions: NSAIDs are frequently used in patients with HF and are associated with increased risk of death and cardiovascular morbidity. Inasmuch as even commonly used NSAIDs exerted increased risk, the balance between risk and benefit requires careful consideration when any NSAID is given to patients with HF.

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S INCE PUBLICATION OF THE Vioxx Gastrointestinal Outcomes Research (VIGOR) Study in 2000,[1] debate has been ongoing about increased cardiovascular risk of nonsteroidal anti-inflammatory drugs (NSAIDs), in particular, the selective cyclooxygenase-2 (COX-2) inhibitors.[2-11] Clinical guidelines discourage use of NSAIDs in patients with chronic heart failure (HF) owing to increased risk of fluid retention and worsening of HF.[12,13] Recent recommendations from the American Heart Association[14] are to avoid administration of selective COX-2 inhibitors in patients with established or increased risk of cardiovascular disease and to consider alternative pain medications before using NSAIDs in this population. Patients receiving NSAIDs are often elderly, frequently have other concurrent medical illnesses, and often have multiple cardiovascular risk factors or established cardiovascular disease. Furthermore, many NSAIDs are sold over the counter (OTC) in pharmacies and convenience stores without expert advice about their use and potential drug interactions or adverse effects, which might give the misconception that NSAIDs are harmless.

The widespread use of NSAIDs and the perception of low risk associated with such OTC drugs prompted us to study an unselected cohort of 107 092 patients surviving a first hospitalization because of HF, with particular focus on risk of death and hospitalization as a result of the use of NSAIDs.

The Danish Data Protection Agency approved this study (No. 2003-54-1269). No ethical approval is required for retrospective registry studies in Denmark.

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Table 1. Baseline Characteristics of the Study Sample According to Exposure Group

Characteristic	Total Population, No. (%)	Treatment Group, No. (%)						
		No NSAID	Rofecoxib	Celecoxib	Ibuprofen	Diclofenac	Naproxen	Other NSAIDs
Total No. of patients	107 092	70 738 (66.1)	6116 (5.7)	5734 (5.4)	16 975 (15.8)	9377 (8.8)	2176 (2.0)	11 488 (10.7)
Age, mean (SD), y	74.8 (11.6)	75.5 (11.5)	75.2 (10.8)	74.6 (10.8)	72.1 (12.1)	71.7 (11.9)	72.2 (12.0)	73.9 (11.2)
Sex								
Male	55 368 (51.7)	36 854 (52.1)	2603 (42.6)	2445 (42.6)	9237 (54.4)	5170 (55.1)	1253 (57.6)	5488 (47.8)
Female	51 724 (48.3)	33 884 (47.9)	3513 (57.4)	3289 (57.4)	7738 (45.6)	4207 (44.9)	923 (42.4)	6000 (52.2)
Year of first hospitalization because of HF								
1995-1996	19 789 (18.5)	11 924 (16.9)	780 (12.8)	619 (10.8)	4345 (25.6)	2226 (23.7)	723 (33.2)	3148 (27.4)
1997-1998	19 996 (18.6)	12 300 (17.4)	1131 (18.5)	920 (16.0)	3817 (22.5)	2254 (24.1)	497 (22.8)	2792 (24.3)
1999-2000	22 588 (21.1)	13 882 (19.6)	1937 (31.7)	1702 (29.7)	3865 (22.8)	2269 (24.2)	472 (21.7)	2601 (22.6)
2001-2002	23 257 (21.7)	15 284 (21.6)	1761 (28.8)	1770 (30.9)	3211 (18.9)	1791 (19.1)	328 (15.1)	1901 (16.5)
2003-2004	21 462 (20.1)	17 348 (24.5)	507 (8.3)	723 (12.6)	1727 (10.2)	837 (8.9)	156 (7.2)	1046 (9.1)
Comorbidity[a]								
MI	14 638 (13.7)	10 040 (14.2)	747 (12.2)	721 (12.6)	2170 (12.8)	1226 (13.1)	259 (11.9)	1393 (12.1)
Peripheral vascular disease	2736 (2.6)	1967 (2.8)	114 (1.9)	117 (2.0)	348 (2.1)	190 (2.0)	37 (1.7)	242 (2.1)
Cerebrovascular disease	7982 (7.5)	5770 (8.2)	385 (6.3)	380 (6.6)	941 (5.5)	519 (5.5)	98 (4.5)	663 (5.8)
COPD	16 534 (15.4)	11 023 (15.6)	933 (15.3)	900 (15.7)	2577 (15.2)	1415 (15.1)	307 (14.1)	1695 (14.7)
Peptic ulcer disease	3638 (3.4)	2644 (3.7)	247 (4.0)	216 (3.8)	321 (1.9)	239 (2.6)	46 (2.1)	336 (2.9)
Diabetes mellitus	13 070 (12.2)	8723 (12.3)	680 (11.1)	711 (12.4)	2088 (12.3)	1043 (11.1)	229 (10.5)	1352 (11.8)
Diabetes mellitus with chronic complications	5862 (5.5)	4051 (5.7)	284 (4.6)	297 (5.2)	856 (5.0)	417 (4.5)	87 (4.0)	560 (4.9)
Renal disease	3364 (3.1)	2571 (3.6)	127 (2.1)	93 (1.6)	392 (2.3)	151 (1.6)	34 (1.6)	260 (1.9)
Rheumatologic disease	1827 (1.7)	1026 (1.5)	212 (3.5)	191 (3.3)	277 (1.6)	146 (1.6)	35 (1.6)	207 (1.8)
Mild liver disease	807 (0.8)	571 (0.8)	46 (0.8)	32 (0.6)	104 (0.6)	64 (0.7)	15 (0.7)	65 (0.6)
Moderate or severe liver disease	40 (0.04)	30 (0.04)	1 (0.02)	0	3 (0.02)	4 (0.04)	0	3 (0.03)
Any malignant tumor	3604 (3.4)	2627 (3.7)	148 (2.4)	143 (2.5)	437 (2.6)	222 (2.4)	58 (2.7)	266 (2.3)
Metastatic tumor	537 (0.5)	410 (0.6)	17 (0.3)	20 (0.4)	57 (0.3)	31 (0.3)	11 (0.5)	32 (0.3)
Hemiplegia or paraplegia	128 (0.1)	93 (0.1)	3 (0.05)	3 (0.05)	17 (0.1)	11 (0.1)	2 (0.1)	11 (0.1)
Dementia	82 (0.1)	60 (0.1)	4 (0.07)	4 (0.07)	8 (0.05)	5 (0.05)	0	6 (0.05)
AIDS	36 (0.03)	25 (0.04)	2 (0.03)	3 (0.05)	6 (0.04)	2 (0.02)	0	3 (0.03)
Charlson Comorbidity Index score, mean (SD)	0.8 (1.2)	0.9 (1.3)	0.8 (1.1)	0.8 (1.2)	0.7 (1.1)	0.7 (1.1)	0.7 (1.0)	0.7 (1.1)
Severity group[b]								
1	26 543 (24.8)	18 814 (26.6)	1281 (20.9)	1265 (22.1)	3669 (21.6)	2088 (22.3)	443 (20.4)	2322 (20.2)
2	42 547 (39.7)	26 228 (37.1)	2804 (45.9)	2615 (45.6)	7658 (45.1)	4264 (45.5)	940 (43.2)	5188 (45.2)
3	24 817 (23.2)	15 927 (22.5)	1500 (24.5)	1406 (24.5)	4099 (24.2)	2207 (23.5)	585 (26.9)	2848 (24.8)
4	13 185 (12.3)	9769 (13.8)	531 (8.7)	448 (7.8)	1549 (9.1)	818 (8.7)	208 (9.6)	1130 (9.8)
Concomitant therapy								
β-Blocker[c]	29 084 (27.2)	19 041 (26.9)	1754 (28.7)	1762 (30.7)	5611 (27.2)	2679 (28.6)	562 (25.8)	2946 (25.6)
ACE inhibitors or ARBs[c]	46 191 (44.1)	29 645 (41.9)	2774 (45.4)	2601 (45.4)	7782 (45.8)	4404 (47.0)	1022 (47.0)	5137 (44.7)
Spironolactone[c]	20 166 (18.8)	13 892 (19.6)	1079 (17.6)	1108 (19.3)	2778 (16.4)	1549 (16.5)	335 (15.4)	1820 (15.8)
Statins[d]	13 084 (12.2)	8611 (12.2)	714 (11.7)	748 (13.0)	2185 (12.9)	1211 (12.9)	240 (11.0)	1218 (10.6)
Antidiabetes agents[e]	13 387 (12.5)	8843 (12.5)	715 (11.7)	752 (13.1)	2187 (12.9)	1134 (12.1)	246 (11.3)	1411 (12.3)
Loop diuretic agents[e]	86 636 (80.9)	57 050 (80.7)	5008 (81.9)	4627 (80.7)	13 725 (80.9)	7556 (80.6)	1784 (82.0)	9451 (82.3)

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin-2 receptor blockers; COPD, chronic obstructive pulmonary disease; HF, heart failure; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug.

[a] As specified by the Charlson Comorbidity Index.

[b] Mean daily dosage of loop-diuretic (furosemide) first 90 days from start of treatment: (group 1, 0-39 mg; group 2, 40-80 mg; group 3, 81-160 mg; and group 4, >160 mg).

[c] At least 1 prescription claimed within 90 days after discharge.

[d] At least 1 prescription claimed within 180 days after discharge.

[e] At least 1 prescription claimed between 90 days before admission and 90 days after discharge.

METHODS

POPULATION

Patients aged 30 years or older who between January 1, 1995, and December 31, 2004, survived their first hospitalization because of HF (*International Classification of Diseases, Tenth Revision*, codes I11.0, I50, I42, and J81 as primary or secondary diagnoses) were identified in the Danish National Patient Registry, which includes records of all hospitalizations in Denmark since 1978. The selection of patients and their characteristics have been described in detail previously.[15] Each patient's vital status as of December 31, 2004, was obtained from the Central Population Registry.

DRUG TREATMENT

The Danish Registry of Medicinal Product Statistics, a national prescription registry, comprises all prescriptions dispensed from Danish pharmacies since 1995, which are directly and automatically linked to reimbursement of medication expenses, ensuring complete registration. Coding is according to the Anatomical Therapeutical Chemical (ATC) Classification System. The national prescription registry does not include information about prescribed daily dosage of medications. Therefore, by calculating mean dosages from up to 3 consecutive prescriptions, the daily dosage was estimated for each new prescription claim. In cases in which only 1 prescription was available, the mean dosage was the minimum predefined dos-

Table 2. Treatment and Outcome According to Exposure Group

		Median (Interquartile Range)			Duration of Exposure to Drug, Person-Years	Risk (95% CI)		
Drug	Patients, No. (%)	Dose, Median (Interquartile Range), mg	Duration of Treatment, d	No. of Deaths		Deaths per 1000 Person-Years	Absolute Risk Increase	NNH[a] per Year
Rofecoxib	6116 (5.7)	25 (12.5 to 25)	42 (14 to 154)	826[b]	2513	329 (310 to 347)	11.1 (9.3 to 13)	9 (8 to 11)
Celecoxib	5734 (5.4)	200 (200 to 200)	60 (20 to 197)	768[b]	2666	288 (271 to 305)	7 (5.3 to 8.8)	14 (11 to 19)
Ibuprofen	16 975 (15.8)	600 (400 to 1200)	97 (30 to 211)	2214	9366	236 (228 to 245)	1.9 (1 to 2.8)	53 (36 to 100)
Diclofenac	9377 (8.8)	75 (50 to 100)	40 (20 to 108)	998[b]	3242	308 (292 to 324)	9 (7.4 to 10.6)	11 (9 to 13)
Naproxen	2176 (2.0)	500 (500 to 550)	64 (25 to 179)	243[b]	1024	237 (211 to 263)	2 (−0.6 to 4.6)	51 (22 to 158)
Other NSAIDs	11 488 (10.7)	. . .	56 (20 to 150)	1061[b]	5454	195 (184 to 205)	−2.4 (−3.4 to −1.3)	43 (29 to 78)
No NSAIDs	70 738 (66.1)	. . .	. . .	54 864	251 682	218 (216 to 220)	. . .	. . .
Total study cohort[c]	107 092	. . .	. . .	**60 974**	**275 947**	221 (219 to 223)	. . .	. . .

Abbreviations: CI, confidence interval; NNH, number needed to harm, that is, number of patients needed to treat to cause 1 additional event (death); NSAID, nonsteroidal anti-inflammatory drug; ellipses, data not available.
[a] Unadjusted for confounders.
[b] Deaths while receiving treatment (exposed to drug).
[c] The values do not sum because there is overlap between the exposure groups.

age for each drug. This method allowed for dosages to be changed at dispensing of a new prescription. The method has been described in detail previously.[15,16]

From the national prescription registry, all claimed prescriptions of NSAIDs (ATC code M01A) by the study cohort were identified. The most frequently used selective COX-2 inhibitors, rofecoxib (M01AH02) and celecoxib (M01AH01), and nonselective NSAIDs, ibuprofen (M01AE01) and diclofenac (M01AB05), were analyzed separately because they represented most of the selective COX-2 inhibitors and nonselective NSAIDs used. In addition, the nonselective NSAID naproxen (M01AE02) was analyzed separately to gain further knowledge about the cardiovascular risk associated with this NSAID. Rofecoxib, celecoxib, ibuprofen, diclofenac, and naproxen were classified as low or high dosages in the analyses. The upper limit of low dosage was defined as the lower recommended daily dose for the individual NSAIDs, that is, 25 mg for rofecoxib, 200 mg for celecoxib, 1200 mg for ibuprofen, 100 mg for diclofenac, and 500 mg for naproxen. Other NSAIDs, not including glucosamine (M01AX05), were categorized as 1 group in the analyses, without dosage specification. We defined concomitant treatment status with the following cardiovascular drugs: angiotensin-converting enzyme inhibitors and angiotensin-2 receptor blockers (ATC C09 ACEi/ARBs), β-blockers (ATC C07), and spironolactone (ATC C03D) as prescriptions claimed within 90 days after discharge, and statins (ATC C10AA) claimed within 180 days after discharge.

To quantify the severity of HF or severity of accompanying renal failure, patients were classified into 4 groups according to the mean daily dose of loop diuretics (ATC C03C) used within the first 90 days after discharge (furosemide equivalent dosage: furosemide, 40 mg=bumetanide, 1 mg): group 1, 0 to 39 mg; group 2, 40 to 80 mg; group 3, 81 to 160 mg; and group 4, more than 160 mg.[15,17] Pharmacologically treated diabetes was identified from prescriptions of glucose-lowering medication (ATC A10) from 90 days before admission to 90 days after discharge.

COMORBIDITY

The Charlson Comorbidity Index, modified for the *International Classification of Diseases, Tenth Revision*, was used to define comorbidity (**Table 1**).[18,19] The Charlson Comorbidity index was estimated at discharge and further enhanced by including diagnoses up to 1 year before the index hospitalization.

STATISTICAL ANALYSIS

Time to death, and hospitalization because of myocardial infarction (MI) or HF were estimated using Cox proportional hazards regression models, including exposure to drug of interest as time-dependent covariates in the models (ie, patients were only considered at risk when they were taking the drug). The models allowed patients to switch from 1 specific NSAID to another specific NSAID, thereby changing exposure status. The models also permitted concomitant use of different NSAIDs; however, combinations were not analyzed specifically. The Cox proportional hazards regression models were adjusted for age, sex, calendar year, duration of exposure, concomitant medical treatment, and comorbidity. The proportional hazard assumption is invalid in time-dependent proportional hazard models; however, the linearity of continuous variables and lack of interaction were tested and found valid unless otherwise indicated.

As a sensitivity analysis, we performed risk-stratified analysis by ranking the patients into tertiles according to an estimated propensity score for death within 1 year after discharge. The propensity score was estimated using logistic regression analysis conditional on baseline covariates. Furthermore, to ensure the robustness of our findings, the analyses were repeated using case-crossover models.[20] The case-crossover analysis includes only patients experiencing an event; however, rather than using matched control subjects, the case serves as its own control, thereby reducing the effect of unmeasured confounders. The case period was defined as 0 to 30 days before the event (death or hospitalization because of MI or HF), and control periods as 60 to 90 days and 90 to 120 days before the event.

Mortality was calculated as deaths per 1000 person-years exposed. The number needed to harm was estimated for each drug from the unadjusted mortality as number needed to harm per 1000 person-years exposed. All statistical calculations were performed using commercially available software (SAS version 9.1; SAS Institute, Inc, Cary, North Carolina).

RESULTS

A total of 107 092 patients with HF were identified and included in the study. Of these, 36 354 patients (33.9%) received at least 1 prescription of either a selective COX-2 inhibitor or a nonselective NSAID. Baseline characteristics are given in Table 1. **Table 2** lists the duration of

Table 3. Hazard Ratios for Death, and Hospitalization Because of HF or AMI

Drug	Death		Hospitalization Because of HF		Hospitalization Because of AMI	
	HR (95% CI)	P Value[a]	HR (95% CI)	P Value[a]	HR (95% CI)	P Value[a]
Rofecoxib						
Any use	1.70 (1.58-1.82)	<.001	1.40 (1.26-1.55)	<.001	1.30 (1.07-1.59)	.01
≤25 mg/d	1.42 (1.31-1.54)	<.001	1.33 (1.20-149)	<.001	1.26 (1.01-1.57)	.04
>25 mg/d	3.54 (3.12-4.02)	<.001	1.86 (1.46-2.35)	<.001	1.59 (0.97-2.61)	.07
Colecoxib						
Any use	1.75 (1.63-1.88)	<.001	1.24 (1.12-1.39)	<.001	1.38 (1.13-1.69)	.001
≤200 mg/d	1.34 (1.22-1.48)	<.001	1.24 (1.09-1.41)	.001	1.33 (1.05-1.69)	.02
>200 mg/d	2.72 (2.45-3.02)	<.001	1.26 (1.04-1.53)	.02	1.50 (1.08-2.10)	.02
Ibuprofen						
Any use	1.31 (1.25-1.37)	<.001	1.16 (1.10-1.23)	<.001	1.33 (1.19-1.50)	<.001
≤1200 mg/d	0.99 (0.94-1.04)	.65	1.16 (1.09-1.23)	<.001	1.31 (1.15-1.48)	<.001
>1200 mg/d	2.83 (2.64-3.02)	<.001	1.18 (1.04-1.33)	.01	1.47 (1.15-1.89)	.002
Diclofenac						
Any use	2.08 (1.95-2.21)	<.001	1.35 (1.24-1.48)	<.001	1.36 (1.12-1.64)	.002
≤100 mg/d	1.31 (1.20-1.42)	<.001	1.34 (1.21-1.48)	<.001	1.14 (0.91-1.43)	.26
>100 mg/d	5.54 (5.08-6.03)	<.001	1.42 (1.17-1.73)	.004	2.43 (1.74-3.40)	<.001
Naproxen						
Any use	1.22 (1.07-1.39)	.004	1.18 (1.00-1.40)	.05	1.52 (1.11-2.06)	.01
≤500 mg/d	0.88 (0.73-1.05)	.15	1.18 (0.97-1.44)	.10	1.47 (1.02-2.10)	.04
>500 mg/d	1.97 (1.64-2.36)	<.001	1.18 (0.88-1.57)	.27	1.62 (0.97-2.72)	.07
Other NSAID	1.28 (1.21-1.35)	<.001	1.27 (1.18-1.36)	<.001	1.32 (1.13-1.54)	.004

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug.
[a] Cox proportional-hazard analysis adjusted for age, sex, year of first hospitalization because of heart failure, comorbidity, severity (loop diuretic dosage), and concomitant medical treatment.
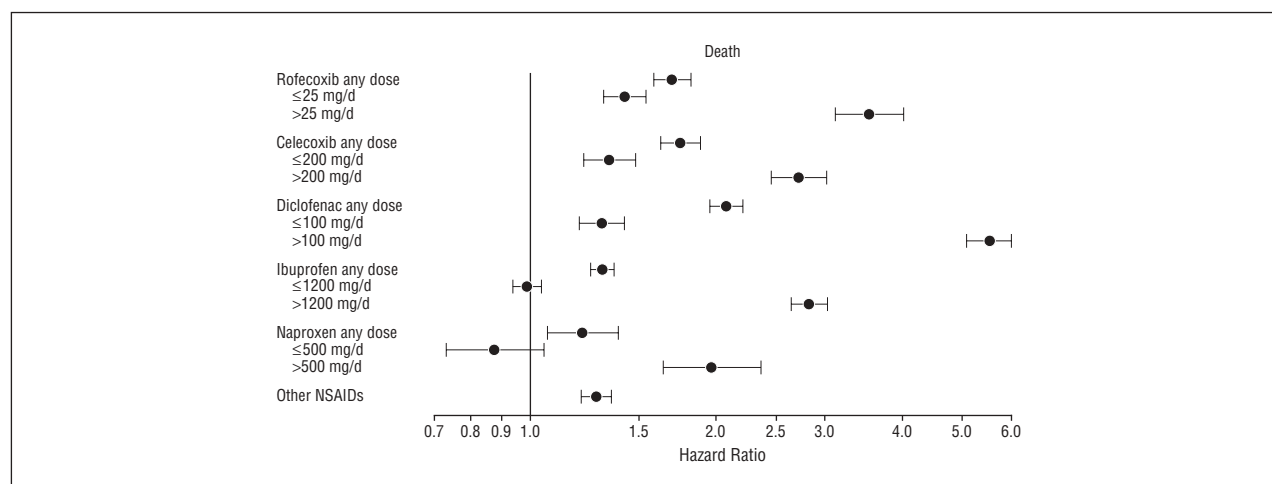

Figure 1. Hazard ratios for death associated with use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with chronic heart failure. Cox proportional hazards regression analysis adjusted for age, sex, calendar year, comorbidity, concomitant pharmacotherapy, and severity of disease. Bars indicate 95% confidence intervals.

treatment with individual drugs and median doses. The median duration of treatment of individual NSAIDs varied between 42 and 97 days (Table 2).

MORTALITY

A total of 60 974 (56.9%) patients died during the study. Mortality, absolute risk increase, and number needed to harm related to each exposure group are listed in Table 2. There was an increased risk of death associated with treatment with most NSAIDs. The increase in risk was highest for rofecoxib, celecoxib, and diclofenac. This was confirmed in multivariate Cox proportional hazards regression

analysis (**Table 3** and **Figure 1**), with a clear dose-dependent increase in risk. Low doses of ibuprofen and naproxen were not associated with increased mortality risk, although high doses of both of these drugs were associated with an increased risk of death.

HOSPITALIZATION BECAUSE OF MI

Hospitalization because of MI occurred in 8970 patients (8.4%). An increased risk of MI was associated with treatment with both selective COX-2 inhibitors and nonselective NSAIDs (Table 3 and **Figure 2**), and hazard ratios were similar for all types of NSAIDs. A dose-
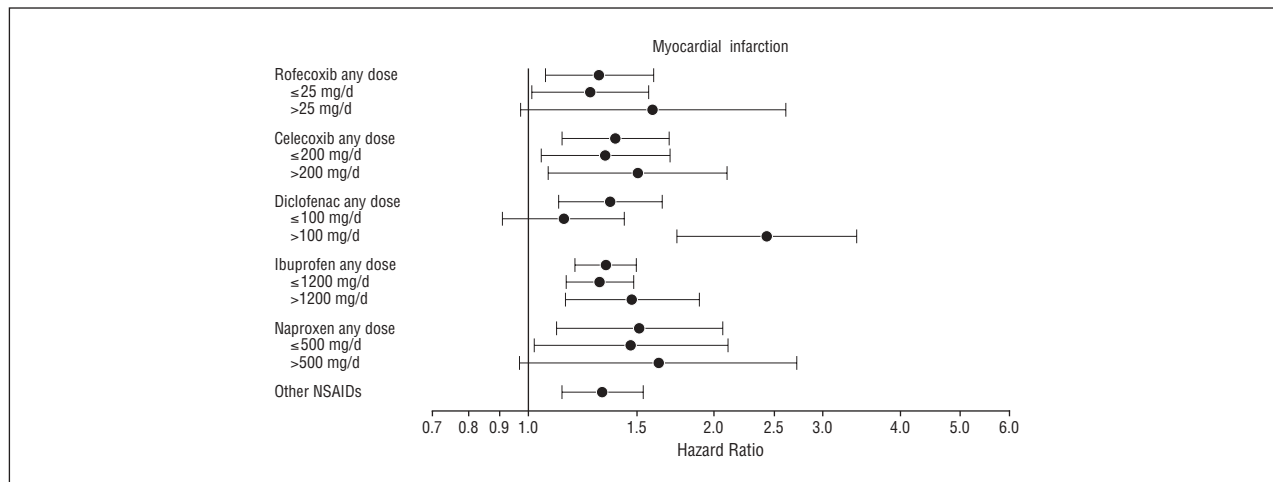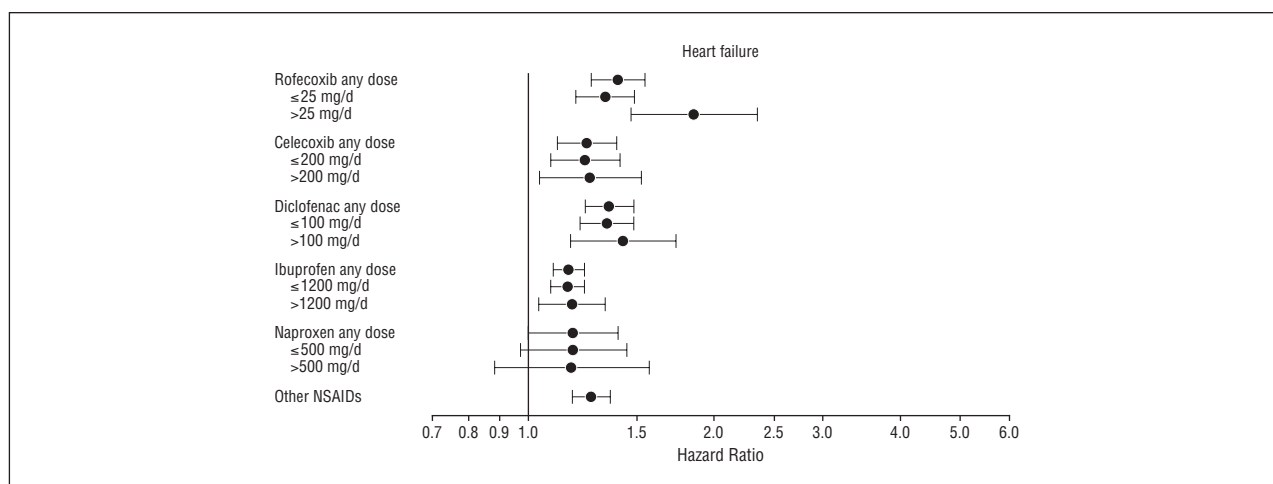
Figure 2. Hazard ratios for hospitalization because of acute myocardial infarction associated with use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with chronic heart failure. Cox proportional hazards regression analysis adjusted for age, sex, calendar year, comorbidity, concomitant pharmacotherapy, and severity of disease. Bars indicate 95% confidence intervals.

Figure 3. Hazard ratios for hospitalization because of heart failure associated with use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with chronic heart failure. Cox proportional hazards regression analysis adjusted for age, sex, calendar year, comorbidity, concomitant pharmacotherapy, and severity of disease. Bars indicate 95% confidence intervals.

dependent increase in risk of MI was evident with rofecoxib and diclofenac.

HOSPITALIZATION BECAUSE OF HF

A total of 39 984 patients (37.5%) were hospitalized because of HF. All of the drugs were associated with an increased risk of hospitalization because of HF (Table 3 and **Figure 3**). Rofecoxib was associated with the highest risk and demonstrated a dose-dependent increase in risk.

CASE-CROSSOVER ANALYSIS

Repeating the analysis using case-crossover models generated similar results (**Table 4**) as with Cox proportional hazards regression analysis.

SENSITIVITY ANALYSES

Figure 4 shows the hazard ratios for death within 1 year after discharge across tertiles of risk of death as defined

by baseline variables. The C statistic was 0.72, indicating good discriminatory power of the models to differentiate strata of risk. The increased risk associated with NSAID therapy was present at all strata.

No important interactions were noted between the different exposure groups and subgroups of patients. In particular, we analyzed subgroups of patients receiving prophylactic evidence-based pharmacotherapy (angiotensin-converting enzyme inhibitors, β-blockers, spironolactone, and statins) and found no indication for effect modification in risk associated with use of these drugs. Also, we found no interaction in risk between patients who did or did not have previous acute MI.

COMMENT

We found increased mortality and increased risk of hospitalization because of MI or HF related to NSAID use in an unselected cohort of patients discharged alive after their first hospitalization because of HF. The risk was

Table 4. Odds Ratios for Death, and Hospitalization Because of HF or AMI[a]

Drug	Death		Hospitalization Because of HF		Hospitalization Because of AMI	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Rofecoxib						
Any use	1.62 (1.40-1.88)	<.001	2.39 (1.89-3.01)	<.001	1.39 (0.93-2.06)	.11
≤25 mg/d	1.19 (1.01-1.40)	.03	2.12 (1.67-2.70)	<.001	1.32 (0.88-1.98)	.18
>25 mg/d	4.99 (3.65-6.84)	<.001	6.17 (3.22-11.82)	<.001	2.73 (0.66-11.32)	.17
Celecoxib						
Any use	1.89 (1.60-2.23)	<.001	1.86 (1.45-2.40)	<.001	1.31 (0.85-2.04)	.23
≤200 mg/d	1.21 (0.99-1.48)	.06	1.95 (1.49-2.56)	<.001	1.26 (0.77-2.04)	.36
>200 mg/d	4.11 (3.15-5.38)	<.001	1.48 (0.87-2.54)	.15	1.51 (0.70-3.27)	.29
Ibuprofen						
Any use	1.50 (1.36-1.65)	<.001	1.41 (1.24-1.61)	<.001	1.47 (1.15-1.88)	.002
≤1200 mg/d	0.89 (0.79-0.99)	.04	1.36 (1.19-1.56)	<.001	1.28 (0.98-1.63)	.07
>1200 mg/d	6.43 (5.26-7.86)	<.001	1.86 (1.33-2.60)	.003	4.51 (2.28-8.91)	<.001
Diclofenac						
Any use	2.50 (2.21-2.82)	<.001	1.97 (1.64-2.34)	<.001	1.64 (1.16-2.30)	.005
≤100 mg/d	1.21 (1.04-1.40)	.01	1.85 (1.52-2.25)	<.001	1.18 (0.81-1.72)	.38
>100 mg/d	14.69 (10.9-19.7)	<.001	2.90 (1.81-4.64)	<.001	9.10 (3.45-23.98)	<.001
Naproxen						
Any use	1.20 (0.91-1.58)	.12	1.02 (0.72-1.46)	.90	1.31 (0.64-2.71)	.05
≤500 mg/d	0.84 (0.60-1.17)	.29	1.03 (0.69-1.53)	.89	1.31 (0.56-3.05)	.54
>500 mg/d	2.35 (1.51-3.65)	.002	1.01 (0.53-1.89)	.98	1.33 (0.39-4.50)	.65
Other NSAID	1.29 (1.15-1.44)	<.001	1.68 (1.44-1.97)	<.001	1.56 (1.16-2.08)	.003

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; HF, heart failure; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio.
[a] Conditional logistic regression by the case-crossover design. Case period, 0 to 30 days before event; control periods, 60 to 90 days and 90 to 120 days before event.

increased for all of the selective COX-2 inhibitors and diclofenac, and for ibuprofen and naproxen in high dosages. A causative relationship was indicated by a dose-dependent increase in risk. The extensive absolute increase in risk of 11.1% for rofecoxib, 7% for celecoxib, and 9% for diclofenac, and the low number needed to harm are worrisome, in particular because 34% of patients with HF received a prescription for an NSAID. Apparently awareness is low among physicians concerning international clinical recommendations that discourage use of NSAIDs in patients with HF.

Most of the current knowledge of the cardiovascular risk with use of NSAID therapy is based on post hoc analyzes and analysis of subgroups of patients from studies designed to examine noncardiovascular diseases[1,5,6,21,22]; however, to our knowledge, with the exception of 1 study,[7] no clinical trials have primarily been designed to address the cardiovascular risk with use of NSAIDs. Focus has primarily been on the COX-2 inhibitors, whereas the cardiovascular risk with use of nonselective NSAIDs is estimated primarily from observational studies and meta-analyses.[3,4,8-11,23] In the future, the discrepancy in results of randomized trials and observational studies may be resolved by the Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen (PRECISION) Trial, which currently is recruiting patients.[24]

The biological effects of NSAIDs have been discussed in detail previously.[25] In brief, NSAIDs inhibit cyclooxygenase, which by 2 separate pathways promotes the synthesis of thromboxanes (COX-1) and prostaglandins (COX-2) from arachidonic acid. It has been proposed that excessive cardiovascular risk with use of NSAIDs is due primarily to an imbalance in inhibition of these pathways. The various NSAIDs have different abilities for inhibition of COX-1 and COX-2, and the more COX-2–selective NSAIDs seem to have a more cardiotoxic effect. Furthermore, there seems to be marked interindividual variability in the response to selective COX-2 inhibition, which might interfere with the susceptibility to cardiovascular risk,[26] which also is more pronounced in patients with established cardiovascular disease.[7,10,27-29] Focus has primarily been on the increased thromboembolic risk, although other properties of NSAIDs could influence the risk in patients with HF. NSAIDs influence renal function and the regulation of fluid balance, causing fluid retention and worsening of HF, in addition to promoting increased risk of hypertension and destabilization of blood pressure.[30] Animal models have demonstrated that COX-2 inhibition can induce structural changes in the myocardium[31] and enhance left ventricular remodeling, impair systolic function, and increase mortality after MI.[32] Regulation of fluid balance and blood pressure is of particular importance in chronic HF; thus, NSAIDs might tip the balance and worsen HF, and in the worst-case scenario, lead to a fatal outcome. A causative relationship between NSAID use and cardiovascular risk in patients with established HF is, therefore, highly plausible.

Agreement is general regarding increased cardiovascular risk with the selective COX-2 inhibitor rofecoxib, whereas the risk with celecoxib has been debated.* We have previously found increased risk with celecoxib in a cohort of patients after MI,[10] and Brophy et al[27] demonstrated that celecoxib was harmful only in patients who had had an MI.[27] Hudson et al[28,36] found that celecoxib

*References 3, 6, 9-11, 21, 23, 27, 28, 33-35.

increased the risk of hospitalization because of HF similarly to conventional NSAIDs.[28,36] In 2 meta-analyses, McGettigan and Henry[11] and Kearney et al[23] did not find increased cardiovascular risk with celecoxib therapy. Hence, it seems that celecoxib may be particularly harmful in patients with established cardiovascular disease. Among the conventional nonselective NSAIDs, the cardiovascular risk with naproxen has been much debated, and some reports have suggested that naproxen was cardioprotective because of its similar ability as aspirin to inhibit COX-1.[37-39] In the present study, naproxen at high dosages was associated with increased mortality and increased risk of hospitalization because of MI and HF. This is in accordance with several other reports,[4,9,34] whereas others have not been able to demonstrate increased risk with use of naproxen.[11,23] However, considering the present results along with the existing evidence, physicians must exert caution in using naproxen in patients with HF, as with other NSAIDs. It is intriguing that the NSAID associated with the highest risk was diclofenac, whose COX-2 selectivity is similar to that of celecoxib.[25] Increased cardiovascular risk with diclofenac has been demonstrated previously,[10,11,23] and the present study extends this finding to patients with HF. Particularly worrisome is that diclofenac is a widely used NSAID, and in many countries it is dispensed OTC, which might be misinterpreted to indicate that diclofenac is a harmless drug. Another common NSAID with OTC status is ibuprofen, which we found harmful in high dosages. Ibuprofen can interact with aspirin by competitively inhibiting COX-1 in the thrombocytes. The inhibition by ibuprofen is reversible, whereas aspirin irreversibly inhibits COX-1; hence, ibuprofen can diminish the cardioprotection of aspirin if taken simultaneously.[40-42] Previous study results have reported an increased risk of hospitalization because of HF associated with NSAID treatment.[28,29,35,36] The present study demonstrates increased mortality and individual differences in risk between the various NSAIDs and dosages. Most patients used NSAIDs for a short time, shortest for the COX-2 inhibitors and diclofenac, which indicates relatively acute cardiotoxic effects of these drugs and is in accord with other reports.[10,43] We found no indication for effect modification by use of evidence-based pharmacotherapy at baseline for the risk exerted by NSAID treatment. Thus, NSAIDs should be avoided in all patients with HF, regardless of baseline pharmacotherapy.

STUDY STRENGTHS AND LIMITATIONS

The main strength of this study is that it includes complete data from an entire nation (Denmark), thus avoiding selection bias by including only subgroups of patients or patients from selected hospitals, medical centers, or health care systems. In Denmark, a government-financed health care system ensures equal access to health care for all inhabitants free. Drug expenses are partially reimbursed, and pharmacies are required to register all dispensed prescriptions in the nationwide prescription registry, ensuring complete registration. Use of OTC NSAID drugs is negligible; ibuprofen is the only NSAID with OTC status in Denmark, and only in low doses (200 mg) and in limited quan-
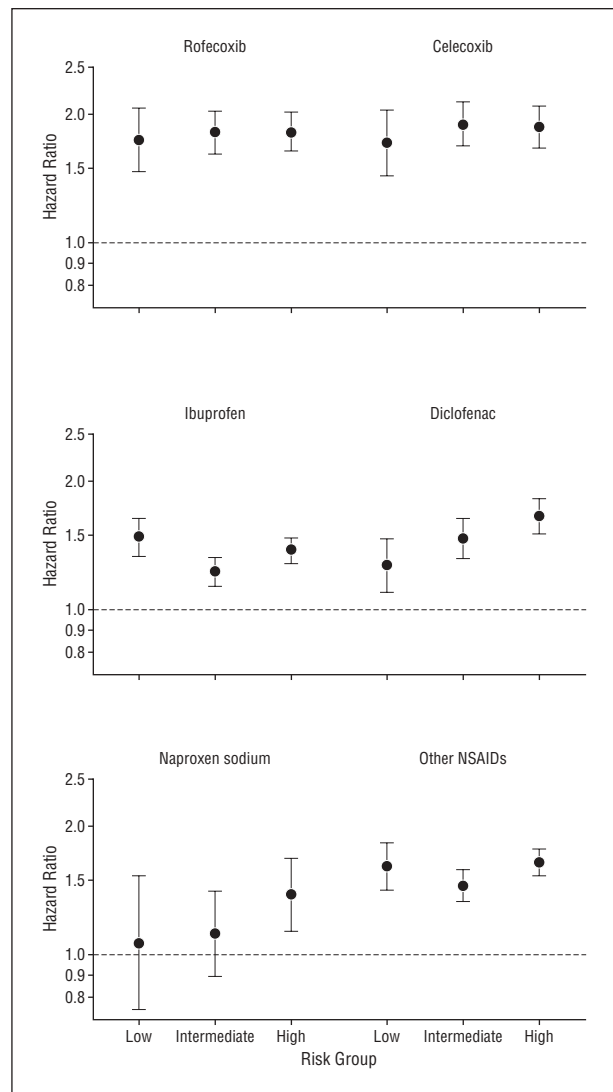

Figure 4. The association between drug use and risk of death according to risk subgroup. The high (>31.4%), intermediate (17.9%-31.4%), and low (<17.9%) mortality risk categories represent tertiles of predicted 1-year mortality risk in a propensity-based analysis. NSAIDs indicates nonsteroidal anti-inflammatory drugs.

tity at each dispensing. Hence, patients needing long-term treatment or higher dosages would have an incentive to get a prescription from their physician because only prescribed drugs are covered by the reimbursement policy. Ibuprofen achieved OTC status in October 2001, and in a sensitivity analysis including data only to January 1, 2001, we achieved similar results (data not shown). Thus, OTC use of ibuprofen is unlikely to have major, if any, effects on the present results.

The main limitation of the present study is its observational design. The discharge coding diagnosis of HF has been validated in the Danish National Patient Registry and, in accord with other studies, found to have high specificity but low sensitivity.[44,45] Thus, the discharge coding diagnosis of HF is suitable to correctly identify patients with HF but not for investigating the prevalence or incidence of HF in a population. Another important limitation is the lack of detailed information about important prognostic factors such as left ventricular ejec-

tion fraction, New York Heart Association classification, smoking, and lipid levels. Although appropriate adjustments were made for comorbidity, the effect of unmeasured confounders can never be fully excluded. In addition, the indication for starting NSAID therapy for each patient is lacking. Thus, the disease or the pain-eliciting condition being treated with an NSAID could indicate a status with increased risk for the patient being treated. However, considering current recommendations that discourage NSAIDs in HF, a channeling bias toward less use of NSAIDs in patients at high risk could be expected because physicians could be more reluctant to use NSAIDs in patients with more severe HF. Comparing baseline characteristics among exposure groups (Table 1), this might be the case because there were fewer patients in severity group 4 using NSAIDs compared with severity groups 1 and 2. The propensity-based risk-stratified analysis yielded similar hazard ratios across all risk groups (Figure 4), with a dose-dependent response (data not shown), and the case-crossover models generated similar results. Thus, confounding by indication alone does not explain the increased risk of NSAID use in this cohort. Furthermore, the difference in risk across different NSAIDS and a dose-dependent increase in risk further supports a causative relationship.

CONCLUSIONS

Treatment with NSAIDs, both selective COX-2 inhibitors and nonselective NSAIDs, in patients with chronic HF is associated with increased mortality and cardiovascular morbidity, with a dose-dependent response. Therefore, patients with HF should, if possible, avoid using any NSAIDs at any dosage for most NSAIDS and at high dosages for ibuprofen and naproxen. Treatment in patients with pain conditions relieved by these drugs should be based on a medically competent evaluation of the benefits vs risks of treatment. Patients who depend on using these drugs should preferably use the NSAIDs that are more COX-1 selective, in as low dosages and for as short a period as possible.

Further research is required to establish the cardiovascular risk associated with all NSAIDs in subgroups of patients with cardiovascular disease, particularly if a low dosage with analgesic effect can be used without increased risk. In the meantime, because of the accumulating evidence, general awareness is required among physicians, health care authorities, and the general public about the potential cardiovascular risk of NSAIDs, in particular in patients with established cardiovascular disease or at increased cardiovascular risk.

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