Risk of Myocardial Infarction and Death Associated With the Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Among Healthy Individuals: A Nationwide Cohort Study

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Use of some nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with increased cardiovascular risk in several patient groups, but whether this excess risk exists in apparently healthy individuals has not been clarified. Using a historical cohort design, we estimated the risk of death and myocardial infarction associated with the use of NSAIDs. Participants in the study were selected from the Danish population and were defined as healthy according to a history of no hospital admissions and no concomitant selected pharmacotherapy. The source population consisted of 4,614,807 individuals, of whom 1,028,437 were included in the study after applying selection criteria. Compared to no NSAID use, hazard ratios (95% confidence limits) for death/myocardial infarction were 1.01 (0.96–1.07) for ibuprofen, 1.63 (1.52–1.76) for diclofenac, 0.97 (0.83–1.12) for naproxen, 2.13 (1.89–2.41) for rofecoxib, and 2.01 (1.78–2.27) for celecoxib. A dose-dependent increase in cardiovascular risk was seen for selective COX-2 inhibitors and diclofenac. Caution should be exercised in NSAID use in all individuals, and particularly high doses should be avoided if possible.

Between 1997 and 2005, 58% of the Danish population used at least one nonsteroidal anti-inflammatory drug (NSAID),[1] and this widespread use is expected to increase even further as more NSAIDs become accessible as over-the-counter drugs. A widespread use of NSAIDs for minor complaints could result in a major public health problem if the excess cardiovascular risk shown for some of the drugs applies to the population in general. However, the possible hazard associated with NSAIDs in apparently healthy people has not been studied. Clinical trials of selected patient groups have documented an increased cardiovascular risk associated with the use of selective cyclooxygenase-2 (COX-2) inhibitors.[2–5] More recently, several large-scale observational studies[6–10] and meta-analyses[11,12] have also suggested an increased cardiovascular risk associated with use of more traditional NSAIDs, such as ibuprofen and diclofenac. The cardiovascular risk associated with NSAIDs seems to be particularly high in patients with established cardiovascular disease.[6,13–15] To address the question of cardiovascular risk of NSAID use in apparently healthy people, we conducted a large-scale study using national administrative registers in Denmark to identify a cohort of individuals without previous hospital admissions or concomitant pharmacotherapy. We investigated whether NSAID use was associated with an increased risk of death and myocardial infarction in these apparently healthy individuals.

RESULTS

The Danish population aged ≥10 years on 1 January 1997 consisted of 4,614,807 individuals. The main study population (population A, **Figure 1**) consisted of 1,028,437 individuals, and the more strictly defined subpopulation (population B) consisted of 153,465 individuals. Baseline characteristics are shown in **Table 1**. In comparison with the entire Danish population, significantly fewer individuals in populations A and B claimed prescriptions for NSAIDs during the study period (57.8%[1] vs. 44.7% for population A and 38.8% for population B, respectively).

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Received 30 June 2008; accepted 29 August 2008; advance online publication 5 November 2008. doi:10.1038/clpt.2008.204

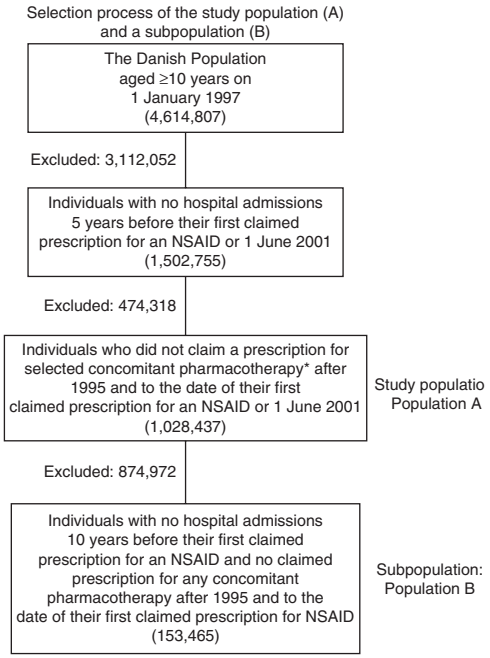

Figure 1 Profile of the study population. *Selected concomitant pharmacotherapy is defined by no prescriptions claimed for one of the following types of drugs: β-blockers, digoxin, angina medication, diuretics, calcium-channel blockers, angiotensin-converting enzyme inhibitors and angiotensin-2 receptor blockers, antithrombotic agents, chronic obstructive pulmonary disease agents, glucose-lowering medication, corticosteroids, analgesics (including morphines), chemotherapy, immunosuppressive agents, disease-modifying antirheumatic agents, and anesthetics. NSAID, nonsteroidal anti-inflammatory drug.

Table 1 Baseline characteristics of two apparently healthy samples of the Danish population

	Population A	Population B
Demographics		
Number of individuals, *n* (% of entire Danish population)	1,028,437 (22.3%)	153,465 (3.3%)
Male sex, *n* (%)	596,920 (58.0%)	110,848 (72.2%)
Median age (IQR)	39 (25–51)	43 (26–56)
Age groups, *n* (%)		
10–30 years	354,167 (34.4%)	49,018 (31.9%)
31–50 years	399,929 (38.9%)	50,730 (33.1%)
51–70 years	227,640 (22.1%)	41,237 (26.9%)
>70 years	46,701 (4.6%)	12,480 (8.1%)
Number of claimed prescriptions for NSAIDs in the study period, *n* (%):		
0 prescriptions	568,525 (55.3%)	109,215 (71.2%)
1 prescription	174,838 (17.0%)	18,470 (12.0%)
2–3 prescriptions	139,551 (13.6%)	14,297 (9.3%)
>3 prescriptions	145,523 (14.2%)	11,483 (7.5%)
Pharmacotherapy 6 months before index date[a]		
Gastric protective agents, *n* (%)	12,688 (1.2%)	—
Antibiotics, *n* (%)	108,353 (10.5%)	—
Cholesterol-lowering drugs, *n* (%)	2,253 (0.2%)	—
Gout agents, *n* (%)	1,705 (0.2%)	—
Osteoporosis drugs, *n* (%)	512 (0.1%)	—
Antidepressants, *n* (%)	16,203 (1.6%)	—
Socioeconomic factors		
Annual family income quartile, *n* (%)		
1 (lowest)	195,675 (22.5%)	40,324 (30.6%)
4 (highest)	252,500 (29.0%)	28,032 (21.3%)

IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs.

[a]Index date is the date of the first claimed prescription for NSAIDs or 1 June 2001, if the individual was not treated with NSAIDs. For individuals who died before 1 June 2001, the index date was set as 1 January 1997.

Population A included significantly more women, and the mean age was lower compared with population B. **Table 2** shows doses, treatment duration, number of deaths, death rates, and numbers needed to harm for the most frequently used NSAIDs. In brief, all NSAIDs were used for a short period, 9–34 days, and most often in low doses. Individuals who received prescriptions for selective COX-2 inhibitors were older compared with those who received nonselective NSAIDs (**Table 2**).

Cox proportional hazard analyses

The relative risk of death and the composite end point of death and myocardial infarction associated with the use of NSAIDs estimated by the Cox proportional hazard analysis are shown in **Table 3**. Results are also given for the more strictly defined population B. The results for the composite end point are illustrated in **Figure 2a** for the main study population (population A). All results are shown for the most frequently used types of selective COX-2 inhibitors and nonspecific NSAIDs. A dose-dependent relation with risk of death and myocardial infarction was seen for all NSAIDs, except naproxen.

Age was an important factor associated with the risk of death and myocardial infarction with NSAID use; for example, ibuprofen and naproxen were associated with an increased risk in 30 to 50-year-olds. The hazard ratios for the composite end point in individuals aged 30 to 50 years for the main study population (within population A) were any use of ibuprofen, 1.76 (95% confidence interval (CI): 1.54–2.01; $P < 0.0001$); diclofenac, 2.80 (95% CI: 2.35–3.34; $P < 0.0001$); rofecoxib, 7.69 (95% CI: 5.67–10.43; $P < 0.0001$); celecoxib, 5.51 (95% CI: 3.93–7.74; $P < 0.0001$); and naproxen, 1.83 (95% CI: 1.30–2.63; $P = 0.001$). There was also a dose-dependent association with the outcomes for all NSAIDs in this age group. In other age groups the results were similar to those reported for the whole study population. A similar association was seen for death alone.

Case-crossover analyses

Odds ratios calculated by the case-crossover method are shown in **Table 4** and illustrated in **Figure 2b** for the main study population (population A). The odds ratios describe the odds of experiencing an event during treatment with an NSAID compared to a previous period. The results were supportive of the trend seen in the Cox analyses for diclofenac, rofecoxib, celecoxib, and naproxen. For these drugs the case-crossover analyses also supported the dose-dependent risk of death and myocardial infarction.

Table 2 Average doses, duration of treatment, and death rates during treatment with selective COX-2 inhibitors and nonselective NSAIDs in two apparently healthy samples of the Danish population

	Number of individuals (%)	Males (%)	Median age (IQR)	Median dose in mg (IQR)	Median treatment duration in days (IQR)	Deaths	Time, person-years	Death rate per 1,000 person-years (95% CI)	NNH (95% CI) per 1,000 person-years
Ibuprofen									
Population A	301,001 (29.3%)	169,472 (56.3%)	40 (27–51)	1,200 (800–1,200)	14 (14–24)	1,052[a]	98,893[b]	11 (10–11)	446 (346–625)
Population B	28,539 (18.6%)	21,834 (76.5%)	42 (28–52)	1,200 (800–1,200)	14 (14–22)	99[a]	6,242[b]	16 (13–19)	432 (184–1,251)
Diclofenac									
Population A	172,362 (16.8%)	97,571 (56.6%)	42 (30–52)	100 (100–100)	14 (9–19)	588[a]	33,007[b]	18 (17–19)	104 (90–122)
Population B	16,103 (10.5%)	12,298 (76.4%)	44 (30–53)	100 (100–100)	14 (9–17)	81[a]	2,632[b]	31 (25–38)	77 (51–158)
Rofecoxib									
Population A	16,079 (1.6%)	7,524 (46.8%)	51 (41–63)	25 (12.5–25)	13 (12–27)	246[a]	4,920[b]	50 (44–56)	24 (21–28)
Population B	1,080 (0.7%)	697 (64.5%)	54 (44–67)	25 (12.5–25)	13 (13–29)	33[a]	378[b]	87 (59–116)	14 (10–25)
Celecoxib									
Population A	15,599 (1.5%)	7,221 (46.3%)	51 (41–62)	200 (200–200)	19 (9–33)	248[a]	4,885[b]	51 (45–57)	24 (21–28)
Population B	1,025 (0.7%)	641 (62.5%)	53 (43–65)	200 (200–200)	19 (9–33)	23[a]	336[b]	68 (41–95)	20 (13–43)
Naproxen									
Population A	40,904 (4.0%)	18,714 (45.8%)	38 (24–50)	500 (472–500)	24 (24–31)	136[a]	14,963[b]	9 (8–11)	1,329 (436–2,450)
Population B	3,961 (2.6%)	2,539 (64.1%)	38 (20–51)	500 (464–500)	24 (19–29)	11[a]	908[b]	12 (5–19)	−165 (−76–(−941))[c]
No NSAID									
Population A	568,525 (55.3%)	340,597 (59.9%)	37 (23–51)	—	—	41,487	4,936,836	8 (8–8)	—
Population B	109,215 (71.2%)	68,562 (72.1%)	43 (25–57)	—	—	16,582	912,477	18 (18–18)	—
Total									
Population A	1,028,437	596,920 (58.0%)	39 (25–51)	—	—	56,305	9,028,028	6 (6–6)	—
Population B	153,465	110,848 (72.2%)	43 (26–56)	—	—	18,579	1,303,821	14 (14–14)	—

95% CI, 95% confidence interval; IQR, interquartile range, NNH, number needed to harm; NSAID, nonsteroidal anti-inflammatory drug.

[a]Deaths during treatment with the specific NSAID. [b]Person-years during treatment with the specific NSAID. [c]A negative NNH represents a drug that has a lower death rate compared to individuals with no NSAID use.

The initial treatment period

The initial treatment period with NSAIDs was characterized by no prior medication or comorbidity at all. The results were similar, as seen in the model in which all treatment intervals were analyzed, and are listed here for the main study population (population A) for the composite end point (Cox proportional hazard analysis): for any use of ibuprofen, the hazard ratio was 1.31 (95% CI: 1.15–1.49; $P < 0.0001$); any use of diclofenac, 2.50 (95% CI: 2.18–2.88; $P < 0.0001$); any use of rofecoxib, 3.50 (95% CI: 2.88–4.26; $P < 0.0001$); any use of celecoxib, 3.05 (95% CI: 2.53–3.68; $P < 0.0001$); and for any use of naproxen, 1.45 (95% CI: 1.08–1.94; $P = 0.01$). Again, there was a dose-dependent relation with risk of death and myocardial infarction (data not shown). Results were similar for death and were confirmed in population B (data not shown). As an additional analysis to describe the distribution of events and the relative risk of death and myocardial infarction in the initial treatment period, we estimated the hazard ratios associated with different time intervals during the treatment period. We found no significant difference in risk associated with the first few days of treatment compared with the rest of the treatment interval (data not shown). Most of the events were distributed later than 10 days into the treatment period.

Additional analyses

Subgroup analyses were performed for patients without a cancer diagnosis following the index date. The results were similar for all types of NSAIDs in both populations (data not shown). Results were also unchanged after excluding individuals who had been hospitalized for up to 30 days before their death (data not shown). Furthermore, all results were similar in subgroups according to sex (no significant interaction between treatment with NSAIDs and sex).

DISCUSSION

Our results demonstrate that use of selective COX-2 inhibitors and nonspecific NSAIDs (particularly in high doses) in a large population of apparently healthy individuals is associated with excess risk of death and myocardial infarction. The novel findings of this study are that previous disturbing results about risk of cardiovascular complications from NSAID use in different patient settings also apply to a cohort of individuals characterized by no comorbidity or concomitant pharmacotherapy, and to short-term use. The results include a dose-dependent relationship between NSAID treatment and risk of death and myocardial infarction. In this apparently healthy population, however, the absolute risk

Table 3 Cox proportional hazard ratios for death and the composite end point of myocardial infarction and death associated with exposure to nonsteroidal anti-inflammatory drugs stratified according to daily dosage in two healthy samples of the Danish population

	Study population (population A), *n* = 1,028,427				Subpopulation (population B), *n* = 153,464			
	Death		Composite end point		Death		Composite end point	
Drug	Deaths[a]	HR (95% CI)	Event[a]	HR (95% CI)	Deaths[a]	HR (95% CI)	Event[a]	HR (95% CI)
Ibuprofen								
No use		1.00		1.00		1.00		1.00
Any use	1,052	0.89 (0.83–0.94)**	1,303	1.01 (0.96–1.07)	99	0.78 (0.64–0.94)*	118	0.88 (0.74–1.06)
≤1,200 mg	835	0.78 (0.73–0.84)**	1,059	0.92 (0.86–0.97)**	76	0.68 (0.54–0.85)**	90	0.76 (0.62–0.94)*
>1,200 mg	217	1.77 (1.55–2.02)**	244	1.84 (1.62–2.08)**	23	1.49 (0.99–2.24)	28	1.75 (1.21–2.53)**
Diclofenac								
No use		1.00		1.00		1.00		1.00
Any use	588	1.47 (1.35–1.59)**	715	1.63 (1.52–1.76)**	81	1.40 (1.13–1.75)**	95	1.58 (1.29–1.93)**
<100 mg	133	0.87 (0.73–1.03)	174	1.05 (0.90–1.21)	11	0.51 (0.28–0.92)*	79	0.71 (0.44–1.16)
≥100 mg	455	1.83 (1.67–2.01)**	541	1.99 (1.83–2.17)**	70	1.93 (1.53–2.44)**	16	2.09 (1.68–2.61)**
Rofecoxib								
No use		1.00		1.00		1.00		1.00
Any use	246	2.12 (1.87–2.40)**	266	2.13 (1.89–2.41)**	33	1.87 (1.33–1.75)**	37	2.03 (1.47–2.81)**
≤25 mg	220	1.97 (1.72–2.25)**	240	2.00 (1.76–2.27)**	27	1.56 (1.07–2.28)*	31	1.74 (1.22–2.47)**
>25 mg	26	6.02 (4.10–8.85)**	26	5.59 (3.81–8.21)**	6	12.85 (5.77–28.64)**	6	12.28 (5.51–27.36)**
Celecoxib								
No use		1.00		1.00		1.00		1.00
Any use	248	2.05 (1.81–2.32)**	262	2.01 (1.78–2.27)**	23	1.56 (1.04–1.75)*	23	1.49 (0.99–2.25)
≤200 mg	170	1.65 (1.42–1.92)**	182	1.64 (1.42–1.90)**	12	1.02 (0.58–1.79)	13	1.05 (0.61–1.81)
>200 mg	78	4.38 (3.50–5.47)**	80	4.16 (3.34–5.19)**	11	3.60 (1.99–6.51)**	10	3.12 (1.68–5.81)**
Naproxen								
No use		1.00		1.00		1.00		1.00
Any use	136	0.80 (0.67–0.94)*	178	0.97 (0.83–1.12)	11	0.76 (0.42–1.36)	13	0.85 (0.49–1.46)
≤500 mg	99	0.70 (0.58–0.86)**	137	0.90 (0.76–1.06)	9	0.73 (0.38–1.41)	11	0.85 (0.47–1.53)
>500 mg	37	1.25 (0.90–1.72)	41	1.28 (0.95–1.74)	2	0.87 (0.22–3.47)	2	0.83 (0.21–3.30)

The analyses are adjusted for age, sex, and calendar year.

HR, hazard ratio; 95% CI, 95% confidence interval.

[a]Deaths or composite end-point events (myocardial infarction or death) during treatment with the specific drug.

*$P < 0.05$. **$P < 0.01$.

of death and cardiovascular events as a result of NSAID intake is low, which was reflected in the high number of patients needed to be treated with NSAIDs to cause harm. This is opposed to previous studies of patients with established cardiovascular disease, in which high baseline risk was associated with low numbers needed to treat to cause harm. However, even in this low-risk population, NSAIDs were significantly associated with increased relative risks of death and cardiovascular events, and because of the large number of individuals who use such drugs, this represents a potential public health concern. The current use of NSAIDs in this study population comprising 1 million people translates into 63 excess deaths per year—a number not much lower than annual traffic deaths in Denmark, which account for ~75 deaths.

To minimize bias, we used two methods to study the relationship between outcome and NSAID treatment. The Cox proportional hazard model has the potential weakness of omitting unidentified and unmeasured confounders. The case-crossover model compared the intake of NSAIDs at the time of an outcome with selected periods before the outcome in the same individual. This method eliminates bias by all covariates that remain constant during the study period. Thus, results that have been found using both methods are regarded as robust, whereas results found using only proportional hazard models are considered less robust, i.e., robust findings of this study were increased risk of death and myocardial infarction when using any dose of diclofenac, rofecoxib, or celecoxib. In addition, a less certain increase in risk was found with high doses of other NSAIDs.

The Vioxx Gastrointestinal Outcomes Research study[2] was the first to show an increased risk of cardiovascular adverse events associated with the selective COX-2 inhibitor rofecoxib. Vioxx

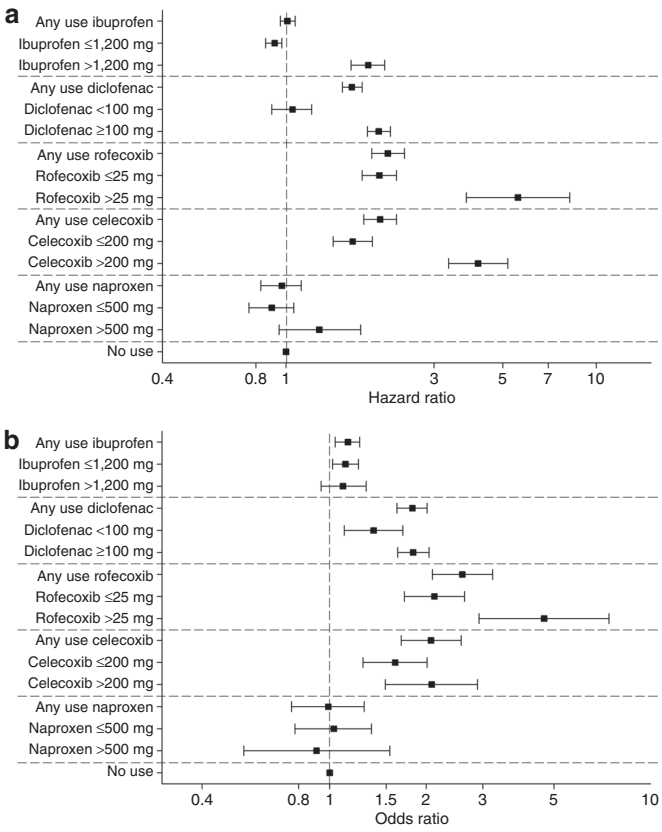

Figure 2 Risk of death or myocardial infarction. (**a**) Cox proportional hazard ratios for the composite end point of death and myocardial infarction associated with exposure to nonsteroidal anti-inflammatory drugs (NSAIDs) in a study population of 1,028,437 individuals characterized by no prior concomitant pharmacotherapy and no comorbidity. Error bars illustrate the 95% confidence interval. (**b**) Odds ratios, derived from the case-crossover analysis, for the composite end point of death and myocardial infarction associated with exposure to NSAIDs in a study population of 1,028,437 individuals characterized by no prior concomitant pharmacotherapy and no comorbidity. Error bars illustrate the 95% confidence interval.

was withdrawn from the market 4 years later, in 2004, after publication of the Adenomatous Polyp Prevention on Vioxx trial, in which similar results to those of the Vioxx Gastrointestinal Outcomes Research were reported.[3] We found comparable relative risk of death and myocardial infarction associated with the use of rofecoxib in this study's population. Since the publication of the Adenomatous Polyp Prevention on Vioxx trial, further evidence has accumulated concerning the use of NSAIDs and increased risk of death and cardiovascular morbidity in a variety of study populations.[2–5,7,9,10,12,13,16–18] In particular, the selective COX-2 inhibitors have caused increased awareness of cardiovascular risk, but recently focus has expanded to cardiovascular risk of the nonselective NSAIDs. The Multinational Etoricoxib and Diclofenac Arthritis Long-term trial found a similar risk of cardiovascular events associated with use of the COX-2 inhibitor etoricoxib and the nonspecific NSAID diclofenac in patients with arthritis.[19] Our results also show that in the general healthy population the risk profile of diclofenac is similar to that of the COX-2 inhibitors. This comparable risk of cardiovascular events could possibly be explained by diclofenac, which has a high COX-2 inhibition profile as compared to COX-1 inhibition, a characteristic most of nonspecific NSAIDs.[18] A systematic review by McGettigan and Henry also raised serious concern about the safety of diclofenac;[12] our results support this notion. Cardiovascular risk associated with the use of ibuprofen, another very widely used nonspecific NSAID, was not as clear compared to that of diclofenac, as risk was observed only at high doses in the Cox proportional hazard analysis. The Therapeutic Arthritis Research and Gastrointestinal Event Trial showed that use of ibuprofen was also suspected to increase the risk of excess cardiovascular events.[20] Studies have also shown an adverse effect of ibuprofen on the protective effect of aspirin therapy in patients with cardiovascular disease.[21,22] This study demonstrated increased risk of death and myocardial infarction associated with only high doses of ibuprofen—and the contrary with low doses. The protective effect of ibuprofen in low doses could be due to an antithrombotic effect of ibuprofen comparable to that of aspirin. In addition, the Therapeutic Arthritis Research and Gastrointestinal Event Trial even suggested that naproxen could be cardioprotective. This was not clearly shown by our results, as we found naproxen to be neutral in almost all analyses. A cardioprotective effect of naproxen cannot be rejected by our results—nor can a cardiovascular risk be ruled out. Thus, this study supports the safety of naproxen in individuals requiring treatment with NSAID as regards cardiovascular morbidity and overall mortality. In a recent scientific statement, the American Heart Association recommended that selective COX-2 inhibitors should be avoided in patients with established cardiovascular disease or who are at high cardiovascular risk, and that alternative pain medications should be considered first.[18] This study raises concern regarding the use of all NSAIDs in an apparently healthy population, and therefore health-care authorities should consider a general caution on use of these drugs, not only in patient groups but also in the general population. Furthermore, previous studies have suggested a dose-dependent increase in risk associated with NSAID use,[5,7,13] and results from clinical trials suggest that continuous use of selective COX-2 inhibitors, in particular, is unfavorable.[3] This is in accordance with our findings. Several clinical trials have also found increased cardiovascular risk associated with the COX-2 inhibitor celecoxib.[5,23,24] The dose-dependent relationship between treatment and cardiovascular events reported in these trials was also confirmed in our study.

Nonspecific NSAIDs are sold over the counter in a number of countries. As a consequence, the general public has easy access to these drugs without medical evaluation of risks and benefits. Recommendations for individuals with cardiac disease state that alternative pain medication should be considered before prescribing an NSAID or a COX-2 inhibitor.[18] Because NSAIDs are sold over the counter, the drugs are perceived as harmless and without need for detailed advice—a convention that needs re-evaluation. In a withdrawal study of rofecoxib, most patients were not shifted to another NSAID; this was interpreted as an increased adherence by the prescribers to current guidelines emphasized by the ongoing controversies of NSAID use.[25] This may underline the importance of a physician's guidance in the balance between risk and benefit when using NSAIDs. We believe that this study raises

Table 4 Case-crossover analysis: odds ratios for death and the composite end point of myocardial infarction and death associated with exposure to nonsteroidal anti-inflammatory drugs stratified according to daily dosage in two healthy samples of the Danish population

	Study population (population A), *n* = 1,028,427				Subpopulation (population B), *n* = 153,464			
	Death		Composite end point		Death		Composite end point	
Drug	Deaths[a]	OR (95% CI)	Event[a]	OR (95% CI)	Deaths[a]	OR (95% CI)	Event[a]	OR (95% CI)
Ibuprofen								
No use		1.00		1.00		1.00		1.00
Any use	1,052	1.06 (0.96–1.17)	1,303	1.14 (1.04–1.24)**	99	1.01 (0.77–1.32)	118	1.06 (0.81–1.38)
≤1,200 mg	835	1.06 (0.96–1.18)	1,059	1.12 (1.02–1.23)*	76	1.01 (0.75–1.35)	90	1.09 (0.81–1.45)
>1,200 mg	217	1.04 (0.88–1.23)	244	1.10 (0.94–1.30)	23	1.04 (0.65–1.66)	28	0.98 (0.62–1.56)
Diclofenac								
No use		1.00		1.00		1.00		1.00
Any use	588	1.81 (1.61–2.04)**	715	1.81 (1.62–2.01)**	81	2.41 (1.77–3.30)**	95	2.34 (1.73–3.17)**
<100 mg	133	1.34 (1.07–1.69)*	174	1.37 (1.11–1.69)**	11	2.06 (1.10–3.88)*	79	2.15 (1.14–4.08)*
≥100 mg	455	1.83 (1.62–2.07)**	541	1.82 (1.63–2.04)**	70	2.26 (1.65–3.10)**	16	2.21 (1.63–3.01)**
Rofecoxib								
No use		1.00		1.00		1.00		1.00
Any use	246	2.74 (2.20–3.43)**	266	2.59 (2.09–3.22)**	33	2.70 (1.34–5.46)**	37	2.70 (1.34–5.46)**
≤25 mg	220	2.22 (1.78–2.78)**	240	2.12 (1.71–2.63)**	27	2.00 (1.03–3.90)*	31	2.00 (1.03–3.90)*
>25 mg	26	4.99 (3.11–7.99)**	26	4.66 (2.92–7.42)**	6	10.22 (2.26–46.23)**	6	20.47 (2.64–158.78)**
Celecoxib								
No use		1.00		1.00		1.00		1.00
Any use	248	1.95 (1.56–2.43)**	262	2.07 (1.67–2.57)**	23	1.09 (0.54–2.23)	23	1.21 (0.62–2.36)
≤200 mg	170	1.46 (1.16–1.84)**	182	1.60 (1.27–2.01)**	12	0.46 (0.22–0.94)*	13	0.49 (0.25–0.99)*
>200 mg	78	2.12 (1.52–2.95)**	80	2.08 (1.49–2.89)**	11	5.44 (1.17–25.21)*	10	5.72 (1.25–26.23)*
Naproxen								
No use		1.00		1.00		1.00		1.00
Any use	136	0.75 (0.56–1.00)*	178	0.99 (0.76–1.28)	11	0.94 (0.40–2.20)	13	0.89 (0.39–2.04)
≤500 mg	99	0.78 (0.58–1.05)	137	1.03 (0.78–1.35)	9	0.82 (0.33–2.00)	11	0.82 (0.34–1.97)
>500 mg	37	0.80 (0.47–1.37)	41	0.91 (0.54–1.54)	2	1.46 (0.19–11.21)	2	1.00 (0.13–8.00)

95% CI, 95% confidence interval; OR, odds ratio.

[a]Deaths or composite end-point events (myocardial infarction or death) during treatment with the specific drug.

*$P < 0.05$. **$P < 0.01$.

concern over whether the safety of unrestricted use of NSAIDs as over-the-counter drugs is sufficient, especially because more NSAIDs are becoming available over the counter. In Denmark, diclofenac has been available over the counter since mid-2008. If NSAID treatment is required, our study suggests little overall risk of death or myocardial infarction in the groups studied for naproxen or ibuprofen, although even these medications carry a significant dose-dependent risk for those aged 30 to 50 years for the composite end point. Thus, our study suggests that these individuals should be advised against taking any of the drugs or else to keep utilization to a minimum.

Strengths and limitations

The main strength of this study is the completeness of data. The data cover the entire population of Denmark independent of race, socioeconomic status, age, or participation in health insurance programs, and notably include citizens both in and out of the labor market. Therefore the risk of selection bias is avoided. The Danish health care system partially reimburses drug expenses, and all Danish pharmacies are thus required to register all dispensed drug prescriptions, which ensures complete registration. During the study period, ibuprofen was the only NSAID that could be purchased as an over-the-counter drug in Denmark, but only in low dosages (200 mg) and in limited quantities. Ibuprofen has been available as an over-the-counter drug in Denmark since 1 November 2001; to confirm our results, we performed a sensitivity analysis ending the study period on this date. The results remained unchanged. Therefore, over-the-counter NSAID use is unlikely to have a significant influence on our results—the exception being that there might be an unregistered use that could have biased our results toward not identifying or diluting the underlying risk

associated with ibuprofen in low doses. Also, as there is partial patient co-payment of drug expenses in Denmark, patients requiring higher doses or long-term treatment would have a financial incentive to obtain a prescription from their physician to receive reimbursement.

The main limitation is inherent in the observational nature of the study. We have no information about the precise indication for initiation of NSAID treatment. Thus, the disease or the pain causing a condition being treated with an NSAID could alone indicate a condition with increased risk of cardiovascular disease or death. To ensure the validity of our results, we performed our analyses with two independent statistical methods and in two populations—the similarity of results from the two methods shows the robustness of our results. We also analyzed the initial treatment period with NSAIDs to stress the association independent of time-dependent confounders that could influence results in the primary analysis. Furthermore, we defined a subpopulation using more conservative criteria and obtained similar findings. However, because this is an observational study, it is important to acknowledge that the effect of unmeasured confounders cannot be fully excluded. In conclusion, this study demonstrated a dose-dependent relationship between NSAID treatment and the composite of death and myocardial infarction in apparently healthy people, most pronounced for the selective COX-2 inhibitors rofecoxib and celecoxib, and also for the nonspecific NSAID diclofenac. The widespread use of these NSAIDs translates into a public health problem of a magnitude similar to that of traffic-related deaths. The evidence accumulating regarding the safety of NSAIDs and their widespread use should result in public warnings of the potential hazards associated with the use of the drugs. Allowing these drugs to be sold over the counter without appropriate counseling should be re-evaluated.

METHODS

All residents in Denmark have a unique and permanent personal civil registration number, which allows linkage on an individual level of data from complete national registers. Information on every dispensed drug prescription from pharmacies in Denmark since 1995 is available in the Danish Register of Medicinal Product Statistics (national prescription register). This register holds information on date of dispensing, quantity dispensed, strength, and the affiliation of the physician issuing the prescription. The drugs are classified according to the international Anatomical Therapeutical Chemical system. Because of partial reimbursement of drug expenses by the health care system, pharmacies in Denmark are required to register all dispensed prescriptions in the national prescription register. This ensures a highly accurate register.[26] Information on previous comorbidity was obtained from the Danish National Patient Register, which holds information on all admissions to Danish hospitals since 1978.[27] Each admission is registered by one primary diagnosis and, if appropriate, one or more secondary diagnoses according to the *International Classification of Diseases* (ICD)—before 1994, the 8th revision (ICD-8), and since 1994, the 10th revision (ICD-10).

Study population. The study population was identified among all Danish residents aged ≥10 years on 1 January 1997. Two study populations were selected based on morbidity and use of other pharmacotherapy, as shown in **Figure 1**. The date of the first claimed prescription for an NSAID was used as the index date. For individuals not prescribed an NSAID, the index date was placed in the middle of the study period (1 June 2001). For individuals who were not prescribed an NSAID and who died before 1 June 2001, the index date was set as 1 January 1997. The main study population (population A) consisted of individuals characterized by having had no hospital admission 5 years before the index date and not having used any of the pharmacological treatments listed below. The subpopulation (population B) was restricted to having had no hospital admission 10 years before the index date and no pharmacotherapy at all for at least 2 years before the index date. The follow-up was 9 years, from 1997 to 2005.

Concomitant pharmacotherapy causing exclusion from population A was defined by records of claimed prescriptions for any of the following drugs (Anatomical Therapeutical Chemical code) from 1 January 1995 to the index date: β-blockers (C07), digoxin (C01A), antiangina medication (C01D), diuretics (C03), calcium-channel blockers (C08), angiotensin-converting enzyme inhibitors or angiotensin-2 receptor blockers (C09), antithrombotic agents (B01), chronic obstructive pulmonary disease agents (R03), glucose-lowering medication (A10), corticosteroids (H02A), analgesics (including morphine) (N02), chemotherapy (L01), immunosuppressive agents (L04), disease-modifying antirheumatic agents (M01C), and anesthetics (N01). Information on the individual use of NSAIDs in the study period was obtained by identifying all claimed prescriptions for NSAIDs. To adjust for socioeconomic status, the population was classified into quartiles according to the annual household income the year before the beginning of the study.

Outcome measures. The primary outcome was a composite of death and myocardial infarction. Risk of death alone was the secondary outcome. Survival status (dead or alive) was obtained from the National Person Register, which is updated at least once every 2 weeks. We identified all individuals admitted to a hospital with myocardial infarction from the Danish National Patient Register (ICD-10 codes I21 and I22).

Dose and duration of treatment. The method that was used to determine the dose and treatment duration has been described previously.[1,28] In brief, for each prescription, the number of pills dispensed was divided by the estimated daily dosage to calculate the treatment duration. High dosage was defined as being above the upper limit of the recommended minimal dosage for each drug: ibuprofen >1,200 mg, diclofenac ≥100 mg, naproxen >500 mg, rofecoxib >25 mg, and celecoxib >200 mg.

Statistics. We used two statistical methods for estimating the risk of death and myocardial infarction associated with exposure to NSAIDs to ensure robustness of the results. First, Cox proportional hazard regression analyses with exposure to NSAIDs entered into the model as time-dependent variables were used for estimating the hazard ratios of death and myocardial infarction. The model was adjusted for age, sex, and calendar year. Sensitivity analyses on individuals with a diagnosed cancer (between the index date and event) were also performed. Subgroup analyses were performed with special focus on sex and age. Second, case-crossover analyses were used. The case-crossover method is based on the case-base paradigm, in which an individual appears as his or her own control in other periods.[29] The effect of unmeasured confounders is thus minimized. In particular, chronic-illness confounders are eliminated from the analyses. We defined the case period as 0–30 days before the event (myocardial infarction or death), and, to enhance the strength of the analyses, we selected two control periods: 60 to 90 and 90 to 120 days before the event. Conditional logistic regression was used in the case-crossover analysis.

The populations were divided into four age groups for subgroup analyses: 10 to 30, 31 to 50, 51 to 70, and >70 years. For each drug, the number needed to harm was estimated from the unadjusted mortality rates as number needed to harm per 1,000 person-years exposed. Last, the Cox proportional hazard analyses were repeated where only the first treatment period was considered as exposure.

For all analyses, a two-sided $P < 0.05$ was considered statistically significant. Cox proportional hazard analyses with time-dependent variables were performed using the STATA statistical package, version 10 (StataCorp LP, College Station, TX). All other analyses and data management were performed using SAS, version 9.1 (SAS Institute, Cary, NC).

Ethics. The Danish Data Protection Agency approved the study (no. 2003-54-1269). Retrospective studies based on data from administrative registers do not require ethical approval in Denmark.

ACKNOWLEDGMENTS

All authors have read and approved the manuscript and contributed to its design, analyses, and/or interpretation of data. In addition, E.L.F., G.H.G., L.K., S.R., and C.T.-P. participated in data management and planning of statistical analyses and were also responsible for the original study idea and design. E.L.F. wrote the first draft of the manuscript. This work was performed at the Department of Cardiology, Gentofte University Hospital, Hellerup, Denmark.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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