Circulation
Cardiovascular Quality and Outcomes
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association
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Circ Cardiovasc Qual Outcomes published online Jun 8, 2010;
DOI: 10.1161/CIRCOUTCOMES.109.861104
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 1941-7705. Online ISSN: 1941-7713

Cause-Specific Cardiovascular Risk Associated With Nonsteroidal Antiinflammatory Drugs Among Healthy Individuals

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Background—Studies have raised concern on the cardiovascular safety of nonsteroidal antiinflammatory drugs (NSAIDs). We studied safety of NSAID therapy in a nationwide cohort of healthy individuals.

Methods and Results—With the use of individual-level linkage of nationwide administrative registers, we identified a cohort of individuals without hospitalizations 5 years before first prescription claim of NSAIDs and without claimed drug prescriptions for selected concomitant medication 2 years previously. The risk of cardiovascular death, a composite of coronary death or nonfatal myocardial infarction, and fatal or nonfatal stroke associated with the use of NSAIDs was estimated by case-crossover and Cox proportional hazard analyses. The entire Danish population age 10 years or more consisted of 4 614 807 individuals on January 1, 1997, of which 2 663 706 (57.8%) claimed at least 1 prescription for NSAIDs during 1997 to 2005. Of these; 1 028 437 individuals were included in the study after applying selection criteria regarding comorbidity and concomitant pharmacotherapy. Use of the nonselective NSAID diclofenac and the selective cyclooxygenase-2 inhibitor rofecoxib was associated with an increased risk of cardiovascular death (odds ratio, 1.91; 95% confidence interval, 1.62 to 2.42; and odds ratio, 1.66; 95% confidence interval, 1.06 to 2.59, respectively), with a dose-dependent increase in risk. There was a trend for increased risk of fatal or nonfatal stroke associated with ibuprofen treatment (odds ratio, 1.29; 95% confidence interval, 1.02 to 1.63), but naproxen was not associated with increased cardiovascular risk (odds ratio for cardiovascular death, 0.84; 95% confidence interval, 0.50 to 1.42).

Conclusions—Individual NSAIDs have different degrees of cardiovascular safety, which must be considered when choosing appropriate treatment. In particular, rofecoxib and diclofenac were associated with increased cardiovascular mortality and morbidity and should be used with caution in most individuals, whereas our results suggest that naproxen has a safer cardiovascular risk-profile. **(*Circ Cardiovasc Qual Outcomes*. 2010;3:00-00.)**

Key Words: nonsteroidal antiinflammatory drugs ■ selective cyclooxygenase-2 inhibitors ■ cause-specific mortality ■ cardiovascular death ■ myocardial infarction ■ stroke ■ bleeding complications

Concerns have been raised regarding the safety of nonsteroidal antiinflammatory drugs (NSAIDs), which have been linked to increased cardiovascular morbidity. This association was first established in large clinical trials investigating the effect of selective cyclooxygenase-2 (COX-2) inhibitors on preventing gastrointestinal ulcers and gastrointestinal polyps.[1–4] Later, these results have been confirmed in several large-scale observational studies[5–9] and meta-analyses,[10,11] which also have suggested an increased cardiovascular risk associated with use of the more traditional nonselective NSAIDs, such as ibuprofen and in particular diclofenac.

The cardiovascular safety of NSAIDs is a major public health issue because NSAIDs are widely used in the general population. We have previously documented that up to 20% of the general population in Denmark at some time have used diclofenac on a prescription basis,[12] which is of major concern because this particular NSAID has been linked to a substantial increased cardiovascular risk in different patient settings. Furthermore, in many countries (ie, the United States, Germany, Sweden, Spain, and others), some NSAIDs (most often ibuprofen, naproxen, and diclofenac) can also be purchased as over-the-counter drugs in supermarkets, at gas

Received March 2, 2009; accepted March 25, 2010.

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Circ Cardiovasc Qual Outcomes **is available at http://circoutcomes.ahajournals.org** **DOI: 10.1161/CIRCOUTCOMES.109.861104**

stations, and convenience stores without any expert advice on their use or potential side effects.[13,14]

Knowledge on the cause of death related to the use of NSAIDs and the general attributable cardiovascular risk to the drugs in healthy people mandates investigation because of the widespread use of these drugs. Risk of bleeding associated with NSAIDs also has great importance when selecting a specific drug, and it is of interest whether the risk of major bleedings is equal among the individual NSAIDs. Therefore, the objective of this study was to investigate the cardiovascular risk in healthy individuals estimated by cause-specific mortality and hospitalizations. We conducted this study to answer whether any specific NSAID carried a risk of cardiovascular adverse events among healthy individuals and to explore if there were safer alternatives within the group of NSAIDs.

WHAT IS KNOWN

- Studies have raised concern about the cardiovascular safety of non-steroidal antiinflammatory drugs (NSAIDs), especially the selective cyclooxygenase-2 inhibitors, which have been linked to an increased cardiovascular risk.
- Almost all evidence regarding the cardiovascular risk of NSAIDs is accumulated through studies performed in populations with increased cardiovascular risk or established disease or from trials testing a noncardiovascular end point.

WHAT THE STUDY ADDS

- This study is the first to our knowledge to study the relationship between cause-specific cardiovascular risk and NSAIDs among healthy individuals.
- In this healthy population, increased cardiovascular morbidity and mortality was observed with the use of rofecoxib, with diclofenac, and with high doses of ibuprofen but not with naproxen.
- The increased risk associated with diclofenac is of particular importance because it is one of the most commonly used NSAIDs worldwide. We hypothesize that this may be because diclofenac is almost as cyclooxygenase-2–selective as rofecoxib.

Methods

Study Design

This study was a population-based historic cohort study in presumably healthy individuals in Denmark. We studied the cause-specific cardiovascular risk in relation to treatment with NSAIDs in this cohort. The study-period lasted from January 1, 1997, to December 31, 2005.

Study Data

All residents in Denmark have a unique personal registration number, which enables linkage of administrative registries on an individual level. Vital status (dead or alive) was obtained from the Central Population Register, which is updated every 2 weeks. Cause of death was obtained from the National Causes of Death Register, in which immediate, contributory, and underlying causes are recorded using the *International Classification of Diseases 10th revision (ICD 10)*. Information on concomitant medication was obtained from the National Prescription Register (the Danish Register of Medicinal Product Statistics), in which all claimed prescriptions in Denmark have been recorded since 1995, ensuring complete data on date of dispensing, strength of the tablets, and number of pills dispensed. The drugs are classified according to the international Anatomic Therapeutical Chemical (ATC) 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 registry.[15] Comorbidity was obtained from the Danish National Patient Registry, which holds information on all admissions to Danish hospitals since 1978.[16] Each admission is registered by 1 primary diagnosis, and, if appropriate, 1 or more secondary diagnoses according to ICD—before 1994, the 8th revision (ICD-8), and since 1994, the 10th revision (ICD-10).

Table 1. Baseline Characteristics

No. of individuals	1 028 437
Male sex, n (%)	596 920 (58.0)
Median age (interquartile range)	39 (25–51)
Age groups, n (%)	
10–30 y	354 167 (34.4)
31–50 y	399 929 (38.9)
51–70 y	227 640 (22.1)
>70 y	46 701 (4.6)
No. of claimed prescriptions for NSAID in the study period, n (%)	
0 prescriptions	568 525 (55.3)
1 prescription	174 838 (17.0)
2–3 prescriptions	139 551 (13.6)
>3 prescriptions	145 523 (14.2)
Pharmacotherapy 6 mo before index date*	
Gastric protective agents, n (%)	12 688 (1.2)
Antibiotics, n (%)	108 353 (10.5)
Cholesterol-lowering drugs, n (%)	2253 (0.2)
Gout agents, n (%)	1705 (0.2)
Osteoporosis drugs, n (%)	512 (0.1)
Antidepressants, n (%)	16 203 (1.6)

*Index date is the date of the first claimed prescription for NSAID or June 1, 2001, if the individual was not treated with NSAID. For nonexposed individuals who died before June 1, 2001, the index date was sat as January 1, 1997.

Study Population

The selection process of the study population has been described in detail previously.[17] In brief, the study population was identified among all Danish residents age 10 years or more on January 1, 1997. The date of the first claimed prescription for an NSAID was used as an index date. For individuals not prescribed with NSAIDs, an index date was placed in the middle of the study period (June 1, 2001) for the groups to have equal length of follow-up time and hence the same possibility for an event to occur. For individuals who did not claim a prescription for NSAID and who died before June 1, 2001, the index date was set as January 1, 1997. The study population consisted of individuals characterized by having no contact with the Danish hospital system 5 years before the index date and with no use of any serious pharmacological treatments (β-blockers, digoxin, antiangina medication, diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin-2 receptor blockers, antithrombotic agents, chronic obstructive pulmonary dis-

Table 2. Number of Individuals Treated With NSAIDs, Average Doses, and Duration of Treatment

	No. of Individuals, n (%)	Males, n (%)	Median Age, y (IQR)	Median Dose, mg (IQR)	Median Treatment Duration, d (IQR)	Time in Person-Years
Ibuprofen	301 001 (29.3)	169 472 (56.3)	40 (27–51)	1200 (800–1200)	14 (14–24)	98 893*
Diclofenac	172 362 (16.8)	97 571 (56.6)	42 (30–52)	100 (100–100)	14 (9–19)	33 007*
Rofecoxib	16 079 (1.6)	7524 (46.8)	51 (41–63)	25 (12.5–25)	13 (12–27)	4920*
Celecoxib	15 599 (1.5)	7221 (46.3)	51 (41–62)	200 (200–200)	19 (9–33)	4885*
Naproxen	40 904 (4.0)	18 714 (45.8)	38 (24–50)	500 (472–500)	24 (24–31)	14 963*
No NSAID	568 525 (55.3)	340 597 (59.9)	37 (23–51)			2 512 502
Total	1 028 437	596 920 (58.0)	39 (25–51)			5 127 474

IQR indicates interquartile range.
*Time exposed to the individual NSAID.

ease agents, glucose-lowering medication, corticosteroids, analgesics including morphine, chemotherapy, immune suppressive agents, disease-modifying antirheumatic agents, and anesthetics). Comorbidity was measured by prescription claims and hospitalizations; hence, individuals without either of these were characterized as having no comorbidities.

Statistical Analysis

We used 2 different statistical methods to estimate the risk of cause-specific death associated with exposure to NSAIDs to increase the robustness of the results. The case-crossover method is based on the case-base paradigm in which an individual appears as his or her own control in other time periods before the event of investigation.[18] The effect of unmeasured confounders is thereby minimized. In particular, chronic illness confounders are eliminated from the analyses when, as in our study, the time periods are of short duration. We defined the case period as 0 to 30 days before an event (death or myocardial infarction), 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. Therefore, this analysis is especially valuable when analyzing the association between short-term exposure and an acute illness or change in medication. Conditional logistic regression analysis was used in the case-crossover analysis. Second, we used Cox proportional-hazard regression analyses with exposure to NSAIDs entered into the model as time-dependent variables to estimate the hazard ratios for the specific outcome. The time-varying exposure covariates were constructed on the basis of the NSAID utilization pattern as done previously.[12,17,19] Daily dosage at each new dispensing was estimated by calculating average dosage from up to 5 consecutive prescriptions before the actual prescription, constituting a treatment interval. The method also allowed dosages to change during a treatment course. Isolated prescriptions (a single prescription not related in time to other prescriptions) were given a standard dosage defined as the minimal recommended dosage used to estimate the daily dose. For each prescription, the number of pills dispensed was divided by the estimated daily dosage to calculate the treatment duration. This treatment duration was then used as the time span in which the individual was classified as being exposed to the individual NSAID. Each individual could have multiple independent treatment courses with the same drug but also with different drugs. Switching between drugs was also possible. In our models, cause-specific fatal events were classified when a death was attributable to the specific cause being analyzed, and subjects were censored in the analysis if death was due to other causes. The following outcome measures were used: cardiovascular death (ICD 10 codes I00-I99), a composite end point of coronary death or nonfatal myocardial infarction (MI) (I20-I25 and I46), and a composite of fatal or

Table 3. Distribution of Specific Primary Causes of Death in Healthy Individuals According to Use of NSAIDS in Relation to Their Death

Specific Causes of Death (ICD-10 Codes)	All Deaths (Excluding Individuals Who Died During NSAID Exposure), n	Deaths During NSAID Exposure, n
All causes	54 101	2204
Malignancy (C00-C97)	16 196	960
Cardiovascular death (I00-I99)	21 415	769
Coronary death (I20-I25+I46)	9771	334
MI (I21-I22)	4230	132
Stroke (I61-I64)	3709	113
Death from other causes	16 490	475

ICD-10 indicates the *International Classifications of Disease, 10th revision.*

Table 4. Number of Individuals in NSAID Treatment During Time of Event (0 to 30 Days Before Event Representing the Case Period), 60 to 90 Days Before the Event, and 90 to 120 Days Before the Event

	90 to 120 Days Before Event	60 to 90 Days Before Event	Case Period (30 Days Before Event)
Ibuprofen			
CVD	587	596	612
Coronary	585	593	601
Stroke	461	451	487
Diclofenac			
CVD	232	254	318
Coronary	241	251	311
Stroke	198	203	242
Rofecoxib			
CVD	90	101	110
Coronary	65	69	76
Stroke	44	44	46
Celecoxib			
CVD	93	93	91
Coronary	57	56	67
Stroke	45	45	49
Naproxen			
CVD	85	82	81
Coronary	77	81	81
Stroke	53	59	66

CVD indicates cardiovascular death; coronary, combined end point of coronary death or nonfatal MI; and stroke, combined end point of fatal or nonfatal stroke.

Table 5. Odds Ratios Estimated by Case-Crossover Analysis for Specific Causes of Death Associated With Exposure to NSAIDs Stratified According to Daily Dosage

	Study Population, n=1 028 427 (56 305 Deaths Overall, of Which 2204 Deaths Occurred During Treatment With NSAIDs)		
Drug	Cardiovascular Death OR (95% CI)	Coronary Death or Nonfatal MI OR (95% CI)	Fatal or Nonfatal Stroke OR (95% CI)
Ibuprofen			
No use	1.00	1.00	1.00
Any use	1.08 (0.90–1.29)	1.52 (1.25–1.85)†	1.29 (1.02–1.63)*
≤1200 mg	1.11 (0.92–1.33)	1.45 (1.19–1.77)†	1.21 (0.95–1.53)
>1200 mg	1.04 (0.74–1.47)	1.44 (0.91–2.27)	1.36 (0.84–2.19)*
Diclofenac			
No use	1.00	1.00	1.00
Any use	1.91 (1.62–2.42)†	1.82 (1.43–2.33)†	1.71 (1.29–2.25)†
<100 mg	1.23 (0.76–1.98)	0.96 (0.59–1.57)	1.16 (0.65–2.08)
≥100 mg	2.04 (1.60–2.60)†	2.01 (1.56–2.59)†	1.70 (1.27–2.27)†
Rofecoxib			
No use	1.00	1.00	1.00
Any use	1.66 (1.06–2.59)*	1.72 (0.95–3.12)	1.14 (0.62–2.12)
≤25 mg	1.52 (0.96–2.41)	1.60 (1.23–2.06)†	1.11 (0.59–2.07)
>25 mg	1.73 (0.75–3.98)	3.02 (1.91–4.78)†	1.62 (0.31–8.40)
Celecoxib			
No use	1.00	1.00	1.00
Any use	0.92 (0.56–1.51)	1.93 (1.06–3.51)*	1.20 (0.59–2.46)
≤200 mg	1.42 (0.86–2.36)	2.13 (1.13–4.02)*	1.16 (0.55–2.42)
>200 mg	0.37 (0.16–0.87)*	0.91 (0.31–2.67)	0.74 (0.20–2.72)
Naproxen			
No use	1.00	1.00	1.00
Any use	0.84 (0.50–1.42)	0.98 (0.59–1.63)	1.91 (1.04–3.50)*
≤500 mg	1.25 (0.75–2.11)	1.37 (0.83–2.27)	1.52 (0.81–2.87)
>500 mg	0.30 (0.08–1.11)	0.24 (0.06–1.03)	2.50 (0.57–10.96)

OR indicates odds ratio; CI, confidence interval; no use, no use of any NSAID; and any use, all use irrespective of dose of the individual drug.

*$P<0.05$.

†$P<0.01$.

nonfatal stroke (I61-I64). We also estimated the risk of a composite of fatal and nonfatal bleedings (ICD-10 codes: intracranial hemorrhage, I60-I62 and S06.4 to 06.6; hemothorax, J94.2; nose bleed R04; gastrointestinal bleeding K25.0, K25.2, K25.4, K26.0, K26.2, K26.4, K27.0, K27.2, K28.0, K28.2, K92.0 to 92.2; urinary-genital bleeding, R31; anemia after bleeding, D62 and D50) to analyze the association between NSAID use and serious bleeding complications. As sensitivity analyses, we evaluated the risk of death caused by malignant causes (C00-C97) and also "other causes." However, because NSAIDs are used in the treatment of pain caused by malignant diseases, these analyses are not performed to establish a cause-specific relation.

The models were adjusted for age, sex, and calendar year. We repeated all the analyses on a cohort of NSAID initiators and age, sex, and time-matched NSAID noninitiators (n=901 596). The match of initiators with noninitiators was performed using the greedy match algorithm (gmatch macro for SAS, Mayo Clinic College of Medicine http://ndc.mayo.edu/mayo/research/biostat/upload/gmatch.sas; last assessed October 1, 2009). Cox analysis performed on the matched cohort was stratified for the matched covariates. For all analyses, statistical significance was defined as a 2-sided probability value below 0.05. The proportional hazard assumption, linearity of continuous variables, and lack of interactions was tested and found valid unless otherwise stated. Cox proportional hazard analyses with time-dependent variables were performed using STATA, version 10 (StataCorp LP, College Station, Tex). All other analyses and data management were performed using SAS, version 9.1 (SAS Institute Inc, Cary, NC).

Ethics

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

Results

The study population comprised 1 028 427 apparently healthy individuals with a median age of 39 years. At least 1 prescription of an NSAID was claimed by 44.7% of the study population from 1997 to 2005. The baseline characteristics are shown in Table 1 and the patterns of use of the respective drugs are shown in Table 2. During the study period, 56 305 individuals died, of whom 2204 died during treatment with an NSAID. The distribution of specific causes of death is shown in Table 3. Table 4 demonstrates the number of individuals

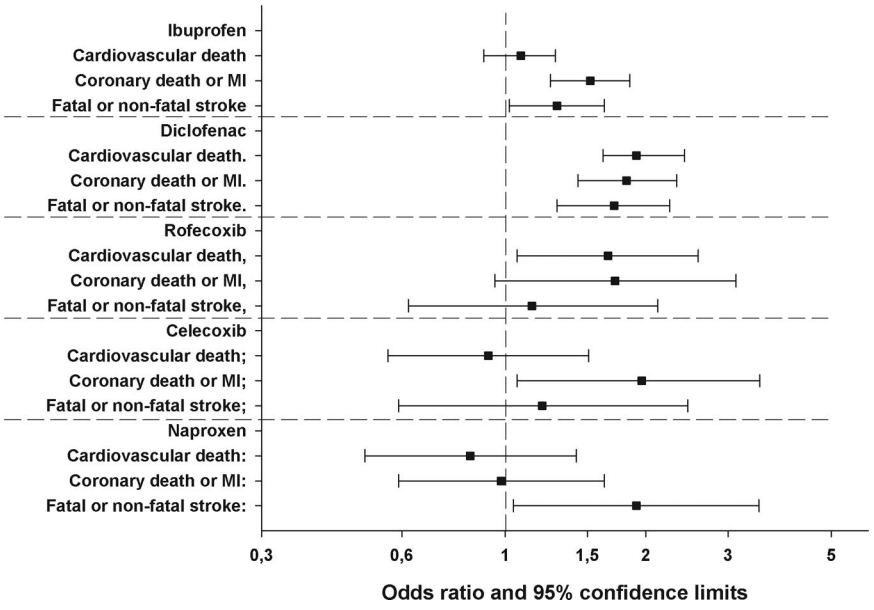

Figure 1. Case-crossover analysis. The estimates and surrounding error bars (representing the 95% confidence intervals) illustrate the association between use of NSAIDs and the listed end points for any use of the specific drugs.

exposed to NSAIDs in different time periods up to an event, explaining the method used to calculate odds ratios in the case-crossover analysis. Figures in the specific time windows are exclusive, meaning that the numbers represent individuals who were exposed to the individual drug only in this time period.

Case-Crossover Analysis

Results from the case-crossover analyses are presented in Table 5 and are illustrated by Figure 1. In these analyses, the use of ibuprofen was associated with a significant increase in risk of coronary death or nonfatal MI and fatal or nonfatal stroke (only in high doses). Use of diclofenac was associated with a significant increase in risk of cardiovascular death, coronary death, or nonfatal MI, as well as fatal or nonfatal stroke (high doses). The results showed a clear dose-dependent relationship. The selective COX-2 inhibitor rofecoxib was significantly related to an increased risk of cardiovascular death and the composite of coronary death or nonfatal MI. Although nonsignificant, there was a trend for increased risk of fatal or nonfatal stroke associated with rofecoxib treatment. Celecoxib was not related to excess cardiovascular death or fatal/nonfatal stroke, and the results showed no trend for a dose-dependent relationship. Finally, use of naproxen was neutral in terms of outcome except for fatal or nonfatal stroke, which showed a trend for increased risk.

Cox Proportional Hazard Analysis

The results from the Cox proportional hazard analysis are shown in Table 6 and are illustrated in Figure 2. Generally, the 2 statistical methods show corresponding results and the Cox proportional hazard analysis thereby substantiate the results from the case-crossover analysis. In the Cox proportional hazard analysis, use of ibuprofen showed a dose-dependent association with risk of coronary events (decreased risk of coronary death or nonfatal MI in low doses and a trend for increased risk in high doses). A similar relationship was seen for ibuprofen and stroke events. Use of low-dose ibuprofen and diclofenac was associated with a decrease in risk of cardiovascular death in the Cox analysis; however, diclofenac was associated with increased risk of cardiovascular death in high doses. Diclofenac was further associated with increased risk of coronary death or nonfatal MI and fatal or nonfatal stroke with a dose-dependent relationship. The results for the selective COX-2 inhibitor rofecoxib demonstrated a similar pattern as diclofenac and ibuprofen for fatal and nonfatal stroke, although the association was not statistically significant. Rofecoxib was related to an increased risk of coronary death or nonfatal MI and cardiovascular death, also in low doses. For the other selective COX-2 inhibitor celecoxib, the results showed a small and statistically insignificant trend toward increased risk of coronary death/nonfatal MI and fatal/nonfatal stroke. Importantly, the results derived from the Cox models on celecoxib were based on relatively few numbers of events (especially the estimates in high doses). Finally, use of naproxen was associated with a trend for neutral or decreased risk of all the examined end points, showing no dose-dependent relationship in the Cox models. As sensitivity analyses, we repeated all the analyses on a population of NSAID initiators and sex-, age-, and time-matched NSAID noninitiators. The results are shown in Table 7 and underline the results of the case-crossover analysis. The analysis on the matched population showed a trend for a higher increase in cardiovascular risk associated with the use of all the drugs. We also performed analyses including only the NSAID users, and the results were similar and the relationship between the individual drugs and attributed risk were the same (data not shown). Hence, individuals who initiated NSAID treatment had an increased cardiovascular risk when exposed to the drugs compared with time of no exposure. None of the drugs were modified by the effect of sex on any of the investigated outcomes (P for interaction >0.05).

Serious Bleedings

Risk of bleedings is a well-known adverse effect of NSAID treatment. To estimate the degree of this problem, we

Table 6. Hazard Ratios Estimated by Cox Proportional Hazard Analysis for Specific Causes of Death Associated With Exposure to NSAIDs Stratified According to Daily Dosage

	Study Population, n=1 028 427 (56 305 Deaths Overall, of Which 2204 Deaths Occurred During Treatment With NSAID)					
	Cardiovascular Death		Coronary Death or Nonfatal MI		Fatal or Nonfatal Stroke	
Drug	Deaths*	HR (95% CI)	Events*	HR (95% CI)	Events*	HR (95% CI)
Ibuprofen						
No use		1.00		1.00		1.00
Any use	453	0.83 (0.75–0.92)‡	465	0.77 (0.70–0.84)‡	412	0.94 (0.85–1.03)
≤1200 mg	362	0.75 (0.67–0.84)‡	394	0.72 (0.65–0.80)‡	348	0.88 (0.79–0.98)†
>1200 mg	91	0.93 (0.75–1.14)	71	1.16 (0.92–1.47)	64	1.45 (1.14–1.86)‡
Diclofenac						
No use		1.00		1.00		1.00
Any use	218	1.03 (0.88–1.20)	229	1.13 (1.00–1.29)†	195	1.34 (1.16–1.55)‡
<100 mg	56	0.62 (0.45–0.86)‡	66	0.88 (0.69–1.12)	51	0.93 (0.71–1.73)
≥100 mg	162	1.28 (1.08–1.53)‡	163	1.28 (1.10–1.50)‡	144	1.59 (1.35–1.88)‡
Rofecoxib						
No use		1.00		1.00		1.00
Any use	78	1.42 (1.09–1.84)‡	61	1.34 (1.04–1.73)†	33	0.90 (0.64–1.27)
≤25 mg	73	1.34 (1.02–1.76)†	58	1.32 (1.02–1.71)†	31	0.88 (0.61–1.25)
>25 mg	5	3.43 (1.43–8.24)‡	3	1.89 (0.61–5.87)	2	1.55 (0.39–6.20)
Celecoxib						
No use		1.00		1.00		1.00
Any use	66	0.95 (0.70–1.30)	52	1.15 (0.87–1.51)	40	1.12 (0.82–1.53)
≤200 mg	54	0.85 (0.65–1.11)	44	1.15 (0.85–1.54)	31	1.02 (0.72–1.45)
>200 mg	12	1.02 (0.58–1.80)	8	1.19 (0.59–2.38)	9	1.73 (0.90–3.34)
Naproxen						
No use		1.00		1.00		1.00
Any use	62	0.74 (0.46–0.98)†	70	0.76 (0.60–0.96)†	59	0.89 (0.69–1.15)
≤500 mg	50	0.73 (0.53–0.99)†	61	0.79 (0.62–1.02)	49	0.89 (0.67–1.18)
>500 mg	12	0.82 (0.44–1.53)	9	0.58 (0.30–1.13)	10	0.89 (0.48–1.66)

The analyses are adjusted for age, sex, and calendar year. Number of censored observations (death from other causes or individuals ending the follow-up without having an event including people immigrating) was 1 003 026, 1 010 860, and 1 015 824 for models performed for cardiovascular death, coronary death or nonfatal MI, and fatal or nonfatal stroke, respectively. HR indicates hazard ratio; CI, confidence interval; no use, no use of any NSAID; and any use, all use irrespective of dose of the individual drug.

*Deaths or events during treatment with the specific drug.

†$P<0.05$.

‡$P<0.01$.

analyzed the risk of serious bleedings associated with NSAID exposure. The results derived from the case-crossover analysis are demonstrated in Figure 3 showing that all NSAIDs except celecoxib were significantly associated with increased risk of fatal or nonfatal major bleedings. The results showed a dose-dependent relationship and were further confirmed by the Cox proportional hazard analysis, which resulted in similar results (data not shown).

Other Analyses

A little more than half of the individuals who died during NSAID treatment died of noncardiovascular causes. Sensitivity analyses showed that NSAID treatment was not associated with increased risk of dying of other causes in both the Cox and case-crossover analyses, and there was no dose-dependent relationship (data not shown). Overall, incidence of noncardiovascular conditions such as musculoskeletal disease (6.4%), lupus erythematosis (0.02%), rheumatic disease (0.04%), AIDS (0.04%), and other infections (2.7%) were low after NSAID treatment was initiated. Risk of malignant death was increased in the Cox analysis but not in the case-crossover analysis (data not shown). Last, switching between drugs was rarely seen (below 1% had overlapping treatment intervals).

Discussion

The present study examined cause-specific cardiovascular mortality and morbidity associated with NSAID treatment in a nationwide cohort of healthy individuals. The main results are that most NSAIDs are associated with increased risk of cause-specific cardiovascular mortality and morbidity. Notably, exposure to 1 of the most commonly used NSAIDs, diclofenac, was associated with a substantial risk of cardio-

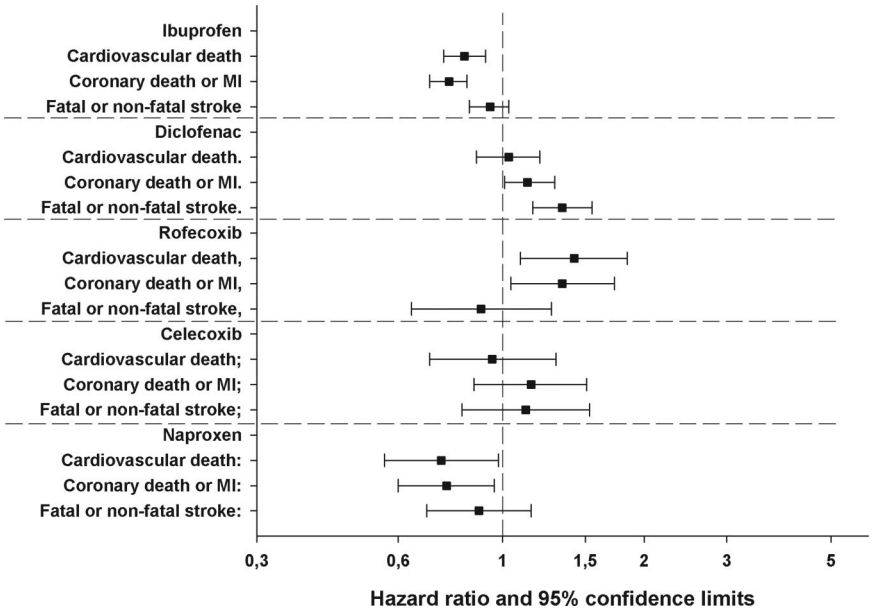

Figure 2. Cox proportional hazard analysis. The estimates and surrounding error bars (representing the 95% confidence intervals) illustrate the association between use of NSAIDs and the listed end points for any use of the specific drugs.

vascular morbidity and mortality including fatal or nonfatal stroke and coronary death or nonfatal MI. Diclofenac has a high COX-2 inhibiting selectivity, and our results demonstrate that diclofenac was associated with a similar increase in cardiovascular risk as the selective COX-2 inhibitor rofecoxib, which was withdrawn from the market in 2004 because of poor cardiovascular safety. More worrying is the fact that the results showed a dose-dependent relationship because diclofenac more often is used in high doses compared with the other drugs. This study moreover indicates that the NSAID with the least cardiovascular risk may be naproxen, which corresponds with recent studies.[20,21] Furthermore, all NSAIDs except for celecoxib were also linked to a substantial increase in risk of serious bleedings, a well-known adverse effect of NSAIDs that needs to be kept in mind. This is highly informative when benefits versus risks associated with NSAID treatment must be assessed before initiating NSAID treatment. We interpret this as a causative relationship because NSAIDs are not used in the treatment of bleedings and this is also the case for cardiovascular risk. We cannot, however, rule out the possibility that the increased risk of bleeding also translates into an increased risk or trend for stroke, which we have observed in the present study for most NSAIDs.

Most of the previous studies performed on the cardiovascular safety of NSAIDs have reported an increase in risk of MI and MI or overall death associated with the use of some of the NSAIDs.[1,2,4,7,10,11,17,22–27] No previous study has reported results on specific cardiovascular endpoints such as fatal/nonfatal stroke or coronary death combined with nonfatal MI. Therefore, our results further strengthen the association between NSAID use and cardiovascular risk by demonstrating effects on all cardiovascular outcomes. Notably, this study is the first to our knowledge to report on the specific cardiovascular risk among healthy individuals.

It is widely accepted that the selective COX-2 inhibitor rofecoxib increases cardiovascular risk. The results regarding the specific cardiovascular risk of celecoxib have been less certain. Observational studies have indicated increased cardiovascular risk in high-risk populations with established cardiovascular disease.[4,17] Solomon et al[4,28,29] have recently analyzed the importance of celecoxib on cardiovascular risk in a large pooled database from 6 clinical trials comparing celecoxib with placebo. The results showed a discrepancy in the importance of celecoxib according to the patients' baseline cardiovascular risk and the dose regimen used. High baseline cardiovascular risk and higher doses predicted worse cardiovascular outcome and low baseline risk, and low doses were not significantly associated with excess cardiovascular risk. Notably, we found no certain association between celecoxib and cardiovascular adverse events among these healthy individuals using 2 independent statistical methods. However, our results are based on few events (especially in high doses) and showed a positive trend for increased cardiovascular risk. Therefore, our analyses of celecoxib are not conclusive. It is also important, from a clinician's point of view, that the results suggest that celecoxib is the only studied NSAID that does not carry excess risk of bleeding. We are currently awaiting results from the ongoing Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION) trial,[30] which we hope will be able to clarify the cardiovascular risk of celecoxib further. The decision of starting celecoxib treatment should therefore be based on individual assessment of cardiovascular risk and the need for high-dosage therapy. In a recent study, Strand[27] concluded that the selective COX-2 inhibitors should be preferred over the traditional NSAIDs in patients with chronic pain. Therefore, in this context, our results may suggest that the use of celecoxib in previously healthy individuals could be safer than previously believed.

Observational studies and meta-analyses have consistently demonstrated an association between diclofenac use and excess cardiovascular morbidity.[6,8,11,22,23,31] Our results confirm this association in healthy individuals, and it is particularly worrying that diclofenac exerts the same risk for cardiovascular adverse events as rofecoxib. This is a major

Table 7. Population of NSAID Initiators and Sex-, Age-, and Time-Matched Controls of Non-NSAID Initiators: Hazard Ratios Estimated by Cox Proportional Hazard Analysis for Specific Causes of Death Associated With Exposure to NSAIDs Stratified According to Daily Dosage

	Study Population, n=901 596					
	Cardiovascular Death		Coronary Death or Nonfatal MI		Fatal or Nonfatal Stroke	
Drug	Deaths*	HR (95% CI)	Events*	HR (95% CI)	Events*	HR (95% CI)
Ibuprofen						
No use		1.00		1.00		1.00
Any use	453	0.88 (0.80–0.96)‡	465	1.31 (1.20–1.44)‡	412	1.47 (1.33–1.63)‡
≤1200 mg	362	0.79 (0.71–0.87)‡	394	1.24 (1.12–1.37)‡	348	1.39 (1.24–1.54)‡
>1200 mg	91	1.63 (1.32–2.00)‡	71	1.94 (1.54–2.45)‡	64	2.22 (1.74–2.84)‡
Diclofenac						
No use		1.00		1.00		1.00
Any use	218	1.20 (1.06–1.38)‡	229	1.83 (1.61–2.09)‡	195	2.00 (1.73–2.30)‡
<100 mg	56	0.80 (0.62–1.05)	66	1.39 (1.09–1.77)‡	51	1.33 (1.00–1.75)†
≥100 mg	162	1.46 (1.25–1.70)‡	163	2.10 (1.81–2.45)‡	144	2.41 (2.04–2.84)‡
Rofecoxib						
No use		1.00		1.00		1.00
Any use	78	1.64 (1.31–2.05)‡	61	1.84 (1.43–2.37)‡	33	1.12 (0.80–1.58)
≤25 mg	73	1.60 (1.27–2.01)‡	58	1.82 (1.41–2.36)‡	31	1.10 (0.77–1.56)
>25 mg	5	2.77 (1.15–6.66)†	3	2.36 (0.76–7.32)	2	1.79 (0.45–7.15)
Celecoxib						
No use		1.00		1.00		1.00
Any use	66	1.24 (0.97–1.58)	52	1.44 (1.10–1.87)‡	40	1.27 (0.93–1.74)
≤200 mg	54	1.19 (0.91–1.56)	44	1.44 (1.07–1.93)†	31	1.16 (0.82–1.65)
>200 mg	12	1.51 (0.86–2.65)	8	1.49 (0.74–2.98)	9	1.95 (1.01–3.75)
Naproxen						
No use		1.00		1.00		1.00
Any use	62	0.86 (0.67–1.10)	70	0.78 (0.61–1.00)	59	1.54 (1.19–1.99)‡
≤500 mg	50	0.84 (0.64–1.11)	61	0.69 (0.51–0.93)†	49	1.55 (1.17–1.05)†
>500 mg	12	0.92 (0.52–1.62)	9	1.22 (0.75–2.00)	10	1.48 (0.80–2.76)

HR indicates hazard ratio; CI, confidence interval.
*Deaths or events during treatment with the specific drug.
†$P<0.05$.
‡$P<0.01$.

public health concern because diclofenac is one of the most widely used NSAIDs worldwide and in some countries dispensed as an over-the-counter drug.[12,32] Furthermore, the separate dose regimens used for the individual drugs are also of importance when comparing the attributable cardiovascular risk and risk of gastric bleeding between the drugs. High-dose treatment with traditional drugs is more frequently used compared with the selective COX-2 inhibitors, and this may also influence our results, for example, introducing channeling bias toward lower dosages of the selective COX-2 inhibitors.

Because treatment with NSAIDs is so widely distributed in the general population, it is also of great importance that a safe alternative is found when NSAID treatment cannot be avoided. The safety of naproxen has been much debated, but it is widely accepted that naproxen is probably the NSAID with the safest cardiovascular risk profile, and our results support this assumption. Ibuprofen is widely sold as over-the-counter medication, which may lead to the assumption that this is a particularly safe NSAID. We found a small trend for increase in cardiovascular risk, with a dose-dependent relationship, associated with ibuprofen therapy. Thus, considering the current results, naproxen may be a safer alternative to ibuprofen in patients needing NSAID treatment. This particularly important for patients taking prophylactic aspirin because studies have shown an interaction between ibuprofen and aspirin if taken simultaneously.[33] Such an interaction has not been demonstrated for naproxen.

We also performed sensitivity analyses regarding the association between NSAID use and other causes of death. NSAID treatment was not related to an increased risk of dying from noncardiovascular causes, which strengthens the observed relationship between exposure and cardiovascular risk. Because NSAIDs are used in the treatment of malignancy, we would expect to find an association with the use of NSAIDs, which also was the case in the Cox model but not in

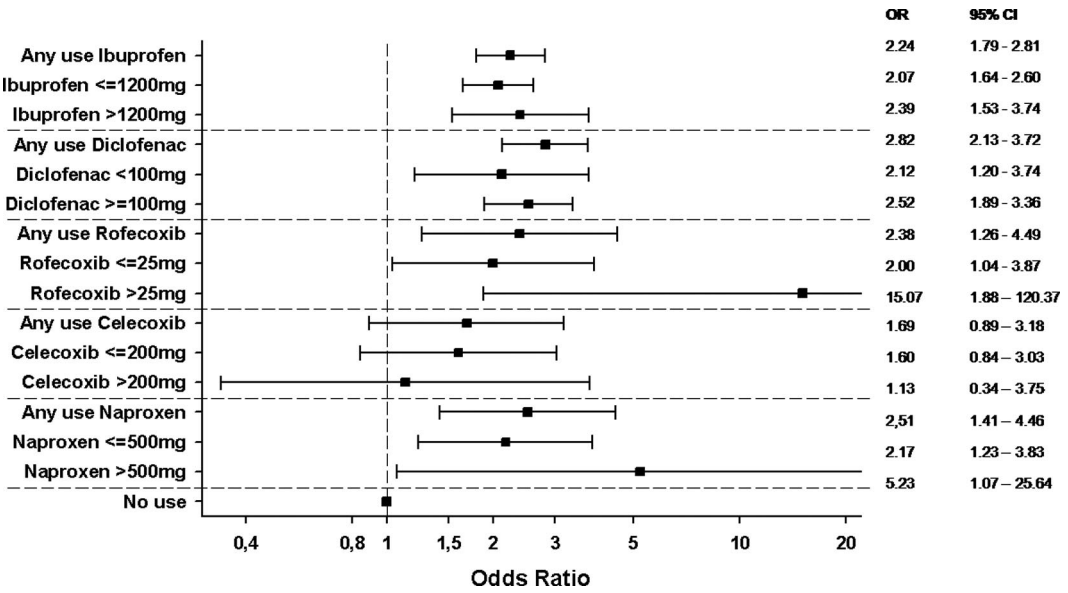

Figure 3. Case-crossover analysis. The estimates and surrounding error bars (representing the 95% confidence intervals) illustrate the association between use of NSAID and fatal or nonfatal major bleedings.

the case-crossover analysis. Hence, we do not interpret this association found in the Cox analysis as a causative relationship.

Strengths and Limitations

The main strength of this study is the size and completeness of data. The data cover the entire population of Denmark independent of race, socioeconomic status, age, or participation in health insurance programs. Therefore, the risk of selection bias is avoided and the study notably includes citizens regardless of participation in the labor market. 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 in low dosages only (200 mg) and in limited quantities. Ibuprofen has been available as over-the-counter drug in Denmark from November 1, 2001, and to confirm our results we performed a sensitivity analysis ending the study period on this date. The results remained unchanged. Also, because there is partial patient copayment of drug expenses in Denmark, patients needing higher doses or long-term treatment would have a financial incentive to obtain a prescription from their physician to receive reimbursement. Therefore, over-the-counter NSAID use is unlikely to have a significant influence on our results.

We used 2 independent and different statistical approaches to examine the relationship between exposure to NSAIDs and the chosen outcomes of interest. The case-crossover analysis uses the same individual as its own control, but at a previous time point. In this way, almost all persisting confounders are excluded from the analysis, which makes the case-crossover analysis particularly robust for chronic confounders. The case-crossover analysis is powerful for analyzing effects of short-time exposure on risk and acute illnesses but less suited for analyzing long-term exposure on risk. The Cox proportional hazard analysis is designed for survival analysis, in which the exposure as well as confounders can change over time. We used time-dependent exposure covariates in our models, indicating that individuals were only considered at risk when they were exposed to NSAIDs. However, the models can be influenced by residual and unmeasured confounding that can affect the results. We tried to underline the results by performing the analyses on an age-, sex-, and time-matched population, and the results derived from this analysis strengthened the overall association between NSAID use and cardiovascular risk. For the purpose of this study, we believe that the case-crossover analysis is the most suited statistical method because the median exposure time to NSAID was 14 days, indicating short-time exposure in most individuals. When both methods give corresponding results, with a dose-dependent increase in risk, the association is further strengthened.

The main limitation is inherited 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 preceding a condition being treated with a NSAID could alone indicate a condition with increased risk of cardiovascular disease or death, thus introducing the risk of confounding-by-indication or prothopathic bias. This condition can possibly raise the cardiovascular risk independently and can therefore be associated with increased cardiovascular risk rather than the drugs or the first symptoms of coronary heart disease could be interpreted as muscular pain and thereafter progress to myocardial infarction. NSAIDs are not recommended or used for the treatment of cardiovascular disease, and angina is not likely to be treated with these drugs as well. However, we cannot completely rule out the possibility that this will happen. A series of sensitivity analyses were performed to test this bias; we found differences in risk between individual NSAIDs, which have the same treatment indication, as well as clear evidence for dose-related response in risk that further strengthens the assumption that NSAIDs

are associated with cardiovascular risk. We therefore find no reason to believe that confounding by indication alone would drive the observed results. Finally, we excluded people because of comorbidity; however, conditions not needing hospitalization or prescription drugs would not be registered as comorbidity and therefore not fully accounted for.

A limitation in this study is the data on mode of death. The Causes of Death Register is based on information obtained from the death certificate filled out by the doctor declaring the individual's death. All deaths are registered in the Causes of Death Register and data are by legislation complete. Validation of coronary and cardiovascular events in similar populations demonstrated acceptable levels of sensitivity, with a tendency to overestimate cardiovascular deaths, although this overestimation would occur in all risk groups in our study.[34,35] The specific diagnosis of myocardial infarction (combined validity of fatal and nonfatal myocardial infarction) has proved to be valid, with a sensitivity of 91% and a positive predictive value of 93%.[36] The nonfatal events are obtained through records on all hospital admissions to Danish hospitals, whereas the fatal events are recorded in the Causes of Death Register based on information gathered from the death certificate. Nonfatal events not resulting in hospital admission would not be recorded and this could in theory introduce bias; however, this is unlikely to influence the results, given the nature of the nonfatal events studied (ie, MI and stroke). The stroke diagnoses (both fatal and nonfatal) used in this study have also been validated with a good result, and it was found that the diagnoses had positive predictive values of 74% to 97%.[37,38] Furthermore, important cardiovascular risk factors such as cardiovascular risk profile, lipid levels, smoking status, blood pressure, or obesity are lacking. 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. However, because this is an observational study, it is important to acknowledge that the effect of unmeasured confounders cannot be fully excluded. Adherence to treatment is also a possible bias in studies using prescription data. No study design can exclude the possibility that the prescribed individuals do not take all the prescribed medication, and especially prescription data must therefore be viewed in the light of the possibility of nonadherence. Nonadherence would influence the results toward the null and hence elude the association between exposure and outcome.

Conclusions

In the present nationwide study of healthy individuals, we found that most NSAIDs are associated with increased cardiovascular mortality and morbidity. In particular, the use of the nonselective NSAID diclofenac and the selective COX-2 inhibitor rofecoxib was associated with a similarly increased risk of cardiovascular mortality and morbidity among healthy individuals. Our results suggest that naproxen could be a safer alternative when NSAID treatment is required.

Diclofenac is widely used in the general population worldwide, and it is also accessible as over-the-counter medication in various countries. Our study suggests that this pharmaceutical strategy represents a major public health issue, potentially exposing a substantial number of individuals to risk of cardiovascular adverse events. Physicians initiating NSAID treatment should always make an individual assessment of cardiovascular risk and carefully consider the balance between benefit and risk before starting treatment with any NSAID.

Disclosures

None.

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