Association of Nonsteroidal Anti-inflammatory Drugs With First Occurrence of Heart Failure and With Relapsing Heart Failure

The Rotterdam Study

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Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with first hospitalization for congestive heart failure (CHF). It is likely, however, that NSAIDs precipitate a relapse but are less likely to induce a first occurrence of (incident) heart failure.

Methods: A total of 7277 participants in the Rotterdam Study were followed up from the interview date until the first of the following events: a diagnosis of incident heart failure, death, removal, or end of the follow-up period. Excluded from the study population were all participants with prevalent heart failure at baseline. Exposure to NSAIDs and other medication was calculated on the basis of automated data on filled drug prescriptions in the pharmacies within the study area. In a second analysis, we followed up all participants with incident heart failure until the first relapse or the end of follow-up.

Results: Incident heart failure was encountered in 345 participants during follow-up. Current use of NSAIDs was associated with a relative risk of incident heart failure of 1.1 (95% confidence interval [CI], 0.7-1.7), after adjustment for age, sex, and concomitant medication. In patients with prevalent heart failure who filled at least 1 NSAID prescription since diagnosis of heart failure, the univariate and adjusted relative risks of a relapse were 3.8 (95% CI, 1.1-12.7) and 9.9 (95% CI, 1.7-57.0), respectively.

Conclusions: The use of NSAIDs is not associated with an increased risk of incident heart failure. In patients with prevalent heart failure, current use of NSAIDs is associated with a substantially increased risk of a relapse.

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HEART FAILURE is a syndrome that results from complex circulatory and neurohormonal responses to cardiac dysfunction.[1,2] The main causes of heart failure are ischemic heart disease and arterial hypertension.[3,4] According to recent guidelines of the European Society of Cardiology, objective evidence of cardiac dysfunction has to be present in addition to symptoms, such as shortness of breath or fatigue at rest or during exercise and ankle swelling, to establish the presence of heart failure.[5]

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with the occurrence of heart failure in several case reports.[6-9] Inhibition of the enzyme cyclooxygenase may result in a decrease in prostaglandin synthesis. Prostaglandins have an important role in renal physiology, and inhibition of their synthesis may give rise to fluid retention.[10] Fluid retention caused by NSAIDs may adversely affect cardiovascular homeostasis, and patients with a propensity for congestive heart failure seem to be particularly susceptible to the cardiovascular effects of NSAIDs. Moreover, NSAIDs may interfere with the cardiovascular effects of angiotensin-converting enzyme inhibitors and diuretics.[10]

Previous studies demonstrated that NSAIDs may precipitate a first hospitalization for heart failure,[11,12] which suggests that NSAIDs may not only induce a relapse of preexisting heart failure but also be a cause of a first occurrence of (incident) heart failure. In view of the pathophysiology of NSAID-induced heart failure, however, there can be doubt whether NSAIDs may induce heart failure in patients without preexisting left ventricular impairment. We tested the hypothesis that NSAIDs do not cause a first occurrence of heart failure but may induce a relapse in patients with prevalent heart failure. We first studied the association between NSAIDs and a first occurrence of (incident) heart failure in a population of elderly patients. Subsequently, we studied the association between NSAIDs and the first relapse in these same patients to

PATIENTS AND METHODS

SETTING

The study was a part of the Rotterdam Study, a population-based prospective cohort study on the prevalence, incidence, and determinants of cardiovascular, neurologic, ophthalmologic, and locomotor diseases in the elderly.[13] The first cross-sectional survey started in June 1990 and was completed in June 1993. All inhabitants of Ommoord, a suburb of the city of Rotterdam, the Netherlands, who were 55 years or older were invited to participate in the Rotterdam Study. Of the 10 275 eligible subjects, 7983 (78%) agreed to participate and signed informed consent. Since the start of the Rotterdam Study, cross-sectional surveys have been carried out periodically by means of home interviews and periodic visits of participants to the research center. In addition, all neurologic, ophthalmologic, cardiovascular, and locomotor diseases that occurred since the start of follow-up in participants of the Rotterdam Study have systematically been gathered.

STUDY POPULATION

From the cohort of 7983 participants in the Rotterdam Study, we excluded participants who were not registered at the pharmacy or who had an unknown date of death (n=48). Participants with prevalent heart failure at study entrance were excluded from the analyses (n=453). In addition, baseline echocardiographic data were available for 2246 participants. We excluded from the analyses 205 participants with a fractional shortening less than 30%, defined as [(left ventricular internal dimension at end diastole – left ventricular internal dimension at end systole)/left ventricular internal dimension at end diastole] × 100%.

A total of 7277 participants were included in the study population for the present study. The study period ran from July 1, 1991, through December 31, 1998. The cohort was followed up from the date of entry in the study until the end point of the follow-up, which was the first of one of the following events: a diagnosis of incident heart failure, death, removal from the study area or institutionalization, and end of the follow-up period. In a second analysis, we followed up all participants with incident heart failure until the first relapse or the end of follow-up as defined.

EXPOSURE DEFINITION

Computerized pharmacy records were available for all participants of the Rotterdam Study as of January 1, 1991. All prescriptions dispensed to participants of the Rotterdam Study by the 3 automated pharmacies in the study area were routinely stored in a database. Drugs were coded according to the Anatomical Therapeutic Chemical Classification.[14] Every prescription included a filling date, the product name, daily dosage, the number of filled tablets or capsules, and the prescribed daily number.

For each member of the study population, exposure to NSAIDs and concomitant cardiovascular and pulmonary medication was assessed during follow-up. The drug-exposure window was defined as the legend duration (prescription length), which was calculated on the basis of the total number of filled tablets divided by the prescribed daily number, plus a carryover period of 7 days. If the drug-exposure windows of consecutive prescriptions of the same drug overlapped, this was considered to be a single period of drug exposure. Hence, the follow-up period for each member of the cohort was divided into periods of exposure and nonexposure to the drugs of interest. Patients were considered to be current users of each drug for which the exposure window overlapped the date of diagnosis of incident heart failure.

OUTCOME DEFINITION

The outcome of the first analysis was considered to be a diagnosis of incident heart failure, defined as the first occurrence of heart failure. Heart failure is one of the areas investigate a potential different effect of NSAIDs on incident and prevalent heart failure.

RESULTS

General characteristics of the study population (n=7277) are presented in **Table 1**. Mean age of the study participants at study entrance was 70 years. Of the study population, 62% were female. Mean follow-up was 6.0 years. Serum creatinine had been assessed in 4882 persons, of whom 563 had a value of 1.1 mg/dL (100 µmol/L) or more. A total of 2356 participants had hypertension, 749 participants had a certain history of myocardial infarction, and 164 patients definitely had atrial fibrillation at study entrance. A diagnosis of incident heart failure during follow-up was made in 345 participants. Age, sex, hypertension, history of myocardial infarction, atrial fibrillation, and a serum creatinine level of 1.1 mg/dL (100 µmol/L) or more were independently associated with incident heart failure.

Table 2 shows that several classes of drugs were associated with the occurrence of incident heart failure. Among the classes with the strongest association were digoxin, antiarrhythmics, vasodilators (mainly nitrates), loop diuretics, and potassium-sparing diuretics. **Table 3** presents the results of the Cox regression model analysis with time-dependent variables. Current use of NSAIDs was univariately associated with a 50% increased risk of incident heart failure (RR, 1.5; 95% CI, 1.0-2.3). In patients with a serum creatinine level less than 1.1 mg/dL (100 µmol/L), the univariate RR of the association between NSAIDs and heart failure was 1.4 (95% CI, 0.8-2.4). In patients with a serum creatinine level of 1.1 mg/dL (100 µmol/L) or more, the RR was 2.0 (95% CI, 1.9-5.5). After adjustment for age, sex, hypertension, history of myocardial infarction, atrial fibrillation, renal function at baseline, and concomitant medication, the RR of the association between current NSAID use and the occurrence of incident heart failure declined to 1.1 (95% CI, 0.7-1.7). Among participants who filled at least 1 NSAID prescription, these RRs were univariately 1.4 (95% CI, 0.9-2.1) and, after adjustment, 1.2 (95% CI, 0.8-1.8). In the second analyses in patients who had been

of special interest in the Rotterdam Study. The continuous follow-up of all participants of the Rotterdam Study, in close cooperation with the participating general practitioners, is aimed at identifying all events of interest, including heart failure. It is part of the routine follow-up procedure that all available data on the events of interest, such as hospital discharge letters and notes from general practitioners, are copied from the records of the general practitioner. Two research physicians independently evaluate all information on cases of heart failure that have occurred during follow-up of the Rotterdam Study. Certainty of diagnosis is rated as possible, probable, or definite, on the basis of the availability of additional information. A definite diagnosis of heart failure is assumed if a medical specialist has diagnosed heart failure on the basis of typical symptoms such as fatigue, ankle edema, orthopnea, nocturnal dyspnea, pulmonary edema on radiography, and a decreased ejection fraction or ventricular hypertrophy on echocardiography. If the 2 research physicians disagree on the certainty of diagnosis, they reevaluate these events during a consensus meeting. When disagreement on the certainty of diagnosis remains, a cardiologist makes a final decision. In addition, a cardiologist reevaluates all potential cases of heart failure on which the 2 research physicians agree during the first evaluation. In the present study, participants were regarded as patients with incident heart failure only if there was a first diagnosis of definite heart failure as defined above.

Apart from the follow-up procedure of the Rotterdam Study, we used hospital discharge diagnoses concerning the study population as gathered from all hospitals in the Rotterdam area. We considered hospital admissions for heart failure after January 1, 1993, as incident heart failure if these patients had not been admitted to the hospital for heart failure in the period from January 1, 1991, through January 1, 1993. If participants were identified in both the follow-up procedure and the hospital discharge database, we took the first date as the date of incident heart failure. For the second analysis, we defined a relapse of CHF as a hospital admission because of heart failure in the patients who had been followed up since the occurrence of incident heart failure. As of that date, these individuals were considered patients with prevalent heart failure.

COFACTORS

Apart from age and sex, we assessed the following independent risk factors for heart failure. Hypertension was defined as systolic blood pressure greater than 160 mm Hg and/or diastolic blood pressure greater than 95 mm Hg, or use of antihypertensive medication for the indication hypertension. If the latter was unsure, the variable was classified as uncertain. History of myocardial infarction was assessed by questionnaire with confirmation on electrocardiography. If patients mentioned myocardial infarction in their history but an electrocardiogram was negative, the history was classified as uncertain. Atrial fibrillation was diagnosed on the basis of a baseline electrocardiogram. Furthermore, a serum creatinine level greater than 1.1 mg/dL (100 µmol/L) was considered a potential risk factor for heart failure.

STATISTICAL ANALYSIS

The statistical analysis was carried out with a Cox regression model with time-dependent covariates. Drug exposure was entered in the model as segmented time-dependent covariates, with different values at different times. The value of the time-dependent covariates could be calculated for each individual member of the cohort on each day during follow-up by splitting up the follow-up time into periods of exposure and nonexposure to the drugs of interest, based on the start date of filled drug prescriptions and the end date plus 7 days. First, we performed univariate analyses with the potential risk factors defined above, NSAIDs, and cardiovascular and pulmonary medication. In the multivariate analyses, we included all risk factors that were univariately associated with heart failure. All tests were 2 sided, with a rejection of the null hypothesis at $P<.05$. All risks were expressed as relative risks (RRs) with 95% confidence intervals (CIs).

followed up since the occurrence of incident heart failure, the crude and adjusted RRs of a relapse of heart failure were 1.4 (95% CI, 0.5-3.8) in both the univariate and the adjusted analyses. As the relapses occurred in those who had had incident heart failure shortly before, baseline hypertension, history of myocardial infarction, a serum creatinine level of 1.1 mg/dL (100 µmol/L) or more, and atrial fibrillation were not associated with a relapse and therefore not adjusted for. Among patients with prevalent heart failure who filled at least 1 NSAID prescription during follow-up, the crude RR of a first relapse of CHF was 3.8 (95% CI, 1.1-12.7). Adjusted for age, sex, and concomitant medication, the RR was 9.9 (95% CI, 1.7-57.0).

COMMENT

This study indicates that current use of NSAIDs is not associated with an increased risk of a first occurrence of heart failure. However, in the analysis of patients who had been followed up since their diagnosis of incident heart failure and who had filled at least 1 NSAID prescription at any time during follow-up, the use of NSAIDs was associated with a substantially increased risk of a relapse of heart failure.

To study the association between NSAIDs and incident heart failure appropriately, one must exclude all patients who might already have had heart failure before the first diagnosis. This may be difficult because a substantial number of the patients with left ventricular impairment appear to be asymptomatic or are undiagnosed despite signs and symptoms of heart failure.[15] Our study population included 345 patients with a certain diagnosis of incident heart failure. We excluded all patients from the study population who might have had a possible or probable diagnosis of heart failure. This could be achieved by means of the intensive follow-up procedure of all participants in Rotterdam Study, which provided the information by which we were able to decide whether participants truly represented incident cases of heart failure. Moreover, we excluded from the analysis 205 patients with a baseline fractional shortening less than

Table 1. General Characteristics of the Study Population*

	No. (%)			
	Total (N = 7277)	Incident Heart Failure (n = 345)	No Heart Failure (n = 6932)	Crude RR (95% CI)
Age, y				
55-64	2435 (33.5)	29 (8.4)	2406 (34.7)	1.0 (Reference)
65-74	2535 (34.8)	122 (35.4)	2413 (34.8)	**4.0 (2.7-6.0)**
≥75	2307 (31.7)	194 (56.2)	2113 (30.5)	**7.1 (4.8-10.4)**
Sex				
Female	4499 (61.8)	188 (54.5)	4311 (62.2)	1.0 (Reference)
Male	2778 (38.2)	157 (45.5)	2621 (37.8)	**1.4 (1.1-1.7)**
Hypertension†				
No	4185 (57.5)	135 (39.1)	4050 (58.4)	1.0 (Reference)
Yes	2356 (32.4)	163 (47.2)	2193 (31.6)	**2.1 (1.7-2.7)**
Uncertain	736 (10.1)	47 (13.7)	689 (10.0)	**1.9 (1.4-2.7)**
History of myocardial infarction‡				
No	5383 (74.0)	190 (55.1)	5193 (74.9)	1.0 (Reference)
Yes	749 (10.3)	79 (22.9)	670 (9.7)	**3.0 (2.3-3.8)**
Uncertain	1145 (15.7)	76 (22.0)	1069 (15.4)	**1.9 (1.5-2.4)**
Atrial fibrillation				
No	7113 (97.7)	325 (94.2)	6788 (97.9)	1.0 (Reference)
Yes	164 (2.3)	20 (5.8)	144 (2.1)	**2.7 (1.8-4.1)**
Serum creatinine, mg/dL (μmol/L)				
<1.1 (<100)	4319 (59.2)	181 (52.5)	4138 (59.7)	1.0 (Reference)
≥1.1 (≥100)	563 (7.7)	46 (13.3)	517 (7.5)	**2.0 (1.4-2.7)**
Unknown	2395 (32.9)	118 (34.2)	2277 (32.8)	1.2 (0.9-1.5)

*RR indicates relative risk; CI, confidence interval; and boldface type, statistically significant values. Mean ± SD follow-up was 6.0 ± 1.6 years.
†Defined as systolic blood pressure greater than 160 mm Hg and/or diastolic blood pressure greater than 95 mm Hg, or use of antihypertensive medication for the indication hypertension.
‡Verified by electrocardiography.

30%, which is regarded as the lower limit of normality.[16,17] Hence, the study population consisted only of patients with a certain diagnosis of truly incident heart failure and patients without heart failure. In this study population, no association between current use of NSAIDs and incident heart failure was present.

Adverse effects of NSAIDs on cardiovascular homeostasis are well established.[10] Particularly in the clinical setting of reduced renal perfusion that can be seen in patients with various disorders such as dehydration, cardiovascular disease, and renal dysfunction, NSAIDs may impair the adequacy of renal prostaglandin production. In patients with reduced left ventricular function, renal prostaglandin production has a crucial role in compensatory renal hemodynamics.[18] Inhibition of cyclooxygenase enzyme activity by NSAIDs will have a substantial inhibitory effect on prostaglandin synthesis that may deteriorate cardiovascular homeostasis in these susceptible patients. Although not statistically significant, the stratified analysis of baseline serum creatinine level also indicated that impaired renal function, defined as serum creatinine level of 1.1 mg/dL (100 μmol/L) or more, seems to be associated with an increased risk of NSAID-associated heart failure.

A number of case reports have been published in which the onset of heart failure was attributed to the use of NSAIDs.[6-9] In most of these reports, patients did have preexisting cardiovascular disease that may have predisposed to the onset of heart failure. An earlier published record-linkage study has shown a 2-fold increased risk of a first hospitalization for heart failure during concomitant use of NSAIDs and diuretics as compared with use of diuretics alone in patients older than 55 years.[11] As this record-linkage study was carried out within a cohort of users of diuretics, it is likely that a number of these patients did have symptomatic left ventricular dysfunction in the period preceding the first hospitalization for heart failure. Many elderly patients are treated by their general practitioner because of mild to moderate signs and symptoms of heart failure before hospital admission is indicated. This may explain the finding in the above-mentioned record-linkage study that the strongest increase in hospitalization risk was seen in patients who were likely to have preexisting heart failure. Hence, a first hospitalization for heart failure is not by definition the same as truly incident heart failure. In our study, we included not only first hospital admissions but also all patients with diagnoses of incident heart failure, irrespective of whether they were admitted to the hospital or not, and excluded all patients with an uncertain diagnosis of incident heart failure.

In a recent matched case-control study,[12] use of NSAIDs in the preceding week was associated with a doubling of the odds ratio of a hospital admission for heart failure. In patients with a first diagnosis of heart failure, a 3-fold increased odds ratio was calculated. A much stronger association was shown in patients with a history of heart disease. In view of the pathophysiology of NSAID-induced heart failure,[18] it seems likely that a substantial part of the cases in this study did have preexisting left ventricular impairment before hospitalization. In

Table 2. Association Between Use of Cardiovascular and Pulmonary Medication and Occurrence of Incident Heart Failure*

	No. (%) of Patients Using Drug During Follow-up		
	Incident Heart Failure (n = 345)	No Heart Failure (n = 6932)	Crude RR† (95% CI)
Digoxin			
No	263 (76.2)	6381 (92.1)	1.0 (Reference)
Yes	82 (23.8)	551 (7.9)	**6.6 (5.0-8.6)**
Antiarrhythmics			
No	315 (91.3)	6719 (96.9)	1.0 (Reference)
Yes	30 (8.7)	213 (3.1)	**5.0 (3.2-7.7)**
Vasodilators			
No	204 (59.1)	5521 (79.6)	1.0 (Reference)
Yes	141 (40.9)	1411 (20.4)	**5.9 (4.7-7.5)**
Thiazides			
No	340 (98.6)	6815 (98.3)	1.0 (Reference)
Yes	5 (1.4)	117 (1.7)	2.3 (0.7-7.2)
Low-ceiling diuretics (thiazides excluded)			
No	333 (96.5)	6699 (96.6)	1.0 (Reference)
Yes	12 (3.5)	233 (3.4)	1.1 (0.4-3.1)
Loop diuretics			
No	211 (61.2)	5822 (84.0)	1.0 (Reference)
Yes	134 (38.8)	1110 (16.0)	**8.0 (6.4-10.2)**
Potassium-sparing diuretics			
No	317 (91.9)	6710 (96.8)	1.0 (Reference)
Yes	28 (8.1)	222 (3.2)	**6.5 (4.1-10.2)**
Loop diuretics or low-ceiling diuretics combined with potassium-sparing diuretic			
No	253 (73.3)	5625 (81.1)	1.0 (Reference)
Yes	92 (26.7)	1307 (18.9)	**1.4 (1.0-2.0)**
β-Blockers			
No	201 (58.3)	4955 (71.5)	1.0 (Reference)
Yes	144 (41.7)	1977 (28.5)	**2.1 (1.7-2.7)**
Calcium entry blockers			
No	246 (71.3)	5738 (81.8)	1.0 (Reference)
Yes	99 (28.7)	1194 (17.2)	**2.9 (2.3-3.8)**
ACE inhibitors			
No	252 (73.0)	5673 (81.8)	1.0 (Reference)
Yes	93 (27.0)	1259 (18.2)	**2.9 (2.2-3.7)**
COPD medication			
No	271 (78.6)	5699 (82.2)	1.0 (Reference)
Yes	74 (21.4)	1233 (17.8)	**2.8 (2.1-3.8)**
Platelet aggregation inhibitors			
No	190 (55.1)	4665 (67.3)	1.0 (Reference)
Yes	155 (44.9)	2267 (32.7)	**2.8 (2.2-3.5)**

*RR indicates relative risk; CI, confidence interval; ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; and boldface type, statistically significant values.

†Crude RR calculated with a Cox regression model with drugs as time-varying exposure variables; RR cannot be calculated directly from columns 2 and 3.

addition, the remarkably high consumption of NSAIDs of nearly 30% in the week before hospitalization among the cases may imply either recall bias or significant comorbidity.

The univariate association between various cardiovascular drugs and the onset of heart failure reflects the presence of preexisting cardiovascular disorders such as hypertension, atrial fibrillation, and ischemic heart disease, which predispose to the development of heart failure. Although we excluded from the analysis all patients who may have had prevalent heart failure, we cannot exclude the possibility that some patients in the study population did use these drugs because of heart failure. However, the presence in the study population of some patients with prevalent heart failure is likely to overestimate the relative risk. Hence, it seems plausible that the risk estimate of the association between incident heart failure and NSAID use might be even lower if we were able to exclude these patients.

The second analysis in our study in patients who were followed up since diagnosis of heart failure (n = 292) demonstrates the different effects of NSAIDs in patients with incident and prevalent heart failure. In patients with prevalent heart failure who filled at least 1 NSAID prescription, current use of NSAIDs was associated with a substantially increased risk of a relapse. From a pathophysiologic point of view, the different effects of NSAIDs with respect to incident and prevalent heart failure seem to be plausible, as cardiovascular homeostasis is much more likely to be prostaglandin dependent in patients with prevalent heart failure than in patients with unimpaired left ventricular function.

Table 3. Association Between Incident Heart Failure and Use of NSAIDs*

	Crude RR (95% CI)	Adjusted RR (95% CI)
Total study population (N = 7277)		
Incident heart failure during current use of NSAIDs†	1.5 (1.0-2.3)	1.1 (0.7-1.7)
Relapse of heart failure during current use of NSAIDs‡	1.4 (0.5-3.8)	1.4 (0.5-3.8)
Participants with ≥1 NSAIDs at any time (n = 5062)		
Incident heart failure during current use of NSAIDs†	1.4 (0.9-2.1)	1.2 (0.8-1.8)
Relapse of heart failure during current use of NSAIDs‡	**3.8 (1.1-12.7)**	**9.9 (1.7-57.0)**

*NSAID indicates nonsteroidal anti-inflammatory drug; RR, relative risk; CI, confidence interval; and boldface type, statistically significant values.

†RR adjusted for age, sex, serum creatinine level 1.1 mg/dL (100 µmol/L) or more, hypertension, history of myocardial infarction, atrial fibrillation, and concomitant cardiovascular and pulmonary medication.

‡RR adjusted for age, sex, and concomitant cardiovascular and pulmonary medication.

A cohort study lacks some of the intrinsic limitations of case-control studies. The availability of prospectively stored drug exposure data from the automated pharmacies in the study area prevents potential differential misclassification of exposure that may occur in case-control studies. Intensive follow-up procedures of participants in the Rotterdam Study provided the possibility of including only patients with definite incident heart failure and excluding from the study population those with an uncertain diagnosis. However, we cannot exclude the possibility that some patients with asymptomatic left ventricular dysfunction were included in our study population.

Several cardiovascular drugs were associated with increased risk of incident heart failure (Table 3). Patients who develop incident heart failure are likely to have potential risk factors such as hypertension or coronary artery disease. The findings in our analysis on the association between NSAIDs and incident heart failure indicate that NSAIDs do not have a substantial additional contribution to the risk but that this is largely caused by cardiovascular comorbidity, as reflected by cardiovascular comedication.

An important source of bias in cohort studies may arise from the degree of accuracy with which participants have been classified regarding their exposure and disease status. In this present study, a diagnosis of incident heart failure could be made only on the basis of information from a medical specialist. Two research physicians independently reviewed all available information before rating the event as definite heart failure. In addition, this decision of the 2 research physicians had to be confirmed by a specialist in cardiovascular medicine. Therefore, substantial misclassification of the diagnosis of definite heart failure seems unlikely, especially as the physicians were unaware of the study hypothesis.

Exposure to NSAIDs was based on the information on filled drug prescriptions in the 3 automated pharmacies in the study area. Information on over-the-counter use of NSAIDs was not available. In the Netherlands, however, since 1995 only a small proportion of total NSAID consumption consists of over-the-counter drugs. Moreover, misclassification of exposure is likely to be nondifferential, as signs and symptoms of heart failure do not prompt the use of NSAIDs.

The NSAIDs are drugs that may have several beneficial effects, particularly for musculoskeletal disease that occurs frequently in the elderly. Despite their potential adverse effects, many patients take advantage of the potent analgesic and anti-inflammatory properties of these drugs. In view of the risk-benefit profile of drugs, our finding that NSAIDs were not associated with an increased risk of incident heart failure in a cohort of patients without preexisting signs or symptoms of heart failure is of clinical significance. This implies that, regarding the risk of heart failure, these drugs can safely be prescribed to elderly patients with uncompromised left ventricular function.

In conclusion, NSAIDs were not associated with incident heart failure in our study population. In patients with prevalent heart failure, however, a substantially increased risk with NSAIDs was demonstrated, implying that NSAIDs should be prescribed with caution to patients with prevalent heart failure.

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