

NSAIDs Associated With Increased Risk of Congestive Heart Failure in Elderly Patients Taking Diuretics

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Background: Both diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used, in particular among the elderly. The use of NSAIDs may decrease the efficacy of diuretics and induce congestive heart failure (CHF) in patients treated with diuretics.

Objective: To investigate the risk of CHF associated with combined use of diuretics and NSAIDs in patients older than 55 years.

Methods: We conducted a study in a base cohort of 10 519 recipients of diuretics and NSAIDs identified in the PHARMO database during the period from 1986 through 1992. The incidence density of hospitalizations for CHF during exposure to both diuretics and NSAIDs (index) was compared with that during exposure to diuretics only (reference).

Results: We found an overall increased risk of hospitalization for CHF during periods of concomitant use of diuretics and NSAIDs compared with use of diuretics only (crude relative risk, 2.2; 95% confidence interval, 1.7-2.9). After adjusting for cofactors including age, sex, history of hospitalization, and drug use, a 2-fold increased risk remained (relative risk, 1.8; 95% confidence interval, 1.4-2.4).

Conclusion: Use of NSAIDs in elderly patients taking diuretics is associated with a 2-fold increased risk of hospitalization for CHF, especially in those with existing serious CHF.

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THERE HAS been evidence of possible risks of concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and diuretics.¹⁻³

The kidney is an important target site for untoward drug reactions associated with the use of NSAIDs, and concomitant use of diuretics may increase the risk of NSAID-associated renal adverse effects.⁴⁻⁸ The interaction between diuretics and NSAIDs is well known.⁸⁻¹⁰ Nonsteroidal anti-inflammatory drugs inhibit the synthesis of renal prostaglandins, which can have serious effects on renal function. Prostaglandins predominantly generated in the kidney are I₂ and E₂, of which prostaglandin E₂ influences sodium resorption in the nephron by causing vasodilation and by directly inhibiting sodium resorption in the thick ascending loop of Henle and in the collecting tubule.⁹ Prostaglandin E₂ also antagonizes the antidiuretic effect of vasopressin in the collecting tubule.^{8,9} Therefore, by inhibiting prostaglandin synthesis, NSAIDs can cause sodium and water retention and blunt the response to di-

uretics. In most users of NSAIDs the inhibition of renal prostaglandins will have no clinical effect, but there have been case reports of patients with a predisposition to sodium retention, in particular because of congestive heart failure (CHF), in which the use of NSAIDs had marked clinical implications.^{8,10-13} Existing CHF may worsen after use of NSAIDs by inhibition of diuretic therapy and by adverse renal effects, especially in elderly patients with renal impairment and cardiovascular comorbidity.¹³ These elderly patients at risk are at the same time the most frequent users of NSAIDs and diuretics, with an estimated 10% of all elderly people having a period of concomitant use of diuretics and NSAIDs in a year.^{14,15}

The objective of this study was to ascertain the risk of CHF associated with the combined use of diuretics and NSAIDs in patients older than 55 years and to identify possible risk factors.

RESULTS

A total of 10 519 patients were found with at least 1 period of concomitant use of a

PATIENTS AND METHODS

SETTING

Data were used from the PHARMO record linkage system, a database containing drug-dispensing records from community pharmacies and linked hospital discharge records of a defined population of 300 000 residents of 6 medium-sized cities in the Netherlands.¹⁶

Medication histories and hospital data were collected from January 1, 1986, through December 31, 1992. Some pharmacies started participation in the study later than 1986, leading to a shorter follow-up time. At the end of 1992, the average period during which data had been collected was 6.0 years. Drugs were coded according to the anatomical-therapeutic-chemical classification.¹⁷ For hospital discharge diagnoses, the *International Classification of Diseases, Ninth Edition, Clinical Modification* codes were used.¹⁸

PATIENTS

All residents aged 55 years or older who had had at least 1 period of concomitant use of a diuretic and an NSAID were included in the study population. The inclusion date was the date of first dispensing of a diuretic. The end point of the study was the first of the following events: (1) first hospitalization for CHF as defined below or (2) last dispensing of any prescription in the pharmacy, indicating a move from the study area, institutionalization, or death.

The definition of follow-up time ensured eligibility for drug use and hospitalization during the study period for each patient. Because of switching or stopping, the index period was defined as the period during which the subjects were exposed to diuretics and NSAIDs concurrently. The control period was defined as the period during which the same subjects were exposed to diuretics but not to NSAIDs.

The anticipated duration of each prescription was calculated from the dosage and prescribed daily dose. Patients were stratified into incidental, irregular, and continuous users of diuretics. Incidental users were defined as subjects with a first prescription of a diuretic in a period of at least 180 days. Continuous users were patients who refilled their prescriptions regularly, ie, with no more than 10 days between the anticipated end date of the prescription and the fill of the next prescription. The remainder were defined as irregular users. Dose was expressed as a fraction of the defined daily dose (DDD) (0.00-0.74, 0.75-1.24, or >1.24 DDDs/d).

VALIDATION OF CASES

The outcome of the study was defined as first hospitalization with a primary (CHF was the reason for hospitalization) or secondary (another reason was given for hospitalization but CHF was present) diagnosis of CHF (*International Classification of Diseases, Ninth Edition, Clinical Modification* code 428). A random sample (n=138) of primary cases from all participating hospitals in 1990 was validated by review of the medical records.¹⁵ The individuals involved in data collection and record abstraction were blinded to the exposure and case-control status, but not to the study hypothesis.

Hospital discharge diagnoses were compared with 2 validated sets of diagnostic models for CHF, the criteria from the Framingham Heart Study and a modification of the Boston criteria.^{19,20} The validity of the hospital discharge diagnosis of CHF was shown to be high. In our study, 81.2% of patients with a hospital discharge code for CHF were identified as true CHF cases by application of the Boston criteria, and 79.7% of the cases were so classified by application of the Framingham criteria. To examine whether misclassification of cases would affect the outcome of the study, we investigated possible differences in drug exposure patterns between the correctly and falsely classified hospitalizations. No differences in age and sex were found between the groups with and without CHF according to the criteria. There was no significant difference in combined use of diuretics and NSAIDs between patients with or without confirmed CHF. Therefore, any possible misclassification in the cases of CHF was most likely nondifferential.

POTENTIAL RISK FACTORS

Basic patient-related cofactors were assessed, ie, age and sex. Drug use in the 180 days preceding the different exposure periods was estimated, including type of drug used, number of days of drug exposure, and number of different prescribers. Comorbidity was assessed by analysis of hospital admissions during the follow-up period.

DATA ANALYSIS

The incidence density of hospitalization for CHF was calculated during exposure to diuretics compared with exposure to diuretics plus NSAIDs, yielding a relative risk (RR) of CHF expressed as the incidence density ratio. Correction for the potential confounding effect of risk factors was performed with Poisson logistic regression analysis.

diuretic and an NSAID during the study period (**Table 1**). The total observation time was 49 512 person-years, which equals an average (\pm SD) of 4.7 \pm 0.17 years of follow-up per patient. The study population was predominantly female (72.2%) and had an average age of 70.8 \pm 9.1 years.

During the observation period, 565 hospitalizations for CHF were found, of which 389 occurred during a period of diuretic use. Of these 389 hospitalizations, 225 (57.8%) had a primary diagnosis and 164 (42.2%) a secondary diagnosis of CHF. During concomitant use of diuretics and NSAIDs, 228 hospitalizations were found, an incidence density of 23.3 per 1000 person-years. During use of diuretics only, 161 hospitalizations

for CHF were found, resulting in an incidence density of 9.3 per 1000 person-years.

Table 2 shows the crude rate ratios of the incidence densities found in the 2 exposure groups. Incidence densities were significantly higher during exposure to both diuretics and NSAIDs than during exposure to diuretics only (RR, 2.5; 95% confidence interval [CI], 2.1-2.9). No significant differences between hospitalizations with a primary diagnosis of CHF and those with a secondary diagnosis were found. Further results will discuss only the hospitalizations with a primary diagnosis of CHF.

To adjust the overall rate ratio for possible confounding variables and to assess the effects of cofactors,

Table 1. Basic Characteristics of Patients Aged 55 Years or Older Who Had Had at Least 1 Period of Concomitant Use of Diuretics and NSAIDs*

Characteristic	Value
Total study population	10 519 (100)
Male	2926 (27.8)
Age, y	
55-64	2963 (28.2)
65-74	3827 (36.4)
75-84	2930 (27.9)
≥85	799 (7.6)
Diuretic prescriptions, No.	178 355
NSAID prescriptions, No.	90 420
Total observation period, person-y (%)	49 512 (100.0)
Diuretics only	17 268 (34.9)
NSAIDs only	8210 (16.6)
Diuretics plus NSAIDs	9778 (19.7)
No diuretics, no NSAIDs	14 256 (28.8)
Average observation period, y	4.7
Admissions for CHF during observation period, No.	565
CHF cases during use of diuretics or diuretics plus NSAIDs, No.	389

*Values are number (percentage) unless otherwise specified. NSAID indicates nonsteroidal anti-inflammatory drug; CHF, congestive heart failure.

Table 2. Rate Ratios of Hospitalizations for CHF in Users of Diuretics and NSAIDs Compared With Users of Diuretics Only*

	No. of Hospitalizations (Incidence Density)†		RR‡ (95% CI)	
	Diuretics Plus NSAIDs	Diuretics Only	RR‡ (95% CI)	
			Crude	Adjusted§
Primary diagnosis of CHF	125 (12.8)	100 (5.8)	2.2 (1.7-2.9)	1.8 (1.4-2.4)
Secondary diagnosis of CHF	103 (10.5)	61 (3.5)	3.0 (2.2-4.0)	2.4 (1.7-3.4)
All diagnoses of CHF	228 (23.3)	161 (9.3)	2.5 (2.1-2.9)	2.1 (1.7-2.5)

*CHF indicates congestive heart failure; NSAID, nonsteroidal anti-inflammatory drug; RR, relative risk; and CI, confidence interval. †Number of hospitalizations for CHF per 1000 person-years. ‡Expressed as the ratio between the incidence densities. §Adjusted for cofactors described in text by Poisson logistic regression.

stratified analyses were made. **Table 3** shows that no differences in risk between female and male patients were found and that there were no significant differences among the various age groups. Risk was highest in the age group of 55 to 64 years (RR, 2.5; 95% CI, 1.1-5.7).

Continuous users of diuretics showed a relatively high risk (RR, 4.3; 95% CI, 2.4-7.9) compared with irregular and incidental users. Patients with patterns of switching diuretic or NSAID therapy showed no higher risk than the overall risk of hospitalization with a primary diagnosis of CHF.

We found no difference in the overall RR in patients with a history of hospitalization (Table 3). Pa-

Table 3. Stratified Analysis of Cofactors*

	No. of Cases/Person-y		
	Diuretics + NSAIDs	Diuretics	RR (95% CI)†
Sex			
Female	83/7763	57/12 763	2.4 (1.7-2.9)
Male	42/2015	43/4505	2.2 (1.4-3.3)
Age, y			
55-64	12/2589	10/5480	2.5 (1.1-5.7)
65-74	44/3562	35/6277	2.2 (1.4-3.4)
75-84	57/2858	44/4404	2.0 (1.4-2.9)
≥85	12/769	11/1107	1.6 (0.7-3.5)
Drug exposure in 180 d preceding			
Diuretic use			
Incidental users	53/2078	39/3140	2.1 (1.4-3.1)
Irregular users	46/5592	47/9160	1.6 (1.1-2.4)
Continuous users	26/2107	14/4933	4.3 (2.4-7.9)
Switching of diuretic therapy	46/1934	38/2888	1.8 (1.2-2.8)
Switching of NSAID therapy	23/1893	1/122	1.5 (0.2-10.8)
Use of cardiovascular drugs			
Digoxin	50/1331	42/2277	2.1 (1.4-3.0)
ACE inhibitors	23/973	21/1754	2.0 (1.1-3.5)
Calcium entry blockers	26/1256	17/2083	2.5 (1.4-4.6)
β-Blockers	21/2761	20/5465	2.1 (1.1-3.8)
Antiarrhythmic	6/283	7/555	1.7 (0.6-4.9)
Other	6/550	5/666	1.5 (0.4-4.7)
Previous hospitalization			
≥9 d in hospital	24/572	13/617	2.0 (1.0-3.9)
Renal diseases	3/42	3/39	1.8 (0.3-9.7)
Cardiovascular diseases	27/1455	41/1010	2.2 (1.4-3.5)

*NSAID indicates nonsteroidal anti-inflammatory drug; RR, relative risk; CI, confidence interval; and ACE, angiotensin-converting enzyme. †Relative risk is expressed as the ratio between the incidence densities. Significant associations are printed in boldface type.

tients with a history of renal disease (nephritis or renal failure) also showed no increase in risk, but the small numbers of patients in this group resulted in wide CIs. Previous hospitalization for cardiovascular diseases other than CHF (in this study, only first hospitalization for CHF was considered) had no effect on risk.

All possible cofactors from the stratified analysis noted in Table 3 were included in a Poisson logistic regression analysis yielding adjusted rate ratios, as shown in Table 2. Rate ratios were slightly lower after adjustment but remained significant. Thus, after correction for possible confounding, an overall 2-fold increase in the risk of hospitalization with a primary diagnosis of CHF remained during concomitant use of diuretics and NSAIDs compared with use of diuretics only.

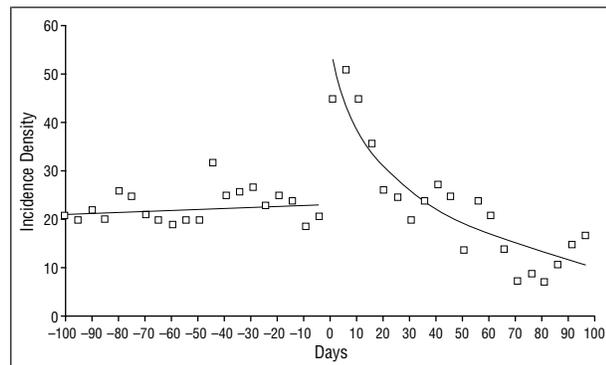
A total of 125 hospitalizations for CHF as primary diagnosis during use of NSAIDs plus diuretics was found. A large part (56.8%) occurred within 1 month of starting of the concomitant use of a diuretic and an NSAID. To investigate the time effect of introducing an NSAID during diuretic therapy, we plotted the incidence of any hospitalization (not only first hospitalizations) with a primary diagnosis of CHF in 10-day intervals before and after the first known use of an NSAID by patients treated with diuretics

(Figure). A fairly stable incidence density was seen in the 100 days preceding concomitant use of an NSAID and a diuretic, whereas there was a sharp increase in incidence density of hospitalization in the first 20 days after initiation of NSAID therapy. After 40 days, the incidence density was back to about the same level as before concomitant use.

Analysis of the NSAID dosages used showed no clear dose-response relationship. The RR in persons taking a relatively low dose of NSAIDs (0.00-0.74 DDDs/d) was 2.4 (95% CI, 1.4-3.0); a medium dose of NSAIDs (0.75-1.24 DDDs/d) showed a lower risk (RR, 1.6; 95% CI, 1.0-2.4) and high dosages of NSAIDs (>1.24 DDDs/d) were associated with a higher risk (RR, 2.3; 95% CI, 1.4-2.9).

Table 4 shows the differences between classes of diuretic drugs. Most frequently used were combinations of thiazide diuretics and potassium-sparing drugs. The incidence density of hospitalizations during use of this combination plus NSAIDs was more than 3 times higher than that for diuretic use only. The incidence density of hospitalizations for CHF was significantly higher during use of loop diuretics than during use of thiazides plus potassium-sparing drugs, ie, 20.4 and 2.8 cases per 1000 person-years, respectively.

The NSAIDs most often used in this population were diclofenac (38.2% of the NSAID prescriptions), ibuprofen (33.1%), naproxen (10.4%), and indomethacin (8.1%). We found no significant differences in the risk of hospitalization for CHF among the different NSAIDs.



Incidence density of hospitalizations for congestive heart failure in 10-day intervals before and after first use of a nonsteroidal anti-inflammatory drug during diuretic therapy. The left line is fitted by linear regression ($r^2=0.65$); the right line, by logistic regression ($r^2=0.85$).

During periods of concomitant use of diuretics and NSAIDs, a 2-fold increased risk of hospitalization for CHF was found compared with periods of diuretic use only. Patients with a history of heavy diuretic use showed an increased risk. This may lead to the hypothesis that an existing condition of CHF that is being treated with diuretics is challenged by the introduction of NSAIDs. Case reports describing CHF after use of NSAIDs almost always mention concurrent use of a diuretic, thus implying an existing CHF condition as an important risk factor.¹⁹ Users of β -blockers did not show an increased risk of CHF during concomitant use of NSAIDs and diuretics, possibly because use of β -blockers is contraindicated in patients with CHF.

The literature suggests that use of NSAIDs may have a more significant impact in patients with diminished renal function,^{1,21-23} but in our study, no increase in risk was found in patients with a history of hospitalization for renal disease. However, as the number of such patients was low, it was difficult to take renal capacity into account in this study. Since diminished creatinine clearance is a relative contraindication to NSAID use, information on renal function should therefore be taken as a cofactor in subsequent studies.

Renal function generally diminishes with age, but we found no age effects in our study. This lack of effect may, however, be explained by a selection bias. In our study, only community-dwelling elderly patients participated, excluding patients who were institutionalized and possibly had a higher morbidity.

Renal function is known to be abnormal in patients with cirrhosis, and several studies describe renal dysfunction in patients with cirrhosis after use of NSAIDs.^{24,25} Of the patients with a hospitalization for CHF in our population, we found a total of 6 patients with a history of liver disease, of whom 2 had a hospitalization for cirrhosis (alcoholic in 1 and nonalcoholic in 1). No evidence was found for a higher risk of CHF after use of an NSAID in patients with a history of cirrhosis.

Murray and Brater¹ described rapid effects of NSAIDs on renal function in susceptible persons. We found a strong temporal relationship between the onset of NSAID therapy and the occurrence of hospitalization for CHF, with the majority of hospitalizations for CHF occurring within 30 days. The highest risk occurred within the first days of NSAID use,

Table 4. Risk of Hospitalization for CHF During Concomitant Use of Different Classes of Diuretics and NSAIDs*

Class of Diuretics	Use, Person-y	No. of Cases (Incidence Density)†		RR (95% CI)‡	
		Diuretics + NSAIDs	Diuretics	Crude	Adjusted§
Thiazides (including combinations)	14 815	26 (5.0)	16 (1.7)	3.0 (1.7-5.4)	2.9 (1.6-6.5)
Loop diuretics	7093	79 (27.8)	66 (15.5)	1.8 (1.3-2.5)	1.7 (1.1-2.5)
Sulfonamides	3208	6 (5.5)	6 (2.8)	1.9 (0.6-6.0)	1.4 (0.2-8.9)
Potassium-sparing drugs (excluding combinations with thiazides)	1040	13 (33.3)	12 (18.4)	1.3 (0.5-3.4)	1.4 (0.6-3.4)

* CHF indicates congestive heart failure; NSAID, nonsteroidal anti-inflammatory drug; RR, relative risk; CI, confidence interval.

† Number of hospitalizations for CHF per 1000 person-years.

‡ Relative risk is expressed as the ratio between the incidence densities. Significant associations are printed in boldface type.

§ Adjusted for cofactors by Poisson logistic regression.

after which it dropped to a level comparable with that before the NSAID initiation. There even appeared to be a slightly decreased risk after 40 days, but this may well be attributed to the fact that patients at high risk had already been admitted to the hospital. These findings are in concordance with clinical data that suggest rapid effects on the kidney.

The therapy most often used, ie, thiazides combined with potassium-sparing drugs, showed a significantly higher risk than the other diuretic therapies. Again, this adds to the theory of destabilizing of treatment of existing CHF by the introduction of an NSAID, for the combination of thiazides and potassium-sparing drugs is used if the thiazide dosage is high, ie, in patients with CHF.²⁶

There was a significantly higher overall incidence of hospitalizations for CHF in patients taking loop diuretics than in those taking other diuretic therapy, indicating that loop diuretics are more often used in patients with more severe CHF. However, in this group, we did not find an increased risk of hospitalization during NSAID use compared with the other diuretic groups. It is possible that NSAIDs affect the site of action of loop diuretics (the loop of Henle) less than that of thiazides (mainly the distal tubule). Many effects of NSAIDs on renal autacoids have been described, but the exact consequences of inhibition of the many prostaglandin production sites in the nephron remain unclear.

It has been suggested that sulindac and piroxicam show decreased renal risk compared with ibuprofen,⁶ although others dispute this claim.^{4,27} In a separate analysis, we found no differences in the risk of hospitalization for CHF among the different NSAIDs, indicating a class effect. However, the rate of use of sulindac was too low in this population to ascertain a possible lower risk.

A possible source of exposure misclassification could be the use of over-the-counter preparations of NSAIDs. However, a previous study that included a cabinet survey of all drugs present in elderly persons' homes showed that use of over-the-counter preparations by elderly people in the Netherlands is relatively low and that NSAIDs available without prescription (low-dose ibuprofen and naproxen) were seldom present as an over-the-counter preparation at the home interview.²⁸ Therefore, it is not to be expected that exposure misclassification had a significant effect on the outcome of this study.

If the reason for prescribing an NSAID in the patients included in this study was associated with the occurrence of the adverse event, ie, worsening of CHF, this would influence the results of the study through confounding by indication. However, this is not likely, as there is no reason to assume that there is an association between the occurrence of CHF and prescription of NSAIDs other than the one found in this study. On the other hand, it is possible that physicians have prescribed fewer NSAIDs in patients especially at risk, which in this study would create a form of confounding by contraindication. This may also account for the lack of a clear dose-response relationship.

In conclusion, we found a 2-fold increased risk of hospitalization for CHF in patients during periods of concomitant use of diuretics and NSAIDs compared with periods of diuretic use only, especially in patients with an existing condition of CHF. The findings in this study call for careful monitoring of patients with a treated CHF in which

NSAID therapy is unavoidable, especially in the first month of NSAID use when the risk of worsening of CHF is high.

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