CARDIOVASCULAR MEDICINE

Non-steroidal anti-inflammatory drugs and risk of first hospital admission for heart failure in the general population

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Heart 2006;**92**:1610–1615. doi: 10.1136/hrt.2005.082388

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Accepted 13 April 2006
Published Online First 22 May 2006

Objectives: To estimate the risk of a first hospital admission for heart failure (HF) associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs).
Methods: Cohort study with a nested case–control analysis based on the UK General Practice Research Database. Overall, 1396 cases of first hospital admission for non-fatal HF were identified (January 1997 to December 2000) and compared with a random sample of 5000 controls.
Results: The incidence rate was 2.7/1000 person years. Prior clinical diagnosis of HF was the main independent risk factor triggering a first HF hospitalisation (relative risk 7.3, 95% confidence interval (CI) 6.1 to 8.8). The risk of a first hospital admission for HF associated with current use of NSAIDs was 1.3 (95% CI 1.1 to 1.6) after controlling for major confounding factors. No effects of dose and duration were found. The relative risk in current users of NSAIDs with prior HF was 8.6 (95% CI 5.3 to 13.8) compared with patients who did not use NSAIDs and without prior clinical diagnosis of HF.
Conclusion: Use of NSAIDs was associated with a small increase in risk of a first hospitalisation for HF. In patients with prior clinical diagnosis of HF, the use of NSAIDs may lead to worsening of pre-existing HF that triggers their hospital admission. This increased risk, although small, may result in considerable public health impact, particularly among the elderly.

Most of the beneficial and harmful effects of non-steroidal anti-inflammatory drugs (NSAIDs) are mechanistically related to their inhibition of prostaglandin synthesis.[1–6] Few studies have examined the association between NSAIDs and serious vascular and renal effects. Results from the few published epidemiological studies evaluating the association of heart failure (HF) with the use of NSAIDs are consistent with an increase in the risk of incident HF, hospitalisation for HF (mostly among patients with previous heart disease) and HF relapse.[7–11]

Although prostaglandins have both vasodilator and vasoconstrictor actions, the overall effects of prostaglandin synthesis inhibition mediated by NSAIDs are to raise peripheral systemic resistance and reduce renal perfusion in susceptible people.[12] These are patients with impaired ventricular function and increased biosynthesis of vasodilator prostaglandins as a compensatory mechanism. Experimental studies have shown that giving NSAIDs to susceptible people can increase systemic vascular resistance and reduce renal blood flow, glomerular filtration and sodium excretion.[13] The combination of these mechanisms can be expected to increase the risk of developing clinical HF in susceptible patients.[14]

HF is a recognised major public health problem in developed countries. The clinical presentation of HF is associated with a reduced life expectancy and it is one of the main reasons for hospitalisation of the elderly.[15 16] Despite recent therapeutic advances, hospital admissions for HF are continuously increasing and case fatality rates remain high.[17–19]

We performed a nested case–control study in a cohort from the general UK population to estimate the risk of a first hospitalisation for non-fatal HF associated with the use of NSAIDs. We decided not to include fatal cases as retrieval of additional information from the general practitioners of patients who have died is limited. We also examined the effect of individual NSAIDs, dose and duration, and whether the risk varies according to antecedents of cardiovascular diseases, other co-morbidities and concomitant drugs.

PATIENTS AND METHODS

Data source

The General Practice Research Database (GPRD) contains computerised medical information entered systematically by general practitioners and sent anonymously to the Medicines and Healthcare products Regulatory Agency (MHRA).[20] The MHRA organises this information for used in research projects. The information recorded includes demographic data, medical diagnoses from general practitioner visits, specialist's referrals and hospitalisations, results of laboratory tests and all prescriptions issued, as well as a free text section. Prescriptions are generated directly from the computer and recorded on the patient's computerised file. An additional requirement is recording of the indication for new courses of treatment. Multiple studies and reviews have been published describing this database in detail and documenting the completeness and validity of the information recorded.[20 21] Over 90% of all referrals are entered on to general practitioners' computers with a code that reflects the specialist's diagnosis.[22] Previous studies have also confirmed the validity of using the GPRD for epidemiological research in the field of HF in association with NSAIDs.[11]

Source population

We identified all patients aged 60–84 years at 1 January 1997 and started follow up from the first day thereafter, once they met the criteria of at least two years' enrolment with the

Abbreviations: ACE, angiotensin-converting enzyme; GPRD, General Practice Research Database; HF, heart failure; MHRA, Medicines and Healthcare products Regulatory Agency; NSAID, non-steroidal anti-inflammatory drug; RR, relative risk; S, synergy index

general practitioner and one year since their first computerised prescription. That date was their start date. We excluded patients with a recorded diagnosis of cancer before the start date. The final study population comprised 228 660 patients. We followed up all source members until the earliest occurrence of one of the following end points: a first-time recorded diagnosis of HF hospitalisation, cancer, age 85 years, or 31 December 2000. The date of the first diagnosis of HF hospitalisation in the study period was used as the index date.

Case ascertainment and validation

We reviewed computerised profiles of all 3495 patients with a code of HF and a mention of hospitalisation detected by the initial computer search. All of the patients' personal identifiers were suppressed and information on NSAID use was removed to allow for a blinded revision of patient profiles. At this stage, we excluded 1104 patients: 690 died in the month after the index date, 38 were hospitalised for a non-cardiac condition in the previous month, 23 had in-hospital HF onset, and 353 were hospitalised with HF with a concomitant diagnosis of an acute coronary syndrome, an exacerbation of asthma or chronic obstructive pulmonary disease, or renal failure. We classified the remainder as probable (n = 1200) and possible cases (n = 1191). Probable cases were patients with a clear computer record of hospitalisation due to HF. We sent a questionnaire to the general practitioners in a random sample of about 10% of probable cases to confirm whether the index hospitalisation was the first one due to HF and the exact admission date. Possible cases were patients who were hospitalised with an unclear HF cause but with visits to a specialist compatible with an HF diagnosis. We sent to the general practitioners a questionnaire for all possible cases. We also requested from the general practitioners all available information related to that hospitalisation, recorded symptoms of HF (New York Heart Association criteria), and tests performed at the time of the first hospitalisation.

Patients were regarded as confirmed cases if the index hospital admission was the first one for HF and no exclusion criteria were found after all the information received from the general practitioners was reviewed.

We received information for 90% of all probable cases, and 75% of them were confirmed as cases. Among the 1191 possible cases the response rate was 96% and among these 246 patients (21%) were confirmed as cases of first hospitalisation due to HF. In the end 1396 patients were regarded as cases of first hospital admission for HF.

Exposure definition

Users of NSAIDs were defined as current users when the supply of the most recent prescription lasted until the index date or ended in the 30 days before the index date. Recent users were defined when the end of the most recent prescription was between 31 and 365 days before the index date. Past users were defined when the end of the most recent prescription was more than one year before the index date. Non-users were defined when no use was recorded before the index date. Current users were subsequently divided into current single users (those who received only one NSAID during the 30 days before the index date) and current multiple users (patients who received prescriptions for different NSAIDs with their respective supply ending within the month before the index date). We also evaluated among current users the duration of treatment, adding the periods of consecutive prescriptions, defined as an interval of less than two months between prescriptions.

Among current single users, we estimated the risk associated with each NSAID and the dose–response relationship on the basis of two dose categories: low–medium and high. We considered the following cut-off limits (in mg) for high dose: aceclofenac > 100, acemetacin > 120, azapropazone > 600, diclofenac > 100, diflusal > 750, etodolac > 400, fenbufen > 900, fenoprofen > 1200, flurbiprofen > 150, ibuprofen > 1200, indomethacin > 75, ketoprofen > 150, mefenamic acid > 1000, meloxicam > 7.5, nabumetone > 1000, naproxen > 750, piroxicam > 10, sulindac > 200, tenoxicam > 10 and tiaprofenic acid > 450. Further, among current single users we classified NSAIDs according to their plasma half life as less than 12 h (aceclofenac, acemetacin, diclofenac, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid and tiaprofenic acid) (short half life) and 12 h or more (long half-life group) (azapropazone, meloxicam, nabumetone, naproxen, piroxican, sulindac and tenoxicam).[23] We also characterised NSAIDs as slow-release formulation and other.

The indication of NSAID treatment was evaluated among current single users through review of computerised patient profiles blinded to the outcome. The same time windows for use and duration were used for other drugs included in the analysis.

Analysis

We computed incidence rates of HF hospitalisation and their 95% confidence intervals (CIs) by using the number of cases as the numerator and the total number of person years as denominator. We performed a nested case–control analysis of all confirmed cases, with the date of the diagnosis as their index date. To select controls, all members from the study population were assigned a random date during the study period. If the random date of a study member was included within his or her observation period (from study entry to end of follow up), this was used as index date and the patient was an eligible control. We applied to controls the same exclusion criteria as for cases. From this pool of eligible controls, we randomly selected 5000 patients frequency matched with cases for age (interval of one year), sex and calendar year.

We estimated crude and adjusted relative risk (RR) of hospitalisation for HF and the 95% CI associated with use of NSAIDs compared with non-use by unconditional logistic regression with Stata (V 7; Stata Corporation, College Station, Texas, USA). Frequency-matching factors were entered into the model. We evaluated the following covariates: body mass index, alcohol, smoking status, number of hospitalisations (cardiovascular and non-cardiovascular related) and specialist visits in the previous year, history of diabetes, anaemia, asthma, chronic obstructive pulmonary disease and cardiovascular disease such us myocardial infarction, angina, hypertension, rhythm disorders, cerebrovascular disease and valvular disease. We also studied the effect of the use of cardiovascular drugs such as diuretics, β blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, other hypertension drugs (centrally acting hypertension drugs, and α adrenoceptor and angiotensin II receptor antagonists), lipid lowering drugs and other drugs such as aspirin, paracetamol, anticoagulants, β2 adrenoceptor agonists, corticosteroids (oral and inhaled), insulin and oral diabetes drugs. Lastly, we studied interactions between NSAIDs and other risk factors, and between NSAIDs and other potential nephrotoxic drugs, by using a single term in the model for the joint effect. We used as a measure of interaction the synergy index (S), as departure from the additivity, with $S = 1$ if there was no interaction.[24] We calculated S (and 95% confidence interval (CI)) by using the β coefficients estimated by the logistic regression. We present only adjusted estimates unless otherwise specified.

Table 1 Risk factors for heart failure (HF) among patients with a first admission for non-fatal HF compared with controls

Risk factor	Cases (n = 1396)	Controls (n = 5000)	RR*	95% CI
Body mass index				
20–24	314	1432	1	
<20	53	212	1.04	0.72 to 1.50
25–29	420	1596	1.14	0.95 to 1.37
⩾30	269	555	2.10	1.69 to 2.61
Unknown	340	1205	1.46	1.16 to 1.83
Alcohol (units)				
Non-use	610	1895	1	
1–9	277	1254	0.77	0.64 to 0.92
10–19	102	396	0.90	0.69 to 1.18
20–29	50	207	0.75	0.52 to 1.09
30–49	33	97	1.16	0.74 to 1.84
⩾50	9	19	1.62	0.66 to 3.98
Unknown	314	1123	0.92	0.72 to 1.18
Smoking				
Non-smoker	785	3030	1	
Smoker	267	746	1.51	1.26 to 1.82
Former smoker	171	549	1.15	0.93 to 1.42
Unknown	173	675	1.14	0.85 to 1.52
Hospitalisations in the previous year				
None	904	4322	1	
⩾1	492	678	2.12	1.81 to 2.47
Referrals in the previous year				
None	436	2642	1	
⩾1	960	2358	1.50	1.29 to 1.73
Prior diagnosis of HF				
No	852	4747	1	
Yes	544	253	7.35	6.10 to 8.85
Myocardial infarction				
No	1118	4673	1	
Yes	278	327	1.88	1.52 to 2.34
Angina				
No	974	4301	1	
Yes	422	699	1.39	1.17 to 1.66
Valvular disease				
No	1275	4898	1	
Yes	121	102	2.94	2.16 to 4.01
Rhythm disorders				
No	981	4520	1	
Yes	415	480	2.68	2.26 to 3.18
Atrial fibrillation and flutter				
No	1111	4765	1	
Yes	285	235	3.48	2.81 to 4.30
Hypertension				
No	770	3281	1	
Yes	626	1719	1.28	1.11 to 1.47
Renal failure				
No	1355	4949	1	
Yes	41	51	1.67	1.04 to 2.66
Asthma				
No	1189	4538	1	
Yes	207	462	0.89	0.67 to 1.20
Chronic obstructive pulmonary disease				
No	1166	4576	1	
Yes	230	424	1.28	1.01 to 1.62
Diabetes				
No	1116	4632	1	
Yes	280	368	2.61	2.15 to 3.17
Anaemia				
No	1355	4953	1	
Yes	41	47	2.83	1.76 to 4.56

*Frequency matched on age, sex and calendar year and adjusted for sex, age, calendar year, body mass index, smoking, alcohol, non-steroidal anti-inflammatory drugs, aspirin, steroids, acetaminophen, anticoagulants, diabetes, coronary heart disease, chronic obstructive pulmonary disease, asthma, valvular diseases, rhythm disorders, renal failure, hypertension and hospitalisations in the previous year.

RESULTS

Of the 1396 patients regarded as cases of first hospital admission for HF, 52% were men and 52% were between 70–79 years old. A prior diagnosis of HF, without hospitalisation, was found in 544 (39%) cases and 253 (5%) controls. The overall incidence rate of a first hospital admission for HF was 2.7/1000 person year.

Independent risk factors for HF

Table 1 presents factors independently associated with the risk of HF hospitalisation. Obesity, current smoking, and recent hospitalisations and specialists' visits were associated with an increased risk of HF hospitalisation. A prior diagnosis of HF, without hospitalisation, was the single risk factor most strongly associated with the risk of hospitalisation due to HF (RR 7.3, 95% CI 6.1 to 8.8), followed by history of atrial fibrillation, valvular disease, myocardial infarction, diabetes and anaemia. History of hypertension and renal failure were associated with a moderate increase in the risk of HF. Diuretics were the drugs most widely used, with close to 60% of cases being current users. Twenty six per cent of cases were taking ACE inhibitors and 12% β blockers. We also looked for the effect of a number of drugs other than cardiovascular drugs or NSAIDs and found a pronounced association only with oral steroids (RR 3.0, 95% CI 2.2 to 4.1).

NSAID use and risk of HF

Table 2 shows the risk of a first hospital admission for HF associated with the use of NSAIDs. Fourteen per cent of cases were current users of NSAIDs compared with 10% of controls. Crude and adjusted risks of HF hospitalisation for current NSAID users relative to non-NSAID users were 1.5 (95% CI 1.1 to 1.6) and 1.3 (95% CI 1.1 to 1.6), respectively. No clear duration effect was found. There was no difference between low–medium dose (RR 1.3, 95% CI 1.0 to 1.7) and high dose (RR 1.4, 95% CI 1.1 to 1.9). The risk was slightly greater for long plasma half-life NSAIDs and slow-release formulations.

Diclofenac and ibuprofen accounted for 35% and 31%, respectively, of NSAID use in this population. The risk of hospitalisation due to HF was 1.1 (95% CI 0.8 to 1.5) for current users of diclofenac and 1.4 (95% CI 1.0 to 2.0) for ibuprofen compared with patients who did not use NSAIDs. The highest risk was observed for users of indomethacin (RR 3.4, 95% CI 1.5 to 7.7). The main indication for NSAID use was osteoarthritis, accounting for more than 70% of cases and controls. There were only minor differences in the risk of HF hospitalisation associated with the various indications of NSAID treatment.

Interaction between NSAIDs and co-morbidity

Table 3 shows how a history of HF modified the effect of NSAIDs. The excess RR for patients with both current use of NSAIDs and prior HF was slightly higher than the sum of the excess RR for each of these two factors, suggesting a small departure from the additivity (S = 1.2, 95% CI 0.6 to 2.2).

We also analysed how the effect of NSAIDs was modified by a history of specific risk factors such as diabetes, hypertension or renal failure. As compared with non-users of NSAIDs with none of the above mentioned conditions, the RR of first admission for HF was 1.7 (95% CI 1.3 to 2.1) for non-users of NSAIDs with any of the conditions, 1.4 (95% CI 1.0 to 1.9) for users of NSAIDs with none of the conditions and 1.9 (95% CI 1.4 to 2.6) for NSAID users with any of the conditions.

Although based on only one exposed case, the RR during the first month of treatment with NSAIDs was 9.1 (95% CI 1.0 to 83.3) in patients with prior HF and a history of diabetes, hypertension or renal failure. No dose effect of NSAIDs was found among patients with a history of these specific risk factors, although numbers were small (data not shown). No interaction was observed with a history of either ischaemic heart disease or rheumatoid arthritis (data not shown).

Concomitant use of NSAIDs and other drugs

We analysed concomitant use of NSAIDs and hypertension drugs (table 4) and estimated S = 1.7 (95% CI 1.0 to 2.9).

Table 2 Relative risk (RR) of hospitalisation for heart failure (HF) associated with non-steroidal anti-inflammatory drug (NSAID) use

Risk factor	Cases (n = 1396)	Controls (n = 5000)	RR*	95% CI
NSAID use				
Non-use	487	2014	1	
Current (0–30 days)	196	524	1.32	1.06 to 1.64
Single use	190	506	1.34	1.08 to 1.68
Multiple use	2	7	0.37	0.06 to 2.27
Switch	4	11	1.15	0.33 to 3.98
Intermediate (31–90 days)	52	188	0.87	0.61 to 1.25
Recent (91–365 days)	131	470	0.90	0.70 to 1.16
Past (≥365 days)	530	1804	0.96	0.82 to 1.13
NSAID duration†				
Non-use	487	2014	1	
1–30 days	49	105	1.64	1.11 to 2.43
31–365 days	54	173	0.98	0.68 to 1.42
365–730 days	28	62	1.59	0.94 to 2.69
≥730 days	65	184	1.37	0.98 to 1.92
NSAID dose†				
Non-use	487	2014	1	
Low–medium	101	288	1.27	0.96 to 1.68
High	89	218	1.44	1.06 to 1.94
NSAID half life†				
Non-use	487	2014	1	
<12 h	116	305	1.29	0.99 to 1.69
≥12 h	39	99	1.44	0.94 to 2.22
Slow release	35	102	1.44	0.93 to 2.22
NSAID indication‡				
Non-use	487	2014	1	
Rheumatoid arthritis	12	20	1.73	0.79 to 3.80
Osteoarthritis	144	386	1.33	1.04 to 1.71
Other pain	104	31	1.13	0.71 to 1.78
Vascular pain	4	4	2.05	0.48 to 8.82
Unknown	10	5	1.36	0.39 to 4.80
NSAID individual use†§				
Non-use	487	2014	1	
Indomethacin	13	16	3.39	1.50 to 7.67
Naproxen	19	38	2.01	1.08 to 3.74
Diclofenac	60	183	1.08	0.76 to 1.52
Ibuprofen	60	159	1.43	1.01 to 2.02
Meloxicam	6	23	0.66	0.24 to 1.83
Ketoprofen	6	18	1.19	0.43 to 3.35
Piroxicam	8	25	1.38	0.58 to 3.28
Other NSAIDs¶	18	44	1.42	0.76 to 2.68

*Frequency matched on age, sex and calendar year and adjusted for sex, age, calendar year, body mass index, smoking, alcohol, aspirin, steroids, acetaminophen, anticoagulants, diabetes, coronary heart disease, chronic obstructive pulmonary disease, asthma, valvular diseases, rhythm disorders, renal failure, hypertension and hospitalisations in the previous year.
†Among current users *v* non-users of NSAIDs. The effect of daily dose, half life and individual drugs was analysed among current users of a single NSAID.
‡In 10 controls and in five cases the indication was unknown.
§Only if there were five or more exposed cases and controls; otherwise categorised as ''other NSAIDs''.
¶Other NSAIDs were aceclofenac, acemetacin, azapropazone, etodolac, fenbufen, fenoprofen, flurbiprofen, mefenamic acid, nabumetone, tenoxicam, tiaprofenic acid and sulindac.

When we studied different classes of hypertension drugs, only concomitant use of NSAIDs and diuretics (RR 5.8, 95% CI 4.1 to 8.4) increased the risk of HF beyond the additivity of NSAIDs (RR 1.2, 95% CI 0.8 to 1.8) and diuretic effects (RR 3.7, 95% CI 2.9 to 4.9), suggesting a small interaction (S = 1.6, 95% CI 1.1 to 2.4). When we restricted the analysis to patients on long term treatment with hypertension drugs, patients starting treatment with NSAIDs (in the first month of use) had an increased risk of having a first hospitalisation for HF (RR 2.4, 95% CI 1.4 to 4.0), and this was true for all classes of hypertension drugs with the exception of calcium channel blocker (data not shown). This increased risk was not observed during the first month of starting NSAIDs together with hypertension drugs.

DISCUSSION

In this study, we found that users of NSAIDs had an overall 30% increased risk of having a first hospital admission for HF in the general population. The risk was slightly higher at the beginning of treatment, especially among patients with pre-existing HF, consistent with the results of previous studies.[7 11] The results are compatible with a minor effect of dose and plasma half life. In two studies, no dose–response relationship was observed[7 11] but a dose effect was observed in patients with prior heart disease in another study.[8] Overall, our results are compatible with results from published epidemiological studies[7–11] indicating that NSAIDs exacerbate symptoms of HF leading to hospitalisation among susceptible patients, such as those with a history of cardiovascular disease, in particular previous HF, but also that NSAIDS trigger the risk of HF hospitalisation in patients without a history of clinical HF.

The risk of hospital admission for HF associated with the use of individual NSAIDs ranged from 1.1 for diclofenac to 3.4 for indomethacin relative to non-use. Of note, indomethacin also had the highest RR in one prior study,[11] as well as in other previous studies analysing the risk of development of acute renal failure.[25]

The risk of HF hospitalisation was associated with known aetiological risk factors consistent with prior investigations.[26–28]

Table 3 Effect of non-steroidal anti-inflammatory drug (NSAID) use among patients with prior heart failure (HF)

NSAID use	History of HF	Cases (n = 1396)	Controls (n = 5000)	Adjusted RR* (95% CI)
No†	No	307	1927	1
Current use	No	121	493	1.28 (0.99 to 1.66)
No	Yes	180	87	7.18 (5.25 to 9.82)
Current use	Yes	75	31	8.60 (5.34 to 13.84)

*Frequency matched on age, sex and calendar year and adjusted for sex, age, calendar year, body mass index, smoking, alcohol, aspirin, steroids, acetaminophen, anticoagulants, diabetes, coronary heart disease, chronic obstructive pulmonary disease, asthma, valvular diseases, rhythm disorders, renal failure, hypertension and hospitalisations in the previous year.
†Includes only non-use (the remaining 713 cases and 2462 controls who were recent and past users of NSAIDs are not included).
RR, relative risk.

Table 4 Effect of concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) and hypertension drugs among current users compared with non-users of either drug

NSAID use	Hypertension drug use	Cases (n = 1396)	Controls (n = 5000)	Adjusted RR* (95% CI)
No†	No	89	1013	1
Current use	No	22	190	1.06 (0.63 to 1.78)
No	Yes	332	764	2.53 (1.90 to 3.35)
Current use	Yes	162	263	3.76 (2.70 to 5.24)

*Matched on age, sex and calendar year and adjusted for sex, age, calendar year, body mass index, smoking, alcohol, aspirin, steroids, acetaminophen, anticoagulants, diabetes, coronary heart disease, chronic obstructive pulmonary disease, asthma, valvular diseases, rhythm disorders, renal failure, hypertension and hospitalisations in the previous year.
†Includes only non-use (the remaining 791 cases and 2770 controls who were recent and past users of NSAIDs or hypertension drugs, or both, are not included).
RR, relative risk.

History of HF, hypertension, diabetes, renal failure, valvular heart disease, atrial fibrillation, anaemia and coronary heart disease were all independently associated with the likelihood of having a first hospital admission for HF. In addition, obesity, smoking and alcohol increased the risk. Recent hospitalisations and consultant visits, both markers of greater co-morbidity, were also independently associated with the risk of HF hospitalisation.

Most of the effects of NSAIDs have been related to their inhibition of cyclo-oxygenase-derived prostaglandins (prostacyclin and thromboxane A_2) with a role in cardiovascular homeostasis, and particularly in renal function.[29 30] Under normal conditions, prostaglandins do not have a major role in the maintenance of renal circulation; however, in the presence of a decreased effective circulating volume, such as in HF or renal insufficiency, prostaglandin synthesis is enhanced to preserve renal perfusion.[29 30]

Our results suggest an immediate worsening effect of NSAIDs in the presence of long-term use of selected cardiovascular drugs. In particular, patients treated with diuretics, ACE inhibitors and β blockers had a greater risk of having a first hospital admission for HF decompensation at the beginning of NSAID use. An interaction between concomitant use of NSAIDs and diuretics has already been suggested in one study.[7] These observations are consistent with a known pharmacodynamic effect of NSAIDs—that is, antagonising the effect of diuretics; NSAIDs, through their inhibition of prostaglandin synthesis, can cause sodium and water retention and blunt the response to diuretics.[30–32] Some authors have found that patients taking NSAIDs and ACE inhibitors are at a greater risk of hyperkalaemia and acute renal deterioration[32 33]; however, we did not find a clear interaction in our study.

Our study has several limitations. Firstly, although information bias on drug use is minimised, as the information was obtained directly from computerised prescription information written before the occurrence of the outcome of interest, over-the-counter drugs are not captured in the database. However, only ibuprofen could be purchased over the counter in the United Kingdom. In addition, misclassification of exposure collected prospectively is usually close to non-differential between cases and controls. This would lead to some minor underestimation of the excess risk under most circumstances. The relatively small impact of missing this information has been previously reported.[11 34 35] Secondly, after our complete case validation process, we were not able to review the original medical notes of 20% of patients to confirm their case status. This misclassification of cases is likely to be non-differential with respect to exposure. We evaluated the impact of this level of misclassification, measured as the percentage change between the reported estimate of RR and the ''true'' corrected estimate of RR. The effect of our misclassification bias would have been an underestimation of the RR by 11%, the true crude RR being 1.7 instead of the 1.5 observed. Thirdly, we assessed the potential confounding by indication among current users of NSAIDs. We did not find clear differences between NSAID indication and the RR of HF admission, suggesting that the observed association was not due to use of an NSAID prescribed to treat early symptoms of HF. Actually, NSAIDs are contraindicated in patients at high risk of HF, and therefore this could have somewhat underestimated the true magnitude of the association between NSAIDs and HF. Lastly, we did not include 30-day fatal cases in this study. The case fatality rate for HF hospitalisation is about 10%.[18] However, a previous study found no indication of a differential effect of NSAIDs between fatal and non-fatal HF[11] (L A García Rodríguez, personal communication, 2004).

The incidence rate of a first hospital admission for HF in our study was 2.7/1000 person years. Assuming that the estimated association with NSAIDS is causal (RR 1.32) and given that 11% of the control population were current users of NSAIDs, the estimated incidence rates of a first hospitalisation for HF/1000 person years were 2.6 and 3.4 among non-users and users of NSAIDs, respectively. This suggests that one extra case of first hospital admission for HF for every 1000 NSAID users aged 60–84 years annually would be attributable to NSAID use. This excess number of first hospital admissions for HF attributed to NSAID use may be even greater in subgroups of high-risk patients. Among patients 70 years and older with hypertension, diabetes or renal failure up to three excess cases were attributed to NSAID use.

HF is a common cause of morbidity and mortality in the elderly and even a small increase in the risk can translate into a significant disease burden in the general population. Therefore, NSAIDs should be used with caution by patients at high risk of hospital admission due to HF such as those with prior clinical HF, diabetes, renal failure or treatment with hypertension drugs.

ACKNOWLEDGEMENTS

We thank the general practitioners for their excellent collaboration and the Boston Collaborative Drug Surveillance Program for providing access to the General Practice Research Database.

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This study was supported by a research grant from Pfizer.

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