Selective COX-2 inhibitors, NSAIDs and congestive heart failure: differences between new and recurrent cases

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Pharmaco-epidemiological studies have shown that in susceptible individuals, nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase (COX)-2 inhibitors increase the risk of developing congestive heart failure (CHF).
- Recently published studies have found lower relative risk (RR) estimates than the initial studies published in 1998–2000.
- It is unclear whether the level of risk is elevated equally in first time and recurrent cases of CHF.

WHAT THIS STUDY ADDS

- This study found low-level, statistically nonsignificant elevations of risk with NSAIDs and COX-2 inhibitors.
- There was a much higher level of recent use of NSAIDs/COX-2 inhibitors among first-time cases than among recurrent cases of CHF.
- The dilution of the RR over successive studies, and the differences between first-time and recurrent cases noted here, suggest that prescribing doctors have heeded advice about the cardiovascular risks of NSAIDs and extended this practice to selective COX-2 inhibitors.

AIMS

To quantify the association between treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase (COX)-2 inhibitors and hospitalization due to congestive heart failure (CHF); to determine if the risk varies between first and subsequent episodes of CHF.

METHODS

We conducted a case–control study of the relationship between recent use of NSAIDs and COX-2 inhibitors and hospitalization with CHF. Cases ($n = 530$) were patients admitted to hospital with a primary diagnosis of CHF. Controls ($n = 1054$) were subjects without CHF who were admitted to the same hospitals as the cases. They were frequency matched to cases on the basis of age and sex. Structured interviews were used to obtain information on a number of study factors, including recent use of NSAIDs and COX-2 inhibitors. Relative risks (RRs) were estimated from exposure odds ratios, adjusted for a range of potential confounders.

RESULTS

Overall, NSAIDs and COX-2 inhibitors had been taken by 249 (23.6%) controls in the week before admission to hospital. Use of any NSAID/COX-2 inhibitor was recorded in 81/285 (28.4%) first-time cases compared with 38/245 (15.5%) in recurrent cases: difference 12.9% (95% confidence interval 5.9, 19.8) ($P = 0.0004$). The adjusted RRs for first hospital admission for CHF with different drug exposures were: NSAIDs 1.1 (0.67, 1.83), rofecoxib 1.29 (0.78, 2.13) and celecoxib 1.47 (0.85, 2.53).

CONCLUSIONS

We found weak and statistically nonsignificant associations between use of NSAIDs and COX-2 inhibitors and hospitalization with CHF. This low RR is consistent with the results of recently published studies, but not with early studies that found an approximate doubling of risk with use of NSAIDs. The dilution of risk and the significantly lower levels of prescribing for recurrent than for first-time cases of heart failure suggest that prescribing doctors heeded messages that NSAIDs may precipitate CHF in vulnerable individuals, and that they have applied the same message to selective COX-2 inhibitors.

Introduction

Congestive heart failure (CHF) is chronic, increasingly prevalent in Western populations and causes substantial morbidity and mortality [1]. The syndrome most commonly occurs against a background of ischaemic myocardial injury and left ventricular systolic dysfunction. A number of drug classes can worsen CHF, either by direct myocardial damage, through salt and water retention by the kidney, or increased peripheral systemic vascular resistance [2, 3]. Nonsteroidal anti-inflammatory drugs (NSAIDs) mainly precipitate heart failure by the latter mechanisms, and it may be significant that there is an increase in cyclooxygenase (COX)-2 expression in the venous endothelium and the myocardium of individuals with decompensated heart failure [4, 5]. NSAIDs have been shown repeatedly to precipitate CHF, particularly in individuals with prior cardiac injury [6–14]. This adverse effect is important for several reasons. Although the estimated relative risk of CHF with NSAIDs from several studies is modest (lying between 1.1 and 2.2), the drugs are widely used, so the resulting disease burden could be high [7]. In addition, episodes of left ventricular dysfunction, even if unaccompanied by direct myocardial injury, may not be completely reversible, and patients can be left with incremental deficits [15]. A large follow-up study of elderly Scottish patients has found that after the first episode of hospitalization with CHF the case fatality rate at 1 year was >40% [16].

In 2000 we published the results of a case–control study in which we found nonselective NSAID use was associated with an approximate doubling of the risk of hospitalization for CHF [7], supporting the findings of an earlier controlled pharmaco-epidemiological study [6] Since then at least seven further studies have been published, confirming the adverse effects of NSAIDs [8–14]. Three of these suggested that selective inhibitors of COX-2 are as likely as nonselective NSAIDs to precipitate CHF [11–13]. This manuscript describes a case–control study performed after the introduction and widespread uptake of COX-2 selective NSAIDs in Australia in 2000/2001. In contrast to the recent studies, which relied on electronic pharmacy billing records, we measured actual consumption of drugs prior to onset of the index episode of CHF. In analysing these data we were particularly interested in whether rofecoxib and celecoxib increase the risk of CHF to the same extent. Three studies have suggested, unexpectedly, that the latter drug is free of this effect [11–13]. We also wished to resolve continuing uncertainty over whether risk is increased both for initial and recurrent episodes of hospitalization with CHF. Although in our previous study we found a higher relative risk of NSAID-induced CHF in those who had not previously suffered from this condition, compared with those who had, this was not confirmed in the study by Mamdani *et al.* [11]. In addition, Feenstra *et al.* found a greater risk of NSAID-induced decompensation in subjects with prevalent heart failure [9].

Methods

Commencing in 2002, we undertook a hospital-based case–control study to investigate the relationship between recent use of selective COX-2 inhibitors and NSAIDs and admission to hospital with a principal diagnosis of CHF. The study methods we used have been described previously [7]. We wished to quantify risk with the class and with individual drugs and to determine whether there were differences in exposure to drugs between cases presenting with a first episode of CHF and those hospitalized with recurrent CHF. If doctors were aware of the risk of precipitating CHF, they might avoid prescribing NSAIDs to 'at risk' subjects. This was a possibility here, because the study commenced 3 years after the first published controlled study of this adverse effect [6]. However, as the drugs had only recently been made available on the Australian national formulary equivalent, the Pharmaceutical Benefits Schedule, we thought that prescribing doctors might be uncertain of the effects of COX-2 inhibitors, which initially were widely portrayed as being 'safer' than the older nonselective drugs.

The study was based at two hospitals in Newcastle, New South Wales, Australia, between them providing most of the acute care for a population of >400 000 people. The study was approved by the research ethics committees of the University of Newcastle and the Hunter Area Health Service. Potential cases were consecutive patients admitted with a primary diagnosis of CHF. Patients admitted for other reasons, who were found incidentally to have CHF, were excluded. Potential cases were identified through scrutiny of daily admission records to the medical wards and coronary care units, attendance at morning report, and enquiries of medical and cardiology ward clinical staff. Eligible cases were those where both the admitting medical officer and the physician responsible for the patient were in agreement that the primary diagnosis was CHF based on clinical and radiological features. Investigations of ventricular function were not undertaken routinely, but when they were available account was taken of such findings to support the diagnosis. A research nurse visited each case, obtained written consent to participate, documented the clinical information in the medical records and assessed the participant's New York Heart Association (NYHA) functional grade.

We attempted to match two controls to each case. Controls were subjects admitted as emergencies to the same hospitals as the cases, but who had no clinical or radiological evidence of CHF. Controls were selected by 'frequency matching' and were recruited contemporaneously with cases to allow for rapid changes in prescribing of the study drugs. Potential controls were excluded if they had a past history of hospital admission with CHF (but not if they had a history of heart disease without CHF). Subjects who had primary admission diagnoses known to be complications of, or indications for, anti-inflammatory drugs, e.g. upper

gastrointestinal bleeding or ulceration, or a rheumatological disorder, were also excluded. Patients admitted for other reasons, but who also suffered from rheumatic diseases, or who had a history of conditions that are known complications of NSAID therapy, were not excluded; this rule also applied to the cases. These methods were based on those used successfully in prior case–control studies of complications of NSAID therapy [7, 17–19].

Information gathering

The index day for cases and controls was the day of admission to hospital. Research nurses used a structured protocol to interview both cases and controls. Information collected included demographic information, medical history, smoking history, alcohol intake, and medicines use, both prescribed and over-the-counter. Ingestion of analgesics was explored through a series of open questions asking about medicines used for painful conditions. These were followed by more direct questions and presentation of 'flash' cards, listing in large type the proprietary and trade names of all relevant products on the Australian market. Each question could be repeated once for clarification. Details of all analgesics ingested within the week and month prior to admission were recorded. Additional clinical and investigation data to corroborate the admission diagnosis and past medical history were collected from the medical records using a standardized data extraction form.

All interviews were conducted within 1 week of admission, the majority within the first 3 days. The interviewers knew whether a subject was a case or control, but understood the importance of adhering strictly to the wording of the protocol. Both case and control subjects understood that we were interested in medicines consumption, particularly medicines for pain, but subjects were unaware of the hypothesis in respect of anti-inflammatory drugs and CHF. Where information on prescribed drug use obtained by interview was unclear, subjects' general practitioners were contacted to confirm the details.

Statistical analysis

In the analyses, it was assumed that the exposure odds ratio is an accurate estimate of the relative risk. The principal analyses involved estimation of the relative risks of admission with CHF in users of selective COX-2 inhibitors or NSAIDs, with non-use of anti-inflammatory drugs as the reference. Univariate logistic regression was used to calculate the ratio of the odds of CHF with and without each of a series of demographic, disease and drug-exposure characteristics. Variables with odds ratios significantly different from one, and clinical variables considered *a priori* to be potential confounders, were included in a multiple logistic regression model. A backward stepwise regression technique was used to generate a parsimonious model that retained age, gender and consumption of selective COX-2 inhibitors and conventional NSAIDs in the week and month before the index day. Variable exclusion was set at a P-value of 0.1. Analyses were repeated with doses of the relevant drugs stratified around the median amount ingested in the previous week by the control subjects. Where appropriate, differences in proportions were analysed by means of the χ^2 test with Yates correction. All analyses were performed with SAS software (SAS Inc., Cary, NC, USA).

With an expected prevalence of anti-inflammatory drug use in the control group of 20% (based on previous studies and market share of COX-2 inhibitors when the study commenced), a sample size of 500, with a ratio of two controls to each case, had 80% power (α 0.05) to detect as significant an exposure odds ratio as low as 1.5. Assuming that around 10% of controls would use COX-2 inhibitors, it was calculated that the study, as planned, would have 80% power (α 0.05) to detect an exposure odds ratio as low as 1.6 with this class of drug. From experience of an earlier study [7], we anticipated that approximately 40% of cases were likely to be first-time admissions with heart failure. In that study, it was found that a prior history of heart disease was strongly associated with a first admission for CHF in users of nonselective NSAIDs. In the current study, we explored this effect with NSAIDs and selective COX-2 inhibitors separately, recognizing that a study confined to first-time cases of CHF would not be capable of detecting an exposure odds ratio much below 2.0.

Results

Between August 2002 and June 2005, 530 cases with CHF and 1054 controls were recruited. Two hundred and eighty-five (53.8%) were first-ever admissions with CHF and 245 participants had been admitted before with this diagnosis (recurrent cases). Their demographic and medical details are presented in Table 1.

Comparison of first-time and recurrent cases of CHF

Recurrent cases were somewhat less likely than first-time cases to present with left heart failure and more likely to present with features of right heart failure (χ^2 7.2; $P = 0.028$). Over 80% of cases in each CHF group were in NYHA functional grades III and IV (short of breath on minimal exertion or at rest). Rates of smoking were generally low, particularly in recurrent cases. Recurrent cases had greater levels of use of antifailure treatments than first-time cases, in particular ACE inhibitors, loop diuretics, digoxin and spironolactone (Table 2). They were also more likely to be users of warfarin. Use of statins by recurrent cases was surprisingly low. There were marked differences between first-time and recurrent cases in their use of some anti-inflammatory drugs. Use of any NSAID was almost twice as high in first-time as in recurrent cases. The differences between first-time and recurrent cases were most

Table 1

Characteristics of cases and controls

Patient characteristics	Cases first admission $n = 285$ (%)	Cases recurrent admission $n = 245$ (%)	Controls $n = 1054$ (%)
Median age (Q1–Q3)	78.2 (70.9–84.0)	80.1 (73.4–86.0)	78.3 (71.0–83.8)
Male	139 (48.8)	115 (46.9)	489 (46.4)
Features of heart failure on admission			
CHF	119 (41.7)	106 (43.3)	
LVF/acute pulmonary oedema	79 (27.7)	39 (15.9)	
RVF	9 (3.2)	20 (8.2)	
APO	78 (27.4)	80 (32.6)	
NYHA grading			
I Not SOB – usual activities	6 (2.1)	3 (1.2)	
II SOB on moderate exertion	48 (16.8)	30 (12.2)	
III SOB on minimal exertion	154 (54.0)	128 (52.2)	
IV SOB at rest	77 (27.0)	84 (34.3)	
Current smoker	30 (10.5)	18 (7.3)	107 (10.2)
Alcohol consumption	94 (33.0)	69 (28.2)	309/1053 (29.3)
Medical history			
Hypertension	209 (73.3)	196 (80.0)	651/1053 (61.8)
Cardiac disease*	180 (63.2)	223 (91.0)	486 (46.1)
Vascular disease†	106 (37.2)	112 (45.7)	368 (34.9)
CAL	53 (18.6)	65 (26.5)	269/1053 (25.5)
Diabetes mellitus	97 (34.0)	75 (30.6)	201 (19.1)
Past peptic ulcer disease	52 (18.2)	49 (20.0)	260 (17.0)
Osteoarthritis	104 (36.5)	69 (28.2)	335/1053 (31.8)
Rheumatoid arthritis and/or ankylosing spondylitis	13 (4.6)	11 (4.5)	59/1053 (5.6)
Gout	79 (27.7)	81 (33.1)	278 (26.4)

*Angina, heart attack, enlarged/dilated heart, valvular disease. †Stroke, cerebral (transient) ischaemic attack, arteriosclerosis, claudication. APO, acute pulmonary oedema; CAL, chronic airways limitation; CHF, congestive heart failure; LVF, left ventricular failure, RVF, right ventricular failure; SOB, short of breath.

marked for celecoxib and rofecoxib (Table 3). These differences were not seen for paracetamol usage. Because of the marked differences between first and recurrent cases in their use of anti-inflammatory drugs, further analyses of the role of these drugs as precipitants of CHF were confined to first-time cases and controls.

Comparison of all cases and controls

Recurrent cases were, on average, 2 years older than first-time cases and controls, and there was a small excess of men in the cases. These residual differences were adjusted for in subsequent multivariate analyses. As expected, cases were more likely than controls to have a history of cardiac disease, hypertension and diabetes. Musculoskeletal disorders, which are the main indications for the drugs of interest, were commonly reported by participants. Around one-third of cases and controls reported a diagnosis of osteoarthritis, and between one-quarter and one-third reported at least one episode of gout. There were no clear differences in the prevalence of these disorders between cases and controls. Unsurprisingly, both groups of cases were more likely than controls to have been using cardiovascular drugs. Use of β-blockers was greater amongst cases than controls, but was lower than use of ACE inhibitors, and in subjects with recurrent heart failure was about

equal to their use of digoxin. Use of angiotensin 2 receptor blocking agents was lower than use of ACE inhibitors and was no greater amongst cases than controls.

Use of selective COX-2 inhibitors and NSAIDs and the risk of CHF

Use of anti-inflammatory drugs by controls in the week prior to the index day was 23.6% (Table 3). Rofecoxib and celecoxib accounted for more than half of this. Of the other NSAIDs, ibuprofen was the most widely used. Overall, use of any NSAID was only slightly higher among first-time cases than controls. Univariate analyses of these differences were not statistically significant (Table 3). We evaluated ingested doses of COX-2 inhibitors in first-time cases and controls who were confident about these details (Table 4). There was no indication that individuals who developed their first episode of CHF had ingested higher doses than control subjects.

Multivariate analyses of risk: first-time cases

Factors that were statistically associated with the development of a first episode of heart failure in the final multivariate model were hypertension, diabetes, a history of heart disease and current use of alcohol. Use of calcium antagonists and drugs for respiratory disorders were negatively

Table 2

Medication use prior to hospitalization

	Cases first admission	Cases recurrent admission	Controls
Cardiovascular drugs			
Digoxin	49 (17.2)	104 (42.4)	144 (13.7)
Loop diuretics	106 (37.2)	180 (73.5)	235 (22.3)
Spironoloactone	13 (4.6)	66 (26.9)	46 (4.4)
ACE inhibitors	113 (39.6)	141 (57.5)	311 (29.5)
Angiotensin II antagonists	53 (18.6)	51 (20.8)	201 (19.1)
Beta adrenoceptor blocking agents	94 (33.0)	99 (40.4)	255 (24.2)
Nitrates	69 (24.2)	98 (40.0)	191 (18.1)
Vasodilators	19 (6.7)	24 (9.8)	46 (4.4)
Thiazide diuretics	37 (13.0)	19 (7.8)	138 (13.1)
Anti-arrhythmics	15 (5.3)	33 (13.5)	22 (2.1)
Alpha adrenoceptor blocking agents	21 (7.4)	15 (6.1)	42 (4.0)
Calcium channel blockers	54 (18.9)	46 (18.8)	226 (21.4)
Aspirin	132 (46.3)	125 (51.0)	455 (43.2)
Antiplatelet drugs excl. aspirin	17 (6.0)	18 (7.3)	89 (8.4)
Statins	94 (34.0)	63 (25.7)	275 (26.1)
Warfarin	41 (14.4)	58 (23.7)	83 (7.9)
Other drugs			
Ulcer-healing drugs	97 (34.0)	106 (43.3)	408 (38.7)
Antidiabetic drugs	70 (24.6)	58 (23.7)	150 (14.2)
Respiratory drugs	113 (39.6)	102 (41.6)	593 (56.3)
CNS drugs	90 (31.6)	78 (31.8)	431 (40.9)

CNS, central nervous system; Statins, HMG CoA reductase inhibitors.

Table 3

Use of anti-inflammatory drugs by cases and controls

Patient characteristics	Cases first admission $n = 285$ (%)	Cases recurrent admissions $n = 245$ (%)	Controls $n = 1054$ (%)
Any anti-inflammatory drug	81 (28.4)	38 (15.5)	249 (23.6)
Selective COX-2 inhibitors*	53 (18.6)	20 (8.2)	160 (15.2)
Other NSAIDs	28 (9.8)	18 (7.3)	89 (8.4)
Celecoxib	25 (8.8)	7 (2.9)	73 (6.9)
Rofecoxib	26 (9.1)	11 (4.5)	79 (7.5)
Naproxen	6 (2.1)	4 (1.6)	26 (2.5)
Diclofenac	5 (1.7)	6 (2.4)	22 (2.1)
Ibuprofen	9 (3.2)	8 (3.3)	33 (3.1)
Meloxicam	2 (0.7)	2 (0.8)	14 (1.3)
Paracetamol	182 (63.9)	160 (65.3)	707 (67.1)
Glucocorticoids	25 (8.8)	17 (6.9)	131 (12.4)

*Celecoxib, rofecoxib, meloxicam.

associated with the development of CHF, and use of loop diuretics had a positive association (assumed to be confounding by indication). After adjustment for these variables there were low-level, statistically nonsignificant, positive associations between use of NSAIDs and COX-2 inhibitors (in the past week) and the development of a first episode of CHF requiring hospitalization (Table 5). Results were no different when use of the drugs in the previous month was analysed (data not displayed). We carried out further multivariate analyses of first-time cases where

ingested doses of celecoxib and rofecoxib were modelled as 'high' or 'low' based on whether they were above or below the median amount ingested by controls in the week prior to hospital admission. The odds ratios for high and low doses of either drug were similar: 1.37 (0.88, 2.1) and 1.36 (0.70, 2.7), respectively. In our final calculations, analysis was confined to subjects with a first episode of heart failure who had a previous history of heart disease (defined as previous myocardial infarction, known dilated or enlarged heart or valvular disease). There were 549 sub-

Table 4

Doses of COX-2 inhibitors ingested by first-time cases and controls

Patient characteristics	Case (first admission) n = 285 (%)	Control n = 1054 (%)
Number of participants who could confidently recall dose (week prior to admission)		
Celecoxib	21	61
Rofecoxib	25	72
Total celecoxib dose in the week prior to admission		
≤600	2/21 (9.5)	4/61 (6.6)
601–1400	15/21 (71.4)	51/61 (83.6)
>1400	4/21 (19.0)	6/61 (9.8)
Total rofecoxib dose (mg) in the week before hospital		
≤75	2/25 (8.0)	4/72 (5.5)
76–175	23/25 (92.0)	66/72 (91.7)
>175	–	2/72 (2.8)

Table 5

Results of multivariate analysis: first-time cases of congestive heart failure and controls

Variable	OR	95% CI (OR)	P-value
Age	0.99	(0.98, 1.01)	0.553
Male	0.98	(0.73, 1.31)	0.591
Hypertension	1.60	(1.18, 2.19)	0.003
Diabetes	2.10	(1.51, 2.81)	<0.001
History of cardiac disease	1.77	(1.32, 2.37)	<0.001
Alcohol consumption	1.49	(1.09, 2.04)	0.013
Use of anti-inflammatory drugs			
None	1.00	reference	
Celecoxib	1.47	(0.86, 2.53)	0.160
Rofecoxib	1.29	(0.78, 2.13)	0.317
Other NSAIDs	1.11	(0.67, 1.83)	0.682
Calcium channel blockers	0.64	(0.45, 0.91)	0.013
Loop diuretics	1.87	(1.37, 2.53)	<0.001
Respiratory drugs	0.66	(0.48, 0.90)	0.010

jects in these analyses. The adjusted odds ratios for use of drugs in the last week were: celecoxib 0.98 (0.39, 2.4); rofecoxib 1.5 (0.70, 3.3); and other NSAIDs 1.6 (0.79, 3.1). In these analyses, no dose effects were found when ingested drugs were stratified around the median values ingested by controls in the previous week (diclofenac 350 mg; ibuprofen 1400 mg; indomethacin 200 mg; meloxicam 105 mg; naproxen 3500 mg; piroxicam 140 mg) (data not shown).

Discussion

This study found weak and statistically nonsignificant relationships between ingestion of selective COX-2 inhibitors, or conventional NSAIDs, and first admission to hospital with CHF. These results contrast with those of our earlier study, which found that recent use of NSAIDs doubled the odds of being admitted to hospital with heart failure. However, they are consistent with results from several recently published papers [11–14]. The latter have documented relative risk estimates ranging from 1.3 to 1.6 for rofecoxib and nonselective NSAIDs. Our findings, although not statistically significant, are generally consistent with these studies. This 'ad hoc' case–control study was smaller than the published studies, which used large administrative datasets. As a result, we lacked the power to detect, as statistically significant, these low-level relative risks; however, the results of this and recently published studies raise a new question: have doctors and patients become more aware of the risks of NSAIDs and become more careful in their use? The early studies, conducted in the 1990s, documented relative risks >2.0 (and considerably higher in some subgroups) [6, 7]. If doctors have become more careful in selecting patients for treatment with NSAIDs, this might act as an effect modifier, leading to a lower average relative risk of developing CHF during drug treatment. If true, this would account for the lower risks observed in studies published since 2003, including this one. The contrasting findings reported here from first-time and recurrent cases also provide some support for this. Recent use of NSAIDs by recurrent cases was only half that seen in those admitted for the first time. In fact, the level of use of NSAIDs was lower among recurrent cases than nonheart failure controls. Our control selection procedures did not change from our previous study, so avoidance of drugs in 'at risk' subjects appears to be the most likely explanation.

The comparisons of prior drug use by first-time and recurrent cases also provide some insights into the adequacy of drug therapy provided to patients who have suffered at least one episode of CHF. Our data indicate rather low use of β-blockers (Table 2). Under one-half of recurrent cases had been using these drugs, possibly

because of continuing unease amongst prescribing physicians, who for many years were taught that the drugs could exacerbate heart failure [20]. Use of ACE inhibitors and/or angiotensin receptor antagonists was high in recurrent cases, and in both sets of case patients consumption was higher than recorded in our previous study [7]. Use of spironolactone by recurrent cases was much higher than in our previous study [7]. Doubtless, this reflects increased awareness of the role of spironolactone following the publication of a large randomized controlled trial [21]. In contrast, use of statins was low, particularly in patients with recurrent heart failure. This may reflect a view that once heart failure has developed there is little gain in prescribing statins to try to reduce the risk of future ischaemic cardiac events. However, this conflicts with a growing body of data supporting the use of statins in patients with established heart failure [22, 23]. The studies demonstrating improved survival have been nonrandomized, but among subjects with non-ischaemic congestive heart failure [24], a small randomized trial has shown an improvement in left ventricular systolic function after 14 weeks of treatment.

Limitations of the study

This study has a number of limitations. Researchers were not blind to the case or control status of participants. This is a potential source of information bias if they questioned cases more thoroughly than controls. In practice, it is very difficult to 'blind' case–control studies, so, like most researchers carrying out 'ad hoc' studies like this, we used carefully structured interviews and trained interviewers to administer the questions in an identical fashion to cases and controls. We have used these techniques in several case–control studies and believe that we minimized this source of potential bias [7, 17–19]. Being a chronic condition, CHF is difficult to study using case–control methods. The index day is hard to specify, with symptoms typically escalating over a period of time before being severe enough to need admission to hospital. This escalation window, however, also provides an opportunity for doctors to recognize the early symptoms of failure and to institute remediation that would avert the need for hospitalization, be this cessation of anti-inflammatory drugs or the augmentation of antifailure treatments. In choosing the day of admission as the index day, we may have underestimated exposure among the cases if the drugs of interest were ceased longer than 1 week prior to admission. We do not believe this was a major issue, however, as there were no great differences between exposure within the week and within the month prior to admission. In our view, it is possible that milder episodes of CHF were recognized as being associated with anti-inflammatory treatment, the drugs were ceased, and admission was thus avoided. As noted earlier, this would lead to reduced hospitalization among the NSAID users and a lower estimated relative risk.

We evaluated only recent use of anti-inflammatory drugs, but believe that this was appropriate. In susceptible individuals, these agents contribute to the development of heart failure largely through their effects on prostaglandin-mediated haemodynamics, and symptoms may develop in days rather than weeks following their introduction. Although a prothrombotic effect of selective COX-2 inhibition is now largely accepted [25], we excluded from the study individuals who were admitted with heart failure in association with acute myocardial infarction.

Our control population was composed of hospital inpatients who might not be truly representative of the community population from which the cases were drawn. Hospital controls will have been in poorer health than comparable community dwellers and, as a result, more likely to have been users of anti-inflammatory drugs. In fact, comparison of the use of a range of drugs by the controls in this study suggested that they were 'sicker' than those recruited into case–control studies that we have previously performed, and their consumption of NSAIDs was higher. This probably reflects the ageing population and the pressure on public hospital beds, resulting in only the sickest patients being admitted. This could have biased our results towards the null. We attempted to minimize such an effect by excluding from the control population patients admitted with conditions requiring treatment with anti-inflammatory drugs and patients admitted with conditions that might have been side-effects of these drugs. Previously we have shown similar levels of use of NSAIDs by hospital and community controls, which appeared to be due to the ubiquitous nature of the drugs, their use for minor ailments, and their availability without prescription [17].

Compared with case–control studies undertaken using linked prescribing and hospital admission databases, our study was modest in size. However, by directly interviewing all cases and controls, it had the advantage of having been able to determine ingested doses of the drugs as opposed to assuming ingestion on the basis of prescriptions issued. The study was also able to examine use of over-the-counter NSAIDs, aspirin and paracetamol, and to obtain information on smoking status and alcohol intake, thus increasing the accuracy of the statistical adjustments that were made.

Conclusions

When this study was commenced, there was little definitive information in the literature on the risks of heart failure associated with the use of selective COX-2 inhibitors. Our finding of a weak association between the use of selective COX-2 inhibitors and the development of heart failure, and a marked difference in drug use between first-time and recurrent cases, is consistent with a growing appreciation of the cardiovascular risks of NSAIDs on the part of prescribers. It appears that they assumed that this risk also

applied to selective COX-2 inhibitors, despite the lack of evidence at the time that these drugs were introduced.

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