Differences in outcomes of patients with congestive heart failure prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs: population based study

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Abstract

Objectives To compare the risk of death and recurrent congestive heart failure in elderly patients prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs (NSAIDs) and to determine whether there are class differences between celecoxib and rofecoxib.
Design Population based retrospective cohort study.
Setting Databases of hospital discharge summaries and prescription drug claims in Quebec.
Participants 2256 patients aged 66 or more prescribed celecoxib, rofecoxib, or an NSAID after an index admission for congestive heart failure between April 2000 and March 2002.
Main outcome measures Time to all cause death and recurrent congestive heart failure, combined and separately.
Results The risk of death and recurrent congestive heart failure combined was higher in patients prescribed NSAIDs or rofexocib than in those prescribed celecoxib (hazard ratio 1.26, 95% confidence interval 1.00 to 1.57 and 1.27, 1.09 to 1.49, respectively). The findings were similar when the outcomes were assessed separately. In pairwise analysis, the risks of death and recurrent congestive heart failure, combined and separate, were similar between patients prescribed NSAIDs and rofecoxib.
Conclusions Celecoxib seems safer than rofecoxib and NSAIDs in elderly patients with congestive heart failure. Differences were found among cyclo-oxygenase-2 inhibitors.

Introduction

The cardiovascular effects of non-steroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase-2 inhibitors have been the subject of much controversy. Studies of NSAIDs, in particular naproxen, have shown decreases, increases, or no effects on the risk of ischaemic heart disease.[1–7] Rofecoxib has been consistently associated with an increased risk of myocardial infarction.[5 8–10] It was withdrawn when data from a trial on benign sporadic colonic adenomas showed a significant increase in the incidence of cardiovascular events compared with placebo (relative risk 1.92, 95% confidence interval 1.19 to 3.11).[11] Although most of the evidence to date shows no association between celecoxib and an increased risk of myocardial infarction,[9 12–15] a meta-analysis[8] and a recent study[16] have cast doubt. Whether cyclo-oxygenase-2 inhibitors have similar or different cardiovascular toxicities remains debatable.[17 18]

The role of cyclo-oxygenase-2 inhibition in congestive heart failure is complex. On the one hand, both NSAIDs and cyclo-oxygenase-2 inhibitors have various renovascular side effects, which include increased volume retention, oedema, and blood pressure, all of which can exacerbate heart failure.[19–22] Data, however, suggest that differences exist between the two types of drugs as well as between the cyclo-oxygenase-2 inhibitors themselves, with some,[23–25] but not all,[26] studies showing that rofecoxib is associated with more renovascular side effects, including increased oedema and blood pressure, than are NSAIDs and celecoxib. On the other hand, the cyclo-oxygenase-2 enzyme is induced in the myocardium of the failing heart and is associated with myocardial scarring.[27 28] Selective cyclo-oxygenase-2 inhibitors can therefore be cardioprotective at the level of the failing myocardium.

Clinically, NSAIDs have been associated with the onset and exacerbation of congestive heart failure.[29–31] Clinical information on the association between cyclo-oxygenase-2 inhibitors and heart failure is, however, scarce.[32–35] In a recent population based study, users of rofecoxib and NSAIDs, but not celecoxib, had a higher risk of admission for congestive heart failure than controls not taking NSAIDs.[36]

Elderly patients are likely to be given cyclo-oxygenase-2 inhibitors for the management of pain and inflammation as these drugs are thought to have fewer gastrointestinal side effects than NSAIDs.[37 38] Yet the risk of cardiovascular disease increases with age. It is therefore important to ascertain the cardiovascular effects of cyclo-oxygenase-2 inhibitors in elderly people at both the patient and the population level. We assessed the effects of celecoxib, rofecoxib, and NSAIDs on the risk of death and recurrent congestive heart failure in elderly patients with known congestive heart failure and we determined whether there are class differences between celecoxib and rofecoxib.

Methods

Information for our population based, retrospective, observational cohort study was derived from the database of hospital discharge summaries for Quebec. The reliability of the coding for congestive heart failure in administrative databases has been shown to be high.[39 40] A similar cohort of patients with congestive heart failure has been used in other pharmacoepidemiological studies.[39 41 42]

Patients were eligible for inclusion if they were discharged with a diagnosis of congestive heart failure (code 428.x; international classification of diseases, 9th revision) between 1 April 2000 and 31 March 2002 (the index admission), they had been prescribed celecoxib, rofecoxib, or a NSAID during that time, and they were aged 66 or more at the time of discharge from the

index admission. Celecoxib became available on the market in late 1999 and rofecoxib on 1 April 2000. We chose the starting date of 1 April 2000 to ensure that both drugs were available throughout the study. Patients were excluded if they were admitted to hospital for congestive heart failure in the preceding three years. The age cut-off point was determined on the basis of the availability of prescription records, to ensure that all participants had at least one full year of observation in the database before entry into the study.

Exposure to drugs

We used the Quebec database for prescription drugs claims to determine exposure to drugs. This database contains information on all drug prescriptions for outpatients aged 65 or more. It has been validated for the accuracy of prescription claims.[43] It also contains information on vital status.[44]

The study groups consisted of patients exclusively given one or more prescriptions for celecoxib, rofecoxib, or any non-selective NSAID after the index admission. Other cyclo-oxygenase-2 inhibitors were not available in Quebec during the study. The NSAIDs of interest were those included on the provincial drug formulary. Patients in the NSAID group could have been dispensed more than one different non-selective NSAID during the study.

Study outcomes and follow-up

The primary outcome was the combined outcome of time to all cause death or time to recurrent congestive heart failure. The secondary outcomes were time to all cause death and time to recurrent congestive heart failure assessed separately. We included episodes of congestive heart failure treated in the emergency room or that required admission. A patient treated in the emergency room and then admitted for the same episode of congestive heart failure was counted only once.

Patients were followed from the time of their first prescription to one of the following censorship times: death, recurrent congestive heart failure, or end of the study (31 December 2002).

Statistical analysis

We generated descriptive statistics to compare patient characteristics according to exposure groups. To compare time to outcome according to group we carried out Cox proportional hazards modelling. We adjusted the models for several possible confounders, including age, sex, comorbidities (diabetes mellitus, cerebrovascular disease, acute and chronic renal failure, cardiac arrhythmias, hypertension, malignancy, and chronic obstructive pulmonary disease), other drugs prescribed before the first prescription for a cyclo-oxygenase-2 inhibitor or a NSAID (β blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, statins, diuretics, digoxin, aspirin, clopidogrel, and warfarin), characteristics of the treating doctor or hospital (cardiologist, internist or other specialist, general practitioner, volume of admissions for congestive heart failure, availability of a catheterisation laboratory), length of stay, year of exposure, acute myocardial infarction in the previous three years, time to first prescription, and episodes of congestive heart failure after the index admission but before the first prescription. All analyses were carried out using SAS version 8.2.

Results

We identified 2256 patients admitted with a diagnosis of congestive heart failure between 1 April 2000 and 31 March 2002 (the index admission) who were given one or more prescriptions for a cyclo-oxygenase-2 inhibitor or NSAID during that time. Of these, 717 (31.8%) received celecoxib, 869 (38.5%) received rofecoxib, and 280 (12.4%) received NSAIDs. Patient characteristics at the index date and prescribing patterns were well balanced between the groups (tables 1 and 2). Overall, 492 patients had recurrent congestive heart failure and 473 died (table 3).

The most commonly used NSAIDs were diclofenac (4.3%), naproxen (2.6%), indomethacin (1.8%), and ibuprofen (1.0%). Other less commonly used NSAIDs included ketoprofen, sulindac, piroxicam, flurbiprofen, tiaprofenic acid, nabumetone, salsalate, and etodolac.

Significantly more patients prescribed celecoxib survived or remained free of recurrent congestive heart failure than those prescribed rofecoxib or NSAIDs (fig 1). The point of divergence occurred early and persisted over time. The difference in survival was persistently significant when assessed as a single end point (fig 2), and the trend was towards those prescribed celecoxib remaining free of recurrent congestive heart failure compared with those prescribed rofecoxib or NSAIDs (fig 3).

In adjusted analysis, we found a significantly higher risk of death or recurrent congestive heart failure in patients prescribed NSAIDs or rofecoxib than in those prescribed celecoxib (hazard ratio 1.26, 95% confidence interval 1.00 to 1.57 and 1.27, 1.09 to 1.49, respectively; fig 4). These increased risks persisted when death was assessed as a separate outcome (NSAIDs, 1.54, 1.17 to 2.04; rofecoxib, 1.44, 1.17 to 1.78). When recurrent congestive heart failure was assessed separately, the trend was towards an

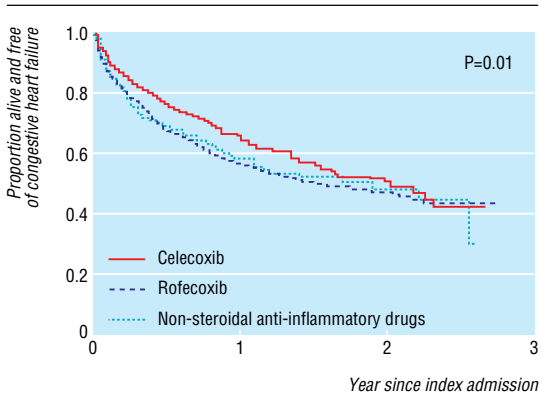

Fig 1 Kaplan-Meier analysis of time to recurrent congestive heart failure or death in patients prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs

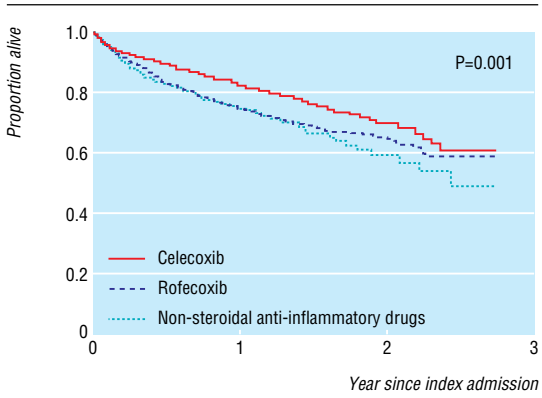

Fig 2 Kaplan-Meier analysis of time to death in patients prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs

Table 1 Baseline characteristics of patients with congestive heart failure prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs (NSAIDs). Values are numbers (percentages) unless stated otherwise

Characteristics	Celecoxib (n=717)	Rofecoxib (n=869)	NSAIDs (n=280)	P value*
Median age (years)	79	78	75.5	0.0017
Men	285 (39.7)	359 (41.3)	156 (55.7)	0.0001
Median length of stay (days)	7	7	7	
Comorbidities:				
Diabetes	254 (35.4)	290 (33.4)	108 (38.6)	
Cerebrovascular disease	62 (8.6)	64 (7.4)	22 (7.9)	
Acute renal failue	65 (9.1)	85 (9.8)	22 (7.9)	
Chronic renal failure	156 (21.8)	194 (22.3)	68 (24.3)	
Cardiac arrhythmia	281 (39.2)	335 (38.6)	104 (37.1)	
Hypertension	320 (44.6)	369 (42.5)	118 (42.1)	
Chronic obstructive pulmonary disease	259 (36.1)	311 (35.8)	99 (35.4)	
Malignancy	38 (5.3)	54 (6.2)	17 (6.1)	
Other cardiac drugs before first prescription of study drug:				
β blockers	325 (45.3)	401 (46.1)	146 (52.1)	
Angiotensin converting enzyme inhibitors	480 (67.0)	554 (63.8)	207 (73.9)	0.03
Calcium channel blockers	276 (38.5)	338 (38.9)	117 (41.8)	
Statins	216 (30.1)	252 (29.0)	102 (36.4)	
Diuretics	655 (91.4)	790 (91.0)	254 (90.7)	
Digoxin	236 (33.0)	287 (33.0)	111 (39.6)	0.045
Aspirin	392 (54.7)	446 (51.3)	168 (60.0)	
Clopidogrel	46 (6.4)	58 (6.7)	22 (7.9)	
Warfarin	198 (27.6)	278 (32.0)	87 (31.1)	
Treating doctors and centres:				
Cardiologist	185 (25.8)	242 (27.8)	87 (31.1)	
Internist or specialist, other than cardiologist	110 (15.3)	135 (15.5)	37 (13.2)	
Family doctor	422 (58.9)	492 (56.6)	156 (55.7)	
Rural hospital	42 (5.9)	52 (6.0)	19 (6.8)	
Teaching hospital	118 (16.5)	134 (15.4)	43 (15.4)	
Hospital with catheterisation laboratory	186 (25.9)	244 (28.1)	69 (24.6)	

*P values are reported for characteristics that significantly differed between NSAIDs and celecoxib. P values not reported are >0.05. Characteristics of patients receiving rofecoxib and celecoxib did not differ significantly.

increase in risk (NSAIDs, 1.21, 0.92 to 1.60; rofecoxib, 1.17, 0.96 to 1.42).

In pairwise analysis, the risk of death and recurrent congestive heart failure, combined and separate, was similar between patients prescribed NSAIDs and those prescribed rofecoxib (combined 0.99, 0.80 to 1.22; death only 1.07, 0.82 to 1.39; recurrent congestive heart failure only 1.04, 0.80 to 1.36; fig 4).

Discussion

The risk of death and recurrent congestive heart failure was higher in elderly patients prescribed non-steroidal anti-inflammatory drugs (NSAIDs) or rofecoxib than in those prescribed celecoxib. In pairwise analysis, we found similar risks of death and recurrent congestive heart failure in patients prescribed rofecoxib or NSAIDs.

An association between cyclo-oxygenase-2 inhibitors and congestive heart failure is emerging, but there seem to be intra-class differences. Case reports have shown worsening heart failure associated with cyclo-oxygenase-2 inhibitors,[45] and data from a small prospective database for disease management suggests that patients who are prescribed a cyclo-oxygenase-2 inhibitor on discharge are more likely to be readmitted for congestive heart failure within a year compared with those not prescribed a cyclo-oxygenase-2 inhibitor (32.5% versus 22.0%, respectively, $P < 0.05$).[46] In that study, the risk of recurrent congestive heart failure differed between rofecoxib and celecoxib (35.5% versus 32.5%, respectively). In a drug safety database, rofecoxib was associated with significantly more reports of cardiac failure than celecoxib.[24] Similarly, in a large, population based study of stable hypertensive patients with no history of heart failure, those who were newly treated with rofecoxib were significantly more likely than those newly treated with celecoxib to have a diagnosis of

Table 2 Prescribing characteristics for patients given celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs (NSAIDs)

Prescription patterns	Celecoxib (n=717)	Rofecoxib (n=869)	P value*	NSAIDs (n=280)	P value*
No (%) of patients given NSAIDs or cyclo-oxygenase-2 inhibitors one year before congestive heart failure	418 (58.2)	474 (54.5)	>0.05	141 (50.4)	0.02
No (%) of patients with congestive heart failure after discharge but before first prescription	102 (14.2)	140 (16.1)	>0.05	62 (22.1)	0.002
Time (days) to first prescription	129	129	>0.05	175	0.03
Dosage (mg/d) of first prescription	200	25	NA	—	NA
Median No of prescriptions during follow-up	2	2	>0.05	1	<0.0001
Median total days of exposure during follow-up	40	30	0.0004	17	<0.0001

NA=not applicable.
*P values reported for variables that significantly differed between rofecoxib and celecoxib and between NSAIDs and celecoxib.

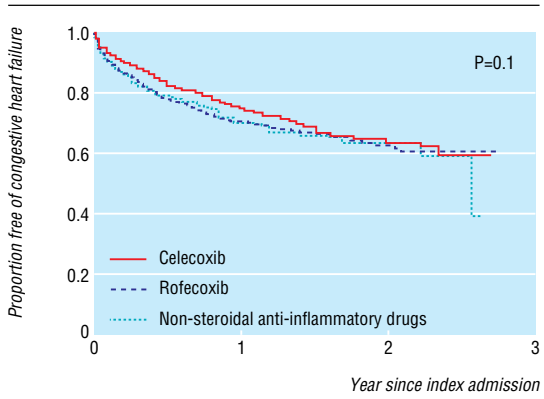

Fig 3 Kaplan-Meier analysis of time to recurrent congestive heart failure in patients prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs

heart failure as an outpatient (rate ratio 1.26, 95% confidence interval 1.06 to 1.48) and as an inpatient (1.52, 1.15 to 2.02).[47] In that study, the rates of heart failure were similar between the celecoxib and NSAIDs groups. Finally, in a recent population based study of cyclo-oxygenase-2 inhibitors and congestive heart failure, users of rofecoxib and NSAIDs, but not celecoxib, had a higher risk of admission for congestive heart failure than controls receiving non-NSAIDs.[36] Findings were similar in a subgroup analysis of patients with a history of admission for congestive heart failure. In pairwise comparisons, they found a significantly higher risk of admission for congestive heart failure in patients prescribed rofecoxib than in those prescribed celecoxib or NSAIDs (adjusted rate ratio 1.8, 95% confidence interval 1.4 to 2.4 and 1.5, 1.1 to 2.1).

Our findings are consistent with these data and are unique because we studied high risk patients with known congestive heart failure and we found a lower risk of death, assessed alone and in combination with recurrent congestive heart failure, in patients prescribed celecoxib compared with those prescribed NSAIDs or rofecoxib. Our data show that celecoxib may be safer than NSAIDs in high risk patients and that there may be important differences between cyclo-oxygenase-2 inhibitors. Differences in selectivity[48] may, at least in part, explain the different results observed in patients prescribed celecoxib compared with those prescribed rofecoxib. NSAIDs also show differences in selectivity. The number of patients prescribed NSAIDs in our study was, however, small so we grouped the NSAIDs. The relative side effects of individual NSAIDs in congestive heart failure remain unknown.

Our study has several limitations. Firstly, patients who were classified as not taking drugs may have been using over the counter aminosalicylic acid or ibuprofen. In 2000, Santé Québec, a government public health agency, estimated that 17.0% and 2.2% of people aged 65 or more bought over the counter NSAIDs or aminosalicylic acid, respectively.[49] Non-differential misclassification on exposure would, however, tend to bias the results towards the null. Secondly, by starting the study on the date that rofecoxib became available (1 April 2000), we included only incident users of rofecoxib but incident and prevalent users of celecoxib. We considered whether the results favouring celecoxib may have been the result of attrition and adherence

Table 3 Unadjusted rates of study events in patients with congestive heart failure who were prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs (NSAIDs)

Events	Person years	Events	Crude event rate/100 person years
Mortality and recurrent congestive heart failure, combined:			
Celecoxib	640.5	266	41.5
Rofecoxib	747.1	387	51.8
NSAIDs	212.5	113	53.2
Deaths:			
Celecoxib	780.7	150	19.2
Rofecoxib	955.4	245	25.6
NSAIDs	265.7	78	29.4
Recurrent congestive heart failure:			
Celecoxib	640.5	177	27.6
Rofecoxib	747.1	242	32.4
NSAIDs	212.5	73	34.4

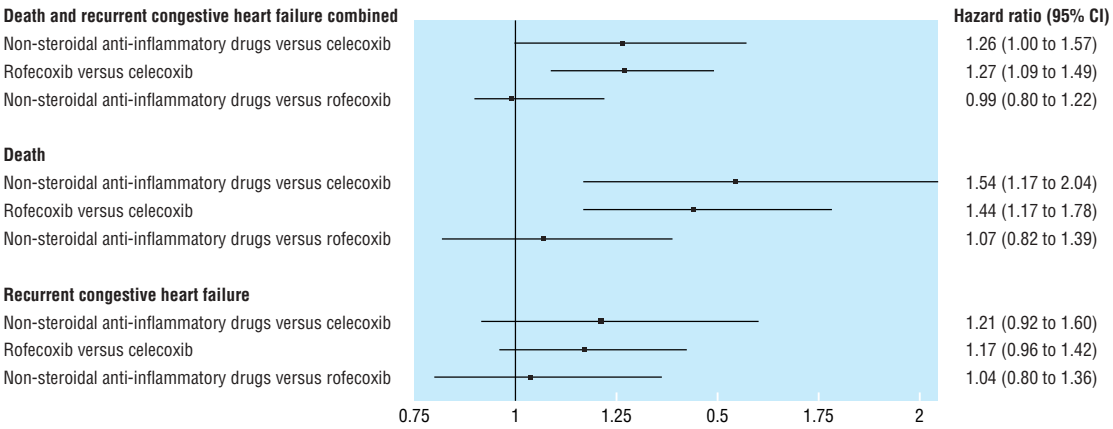

Fig 4 Adjusted hazard ratios (95% confidence intervals) for death and recurrent congestive heart failure, combined and alone, according to exposure group

What is already known on this topic

Non-steroidal anti-inflammatory drugs (NSAIDs) increase the risk of congestive heart failure

Little is known about the safety of cyclo-oxygenase-2 inhibitors in patients with congestive heart failure

What this study adds

Celecoxib seems to be a safer alternative to rofecoxib and NSAIDs in elderly patients with congestive heart failure

Class differences seem to exist between NSAIDs and cyclo-oxygenase-2 inhibitors and between cyclo-oxygenase-2 inhibitors

biases.[50] We carried out a sensitivity analysis in which we included only new users of celecoxib (and excluded those with a prescription before 1 April 2000). Time to all cause death or recurrent congestive heart failure was similar to that reported in the main analysis (hazard ratio 1.27, 95% confidence interval 1.07 to 1.52 versus 1.27, 1.09 to 1.49).

NSAIDs are known to be associated with congestive heart failure, but such information is scarce for cyclo-oxygenase-2 inhibitors. No head to head comparisons in randomised trials are available to determine the relative risks between NSAIDs and cyclo-oxygenase-2 inhibitors. We used an observational design and compared a cohort of patients with congestive heart failure who used NSAIDs or cyclo-oxygenase-2 inhibitors, and we found that celecoxib was associated with a lower risk of death and recurrent congestive heart failure than were NSAIDs and rofecoxib. All our patients received either NSAIDs or a cyclo-oxygenase-2 inhibitor and the reference group received celecoxib. Since we had no unexposed group, we were unable to estimate whether, and by how much, celecoxib increases the risk of recurrent congestive heart failure and death compared with non-users of NSAIDs and cyclo-oxygenase-2 inhibitors. We conclude that important class differences seem to exist between NSAIDs and cyclo-oxygenase-2 inhibitors and among cyclo-oxygenase-2 inhibitors themselves. Celecoxib seems to be a safer alternative to rofecoxib and NSAIDs in elderly patients with congestive heart failure.

Contributors: LP gathered the data. MH and LP planned the study and drafted the manuscript. HR was responsible for data programming. All authors were responsible for data analysis and interpretation. All authors will act as guarantors for the paper.

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Competing interests: None declared.

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