

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 a 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 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). 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. Rofecoxib has been consistently associated with an increased risk of myocardial infarction.¹⁻⁵ Although most of the evidence to date shows no association between celecoxib and an increased risk of myocardial infarction,³⁻⁶⁻⁹ a meta-analysis² and a recent study¹⁰ have cast doubt. Whether cyclo-oxygenase-2 inhibitors have similar or different cardiovascular toxicities remains debatable.¹¹⁻¹²

Both NSAIDs and cyclo-oxygenase-2 inhibitors have renovascular side effects, all of which can exacerbate heart failure.¹³⁻¹⁶ The cyclo-oxygenase-2 enzyme, however, is induced in the myocardium of the failing heart and is associated with myocardial scarring.¹⁷⁻¹⁸ 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.¹⁹⁻²¹

Clinical information on the association between cyclo-oxygenase-2 inhibitors and heart failure is however, scarce.²²⁻²⁵

Elderly patients are likely to be given cyclo-oxygenase-2 inhibitors for pain and inflammation as these drugs are thought to have fewer gastrointestinal side effects than NSAIDs.²⁶⁻²⁷ Yet the risk of cardiovascular disease increases with age. 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

Our cohort was derived from the database of discharge summaries for Quebec. 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 the availability of both drugs. The age cut-off point ensured that all participants had at least one full year of observation in the database before entry into the study.

We used the Quebec database for claims for prescription drugs to determine exposure to drugs. This database contains information on all drug prescriptions for outpatients aged 65 or more.

The study groups consisted of patients exclusively given one or more prescriptions for celecoxib, rofecoxib, or any non-selective NSAID after the index admission. Patients in the NSAID group could have been dispensed more than one different non-selective NSAID during the study.

The primary outcome was the combined outcome of time to all cause death or to recurrent congestive heart failure. The secondary outcomes were time to all cause death and time to recurrent congestive heart failure assessed separately.

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



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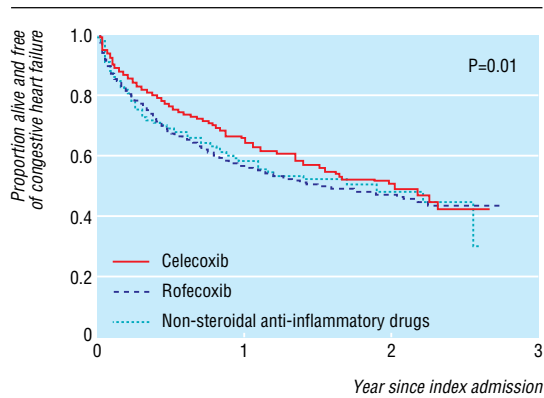


Fig 1 Kaplan-Meier analysis of time to recurrent congestive heart failure or death in patients prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs

Statistical analysis

We generated descriptive statistics to compare patient characteristics according to exposure groups. To compare time to outcome we carried out Cox proportional hazards modelling. We adjusted the models for possible confounders, including age, sex, comorbidities, other drugs prescribed before the first prescription for a study drug, characteristics of the treating doctor or hospital, 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.

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 coxib 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 (see *bmj.com*). Overall, 492 patients had recurrent congestive heart failure and 473 died (table).

The most commonly used NSAIDs were diclofenac (4.3%), naproxen (2.6%), indomethacin (1.8%), and ibuprofen (1.0%).

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 (see *bmj.com*), and the trend was towards those prescribed celecoxib remaining free of recurrent congestive heart failure compared with those prescribed rofecoxib or NSAIDs (see *bmj.com*).

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 2). 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 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 2).

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 intraclass differences. 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, $P < 0.05$).²⁸ In that study, the risk of recurrent congestive heart failure differed between rofecoxib and celecoxib. In a drug safety database, rofecoxib was associated with significantly more reports of cardiac failure than celecoxib.²⁹ 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 not receiving NSAIDs.³⁰ 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

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

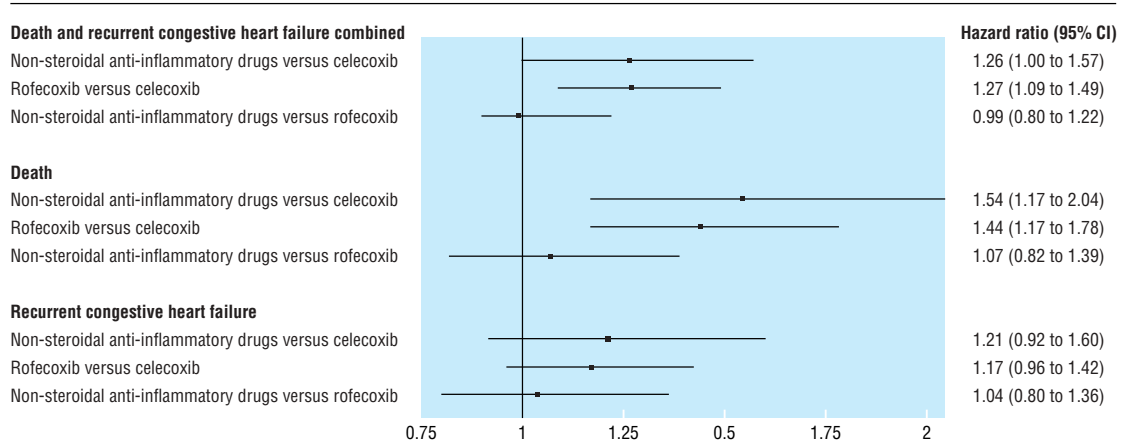


Fig 2 Adjusted hazard ratios (95% confidence intervals) for death and recurrent congestive heart failure, combined and alone, according to exposure group

recurrent congestive heart failure, in patients prescribed celecoxib compared with those prescribed NSAIDs or rofecoxib. Celecoxib may be safer than NSAIDs in high risk patients and there may be important differences between cyclo-oxygenase-2 inhibitors. Differences in selectivity³¹ may, at least in part, explain the different results observed in patients prescribed celecoxib compared with those prescribed rofecoxib.

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. Such non-differential misclassification 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 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).

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. 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.

Contributors: See bmj.com

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Competing interests: None declared.

Ethical approval: Not required.

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

- Graham DJ, Campen D, Hui R, Spence M, Cheatham C, Levy G, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *Lancet* 2005;365:4996.
- Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 2001;286:954-9.
- Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet* 2002;360:1071-3.
- Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet* 2004;364:2021-9.
- Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352:1092-102.
- Konstam MA, Weir MR, Reicin A, Shapiro D, Sperling RS, Barr E, et al. Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib. *Circulation* 2001;104:2280-8.
- Reicin A, Shapiro D, Sperling RS, Barr E, Yu Q. Comparison of cardiovascular thrombotic events in patients with osteoarthritis treated with rofecoxib versus nonselective nonsteroidal anti-inflammatory drugs (ibuprofen, diclofenac, and nabumetone). *Am J Cardiol* 2002;89:204-9.
- White WB, Faich G, Whelton A, Maurath C, Ridge NJ, Verburg KM, et al. Comparison of the thromboembolic events in patients treated with celecoxib, a cyclo-oxygenase-2 specific inhibitor, versus ibuprofen and diclofenac. *Am J Cardiol* 2002;89:425-30.
- Mamdani M, Rochon P, Juurlink DN, Anderson GM, Kopp A, Naglie G, et al. Effect of selective cyclooxygenase 2 inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly. *Arch Intern Med* 2003;163:481-6.
- Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;352:1071-80.
- Topol EJ. Failing the public health—rofecoxib, Merck, and the FDA. *N Engl J Med* 2004;351:1707-9.
- Fitzgerald GA. Coxibs and cardiovascular disease. *N Engl J Med* 2004;351:1709-11.

- 13 Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med* 1993;153:477-83.
- 14 Johnson AJ, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Ann Intern Med* 1994;121:289-300.
- 15 Brater DC, Harris C, Redfern JS, Gertz BJ. Renal effects of selective COX-2 inhibitors. *Am J Nephrol* 2001;21:1-15.
- 16 Perazella MA, Tray K. Selective cyclooxygenase-2 inhibitors: a pattern of nephrotoxicity similar to traditional nonsteroidal anti-inflammatory drugs. *Am J Med* 2001;111:64-7.
- 17 Wong SC, Fukuchi M, Melnyk P, Rodger I, Giaid A. Induction of cyclooxygenase-2 and activation of nuclear factor- κ B in myocardium of patients with congestive heart failure. *Circulation* 1998;98:100-3.
- 18 Zhang Z, Vezza R, Plappert T, McNamara P, Lawson JA, Austin S, et al. COX-2-dependent cardiac failure in Gh/ITG transgenic mice. *Circ Res* 2003;92:1153-61.
- 19 Feenstra J, Heerdink ER, Grobbee DE, Stricker BH. Association of nonsteroidal anti-inflammatory drugs with first occurrence of heart failure and with relapsing heart failure: the Rotterdam Study. *Arch Intern Med* 2002;162:265-70.
- 20 Rodriguez LA, Hernandez-Diaz S. Nonsteroidal anti-inflammatory drugs as a trigger of clinical heart failure. *Epidemiology* 2003;14:240-6.
- 21 Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem. *Arch Intern Med* 2000;777-84.
- 22 Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib long-term arthritis safety study. *JAMA* 2000;284:1247-55.
- 23 Data presented to the FDA arthritis advisory committee, Feb 2001. www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_03_med.pdf (accessed 13 Apr 2005).
- 24 Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;343:1520-8.
- 25 Data presented to the FDA arthritis advisory committee, Feb 2001. www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_01_merck.pdf (accessed 13 Apr 2005).
- 26 Lipsky PE, Abramson SB, Breedveld FC, Brook P, Burmester R, Buttgerit F, et al. Analysis of the effect of COX-2 specific inhibitors and recommendations for their use in clinical practice. *J Rheumatol* 2000;27:1338-40.
- 27 Tannenbaum H, Peloso PM, Russell AS, Marlow B. An evidence-based approach to prescribing NSAIDs in the treatment of osteoarthritis and rheumatoid arthritis: the second Canadian consensus conference. *Can J Clin Pharmacol* 2000;7(Suppl A):A4-16.
- 28 Jassal DS, Howlett J, Cox JL. Are COX-2 inhibitors safe in congestive heart failure? American Heart Association: scientific sessions. Orlando, FL: Nov 9-12, 2003. *Circulation* 2003;108:665.
- 29 Zhao SZ, Reynolds MW, Lejkowith J, Whelton A, Arellano FM. A comparison of renal-related adverse drug reactions between rofecoxib and celecoxib, based on the World Health Organization/Uppsala Monitoring Centre safety database. *Clin Ther* 2001;23:1478-91.
- 30 Mamdani M, Juurlink DN, Lee DS, Rochon PA, Kopp A, Naglie G, et al. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. *Lancet* 2004;363:1751-6.
- 31 FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001;345:433-42. (Accepted 29 April 2005)

Endpiece

Discredit into which physic was brought

The emperor Adrian ordered it to be inscribed on his tomb, that he died by the hands of his physicians. My son Marcellus, says Cato, if physicians are brought from Greece to Rome, advise the fathers of the Senate that they suffer them not to read or teach physic, or to practise it in the Common Wealth; because the art is too dangerous and difficult, that though it is professed by many it is understood by few.

Miller J. Observations on the management of the prevailing diseases of Great Britain, 1779

Jeremy Hugh Baron,
honorary professorial lecturer,
Mount Sinai School of Medicine, New York

The first and last days of medical school

On my father's first day of medical school, so I am told, the dean of medicine, perched high on a stage, looked down on the eager group of new recruits and instructed: "Look to your left." They did so.

"Look to your right." They did that too.

"Someone sitting beside you will not be seen at convocation, unless, of course, that person is you." The dean, in self fulfilling prophecy, turned out to be correct each year.

In contrast, my first day at medical school involved a barbeque, and the faculty volunteered to cook. I have never heard the pessimism that accompanied my father's educational experience. Despite this welcoming atmosphere, however, the dean's prediction still held true.

It was in the gross anatomy lab, over the dissected thorax of our cadaver, that I realised that my class would soon lose its first person to stress and burnout. Holding a sectioned specimen tightly, my classmate went through the borders, surfaces, vascular supply, and lymphatic drainage of the lungs with fantastic speed and passionate fervour. There was an upcoming quiz. Somebody, in an attempt to help, pointed out that she had forgot the lingula. This omission caused her to lose sleep for many days.

To seem as intelligent as she thought the rest of us were, she began to ask the professors to lecture faster and in greater detail, thereby ostracising herself from the rest of the class. We were already struggling to keep up, and this recommendation made her especially unpopular. By Christmas, she left. Buoyed by the excellent results of our first term results and with a

sense of satisfaction that comes with survival, the rest of the class forged ahead.

Nobody mentions her name anymore, but many of us wonder where she went, what she is doing, and whether she finally found a fulfilling career outside medicine. As convocation approaches, it seems unlikely that we will ever hear.

I do wish that someone had the gall to tell us it would be rough, that our classmates would leave, and that many who stayed would become less certain of their decisions with time. The current literature is filled with excellent research on attrition rates, doctors' wellbeing, resident work hours, and socioeconomic trends of admissions. Reports are commissioned, and experts are hired to point out the pitfalls. None of these papers prepare you for that time when your lab partner forgets to breathe.

Farrah J Mateen *final year medical student, College of Medicine, University of Saskatchewan, Saskatoon, Canada* (farrah_mateen@hotmail.com)

We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. Please submit the article on <http://submit.bmj.com> Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.