Cardiovascular safety of celecoxib in acute myocardial infarction patients: a nested case-control study

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Abstract

The objective was to measure the impact of exposure to coxibs and non-steroidal anti-inflammatory drugs (NSAID) on morbidity and mortality in older patients with acute myocardial infarction (AMI). A nested case-control study was carried out using an exhaustive population-based cohort of patients aged 66 years and older living in Quebec (Canada) who survived a hospitalization for AMI (ICD-9 410) between 1999 and 2002. The main variables were all-cause and cardiovascular (CV) death, subsequent hospital admission for AMI, and a composite end-point including recurrent AMI or CV death. Conditional logistic regressions were used to estimate the risk of mortality and morbidity. A total of 19,823 patients aged 66 years and older survived hospitalization for AMI in the province of Quebec between 1999 and 2002. After controlling for covariables, the risk of subsequent AMI and the risk of composite end-point were increased by the use of rofecoxib. The risk of subsequent AMI was particularly high for new rofecoxib users (HR 2.47, 95% CI 1.57-3.89). No increased risk was observed for celecoxib users. No increased risk of CV death was observed for patients exposed to coxibs or NSAIDs. Patients newly exposed to NSAIDs were at an increased risk of death (HR 2.22, 95% CI 1.30-3.77) and of composite end-point (HR 2.28, 95% CI 1.35-3.84). Users of rofecoxib and NSAIDs, but not celecoxib, were at an increased risk of recurrent AMI and of composite end-point. Surprisingly, no increased risk of CV death was observed. Further studies are needed to better understand these apparently contradictory results.

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Introduction

COX-2 inhibitors offer a significant gastrointestinal safety advantage over non-selective non-steroidal anti-inflammatory drugs (NSAIDs).[1] However, as with any other therapy, potential risks associated with treatment (in this case, increased risk of cardiovascular events) must be weighed against potential benefits (fewer gastrointestinal complications). In fact, the adverse effect of rofecoxib (VIOXX) on the cardiovascular system became apparent with the VIGOR randomized clinical trial and seems to have now reached consensus.[2-6] The effect of celecoxib on the cardiovascular system is less clear. Recent meta analyses show that the risk of acute myocardial infarction (AMI) associated with celecoxib is increased in patients with a history of AMI,[5,7] but not in patients without a history of AMI.[2,3] Nevertheless, few studies show the impact of these drugs on mortality in the general population and in the high-risk population of patients who survived an AMI. Moreover, among observational studies evaluating the impact of COX-2 on mortality, the results are very inconsistent. In Gislason *et al.* (2006),[5] a very high risk of death is associated with both celecoxib and rofecoxib in patients with prior myocardial infarction, whereas the results presented in Lee *et al*.[8] show a protective effect of coxibs on overall mortality in patients suffering from osteoarthritis. In a meta analysis of randomized clinical trials, Kearney *et al.*[9] show a non-statistically significant increased risk of vascular death associated with the use of COX-2 inhibitors.

Traditional NSAIDs have also raised concerns based on several studies reporting an increased risk of cardiovascular events in users of these drugs,[2,3,5] particularly in non-naproxen users. Although two recent meta analyses[2,3] show increased cardiovascular risk in the general population, few studies show the impact of NSAIDs on all-cause and cardiovascular mortality in the general population, and even fewer in the high-risk population of patients who survived an acute myocardial infarction. Moreover, among those that specifically studied mortality, we find contradictory results. In Lee *et al.*,[8] the risk of all-cause death was reduced among NSAID users, even in the high-risk population with a preexisting coronary artery disease, and do not seem to depend on the NSAID used (naproxen, ibuprofen, diclofenac, other NSAID). Similarly, Stürmer *et al.*[10] showed a significant decreased death risk associated to NSAIDs. On the other hand, Gislason *et al.*[5] found a significant increased risk of death associated with both ibuprofen and diclofenac in an AMI population; but this risk seemed to be effective in high daily dosage only. In low-dosage ibuprofen, the risk of death was even significantly decreased. Finally, MacDonald *et al.*[11] showed a significant increased risk of both all-cause and cardiovascular death among aspirin and ibuprofen users as compared to aspirin alone, but a non-significant decrease among aspirin and diclofenac users.

The method used to measure exposure to drug varied widely. Some studies considered that an individual was exposed to a specific drug when the drug prescription overlaps the index date,[5,12-14] when the drug has been used within seven days before the index date,[15,16] when the supply of the last prescription lasted until the index date or ended in the 30 days before the index date,[17] or when the drug has been prescribed within 90 days before the index date.[18] Other studies[6,19,20] also considered new coxib users defined as current users who were taking the drug for the first time in a predetermined time period. Several of these studies also categorized coxibs according to low- or high-dosage and show that higher dosages imply higher risk of acute myocardial infarction.[5,12-14]

The objective of this naturalistic study was to measure the impact in real life of exposition to coxibs (rofecoxib, celecoxib) and NSAIDs on morbidity and mortality in older acute myocardial infarction (AMI) patients. Secondary objectives were to explore several methods for measuring drug exposure.

Materials and Methods

Design and data sources

We used a retrospective population-based cohort study with a nested case-control analysis. Patients' data were obtained from the Quebec's provincial hospital discharge register (MED-ECHO)[21] and Québec's provincial demographic database which contains dates and causes of death. These data were obtained from the *Ministère de la santé et des services sociaux* (MSSS). The drug register was obtained from the *Régie de l'assurance maladie du Québec* (RAMQ)[22] and contains all drugs claimed by individuals in the public drug insurance plan, which covers more than 95% of all people aged 65 years and older in the province. This database may represent one of the most accurate means of determining drugs dispensed to individuals in real life.[23] The coding systems differ according to registers: the demographic register used the International Disease Classification (ICD) -9th revision before 2000 and the ICD-10 since 2000 for the cause of death, while the MED-ECHO register uses the ICD-9 coding system for diagnoses. Using a unique encrypted identifier, patients' files were linked to provide individual level information on demographic characteristics, medical and drug histories, as well as vital status.

Table 1. Characteristics of cases and controls by outcome.

	ALL-cause death			CVD death		
	Cases	Controls	p	Cases	Controls	p
Number	4,146	82,784		1,963	39,177	
Age (y),[a] mean (SD)	79.9(7.2)	79.1 (6.8)	<0.001	80.5 (7.1)	79.6 (6.7)	<0.001
Gender, %						
Female	48.0	48.0	0.979	48.2	48.2	1.000
Male	52.0	52.0		51.8	51.8	
Revascularization, %	10.2	24.0	<.001	9.2	22.9	<0.001
Length of stay (days), mean (SD)	17.2 (20.3)	14.9 (16.3)	<0.001	16.8 (18.2)	14.9 (16.3)	<0.001
Comorbidities, mean (SD)	3.3 (2.4)	2.1 (2.0)	<0.001	3.1 (2.1)	2.0 (2.0)	<0.001
Cardioprotective drug,[b] %						
Aspirin	30.1	58.2	<0.001	34.3	58.2	<0.001
Beta-blockers	27.1	54.5	<0.001	30.5	54.1	<0.001
ACE inhibitors	29.5	54.6	<0.001	35.7	54.2	<0.001
Statins	16.7	40.0	<0.001	20.7	38.4	<0.001
	AMI Readmission			AMI event		
	Cases	Controls	p	Cases	Controls	p
Number	1,759	35,167		3,240	64,695	
Age (y), mean (SD)	78.6 (7.2)	78.1 (6.8)	<0.001	79.4 (7.3)	78.8 (6.8)	<0.001
Gender, %						
Female	46.8	46.9	0.994	47.1	47.1	0.994
Male	53.2	53.1		52.9	52.9	
Revascularization, %	13.8	25.6	<0.001	11.7	24.7	<0.001
Length of stay (days), mean (SD)	13.3 (13.0)	14.8 (16.0)	<0.001	15.3 (16.2)	15.0 (16.5)	<0.001
Comorbidities, mean (SD)	2.6 (2.1)	2.0 (2.0)	<0.001	2.9 (2.2) 2.0	(2.0)	<0.001
Cardioprotective drug, %						
Aspirin	55.9	58.6	0.028	45.2	58.4	<0.001
Beta-blockers	54.5	55.2	0.584	42.4	54.7	<0.001
ACE inhibitors	57.5	54.5	0.015	47.0	54.4	<0.001
Statins	37.4	41.1	0.002	29.3	39.8	<0.001

[a]Age at cohort entry; [b]exposition at index time

Studied population

The study population included all patients 66 years and older, living in the province of Quebec who have been hospitalized with a main diagnosis of AMI (ICD-9: 410) between January 1999 and December 2002. The first such hospitalization during the study period was considered as the index hospitalization. Studies confirming the validity of the administrative hospital discharge data concerning AMI have been previously published.[24,25] In order to have only "new" AMI patients, we excluded patients who have been previously hospitalized for an AMI in the four years before the index hospitalization. We also excluded patients discharged from index hospitalization after a stay of less than four days because they were more likely to have been misclassified as having an AMI, and those who died within 30 days from index hospital discharge, in order to allow some time for patients to receive medication. A 2-year follow-up period was used in order to collect dates and causes of death as well as dates and causes of subsequent hospitalization.

The outcomes were all-cause death, cardiovascular death (ICD-9: 410-414, 426-429; ICD-10: I20-I25, I44-I52), and rehospitalization for AMI (ICD-9: 410) occurring anytime within two years after cohort entry. A composite endpoint, named AMI event, was also defined and included cardiovascular death and rehospitalization for AMI. Otherwise, a drug associated with an increased mortality rate could appear to protect against non-fatal AMI.

Selection of cases and controls

We used nested case-control approaches with 20 controls per case. We used 20 controls per case to optimize statistical efficiency.[26] For each outcome, all individuals who had the outcome during the study follow-up were considered as cases. The controls were matched to cases according to age (within five years), gender and date of cohort entry (within 30 days). For each case, the controls were randomly drawn from the case's matched risk set, and the index time refers to the time between the case's cohort entry and the event date. For controls, the index time is the same as their respective case.

Drug exposure

We considered that every patient who filled a prescription at a pharmacy was exposed to the drug for the length of time of the prescription. Cases and controls were considered currently exposed if they were exposed to the drug at index time. Past users refer to those who were not currently exposed but have been exposed in the year preceding index time, and non-users refer to those with no prescription of coxib or NSAIDs during that time. Another set of analyses were performed using another categorization: new, past and never users. New users refer to patients who were currently exposed for the first time in one year, past users to those who were users but not for the first time and non-users refer to the same definition as before. The drug classes considered were rofecoxib, celecoxib and NSAIDs.

Covariables

Other variables included revascularization at index hospitalization, index hospitalization length of stay (including all hospital transfers), current exposure to cardioprotective drugs after hospitalization discharge (ASA, ACE inhibitors, beta-blockers or statins), and a comorbidity index. The comorbidity index,[27] which is an adaptation of the Charlson comorbidity index,[28] is a weighted score of comorbid conditions; these conditions being defined by the 16 diagnoses available in the hospital discharge database in the year preceding and including the index hospitalization. The predictive performance of several comorbidity scores (including the D'Hoore index) for use in epidemiological research with administrative databases was studied by Schneeweiss *et al.*[29] in 2001. They show that the four scores based on the ICD-9 generally performed better at predicting 1-year mortality than medication-based Chronic Disease Score.

Statistical analyses

For each outcome, conditional logistic regression model was used to estimate the hazard ratios (HR) of the outcome events associated with coxibs and NSAIDs. To take into account differences in population characteristics, all models were adjusted for revascularization, hospital length of stay, comorbidity and current exposition to NSAIDs, aspirin, ACE inhibitors and statins. All analyses were performed using SAS 9.1.

Results

A total of 19,823 patients satisfied the inclusion and exclusion criteria. During the 2-year follow-up period, 4,146 (20.9%) patients died,

Table 2. Adjusted[c] hazard ratios of all-cause death according to coxib and NSAID exposition: results from the conditional logistic regression analyses.

ALL-cause death	Cases	Controls	Crude HR	Adjusted HR (95% CI)
New use				
Rofecoxib	20	429	0.91	1.18 (0.74; 1.86)
Celecoxib	17	383	0.86	1.08 (0.66; 1.78)
NSAID	17	185	1.79	2.22 (1.30; 3.77) *
Past use	947	20587	0.96	1.09 (1.01; 1.18) *
No use	3145	61200	1.00	1.00 (reference)
Current use				
Rofecoxib	56	1366	0.80	1.13 (0.86; 1.49)
Celecoxib	61	2138	0.56	0.76 (0.59; 0.99) *
NSAID	36	782	0.90	1.37 (0.97; 1.94)
Past use	838	17048	0.96	1.13 (1.04; 1.22) *
No use	3155	61450	1.00	1.00 (reference)
Use in last week				
Rofecoxib	70	1565	0.87	1.19 (0.93; 1.52)
Celecoxib	88	2418	0.71	0.95 (0.76; 1.19)
NSAID	41	897	0.89	1.28 (0.93; 1.78)
Past use	795	16537	0.94	1.11 (1.02; 1.20) *
No use	3152	61367	1.00	1.00 (reference)
Use in last month				
Rofecoxib	106	2109	0.98	1.28 (1.04; 1.57) *
Celecoxib	120	3006	0.78	1.00 (0.82; 1.21)
NSAID	55	1236	0.87	1.23 (0.93; 1.62)
Past use	720	15233	0.92	1.09 (1.00; 1.19)
No use	3145	61200	1.00	1.00 (reference)

* $p<0.05$; ** $p<0.001$; *** $p<0.0001$; [c]Adjusted for age, gender, time of cohort entry, revascularization and length of stay at index hospitalization, comorbidity index, and exposure to aspirin, beta-blockers, ACE inhibitors and statins; HR, hazard ratios.

Table 3. Adjusted[d] hazard ratios of cardiovascular death according to coxib and NSAID exposition: results from the conditional logistic regression analyses.

CV death	Cases	Controls	Crude HR	Adjusted HR (95% CI)
New use				
Rofecoxib	8	211	0.73	0.85 (0.42; 1.76)
Celecoxib	9	196	0.88	1.03 (0.52; 2.05)
NSAID	7	82	1.64	2.13 (0.95; 4.76)
Past use	430	9705	0.85	0.99 (0.89; 1.11)
No use	1509	28983	1.00	1.00 (reference)
Current use				
Rofecoxib	21	611	0.66	0.86 (0.55; 1.34)
Celecoxib	38	994	0.74	0.94 (0.67; 1.31)
NSAID	17	317	0.89	1.35 (0.82; 2.21)
Past use	375	8090	0.89	1.02 (0.90; 1.14)
No use	1512	29115	1.00	1.00 (reference)
Use in last week				
Rofecoxib	24	716	0.64	0.82 (0.54; 1.24)
Celecoxib	45	1109	0.78	0.98 (0.72; 1.33)
NSAID	17	435	0.75	1.09 (0.66; 1.78)
Past use	366	7850	0.90	1.02 (0.91; 1.15)
No use	1511	29067	1.00	1.00 (reference)
Use in last month				
Rofecoxib	40	968	0.79	0.99 (0.71; 1.37)
Celecoxib	61	1384	0.85	1.03 (0.79; 1.35)
NSAID	26	603	0.83	1.12 (0.75; 1.68)
Past use	327	7239	0.87	0.99 (0.87; 1.12)
No use	1509	28983	1.00	1.00 (reference)

[d]Adjusted for age, gender, time of cohort entry, revascularization and length of stay at index hospitalization, comorbidity index, and exposure to aspirin, beta-blockers, ACE inhibitors and statins; HR, hazard ratios; CV, cardiovascular.

1,963 (9.9%) died from a cardiovascular disease, 1,759 (8.9%) were rehospitalized for AMI, and 3,240 (16.3%) either died from a cardiovascular disease or were rehospitalized for AMI. For each of these four end-points, cases and controls were selected and are described in Table 1. Since we matched cases and controls according to gender and age, with a maximum difference of five years, we observe only a slight difference in gender repartition and average age between cases and controls. For all study end-points, cases had less revascularization, more comorbid conditions, and were generally less exposed to cardioprotective treatments than controls.

The nested case-control analyses (Tables 2-5) revealed that, after controlling for age, gender, time of cohort entry, revascularization and length of stay at index hospitalization, as well as exposure to cardioprotective drugs, the risk of subsequent AMI and the risk of AMI event was increased with the use of rofecoxib, and this was true whatever the definition of exposure used (Tables 4 and 5).

The risk of subsequent AMI was particularly high for new rofecoxib users (HR 2.47, 95% CI 1.57-3.89, p<0.0001). Despite these findings, the risk of cardiovascular death for patients exposed to rofecoxib was not higher than for patients not exposed to NSAIDs in the last year. The results also show that celecoxib was not associated with a statistically significant increase in the risk of any of the four end-points. Patients newly exposed to NSAIDs were at increased risk of death (HR 2.22, 95% CI 1.30-3.77, p=0.003) and in increased risk of AMI event (HR 2.28, 95% CI 1.35-3.84, p=0.002), compared to non-users of NSAIDs.

Discussion

This study aimed to evaluate the impact of exposition to coxibs (rofecoxib, celecoxib) and NSAIDs on mortality and morbidity in AMI patients. First, our results confirm that exposition to rofecoxib increases the risk of subsequent AMI. Second, as opposed to other studies,[5,7] the exposition to celecoxib is not associated with an increased risk of recurrent AMI for patients with a previous history of AMI, and this is true for all drug exposition measures. Furthermore, new users of rofecoxib or NSAIDs are at increased risk of recurrent AMI and cardiovascular event as compared to non-users of coxibs/NSAIDs. Other studies[6,20] have also shown an increased AMI risk for first time users or new users of rofecoxib. The study of Levesque *et al.*[6] also shows a decreased trend in AMI risk with increasing length of treatments. In our study, neither exposition to rofecoxib nor exposition to celecoxib were associated with an

Table 4. Adjusted[e] hazard ratios (HR) of recurrent AMI according to coxib and NSAID exposition: results from the conditional logistic regression analyses.

Recurrent AMI	Cases	Controls	Crude HR	Adjusted HR (95% CI)
New use				
Rofecoxib	29	325	1.73	2.47 (1.57; 3.89)***
Celecoxib	18	329	1.06	1.22 (0.66; 2.25)
NSAID	16	166	1.87	1.83 (0.92; 3.64)
Past use	734	16462	0.87	0.95 (0.85; 1.07)
No use	2443	47413	1.00	1.00 (reference)
Current use				
Rofecoxib	61	1015	1.16	1.68 (1.24; 2.28)**
Celecoxib	69	1664	0.80	1.01 (0.74; 1.37)
NSAID	37	626	1.15	1.18 (0.75; 1.84)
Past use	616	13776	0.87	0.91 (0.81; 1.03)
No use	2457	47614	1.00	1.00 (reference)
Use in last week				
Rofecoxib	65	1175	1.07	1.55 (1.16; 2.09)*
Celecoxib	83	1838	0.88	1.08 (0.81; 1.43)
NSAID	41	749	1.06	1.18 (0.78; 1.78)
Past use	600	13386	0.87	0.92 (0.81; 1.04)
No use	2451	47547	1.00	1.00 (reference)
Use in last month				
Rofecoxib	88	1587	1.08	1.46 (1.12; 1.91)*
Celecoxib	107	2334	0.89	1.03 (0.80; 1.34)
NSAID	57	1049	1.05	1.27 (0.90; 1.79)
Past use	545	12312	0.86	0.91 (0.79; 1.03)
No use	2443	47413	1.00	1.00 (reference)

* p<0.05; ** p< 0.001; *** p< 0.0001. [e]Adjusted for age, gender, time of cohort entry, revascularization and length of stay at index hospitalization, comorbidity index, and exposure to aspirin, beta-blockers, ACE inhibitors and statins; HR, hazard ratios.

Table 5. Adjusted[f] hazard ratios of AMI event (recurrent AMI or CV death) according to coxib and NSAID exposition: results from the conditional logistic regression analyses.

AMI event	Cases	Controls	Crude HR	Adjusted HR (95% CI)
New use				
Rofecoxib	20	429	0.91	1.94 (1.32; 2.86)**
Celecoxib	17	383	0.86	1.19 (0.74; 1.93)
NSAID	17	185	1.79	2.28 (1.35; 3.84)*
Past use	947	20587	0.96	0.95 (0.87; 1.03)
No use	3145	61200	1.00	1.00 (reference)
Current use				
Rofecoxib	56	1366	0.80	1.36 (1.04; 1.77)*
Celecoxib	61	2138	0.56	0.93 (0.73; 1.19)
NSAID	36	782	0.90	1.39 (0.99; 1.94)
Past use	838	17048	0.96	0.93 (0.85; 1.02)
No use	3155	61450	1.00	1.00 (reference)
Use in last week				
Rofecoxib	70	1565	0.87	1.23 (0.95; 1.59)
Celecoxib	88	2418	0.71	1.00 (0.80; 1.26)
NSAID	41	897	0.89	1.28 (0.93; 1.76)
Past use	795	16537	0.94	0.94 (0.86; 1.03)
No use	3152	61367	1.00	1.00 (reference)
Use in last month				
Rofecoxib	106	2109	0.98	1.20 (0.96; 1.50)
Celecoxib	120	3006	0.78	0.99 (0.81; 1.21)
NSAID	55	1236	0.87	1.28 (0.98; 1.69)
Past use	720	15233	0.92	0.93 (0.84; 1.02)
No use	3145	61200	1.00	1.00 (reference)

* p<0.05; ** p<0.001; *** p<0.0001; [f]Adjusted for age, gender, time of cohort entry, revascularization and length of stay at index hospitalization, comorbidity index, and exposure to aspirin, beta-blockers, ACE inhibitors and statins; HR, hazard ratios.

increased risk of cardiovascular mortality. These surprising results raise some questions. What mechanisms can explain the increased risk of AMI associated with exposure to rofecoxib that is not translated to an increased risk of cardiovascular death. A possible explanation that has been raised by Lee *et al.*[8] is that the increased risk of AMI may be counterbalanced by a possible protective effect of improved vitality or increase in physical activity because of a more optimal control of pain. Further studies are needed to clarify this point.

The major strength of our study is that we explored cardiovascular mortality as well as cardiovascular morbidity when most of the studies and meta analyses explored only the risk of AMI. We also explored several definitions of coxibs exposure, which reveal that the magnitude of the risk estimates is sensitive to the definition used to measure the drug exposure but the direction remains the same. We also performed several Cox regression analyses and we found essentially the same results (*data not shown*).

Our study has some limitations. First, there may exist differences in population characteristics among users and non-users of coxibs and NSAIDs, but our analyses were all adjusted for age, gender, time of cohort entry, revascularization and length of stay at index hospitalization, comorbidity index, and exposure to cardio-protective drug use. However, the use of a comorbidity index that captures within a unique variable all comorbidities can dilute potential confounding factors. Second, the use of administrative data did not allow us to have information on risk factors such as smoking status, body mass index, cholesterol levels, blood pressure measurements, as well as other known major cardiovascular risk factors, but there is no reason to believe that these risk factors would not be evenly distributed among users and non-users. Some studies have found a positive statistically significant association between high doses of coxib and cardiovascular risk.[5,12-14] Unfortunately, we were unable to take into account dosage in our analyses due to the limited number of patients using high-dose coxib.

Finally, a major limitation could also be a possible information bias related to the assumption that a patient starts using the drug the day the prescription was filled at the pharmacy, takes the drug regularly, and is compliant to the posology. COX-2 inhibitors were drugs dispensed by prescription only. However, the NSAID ibuprofen was the only non-aspirin NSAID available over the counter. Since the public drug insurance plan covers more than 95% of all people aged 65 years and older in the province, we can assume that only a small part of these patients would acquire medication without having data registered in the provincial database.

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