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ORIGINAL REPORT

Risk of acute myocardial infarction with real-world NSAIDs depends on dose and timing of exposure

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Abstract

Purpose: Real-life use of nonsteroidal anti-inflammatory drugs (NSAIDs) is dynamic. This study aimed to characterize the temporal association between time-varying NSAID exposure and acute myocardial infarction (MI).

Methods: Nested case-control analyses were conducted on a Quebec administrative health cohort. NSAID dose, confounders, and outcome status were determined for each day of follow-up. To better account for dose and timing of past exposures, flexible weighted cumulative exposure models were also fitted.

Results: The cohort consisted of 233 816 older adults including 21 256 acute MI cases. Dose-related increased risks of MI were found with current use of all NSAIDs. In models not accounting for duration of use, ORs (95%CI) for the most common current daily dose vs. no current exposure were: celecoxib 200 mg: 1.16 (1.10, 1.22), diclofenac 150 mg: 1.59 (1.38, 1.84), ibuprofen 1200 mg: 1.42 (1.17, 1.74), naproxen 750 mg: 1.38 (1.21, 1.58), and rofecoxib 25 mg: 1.54 (1.43, 1.66). Weighted cumulative exposure models confirmed that all NSAIDs—including naproxen—are associated with an increased risk of MI and suggested that doses taken up to 3 weeks ago for rofecoxib, ibuprofen, and naproxen and up to 75 days ago for diclofenac and celecoxib may contribute to the current MI risk. However, the celecoxib risk seems to require continuous use for more than 30 days, whereas for other NSAIDs, a heightened MI risk occurs within 7 days.

Conclusions: Weighted cumulative exposure analysis uncovered NSAID-specific differences in the immediate MI risk and how this risk seems to accumulate.

KEYWORDS

acute myocardial infarction (MI), cumulative effects, nonsteroidal anti-inflammatory drugs (NSAIDs), pharmacoepidemiology

1 | INTRODUCTION

Whereas it is generally accepted that oral nonsteroidal anti-inflammatory drugs (NSAIDs) can increase the risk of acute myocardial infarction (MI), their comparative cardiovascular (CV) safety remains incompletely characterized. The Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen Or Naproxen (PRECISION) trial[1] found that celecoxib (209 ± 37 mg) was noninferior to ibuprofen (2045 ± 246 mg) and naproxen (852 ± 103 mg) for adverse CV events in arthritis patients at moderate CV risk.[1,2] PRECISION challenges the conventional orthodoxy[3] that all selective COX-2 inhibitors share the same heightened CV risk as rofecoxib, and it does not support that naproxen results in better cardiovascular outcomes than other NSAIDs.[1]

In PRECISION and other trials,[4] NSAIDs were typically taken on a continuous basis in high standardized doses. This may not represent the clinical reality[5] of many patients who use NSAIDs in low or varying doses or intermittently.[6,7] Unresolved issues about risk of acute MI with NSAIDs include the dose relationship, precise timing of risk onset, and the existence of a cumulative effect, whereby MI risk depends

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both on past and current use. Population-based observational studies are well suited to address the above questions.

To further explore aspects of NSAID exposure that are etiologically relevant, we assembled a population-based cohort reflecting the dynamics of routine use in older adults. We documented the MI risk-NSAID relationship by standard nested case-control (NCC) analysis and then used a novel weighted cumulative exposure (WCE) model[8] to gain additional insights into the temporal relationship between NSAID exposure and acute MI.

KEY POINTS

- Accurate assessment of drug safety requires an etiologically correct model encompassing all relevant aspects of exposure.
- Weighted cumulative exposure models suggest that the relative importance of past doses on the risk of MI differs among NSAIDs.
- All common NSAIDs are associated with an increased MI risk.
- Celecoxib MI risk seems to depend on continuously using the drug for more than 30 days, whereas for ibuprofen, rofecoxib, diclofenac, and naproxen, a heightened MI risk occurs within 7 days of use.

2 | METHODS

2.1 | Data source

We used the universal public insurance databases of Quebec, Canada (RAMQ). Each person's identifier allowed linking individual data involving demographic information, medical services claims, dispensed outpatient prescription drugs, hospitalization data, indicator of hospital mortality, and long term vital statistics. These databases were shown to be valid for this purpose[9,10] including for cardiovascular research.[11,12]

2.2 | Study participants

We assembled an older adult cohort of new NSAID users (first time users or newly treated after a 1-year baseline). Cohort entry was the first NSAID prescription after study start (January 1, 1993), and cohort exit was the earliest of the following dates: study outcome, death, end of insurance coverage, or study end (September 30, 2004). The calendar time frame allowed for comparison with rofecoxib, which is important given the consistency and strength of randomized controlled trial (RCT) evidence for MI risk with this drug.[13-16]

2.3 | Outcome ascertainment

The outcome was the first hospitalization for acute MI, ICD-9[17] code 410.x (positive predictive value 0.979; 95% CI, 0.970-0.985).[11] For nonfatal MI cases, we used a validated definition[18,19] corresponding to local practice relevant to study years. Length of hospital stay had to be at least 3 days, unless the patient was transferred to or from another institution or underwent percutaneous coronary angioplasty.

2.4 | Design of NCC study

We performed an individually matched NCC analysis by randomly selecting 10 controls matched on age ± 1 year, sex, and month/year of cohort entry. Hospital admission date for acute MI was the index date for cases. For their controls, the date that resulted in the same cohort follow-up time was the assigned index date, thereby controlling for potential calendar time effects.

2.5 | Drug exposure ascertainment

NSAID exposure was determined for each day of follow-up for each of the following drugs: celecoxib, diclofenac, ibuprofen, naproxen, rofecoxib, and all other NSAIDs grouped together. Computer-recorded variables allowed the direct calculation of daily dose of NSAIDs as pill strength times number of pills divided by number of days supplied. Days supplied and consecutive prescription dates confirmed the duration of each dispensing and allowed identifying gaps between the end of a prescription and the start of a next one. A priori rules (Tables S1 and S2) were specified to capture behaviors such as intermittent use, dose changes, and drug switches such that patients could not be concurrently exposed to more than one NSAID.

2.6 | Assessment and measurement of covariates

We identified risk factors for the outcome and potential confounders based on substantive knowledge and literature search.[20-23] Via a simplified causal graph,[24] we mapped relationships between variables,[25] including time-dependent confounders that are mediating intermediates on the causal pathway between NSAID exposures and acute MI,[26] then confirmed the final set of confounders (Figure S1). Comorbidities were defined according to validation studies[27-32] and treatment guidelines.[33-36] We relied on ICD-9 codes recorded during hospitalization and on outpatient medications (Table S3). To increase specificity for hypertension, coronary heart disease, congestive heart failure, or rheumatoid arthritis, we used algorithms based on drug dispensing dates. The presence of a comorbidity was confirmed using the first occurrence of ICD-9 codes in the hospital discharge summary or by dispensed drugs over the cohort period preceding the index date, with the following exceptions: (1) potentially mediating comorbidities—hypertension, congestive heart failure, and renal failure—were assessed only before cohort entry and (2) ambulatory claims for comorbidities without any algorithm to overcome the low specificity of drug treatment—chronic pulmonary obstructive disease and gastrointestinal ulcer disease—were considered for the 1-year preceding the index date. Treatment with oral corticosteroids, clopidogrel, and cardioprotective aspirin was ascertained for the 30-day period prior to index date (Figure S2). Ascertainment of aspirin use was done similarly to NSAID exposure. Medication adherence is a strong determinant of effective cardioprotection[37] such that we allowed a grace period of 7 days between 2 refills when defining continuous aspirin exposure status. Indication for cardioprotection was assumed for dosages ranging from 80 mg every other day to 650 mg daily.[38]

2.7 | NSAID exposure and standard NCC analysis

We prespecified 2 alternative definitions of time windows for exposure to each common NSAID (celecoxib, diclofenac, ibuprofen, naproxen, and rofecoxib) and to other NSAIDs grouped together. In the first model, the mutually exclusive binary indicators of use for each NSAID were (1) current use on the index date, (2) recent use 1 to 30 days ago, (3) past use 31 to 180 days ago, or (4) no use in the last 180 days before the index date. In the second model, (1) current use corresponded to index date or up to 7 days before, (2) recent use was 8 to 30 days ago, and (3) and (4) were identical to above. Categories were assessed from (1) to (4) for each NSAID, and once a category was set to 1, the subsequent categories were set to 0, ensuring they were mutually exclusive. These 2 models were repeated by replacing the current use in (1) by current daily dose (continuous variable). Recent and past use in (2) and (3) were not replaced by daily dose because it may vary over the time windows.

An NCC analysis of the cohort was chosen for computational convenience.[39] We estimated the odds ratio (ORs) of acute MI for NSAID exposure-related variables described above, for each NSAID, while adjusting for exposure to the other NSAIDs and potential confounders.

The fit of standard NCC models was compared through the Akaike information criterion (AIC).[40]

2.8 | WCE analysis

NCC data were also analyzed with the WCE model.[8] This model adapts earlier approaches, proposed by Breslow et al,[41] Thomas,[42] Vacek,[43] and Hauptman et al[44,45] to flexible time-to-event or NCC analyses of time-varying exposures.

A WCE combines information about doses, duration, and timing of past treatment into a summary exposure metric, defined as a weighted sum of daily doses from the index date to a specified past time. The WCE metric thus incorporates current, recent, and past use of the drug of interest. The estimated weight function reflects the relative importance of doses taken at different times in the past on the current risk of outcome (see Table S4 for details). Weighted cumulative exposure to each NSAID was modeled in a separate WCE NCC model, while adjusting for the other NSAIDs (using the best-fitting parameterization of standard NCC models described above) and for the same confounders.

In preliminary analyses, we estimated alternative WCE models over time windows ranging from 20 to 180 days, to consider the possibility that NSAID exposure as remote as 180 days might affect the current risk of acute MI, and compared their fit with AIC. In accordance with previous work,[46] we considered differences in AIC below 4 points as minor and differences above 10 points as important.

All analyses were performed in R version 3.0.3.[47,48]

3 | RESULTS

Analyses were conducted with 233 816 individuals, of which 21 256 were acute MI cases (Figure S3). Table S5 presents the prevalence of confounders at index date, which indicates that this older cohort (mean age 77.8 ± 6.1 years) had high baseline coronary risk.

The overall best fit to the data was for the standard NCC model representing current NSAID exposure by daily dose on the index date or any of the 7 prior days (Table S6). Therefore, characterizing NSAID by its dose had a better fit than modeling NSAID use. The fit of WCE dose models was inferior to the best standard NCC model.

3.1 | Standard models

In the standard NCC model, ORs (95% CI) for current exposure to the most common daily dose in this study, taken for any duration of time before the index date, versus no current exposure (dose 0 mg), were celecoxib 200 mg, 1.16 (1.10, 1.22); diclofenac 150 mg, 1.59 (1.38, 1.84); ibuprofen 1200 mg, 1.42 (1.17, 1.74); naproxen 750 mg, 1.38 (1.21, 1.58); and rofecoxib 25 mg, 1.54 (1.43, 1.66) (Table 1).

3.2 | WCE models

Preliminary WCE analyses indicated that the model with a 90-day window was either the best-fitting or yielded an AIC within 5 points of the best model for all five NSAIDs (Figure S4). In addition, weight functions estimated for the alternative time windows within 5 points of the best-fitting were generally similar to the 90-day estimate for the same NSAID, leading to similar interpretation of the results. Therefore, to enhance comparability of results, Figure 1 displays weight functions estimated with a 90-day window, for each NSAID, against time (t) before the index date. By examining plots of WCE weights in Figure 1, we may gain insights on the relative importance of doses taken at different times (eg, 7 vs 30 days before the index date).[8,49-51] Weights close to 0 indicate no impact of the dose taken at that time on current acute MI risk. For all NSAIDs, current and very recent exposure had the greatest impact on MI risk, as reflected by weight peaks near $t = 0$.

For celecoxib and diclofenac, the plots of weights suggest an effect for a dose taken up to 75 days ago (Figure 1). However, WCE weights are not significantly different from constant weights (see Table S7 for details), suggesting that doses from the past 75 days had similar importance. In contrast, for rofecoxib and ibuprofen, the WCE models fitted significantly better than the constant weight models (Table S7). For rofecoxib, ibuprofen, and naproxen, past exposure seems to become practically irrelevant after approximately 3 weeks in the past (Figure 1).

We assessed the MI risk for NSAID common doses with various clinical patterns of NSAID exposure corresponding to only a few days use or to chronic use (Table 2). Odds ratio (95% CI) for the most common current daily dose, taken for the last 90 days before the index date, versus a dose of 0 mg, were celecoxib 200 mg, 1.20 (1.13, 1.27); diclofenac 150 mg, 1.93 (1.59, 2.34); ibuprofen 1200 mg, 1.65 (1.27, 2.16); naproxen 750 mg, 1.39 (1.16, 1.66); and rofecoxib 25 mg, 1.53 (1.39, 1.69) (Table 2). Increasing the NSAID dose was associated with greater MI risk. We also assessed the MI risk with shorter durations of NSAID use. For celecoxib 200 mg taken for 30 days, ORs were 1.06 (0.97, 1.16). An OR approximately 1.20 was noted only after longer term treatment for 75 days with daily celecoxib 200 mg but was observed after short-term treatment of 14 days for diclofenac 100 mg or naproxen 500 mg, and 7 days for ibuprofen 600 mg in this population of older adults. (Table 2).

TABLE 1 Adjusted ORs (with 95% CI) for the association between MI risk and NSAID exposure—standard nested case-control analyses of a RAMQ cohort of older adults

NSAID Exposure[a,b]	OR [95% CI][c,d,e]
Celecoxib	
Past use	1.07 [1.00-1.15]
Recent use	1.26 [1.12-1.41]
Current 100 mg/day	1.08 [1.05-1.10]
Current 200 mg/day	1.16 [1.10-1.22]
Current 400 mg/day	1.34 [1.21-1.48]
Diclofenac	
Past use	1.12 [1.03-1.22]
Recent use	1.29 [1.10-1.51]
Current 75 mg/day	1.26 [1.17-1.36]
Current 100 mg/day	1.36 [1.24-1.50]
Current 150 mg/day	1.59 [1.38-1.84]
Ibuprofen	
Past use	1.13 [0.98-1.30]
Recent use	1.30 [0.98-1.72]
Current 600 mg/day	1.19 [1.08-1.32]
Current 1200 mg/day	1.42 [1.17-1.74]
Current 1800 mg/day	1.70 [1.26-2.29]
Naproxen	
Past use	1.15 [1.04-1.26]
Recent use	1.28 [1.06-1.54]
Current 500 mg/day	1.24 [1.14-1.36]
Current 750 mg/day	1.38 [1.21-1.58]
Current 1000 mg/day	1.54 [1.29-1.84]
Rofecoxib	
Past use	1.07 [0.99-1.15]
Recent use	1.12 [0.98-1.29]
Current 12.5 mg/day	1.24 [1.20-1.29]
Current 25 mg/day	1.54 [1.43-1.66]
Current 50 mg/day	2.38 [2.05-2.76]

Abbreviations: CI, confidence interval; MI, myocardial infarction; NSAID(s), nonsteroidal anti-inflammatory drug(s); OR, odds ratio.

[a]For each NSAID use was characterized as current daily dose = dose of a prescription supply that covered the index date or any of the 7 days before; recent use = duration of prescription supply ended 8 to 30 days before the index date; past use = duration of prescription supply ended 31 to 180 days before the index date; nonuse = no use in the 180 days preceding the index date. For a given NSAID, "current," "recent," "past" use, and "nonuse" categories are mutually exclusive.

[b]A current dose could have been taken for any duration. Past use (31-180 days ago) or recent use (8-30 days ago) could be for any dose and any duration within the time period.

[c]The reference for ORs for past and recent uses for a given NSAID was set to nonuse in the last 180 days of this NSAID. Current dose was modeled a single continuous variable, and ORs were calculated for different typical doses by multiplying the parameter estimate by the doses specified. The OR for a given current dose estimates the change in the MI risk associated with a corresponding increase in the current daily dose, and compares, for example, the current daily dose indicated versus no current exposure (0 mg/day).

[d]Adjusted for current daily dose of each NSAID in this table and for recent and past use of each NSAID in this Table; also adjusted for current, recent, and past use of other prescription NSAIDs grouped as "other NSAIDs".

[e]Adjusted for age at index date, diabetes, hyperlipidemia, hypertension, previous myocardial infarction, coronary heart disease, cerebrovascular disease, congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, gastrointestinal ulcer disease, gastrointestinal bleeding, acute or chronic renal failure, and rheumatoid arthritis, concomitant use of oral corticosteroids, clopidogrel, and cardioprotective aspirin.

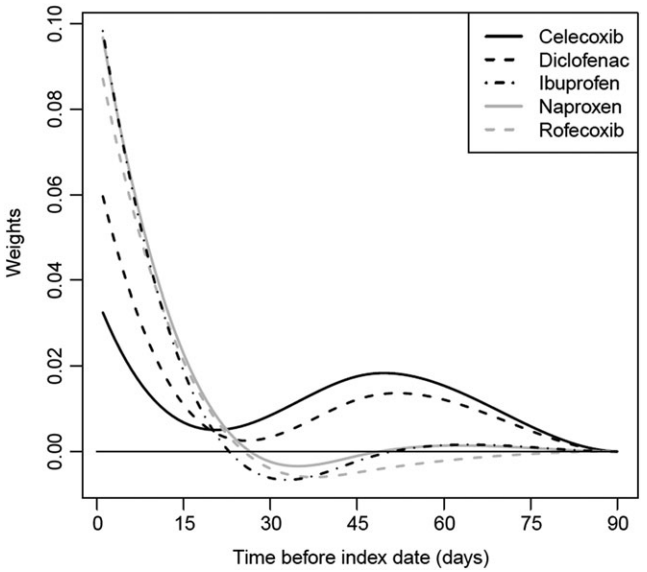

FIGURE 1 Weight functions representing the relative importance of past doses of each NSAID on the current risk of MI against time before the index date in the weighted cumulative exposure nested case-control analyses of a RAMQ cohort of older adults. To plot on the same scale, weight functions were standardized to have an area under the curve (in absolute value) equal to 1. The NSAID-specific weight functions can be compared in terms of the duration but not the strength of the effect. Abbreviations: MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug

4 | DISCUSSION

4.1 | Summary of findings

The methods used in this study provided additional insights into the effect of dose and temporal relationship of risk of acute MI associated with NSAIDs. Our results indicate that all NSAIDs are associated with a dose-related increased risk of acute MI. For celecoxib, unlike for other NSAIDs, previous use over a long period seems to be needed to observe an increase in MI risk (Table 2).

4.2 | Comparison with other research

A meta-analysis of patient-level data (NSAIDs IPD MA),[52] which included the RAMQ data studied herein, found that all commonly prescribed NSAIDs were associated with a dose-related increased risk of acute MI. Onset of risk was in the first week. Use in the first month at a high daily dose was associated with the greatest harms. With treatment for longer than 1 month, MI risk remained elevated but did not seem to continue to increase even further. However, the NSAIDs IPD MA could not further characterize the temporal association of NSAIDs with MI or ascertain whether the effect of past doses of NSAIDs persisted and affected current risk.[52] The ORs calculated from WCE models (Table 2) estimated the risk of acute MI for daily dose of the NSAID used during the last "x" days before the index date and nonuse for the preceding days (e.g., use of the NSAID for the last 7 days and nonuse for the preceding 83 days) (OR numerator) versus nonuse of this NSAID over a full 90-day period (OR denominator). Findings of the WCE analysis therefore allowed disentangling the

TABLE 2 Adjusted ORs (with 95% CI) for the association between MI risk and various clinical patterns of NSAID exposure—weighted cumulative exposure nested case-control analyses of a RAMQ cohort of older adults

	OR [95% CI][a, b]							
NSAID and daily dose	Use for the last 1 day	Use for the last 3 days	Use for the last 7 days	Use for the last 14 days	Use for the last 21 days	Use for the last 30 days	Use for the last 75 days	Use for the last 90 days
Celecoxib								
100 mg	1.00 [1.00-1.01]	1.01 [0.99-1.03]	1.02 [0.98-1.05]	1.02 [0.98-1.07]	1.03 [0.98-1.07]	1.03 [0.99-1.08]	1.09 [1.06-1.13]	1.09 [1.06-1.13]
200 mg	1.01 [0.99-1.02]	1.02 [0.98-1.05]	1.03 [0.97-1.10]	1.05 [0.96-1.14]	1.05 [0.97-1.15]	1.06 [0.97-1.16]	1.19 [1.12-1.27]	1.20 [1.13-1.27]
400 mg	1.01 [0.98-1.04]	1.03 [0.96-1.11]	1.06 [0.93-1.21]	1.09 [0.92-1.29]	1.11 [0.93-1.32]	1.13 [0.95-1.35]	1.42 [1.26-1.60]	1.44 [1.26-1.62]
Diclofenac								
75 mg	1.02 [1.00-1.04]	1.06 [1.01-1.11]	1.11 [1.02-1.21]	1.16 [1.04-1.30]	1.18 [1.05-1.32]	1.19 [1.06-1.34]	1.38 [1.25-1.51]	1.39 [1.26-1.53]
100 mg	1.03 [1.00-1.05]	1.07 [1.01-1.15]	1.15 [1.02-1.29]	1.22 [1.05-1.42]	1.25 [1.07-1.45]	1.26 [1.08-1.48]	1.53 [1.35-1.74]	1.55 [1.36-1.76]
150 mg	1.04 [1.00-1.08]	1.11 [1.01-1.23]	1.23 [1.03-1.47]	1.35 [1.08-1.69]	1.39 [1.11-1.75]	1.42 [1.12-1.79]	1.90 [1.57-2.29]	1.93 [1.59-2.34]
Ibuprofen								
600 mg	1.03 [1.01-1.06]	1.09 [1.02-1.17]	1.19 [1.04-1.35]	1.29 [1.09-1.52]	1.32 [1.11-1.56]	1.30 [1.10-1.55]	1.28 [1.12-1.46]	1.29 [1.13-1.47]
1200 mg	1.07 [1.01-1.12]	1.19 [1.03-1.37]	1.41 [1.09-1.82]	1.65 [1.19-2.30]	1.73 [1.24-2.42]	1.70 [1.20-2.41]	1.65 [1.26-2.14]	1.65 [1.27-2.16]
1800 mg	1.10 [1.02-1.19]	1.30 [1.05-1.61]	1.67 [1.14-2.46]	2.13 [1.30-3.49]	2.28 [1.38-3.77]	2.22 [1.32-3.73]	2.11 [1.42-3.13]	2.12 [1.42-3.16]
Naproxen								
500 mg	1.02 [1.00-1.05]	1.07 [1.00-1.13]	1.14 [1.02-1.27]	1.22 [1.06-1.40]	1.25 [1.08-1.44]	1.25 [1.07-1.45]	1.24 [1.11-1.40]	1.25 [1.11-1.40]
750 mg	1.04 [1.00-1.07]	1.10 [1.01-1.21]	1.21 [1.03-1.43]	1.34 [1.08-1.65]	1.39 [1.12-1.72]	1.39 [1.11-1.75]	1.39 [1.17-1.65]	1.39 [1.16-1.66]
1000 mg	1.05 [1.00-1.10]	1.14 [1.01-1.29]	1.30 [1.04-1.62]	1.48 [1.11-1.96]	1.55 [1.16-2.07]	1.56 [1.15-2.11]	1.55 [1.23-1.96]	1.55 [1.22-1.97]
Rofecoxib								
12.5 mg	1.03 [1.02-1.04]	1.08 [1.05-1.11]	1.17 [1.11-1.22]	1.27 [1.19-1.34]	1.30 [1.22-1.38]	1.30 [1.22-1.38]	1.24 [1.18-1.30]	1.24 [1.18-1.30]
25 mg	1.06 [1.04-1.08]	1.17 [1.11-1.23]	1.36 [1.24-1.50]	1.59 [1.41-1.79]	1.69 [1.50-1.90]	1.69 [1.49-1.91]	1.53 [1.39-1.69]	1.53 [1.39-1.69]
50 mg	1.12 [1.07-1.16]	1.36 [1.22-1.51]	1.85 [1.53-2.24]	2.54 [2.00-3.22]	2.86 [2.25-3.63]	2.85 [2.22-3.67]	2.35 [1.94-2.85]	2.34 [1.93-2.85]

Abbreviations: CI, confidence interval; OR, odds ratio; MI, myocardial infarction; NSAID), nonsteroidal anti-inflammatory drug).

[a]The OR estimates the risk of acute MI for daily dose of the NSAID used during the last "x" days (as indicated for each column) and, where applicable, nonuse (dose of 0 mg) for the preceding days of the 90-day time window (OR numerator), versus nonuse of this NSAID over the 90-day time window (OR denominator).

[b]Refer to Table 1 for description of adjustments.

effect of current dosing from that of a previous use of the NSAID in the recent or remote past. Assuming that misclassification and residual confounding similarly affected both studies, we surmise that the reason why the NSAIDs IPD MA found an increased MI risk with use of celecoxib for less than 1 week (which corresponds to initiating celecoxib or restarting its use) while the WCE model did not is that the NSAIDs IPD MA was also capturing the MI risk from previous histories of celecoxib use.

The overall findings from our study are aligned with the PRECISION trial[1] and do not support that naproxen has a lower MI risk. Nondifferential NSAID exposure misclassification may explain why there was no evidence of MI risk increase with naproxen in the Safety Of non-Steroidal anti-inflammatory drugs meta-analysis of observational studies,[53] which included studies for which the reference group was NSAID users in the recent past (>60 days before index date)[54,55] and studies defining as "current use" any use in a time window possibly remote (90 days[56] or 180 days[57]) from the event date.

Summaries of risk for acute MI with NSAIDs obtained in placebo-controlled RCTs are available from 2 network meta-analyses, one with aggregate data (Trelle et al)[4] and the other with IPD (Coxib and traditional NSAID Trialists' (CNT) Collaboration).[3] The bulk of placebo-controlled direct evidence suggesting a neutral effect for naproxen came from clinical trials in populations with, or at risk of, Alzheimer disease.[4] Nonadherence bias, documented in such patient populations,[58] may translate into an underestimation of the risk with naproxen in meta-analyses of RCTs. Moreover, these previous meta-analyses of trials[3,4] were underpowered to determine MI risk with naproxen and were inconclusive. While the rate ratio was <1 in the CNT meta-analysis,[3] confidence interval was too wide to exclude a clinically meaningful MI risk increase of 35%. As for celecoxib, the risk of MI was not considered separately for the various selective COX 2 inhibitors in the CNT meta-analysis.[3] Our results indicate that there seems to be differences between rofecoxib and celecoxib on risk of acute MI, which agrees with the findings for celecoxib in the PRECISION trial.[1]

4.3 | Strengths

The design of this study offered gains in accuracy and precision compared with many previous studies of NSAIDs and acute MI risk. We found a marked MI risk increase with rofecoxib, for which numerous RCTs[16,59] have reliably shown an increased cardiovascular risk. Confounding was controlled by matching on demographics and calendar time and by multivariable regression on comorbidities and concomitant treatments selected based on a causal diagram. Setting the study before withdrawal of rofecoxib—a timeframe during which the choice of NSAID by a typical prescriber was unrelated to a patient's MI risk—further minimized the possibility of confounding by indication (ie, prescribing naproxen for cardioprotection) or by contraindication (ie, not prescribing a COX-2 selective inhibitor to patients with preexisting cardiovascular disease).

4.4 | Limitations

Future analyses may consider using continuous doses for current, recent, and past exposure based on the piecewise constant latency model described by Langholz et al. [60] This approach might improve the accuracy of our standard NCC analyses and, by accounting for both the latency and dose, may approximate the results of the WCE models.

There is no obvious correlate between weight functions in this study and the documented pharmacokinetics or pharmacodynamics of NSAIDs. Examining WCE weight functions with a suitable biological marker of immediate and cumulative effects on MI risk might reveal further pharmacological differences between NSAIDs. This requires additional research.

Although measuring confounder and exposure status for each follow-up day helped reduce misclassification, the actual use of NSAIDs may differ from drug dispensing records.[61] However, this study does not systematically overestimate MI risks because this would mean that misclassification resulting from prescriptions being a proxy for actual intake affected cases and controls in a differential manner. Underascertainment of OTC ibuprofen and cardioprotective aspirin use may have occurred although the older adults enrolled in this study likely sought a prescription to be reimbursed for the cost of these medications.[62] Whereas exposure to ibuprofen may have been underestimated due to OTC use, especially for short-term low doses, it may have been overestimated when ibuprofen was prescribed "as needed." Overall, the combined influence of various sources of exposure measurement error may have biased results towards the null. No sensitivity analyses were done to assess whether the rules that were applied to resolve inconsistent or complicated dispensing profiles (Tables S1 and S2) might have affected the results.

We suspect that there is residual confounding because substantive knowledge[63-65] ascertains that there are mediating variables between NSAID exposures and acute MI (Figure S1). Since we had no access to data collected during routine health encounters, we were unable to adjust for NSAID-related blood pressure increases or renal deterioration over time, which are known to occur and may differ among NSAIDs.[1] Previous work[54,66] provides insight on the risk of bias due to unobserved confounders in database studies (obesity, OTC aspirin or NSAID use, smoking, income, or educational attainment), which suggests that failure to adjust for these confounders might slightly underestimate MI risk.[67] Based on literature[20,23,68] (and the anticipated direction of bias to the null) and because unadjusted and confounder-adjusted estimates of acute MI risk are quite similar (Table S8), we believe that unmeasured and incompletely measured confounders are unlikely to affect the substantive conclusions of this study.

Some patients who did not seek contact with the healthcare system may possibly have taken an NSAID (purchased OTC or previously dispensed) to try alleviating chest pain. However, we believe that physicians correctly identified prodromal symptoms of MI and that patients with chest pain who sought medical help and were subsequently diagnosed with acute MI did not self-medicate with NSAIDs. Although these could not be studied, we do not expect that silent MIs or out-of-hospital fatal MIs would differ from documented MI by exposure to NSAIDs.

4.5 | Implication for policy and research

Odds ratio of acute MI for current exposure to commonly available NSAIDs at their defined daily dose,[69] taken for any duration of

time before the index date, indicates an associated increase in risk of 15% for celecoxib (200 mg), 25% for naproxen (500 mg), 35% for diclofenac (100 mg), 40% for ibuprofen (1200 mg), and 55% for rofecoxib (25 mg) (Table 1). Depending on the NSAID, given the baseline coronary risk of the studied population, the absolute risk of MI associated with NSAID use can be estimated to about 0.5% to 1% per year. Although this absolute MI risk increase is small, NSAID use is very prevalent in older adults. The novel aspect of this work, revealed by the WCE analysis, is the suggestion that celecoxib is the safest NSAID on an MI endpoint, if used for 30 days or less (Table 2).

This study also highlights the importance of appropriately selecting the comparison group. Nonuse may be inappropriate when it implies a contraindication for use such that nonusers are fundamentally different from users,[70] which is not the case for NSAIDs. The conservative definition of nonuse reduced the possibility of confounding that might arise if sicker patients recently stopped taking NSAIDs.

Weighted cumulative exposure modeling proved to be useful as a companion analysis tool. The standard model suggested that timing of past NSAID exposure mattered and WCE models emphasize a key epidemiological concept:[71,72] Risk should be assessed over a time window that is etiologically relevant.

5 | CONCLUSION

Despite the wealth of literature published since the 2004 withdrawal of rofecoxib, this is the first study precisely characterizing the time course of acute MI risk with NSAIDs. Results suggest that determining the onset of risk, effect of dose, and impact of past exposure on current risk is valuable when investigating unintended drug effects.

ETHICS STATEMENT

The study was approved by the McGill University Health Centre Research Ethics Board (13-380-SDR).

CONFLICT OF INTEREST

JMB receives salary support from the Fond de Recherche du Québec – Santé (FRQS). The authors declare no other conflict of interest.

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SUPPORTING INFORMATION

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