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ORIGINAL ARTICLE

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Risk of myocardial infarction associated with non-steroidal anti-inflammatory drugs: Impact of additional confounding control for variables collected from self-reported data

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Summary

What is known and objective: Important risk factors and over-the-counter (OTC) dispensing of non-steroidal anti-inflammatory drugs (NSAIDs) are often not routinely recorded in electronic health records. This study aimed to assess the impact of patient's reports on these factors on the risk of acute myocardial infarction (AMI) for NSAID use.

Methods: A nested case-control study was conducted among adults in the Utrecht Cardiovascular Pharmacogenetics study. Cases were patients with a first diagnosis of AMI as a hospital discharge diagnosis and controls were those without AMI. NSAID exposure was either current use of selective COX-2 inhibitors or conventional NSAIDs. Information was collected from The Dutch PHARMO Database Network (pharmacy records of drug dispensing linked to hospitalization records) and the patient's questionnaire (lifestyle factors, body mass index and history of cardiovascular diseases). Unconditional logistic regression analysis was used to calculate odds ratios (ORs) and to control for confounding factors.

Results: We identified 970 AMI cases and 2974 controls. Among cases, 11 (1.1%) and 185 (19.1%) were exposed to selective COX-2 inhibitors and conventional NSAIDs, respectively. Compared to non-use, none of these drug classes were associated with an increased risk of AMI (adjusted OR 1.07, 95% CI: 0.52-2.18 and 0.93, 95% CI: 0.77-1.12, respectively). Additional adjustment for potential confounders from patient's reports did not change the risk estimates (adjusted OR 1.08, 95% CI: 0.53-2.22 and 0.89, 95% CI: 0.73-1.09, respectively).

What is new and conclusion: Additional confounding control for variables from self-reported data or considering self-reported OTC NSAID use did not change the risk estimates for the association between NSAIDs and AMI.

KEYWORDS

acute myocardial infarction, conventional NSAIDs, patient's reports, pharmacoepidemiology, pharmacy records, selective COX-2 inhibitors, Utrecht cardiovascular pharmacogenetics study

1 | WHAT IS KNOWN AND OBJECTIVES

Previous studies demonstrated that individuals taking non-steroidal anti-inflammatory drugs (NSAIDs) have an increased risk of cardiovascular (CV) adverse events compared to either non-users or past users.[1,2] Both conventional NSAIDs and selective cyclooxygenase-2 (COX-2) inhibitors increase the risk of stroke and CV death.[3] The latter drugs are also associated with an increased risk of acute myocardial infarction (AMI).[3,4]

Several observational studies utilize databases containing prescription data from general practices, dispensing data from pharmacy records or claims data from the health insurance companies to assess the association between NSAIDs and the risk of CV toxicity.[5-7] Although these databases routinely collect information on age, sex, medication use and comorbidities, they often do not record over-the-counter (OTC) NSAID use.[8,9] As a consequence, estimating the actual NSAID use is difficult and then might cause an exposure misclassification. Furthermore, these databases often do not either have information on important risk factors for CV diseases such as lifestyle factors (smoking, alcohol use and physical activity), body mass index (BMI) and familial history of CV diseases.[10] When these potential confounders are not taken into account, risk estimates for the association between NSAIDs and CV toxicity might be less accurate. To complement information on these confounding factors, patient's self-reports could be utilized.

Our objectives were as follows: to assess the impact of adjustment for additional potential confounders collected from patient's reports on the risks of AMI associated with either selective COX-2 inhibitors or conventional NSAIDs compared to non-use; and to evaluate the effect of integrating OTC NSAID use collected from patient's report to pharmacy record on this association.

2 | METHODS

2.1 | Design and data sources

We used The Utrecht Cardiovascular Pharmacogenetics (UCP) study. This nested case-control study consisted of a cohort of patients 18 years old or older and at least 1 year in the Dutch PHARMO Database Network. They received a dispensing of at least one of anti-hypertensive drugs (low-ceiling diuretics, β-blockers, angiotensin-converting enzyme [ACE] inhibitors, calcium antagonists, angiotensin II type I receptor blockers [ARB], other anti-hypertensive drugs or combination of anti-hypertensive drugs), cholesterol-lowering drugs (statins) and/or had total cholesterol >5 mmol/L. This network includes 2 million Dutch inhabitants and links drug dispensing histories from community pharmacies to The National Registration of Hospital Discharge Diagnoses and laboratory data. The UCP study was initially aimed to evaluate the interaction between patients' genetic profile and CV drug use on the risk of AMI. The eligible cases and controls in the UCP study were then contacted to participate through their community pharmacies. If they agreed, they were asked to return a filled-in questionnaire and informed consent (Appendix S1). Information on height, weight, history of coronary artery diseases and stroke, alcohol consumption, smoking habits and physical activity, and familial history of AMI and stroke was collected. In the questionnaire, information was collected using both closed and open-ended questions. Closed questions (yes/no) were used for the status of hypertension, hypercholesterolaemia and other comorbidities, and open-ended questions for the type of drugs. Participants were asked to list drugs they used as either branded or generic names. We then grouped branded drugs and their generic ones to the substance names. We excluded patients with a discrepancy in age or sex between The Dutch PHARMO Database Network and filled-in questionnaires, or who had had a previous AMI. The Medical Ethics Committee of the University Medical Center Utrecht, The Netherlands, has approved this study and written informed consent was obtained from participants.

2.2 | Outcome

Cases included patients with a hospital discharge diagnosis as first AMI according to the International Code for Diseases (ICD-9 code 410) during the period August 1986-December 2005. AMI diagnosis in the Dutch PHARMO Database Network has high sensitivity and positive predictive values by 84% and 97%, respectively.[11] The date of a patient hospitalized with first AMI was the index date. Controls were patients without AMI before and at the index date. They should be active in the database at the index date. One case was matched to up to 13 controls on sex and age (±1 year) at the index date.

2.3 | Exposure definition

Based on pharmacy records, cases and controls were classified as current NSAID users if the index date fell between the dispensing date of last NSAIDs and its theoretical end-date. The end-date was determined from the dispensing date plus the total duration of NSAID use (days), that is, the total numbers of drug dispensed divided by the frequency of NSAID use per day. We considered current use as the closest exposure to the index date for those who switched medications from conventional NSAIDs to selective COX-2 inhibitors, or vice versa. Those who were not current NSAID users, but dispensed any NSAIDs before the index date, were defined as past users. Non-users were those who were not dispensed any NSAIDs before and at the index date.

Based on patient's questionnaire, NSAID use was defined as any NSAIDs taken within 2 months before the index date from both pharmacy dispensing and OTC medications, whereas non-users were defined as those who were not taking any NSAIDs within this period. This period is considered a maximum duration for patients to recall information accurately. Information on NSAID use from patient's reports was also integrated into pharmacy records to analyse the risk of AMI. Since we had no information about NSAID use more than 2 months prior to the AMI event from self-reported questionnaire data, and also to minimize recall bias, we excluded past users of NSAIDs from the analyses. Those who were dispensed or used

selective COX-2 inhibitors and conventional NSAIDs concomitantly were also excluded. Probably, the patients who had an overlap in the dispensing of selective COX-2 inhibitors and conventional NSAIDs, in reality, did not use both drugs together but switched from one to the other. Unfortunately, it is not clear when a switch took place. NSAIDs were defined according to The Anatomical Therapeutic Classification (ATC), including selective COX-2 inhibitors (M01AH) and conventional NSAIDs (M01AA, M01AB, M01AC, M01AE, M01AG and M01AX01).

2.4 | Potential confounders

We considered several potential risk factors for CV diseases to evaluate the risk of AMI for NSAID use. From pharmacy records, we included CV drug use within 3 months before the index date including diuretics, beta-blockers, calcium channel blockers, ACE inhibitors, ARB, antithrombotic agents (vitamin K antagonists and platelet aggregation inhibitors), cholesterol-lowering drugs and anti-diabetic agents (including insulin). A history of angina was defined as a dispensing of at least two prescriptions of nitrates within the year before the index date as validated in our previous study.[12] Since patients with angina are not automatically hospitalized, and nitrates are almost exclusively given for coronary artery diseases, the dispensing of nitrates was then used as a proxy of a diagnosis of stable angina pectoris. A history of ischaemic heart diseases and stroke was defined from the hospital discharge registries (ICD-9 430-436, except for 435) before the index date. From the questionnaire, we considered height, weight, medication use, lifestyle factors and history of CV diseases. Ideally, these variables collected from the questionnaires are assessed at the initiation of exposure. Since questionnaires did not accommodate this assessment, this information is considered as a proxy for the actual variable status at the time of exposure.

2.5 | Data analyses

Characteristics of cases and controls were compared using a *t* test or a chi-square test for continuous variables and categorical variables, respectively. Since we excluded past use and concomitant use of conventional NSAIDs or selective COX-2 inhibitors, the original matching between cases and controls was lost. Therefore, we applied an unconditional logistic regression analysis to estimate the crude and adjusted odds ratios (ORs) of AMI. In all analyses, we adjusted for matching factors. We used two different sources of exposure: first from pharmacy records only and second from pharmacy records complemented with patient's reports.

We applied multiple adjustment methods to assess the ORs. Initially, the ORs were determined without adjustment (crude). We then adjusted for potential confounders collected from pharmacy records. We then additionally adjusted for BMI, lifestyle factors and history of CV diseases from patient's reports. Finally, the latter adjustment method was repeated, but information on co-medications and history of CV diseases from patient's reports was added to such information from pharmacy records. These statistical models were presented in Appendix S2. Missing values were handled by multiple imputation methods with fully conditional specification using five sets of the data set. In this iterative method, all other available variables in the model are used as predictors. We also evaluated the interaction of the exposures to age and sex as a function of the synergy index (SI). This SI measures whether the effect of this interaction exceeds the product of the individual effects of the two exposures. The interaction is positive if the SI > 1 and negative if the SI < 1. The precision of the interaction is determined by a 95% CI of SI. This interaction term was assessed only for the total study population because of the small sample size for participants who returned the questionnaires. All statistical analyses were performed by statistical software IBM SPSS version 25, and the significance threshold was 5%.

3 | RESULTS

3.1 | Characteristics of the study population

A total of 45 981 eligible patients were identified in the Dutch PHARMO Database Network for UCP study including 4843 AMI cases and 41 138 non-cases. The median number of controls per case was 11. Of cases, 2372 patients were dispensed anti-hypertensive drugs, 1302 patients had hypercholesterolaemia, and other 1169 patients had both. We excluded 5797 patients (12.61%) as either they were concomitant or past users of selective COX-2 inhibitors or conventional NSAIDs leaving 4106 cases and 36 078 controls. Compared to controls, cases were slightly older (66.6 years old vs 66.0 years old) and more likely to be male (66.2% vs 62.8%). In general, cases were unlikely to take CV drugs, but more likely to take insulin and to have a history of angina.

Of the total population, 4536 patients (9.9%) returned the questionnaire, consisting of 23.7% and 8.2% for cases and controls, respectively. We excluded 115 concomitant or 477 past users of conventional NSAIDs or selective COX-2 inhibitors leaving 970 cases and 2974 controls (Figure 1). Compared to controls, cases were older (63.7 years old vs 63.3 years old), more likely to be male (74.5% vs 74.3%) and to have a history of CV diseases, but unlikely to take CV and anti-diabetic agents. No significant differences were found between cases and controls with regard to BMI, lifestyle factors and familial history of CV diseases. Missing values were found for BMI, lifestyle factors and a history of CV diseases. The highest proportion of missing values was found for alcohol use by 18.6% and 17.5% for cases and controls, respectively.

For cases who returned the questionnaire, the mean age was lower, but the proportion of males was higher compared to cases regardless of the completion of the questionnaire. They were less likely to be exposed to cardiovascular and anti-diabetic agents or to have a history of cardiovascular diseases (Table 1). According to pharmacy record data, cases who returned the questionnaire were more likely to take CV drugs, but unlikely to take anti-diabetic agents or to have a history of CV diseases compared to patient's reports (Appendix S3).

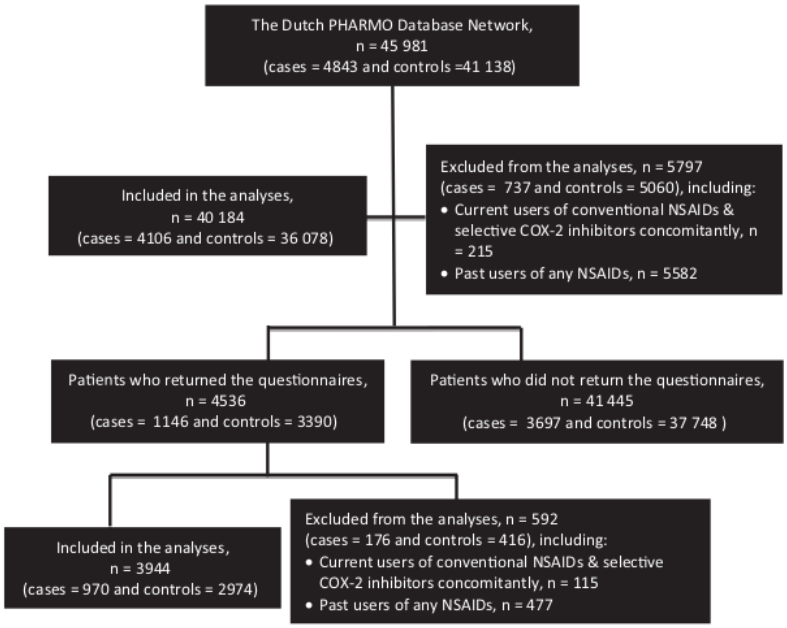

FIGURE 1 Flow chart of study

3.2 | Risks of AMI and the impact of additional confounding control for variables

For patients regardless of completion of the questionnaire, selective COX-2 inhibitors increased the risk of AMI by 38% (adjusted OR 1.38, 95% CI: 1.08-1.77) compared to non-use after adjustment for potential confounders from pharmacy records. In contrast, conventional NSAIDs did not increase the risk (adjusted OR 0.98, 95% CI: 0.90-1.07). Additional adjustment for potential confounders collected from patient's report did not change the risk for both selective COX-2 inhibitors and conventional NSAIDs compared to non-use (Table 2).

However, when the analyses were performed among those who returned the questionnaire with information on NSAID use was retrieved from pharmacy records, the estimated risks changed. Neither selective COX-2 inhibitors nor conventional NSAIDs increased the risk of AMI (adjusted OR 1.00, 95% CI: 0.46-2.17 and adjusted OR 0.81, 95% CI: 0.66-1.00), respectively, compared to non-use after adjustment for potential confounders from pharmacy records. These estimated risks did not change after additional adjustment for potential confounders collected from patient's reports nor incorporating information on co-medications and history of CV diseases from patient's reports to pharmacy records. Incorporating information on the exposures from patient's reports into pharmacy records did not seem to change the ORs for any of the adjusted models. Interestingly, the AMI risk for selective COX-2 inhibitors collected from the pharmacy records and the questionnaire decreased from OR 1.08 (95% CI; 0.53-2.22) to OR 0.74, (95% CI; 0.31-1.74) after incorporating information on co-medications and history of CV diseases from patient's report to pharmacy records (Table 3).

3.3 | Effect modification

In all patients regardless of completion of the questionnaire, selective COX-2 inhibitors were associated with a higher risk for the elderly (≥65 years old) but a similar risk of AMI for adults (18-64 years old). In contrast, conventional NSAIDs were associated with lower risk compared to non-use for adults, but a similar risk for the elderly. Selective COX-2 inhibitors were also associated with a higher risk compared to non-use for females, but a similar risk for males. The similar risk was found for both sex dispensed conventional NSAIDs. The interaction between age and conventional NSAIDs was statistically significant, but not between age and selective COX-2 inhibitors nor between sex and either selective COX-2 inhibitors and conventional NSAIDs. Additional adjustment for potential confounders collected from patient's reports did not change the ORs in each subgroup for both selective COX-2 inhibitors and conventional NSAIDs (Tables 4 and 5).

4 | DISCUSSION

Our results showed that for all participants regardless of the completeness of questionnaire, selective COX-2 inhibitors, but not conventional NSAIDs, increased the risk of AMI after adjustment for potential confounders collected from pharmacy records. Our findings supported previous systematic reviews of clinical trials and observational studies.[1,2,4] However, among patients who returned the questionnaire, both selective COX-2 inhibitors and conventional NSAIDs were not associated with an increased risk. The issue of selection bias might explain these findings. Of those who returned the questionnaire, cases were more likely to participate than controls (23.7% vs 8.2%).

TABLE 1 Characteristics of the study population based on data sources

Variable	PHARMO database[a]			Patient's reports		
	Cases (n = 4106)	Controls (n = 36 078)	*P*-value	Cases (n = 970)	Controls (n = 2974)	*P*-value
Age, mean (years ± SD)	66.58 ± 11.72	66.00 ± 11.39	0.002*	63.65 ± 10.30	63.31 ± 9.28	0.341
Male, n (%)	2720 (66.2)	22 665 (62.8)	0.000*	723 (74.5)	2211 (74.3)	0.905
Body mass index, n (%)						
>30 (kg/m^2)	–	–	–	194 (20.0)	521 (17.5)	0.135
Unknown	–	–		32 (3.3)	153 (5.1)	
Co-medications						
Cardiovascular drugs, n (%)						
Diuretics	1061 (25.8)	11 609 (32.2)	0.000*	113 (11.6)	476 (16.0)	0.001*
Beta-blockers	1611 (39.2)	14 547 (40.3)	0.179	339 (34.9)	990 (33.3)	0.342
Calcium channel blockers	982 (23.9)	6906 (19.1)	0.000*	215 (22.2)	637 (21.4)	0.624
ACE inhibitors	813 (19.8)	9211 (25.5)	0.000*	190 (19.6)	718 (24.1)	0.003*
ATII receptor antagonists	300 (7.3)	3394 (9.4)	0.000*	104 (10.7)	404 (13.6)	0.021*
Cholesterol-lowering drugs	917 (22.3)	9436 (26.2)	0.000*	298 (30.7)	727 (24.4)	0.000*
Vitamin K antagonists	242 (5.9)	2436 (6.8)	0.037*	137 (14.1)	320 (10.8)	0.004*
Platelet aggregation inhibitors	1,228 (29.9)	9503 (26.3)	0.000*	244 (25.2)	475 (16.0)	0.000*
Anti-diabetic agents, n (%)						
Insulin	572 (13.9)	4359 (12.1)	0.001*	86 (8.9)	178 (6.0)	0.002*
Oral anti-diabetic agents	423 (10.3)	3384 (9.4)	0.056	77 (7.9)	249 (8.4)	0.670
Lifestyle factors						
Smoking status, n (%)						
Current smoker	–	–	–	131 (13.5)	318 (10.7)	0.056
Past smoker	–	–		358 (36.9)	1151 (38.7)	
Non-smoker	–	–		437 (45.1)	1361 (45.8)	
Unknown	–	–		44 (4.5)	144 (4.8)	
Exercise level (h/wk), n (%)						
>4	–	–	–	411 (42.4)	1308 (44.0)	0.357
≤4	–	–		450 (46.4)	1362 (45.8)	
No-exercise	–	–		97 (10.0)	256 (8.6)	
Unknown	–	–		12 (1.2)	48 (1.6)	
Alcohol use (glass/d), n (%)						
>2	–	–	–	62 (6.4)	252 (8.5)	0.173
1-2	–	–		258 (26.6)	743 (25.0)	
<1	–	–		349 (36.0)	1100 (37.0)	
Non-drinker	–	–		121 (12.5)	358 (12.0)	
Unknown	–	–		180 (18.6)	521 (17.5)	
A history of cardiovascular diseases, n (%)						
Coronary artery diseases (angina & myocardial infarction)	262 (27.0)	413 (13.9)	0.000*	1164 (28.3)	5159 (14.3)	0.000*
Stroke	50 (5.2)	162 (5.4)	0.726	308 (7.5)	1986 (5.5)	0.000*
Familial history of cardiovascular diseases						
Myocardial infarction, n (%)						
Yes	–	–	–	321 (33.1)	902 (30.3)	0.110
Unknown	–	–		26 (2.7)	84 (2.8)	

(Continues)

TABLE 1 (Continued)

Variable	PHARMO database[a] Cases (n = 4106)	Controls (n = 36 078)	*P*-value	Patient's reports Cases (n = 970)	Controls (n = 2974)	*P*-value
Stroke, n (%)						
Yes	–	–	–	317 (32.7)	935 (31.4)	0.455
Unknown	–	–		33 (3.4)	98 (3.3)	

ACE, Angiotensin-converting enzyme; ATII, angiotensin II antagonist; COX, cyclooxygenase; NSAIDs, non-steroidal anti-inflammatory drugs.
[a]patients in pharmacy records regardless of the completion of questionnaires
*Statistically significant ($P < 0.05$).

TABLE 2 Odds ratios of acute myocardial infarction for non-steroidal anti-inflammatory drug users among all patients regardless the completeness of questionnaire

Exposures	Cases (n = 4106)	Controls (n = 36 078)	Crude OR (95% CI)	Adj. OR[a] (95% CI)	Adj. OR[b] (95% CI)
Non-use, n (%)	3327 (81.0)	29 386 (81.5)	1	1	1
Selective COX-2 inhibitors, n (%)	78 (1.9)	512 (1.4)	1.35 (1.06-1.71)*	1.38 (1.08-1.77)*	1.39 (1.09-1.77)*
Conventional NSAIDs, n (%)	701 (17.1)	6180 (17.1)	1.00 (0.92-1.09)	0.98 (0.90-1.07)	0.98 (0.94-1.03)

Adj., Adjusted; CI, confidence interval; COX, cyclooxygenase; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio.
[a]Adjusted for age, sex, the index date, co-medications and a history of cardiovascular diseases routinely collected in pharmacy records.
[b]Adjusted for [a]plus body mass index, lifestyles and familial history of cardiovascular diseases collected from patient's reports.
*Statistically significant ($P < 0.05$).

Our study also found that additional adjustment for potential confounders or additional information on NSAID use collected from patient's reports did not change the risk estimates for either all patients regardless the completeness of questionnaire or patients who returned the questionnaire. These results may be explained by the fact that these confounders might be relatively minor for this association or are already adjusted by proxy (captured by recorded information), or inaccurate measurement of confounders.[13] The latter explanation is unlikely as we previously demonstrated that several lifestyle factors that were measured in our study were associated with the risk of AMI.[14] Our findings supported earlier observational studies on the impact of lifestyle factors on the association between drugs affecting the nervous systems and fractures, and statin and joints revision.[15-17] It might also be caused by incorporating the patient's information on NSAID use into pharmacy records did not substantially change the proportion of NSAID use among cases and

TABLE 3 Odds ratios of acute myocardial infarction for non-steroidal anti-inflammatory drug users among patients who returned the questionnaire

	Cases (n = 970)	Controls (n = 2974)	Crude OR (95% CI)	Adj. OR[a] (95% CI)	Adj. OR[b] (95% CI)	Adj. OR[c] (95% CI)
Exposures from pharmacy records						
Non-use, n (%)	821 (84.6)	2432 (81.8)	1	1	1	1
Selective COX-2 inhibitors, n (%)	9 (1.0)	28 (0.9)	0.95 (0.45-2.03)	1.00 (0.46-2.17)	1.00 (0.46-2.19)	1.11 (0.36-3.36)
Conventional NSAIDs, n (%)	140 (14.4)	514 (17.3)	0.81 (0.66-0.99)*	0.81 (0.66-1.00)	0.82 (0.66-1.01)	0.85 (0.63-1.16)
Exposures from pharmacy records and questionnaire						
Non-use, n (%)	774 (79.8)	2336 (78.5)	1	1	1	1
Selective COX-2 inhibitors, n (%)	11 (1.1)	32 (1.1)	1.04 (0.52-2.07)	1.07 (0.52-2.18)	1.08 (0.53-2.22)	0.74 (0.31-1.74)
Conventional NSAIDs, n (%)	185 (19.1)	606 (20.4)	0.92 (0.77-1.11)	0.93 (0.77-1.12)	0.89 (0.73-1.09)	0.87 (0.68-1.11)

Adj., Adjusted; CI, confidence interval; COX, cyclooxygenase; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio.
[a]Adjusted for age, sex, the index date, co-medications and a history of cardiovascular diseases routinely collected in pharmacy records.
[b]Adjusted for [a]plus body mass index, lifestyles and familial history of cardiovascular diseases collected from patient's reports.
[c]Adjusted for [b]complemented with data from patient's reports for co-medications and history of cardiovascular diseases.
*Statistically significant ($P < 0.05$).

TABLE 4 Odds ratios for acute myocardial infarction among total participants regardless of the completion of the questionnaire in pharmacy records exposed to NSAIDs stratified by age

	Cases	Controls	Crude OR (95% CI)	Crude SI (95% CI)	Adj. OR[a] (95% CI)	Adjusted SI[a] (95% CI)	Adj. OR[b] (95% CI)	Adjusted SI[b] (95% CI)
18-64 y old				1.29 (0.76-2.19)		1.32 (0.77-2.25)		1.16 (0.74-1.81)
Non-use, n (%)	1379 (81.6)	12 302 (79.9)	1		1		1	
Selective COX-2 inhibitors, n (%)	22 (1.3)	174 (1.1)	1.13 (0.72-1.76)		1.16 (0.74-1.82)		1.16 (0.74-1.82)	
≥65 y old								
Non-use, n (%)	1948 (80.6)	17 084 (82.6)	1		1		1	
Selective COX-2 inhibitors, n (%)	56 (2.3)	338 (1.6)	1.45 (1.09-1.94)*		1.49 (1.12-2.00)*		1.49 (1.12-2.00)*	
18-64 y old				1.26 (1.06-1.50)*		1.26 (1.06-1.50)*		0.86 (0.75-0.98)*
Non-use, n (%)	1379 (81.6)	12 302 (79.9)	1		1		1	
Conventional NSAIDs, n (%)	288 (17.1)	2912 (18.9)	0.88 (0.77-1.01)		0.86 (0.75-0.99)*		0.86 (0.75-0.99)*	
≥65 y old								
Non-use, n (%)	1948 (80.6)	17 084 (82.6)	1		1		1	
Conventional NSAIDs, n (%)	413 (17.1)	3268 (15.8)	1.11 (0.99-1.24)		1.08 (0.96-1.21)		1.08 (0.96-1.21)	

Adj., Adjusted; CI, confidence interval; COX, cyclooxygenase; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; SI, synergy index.
[a]Adjusted for sex, index date, co-medications, lifestyle factors and a history of cardiovascular diseases routinely collected in pharmacy records.
[b]Adjusted for [a]plus body mass index, lifestyles and familial history of cardiovascular diseases collected from patient's reports.
*Statistically significant ($P < 0.05$).

controls. However, the AMI risk for selective COX-2 inhibitors collected from the pharmacy records and the questionnaire decreased after incorporating information on co-medications and history of CV diseases from patient's report to pharmacy records. A potential explanation might be the discrepancies between information collected from pharmacy records and patient's report, especially patients reported to have a history of coronary artery diseases more than three times higher than derived from pharmacy records (85.7% vs 28.3%).

Utilizing an electronic health database for conducting pharmacoepidemiological studies has advantages. As data collected routinely, prospectively are not linked to specific research questions, recall bias is minimal. When direct information about comorbidities is not available, information on drug use might be applied as a proxy.[18,19] Nevertheless, this database has several limitations. For instance, the actual drug use is not ascertained in pharmacy dispensing records. Thus, medication use might be overestimated (if patients do not take or stop the medications) or underestimated (if OTC drug use is not recorded). Likewise, significant risk factors for CV events, often, are not routinely recorded.[20,21]

Incorporating patient's reports on information that is not routinely available in electronic databases can increase the accuracy in the risk estimate. Nevertheless, this data source is subject to limitations. A significant limitation of patient's reports is an issue of recall bias. A low concordance between information collected from pharmacy records and patient's reports was found in our study, as well as other studies.[22-24] The gap between the event occurred and the time to recall partly affected the patient's ability to recall information. The later the event they recall, unlikely the valid the information is.[25] Patients might also conceal information because of social or medical desirability.[26] Missing values on important risk factors such as alcohol use might lead to under- or overestimated risks as alcohol was significantly associated with CV events.[27] Thus, self-reporting data are not recommended as a single instrument to collect information.[23,26]

4.1 | Strengths and limitations

We identified several strengths. First, we minimized an exposure misclassification as NSAIDs were stratified into selective COX-2 inhibitors and conventional NSAIDs, and OTC NSAID use was considered. Second, we reduced the unmeasured confounding effect by including important potential confounders that are not available in the Dutch PHARMO Database Network. Lastly, the diagnosis of AMI in this database has high sensitivity and positive predictive values.[11]

Nevertheless, this study has some limitations. First, an issue of selection bias is our primary concern. Some characteristics of the total population are different from those who returned the questionnaire. We did not include patients who were naïve of using anti-hypertensive drugs or of having hypercholesterolaemia or those who had died

TABLE 5 Odds ratios for acute myocardial infarction among total participants regardless the completion of the questionnaire in pharmacy records exposed to NSAIDs stratified by sex

	Cases	Controls	Crude OR (95% CI)	Crude SI (95% CI)	Adj. OR[a] (95% CI)	Adjusted SI[a] (95% CI)	Adj. OR[b] (95% CI)	Adjusted SI[b] (95% CI)
Female				0.63 (0.38-1.02)		0.65 (0.40-1.06)		0.65 (0.39-1.06)
Non-use, n (%)	1063 (76.7)	10 648 (79.4)	1		1		1	
Selective COX-2 inhibitors, n (%)	45 (3.2)	260 (1.9)	1.73 (1.26-2.39)*		1.66 (1.20-2.31)*		1.66 (1.19-2.31)*	
Male								
Non-use, n (%)	2264 (83.2)	18 738 (82.7)	1		1		1	
Selective COX-2 inhibitors, n (%)	33 (1.2)	252 (1.1)	1.08 (0.75-1.56)		1.10 (0.77-1.61)		1.11 (0.77-1.61)	
Female				0.86 (0.72-1.02)		0.88 (0.73-1.05)		0.88 (0.73-1.05)
Non-use, n (%)	1063 (76.7)	10 648 (79.4)	1		1		1	
Conventional NSAIDs, n (%)	278 (20.1)	2505 (18.7)	1.12 (0.97-1.28)		1.06 (0.92-1.22)		1.06 (0.92-1.22)	
Male								
Non-use, n (%)	2264 (83.2)	18 738 (82.7)	1		1		1	
Conventional NSAIDs, n (%)	423 (15.6)	3675 (16.2)	0.95 (0.85-1.06)		0.93 (0.83-1.04)		0.93 (0.83-1.04)	

Adj., Adjusted; CI, confidence interval; COX, cyclooxygenase; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; SI, synergy index.
[a]Adjusted for age, index date, co-medications, lifestyle factors and a history of cardiovascular diseases routinely collected in pharmacy records.
[b]Adjusted for [a]plus body mass index, lifestyles and familial history of cardiovascular diseases collected from patient's reports.
*Statistically significant ($P < 0.05$).

because of complication from first AMI. Hence, extrapolation of our findings to patients with first AMI without hypertension and/or hypercholesterolaemia is not easily possible. Our previous study demonstrated that some characteristics of responders were also different from non-responders. Females were less likely to participate, as well as the elderly. However, no differences were found for anti-hypertensive drug use and history of cardiovascular diseases.[28] Second, recall bias may be an issue because we found discrepancies on information collected from patient's reports and pharmacy records. Information bias due to recall bias might cause a differential misclassification. Misclassification of confounders may lead to residual confounding. Third, we might overestimate NSAID use. All dispensing NSAIDs were considered a regular use medication. Likewise, the survey did not assess the frequency of NSAID use. Hence, it did not allow us to distinguish between incidental and regular use. Forth, we had a small sample size that led to insufficient power to detect a relatively weak association between NSAIDs and AMI. Finally, we did not consider the dosage of NSAID use. A recent meta-analysis showed that the dosages of NSAIDs modified the risk of AMI.[29]

5 | WHAT IS NEW AND CONCLUSION

Additional adjustment for potential confounders collected from patient's reports and complementing information of pharmacy records on NSAID use with patient's report did not affect the risk estimate of AMI for either selective COX-2 inhibitors or conventional NSAIDs. Additional information collected from patient's reports, including information about OTC NSAID use, apparently did not give an added value for the study on the association between NSAIDs and the risk of AMI. Our findings indicated that pharmacy record data might be used as a single data source to obtain valid estimated risks.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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