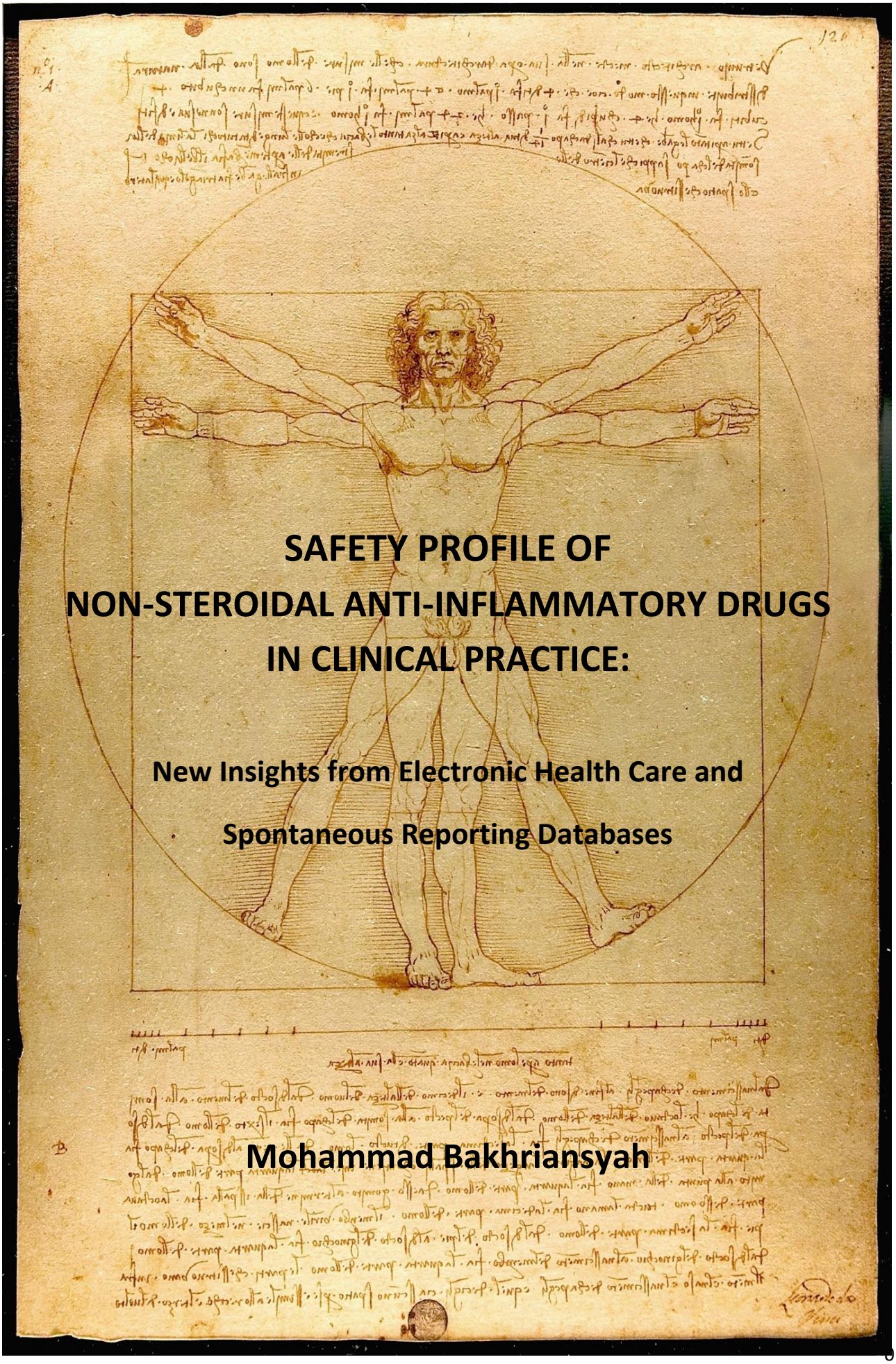

SAFETY PROFILE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN CLINICAL PRACTICE:

New Insights from Electronic Health Care and Spontaneous Reporting Databases

Mohammad Bakhriansyah

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Veiligheidsprofiel van Niet-Steroide Ontstekingsremmers in de Klinische Praktijk:

Nieuwe Inzichten van Elektronische Gezondheidszorg en Spontane Rapportage Databases

(met een samenvatting in het Nederlands)

Profil Keamanan Obat Anti-inflamasi Non-Steroid di Praktek Klinik:

Kajian Baru Menggunakan Pangkalan Data Elektronik Layanan Kesehatan dan Pelaporan Spontan

(dengan ringkasan dalam Bahasa Indonesia)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van
de rector magnificus, prof. dr. H.R.B.M Kummeling, ingevolge het besluit
van het college voor promoties in het openbaar te verdedigen
op woensdag 6 november 2019 des middags te 2.30 uur

door

Mohammad Bakhriansyah
geboren op 25 december 1973 te Amuntai, Indonesië

Promotoren : Prof.dr. A. de Boer

Prof.dr. O.H. Klungel

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“Education makes a people easy to lead, but difficult to drive;

easy to govern, but impossible to enslave”

– Henry Peter Brougham

“Live as if you were to die tomorrow.

Learn as if you were to live forever.”

- Gandhi

CHAPTER I

GENERAL INTRODUCTION

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are potent drugs with anti-inflammatory, pain-killing, and anti-pyretic effects (1, 2). These drugs are useful in the treatment of musculoskeletal problems such as rheumatoid arthritis, osteoarthritis, and chronic low back pain (3-5). Two types of NSAIDs are now known namely conventional NSAIDs and selective cyclooxygenase (COX)-2 inhibitors (1, 2). Selective COX-2 inhibitors were developed later with minimal gastrointestinal (GI) complications that are often found among conventional NSAID users (6, 7). More than 30 million people worldwide use NSAIDs daily as either on a prescription basis or an over-the-counter (OTC) purchase (8). In the US alone, >1000 million courses of NSAIDs are prescribed annually (9). Now, a large number of NSAIDs is available; a few of them such as mefenamic acid, ibuprofen, diclofenac, and naproxen can be purchased as OTC analgesics in certain countries (10).

According to their relative inhibitory potency towards COX enzymes, NSAIDs are classified into 1) conventional or non-selective NSAIDs, i.e., NSAIDs that inhibit both COX-1 and COX-2 enzymes, and 2) selective COX-2 inhibitors, .i.e., NSAIDs that are more likely to inhibit COX-2 than COX-1 enzyme (2). Conventional NSAIDs inhibit COX enzyme activities that are responsible for the formation of prostaglandin (PG) H_2 from arachidonic acid. Prostaglandin H_2 is the direct precursor for various PGs and thromboxane (TXA_2) (11). Both COX-1 and COX-2 enzymes are physiologically found in some organs, including the blood vessels, stomach, kidneys, spinal cords, and brain, but COX-2 enzyme is mainly expressed in the kidneys and brain (1, 10, 11). The COX-1 enzyme is responsible for the physiological regulation and production of prostanoids for inflammatory responses and platelet aggregation. TXA_2 synthesized by COX-1 enzyme in platelets promotes vasoconstriction, smooth muscle proliferation, and platelet aggregation. PGI_2 in vessel walls plays an essential role in homeostatic defense mechanism that causes vasodilatation and inhibits platelet aggregation. Conventional NSAIDs inhibit COX enzymes that block TXA_2 and PGI_2, while selective COX-2 inhibitors create an imbalance between these chemical mediators and shift the protective effects attributable to PGI_2. These mechanisms might increase the risk of thrombosis. In the GI mucosa, COX-1 enzyme produces bicarbonate and mucus and regulates blood flow and epithelial proliferation. In the

urinary systems, PGs are involved in sodium reabsorption in renal tubules and antagonize antidiuretic effects of vasopressin. The imbalance between PGs and leukotriene is responsible for the clinical features of hypersensitivity reactions (HSRs) (1, 12, 13). The COX-2 enzyme is released as a response to the inflammatory or mitogenic stimulus of monocytes, macrophages, neutrophil, and endothelial cells (10, 14). In the musculoskeletal system, the production of PGs triggers local activities of COX enzymes that promote bone formation and resorption. COX enzymes, especially COX-2 stimulate the formation of osteoclasts, inflammatory proteins, hormones, and growth factors. COX-2 enzyme increases the expression of receptor activator for nuclear factor-kappa β and decreases osteoprotegerin in bone metabolism (15).

NSAIDs can also be categorized based on their chemical groups in accordance to The Anatomical Therapeutic Chemical (ATC) Classification System, i.e., butylpyrazolidines, acetic acid derivatives and related substances (AADs), oxicams, propionic acid derivatives (PADs), fenamates, coxibs, and any other NSAIDs that are not included elsewhere. Another chemical classification that is often used is based on the presence/absence of a sulfonamide functional group in their chemical structures (3, 4, 16-19). The varying degrees of inhibitory potency of NSAIDs against COX enzymes (6) and the differences in the chemical groups are suspected of playing a role in the differences in their both therapeutic and adverse effects, including in sensitizing capacities and hypersensitivity risks. Hence, these both effects of NSAIDs can be predicted based on these characteristics.

A significant concern about NSAIDs is that NSAIDs are one of the most reported drug classes associated with adverse events in various human body systems (16, 17). The short and long-term beneficial effects of NSAID use are partly counterbalanced by their adverse drug reactions (ADRs), especially in susceptible individuals, with either atopy, pre-existing risk profiles, or co-medications (10, 20). These ADRs range from minor to severe toxicities such as stomach perforation, ulcer, and bleeding (PUB) in the GI system (21, 22), acute renal failure and glomerulonephritis in the urinary system (23-25) especially for conventional NSAID use, and acute myocardial infarction (AMI), atrial fibrillation, stroke, and CV death in the CV system especially for selective COX-2 inhibitor use (26-31). NSAIDs have also been associated with ADRs in the immunological system such as a higher risk of allergy and anaphylaxis (32). NSAIDs are known

to affect the musculoskeletal system by increasing the risk of joint replacement, fracture, and its following events such as non-union and secondary fracture (33-37). In the urinary system, the percentage of patients exposed to NSAIDs develop ADRs are considered low (1-5%) (38). However, NSAIDs are among the most prescribed drugs, and some of them are available OTC, these small increases in risk can affect a high absolute number of patients.

Many studies have demonstrated ADRs of NSAID use in the human body. However, still much is unknown with regards to the risk of various adverse events related to the CV and urinary systems. Other non-cardiorenal adverse effects also require further investigation, for instance, HSRs and bone implant-related effects. Although well-established, even the association between NSAID use and the risk of GI toxicity remains of interest, because these associations were assessed in separate studies. Hence, they differed in various aspects such as study design, exposure, and outcome definitions that lead to heterogeneity for deriving conclusions.

THESIS OBJECTIVES

In general, the objectives of this thesis are to evaluate the association between NSAID use and the risk of several adverse outcomes in various human body systems by using electronic health care databases. More specifically, our primary objectives are to assess the risk of adverse events related to the cardio-renal, immune, GI, and musculoskeletal systems either within NSAID users or in comparison to non-users.

THESIS OUTLINE

This thesis consists of five chapters. Following the General Introduction (**Chapter 1), Chapter 2-7** present the clinical perspectives of NSAIDs-associated adverse events in various human body systems, including the risk of out-of-hospital cardiac arrests with documented ventricular tachycardia/ventricular fibrillation (VT/VF-OHCA) **(Chapter 2**), nephrotic syndrome (NS) **(Chapter 3**), PUB **(Chapter 4**), HSRs

(**Chapter 5**), and revision surgery of lower joint replacements (LJRs) (**Chapter 6**). In **Chapter 7**, we present methodological aspects of observational studies on the adverse events of NSAID use, i.e., the impact of additional confounding control for variables collected from self-reported data on the risk of AMI during NSAID use. Finally, in the General Discussion **(Chapter 8),** we discuss the main findings of the studies presented in this thesis from the perspective of existing literature. We also identify strengths and limitations and discuss potential clinical implications and future research.

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CHAPTER 2

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

AND THE RISK OF OUT-OF-HOSPITAL CARDIAC ARRESTS:

A CASE-CONTROL STUDY

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ABSTRACT

Background: Non-steroidal anti-inflammatory drugs (NSAIDs), particularly selective COX-2 inhibitors, are associated with an increased risk of cardiovascular adverse events. However, the association between these drugs and out-of-hospital cardiac arrest with electrocardiogram-documented ventricular tachycardia/ventricular fibrillation (VT/VF-OHCA) has not been studied yet.

Purposes: This study was aimed to evaluate the association between the use of selective COX-2 inhibitors or conventional NSAIDs and VT/VF-OHCA compared to nonuse.

Methods: A case-control study was conducted among 2,483 cases with VT/VF-OHCA from the AmsteRdam REsuscitation STudies (ARREST) registry, an ongoing Dutch registry of OHCA, and 10,441 non-VT/VF-OHCA-controls from the Dutch PHARMO Database Network, containing drug dispensing records of community pharmacies, over the period July 2005 – December 2011. Up to 5 controls were matched for age and sex to one case at the date of VT/VF-OHCA (index date). Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated by conditional logistic regression analysis.

Results: Of the cases, 0.5% was currently exposed at the index date to selective COX-2 inhibitors and 2.5% to conventional NSAIDs. Neither current use of selective COX-2 inhibitors nor conventional NSAIDs were associated with an increased risk of VT/VF-OHCA (adjusted OR 1.11, 95%CI: 0.79-1.56 and adjusted OR 0.97, 95%CI: 0.86-1.10, respectively) compared to nonuse. Stratification for VT/VF-OHCA with presence/absence of acute myocardial infarction did not change these results.

Conclusions: Exposure to selective COX-2 inhibitors or conventional NSAIDs was not associated with an increased risk of VT/VF-OHCA compared to nonuse.

INTRODUCTION

Cardiovascular diseases are a major cause of death in adults, with sudden cardiac arrest as the main cause (1). In the Netherlands, according to data published in 2010, the yearly incidence of out-of-hospital cardiac arrest (OHCA) was 9.7 per 10,000 persons, contributing to 17.8% of total morbidity (2).

Previously, we found that, in the Netherlands, 19.8% of OHCA cases were taking anti-inflammatory agents including non-steroidal anti-inflammatory drugs (NSAIDs) (3). NSAIDs are associated with an increased risk of cardiovascular adverse events. *In vivo* and *in vitro* studies indicated that NSAIDs influence cardiac electrophysiological properties by impacting various cardiac ion channels such as the Na channel (4), various K channels (5, 6), and the L-type Ca channel (4, 5). The effects on these properties may lead to cardiac arrhythmia such as ventricular tachycardia (VT) and/or ventricular fibrillation (VF), the main causes of OHCA (7).

We aimed to establish the risk of OHCA with documented VT/VF (VT/VF-OHCA) for the use of selective COX-2 inhibitors or conventional NSAIDs. Since acute myocardial infarction (AMI) is an important underlying cause of VT/VF-OHCA (8, 9), we also stratified the analyses of VT/VF-OHCA cases for patients according to their AMI status. Finally, we assessed whether the association between NSAIDs and VT/VF-OHCA was different for various durations of drug exposure, and subgroups of age and sex.

METHODS

Study design

A population-based case control study was performed using the AmsteRdam REsuscitation STudies (ARREST) registry and the Dutch PHARMO Database Network. OHCA cases were obtained from ARREST and age/sex/index-date matched non-OHCA controls were selected from the PHARMO. The date of the OHCA was defined as the index date.

Consent

The ARREST study is conducted based on the principles of the Declaration of Helsinki and has been approved by the Ethics Committee of The Academic Medical Center, Amsterdam. Written informed consent was obtained from all patients who survived OHCA. For patients who did not survive, the use of their data was approved by the Ethics Committee.

Data sources

The ARREST registry is an ongoing, prospective community-based database to evaluate determinants of OHCA including genetic, clinical, environmental and pharmacological information. Patients with an OHCA in the North Holland province of the Netherlands are included in the database. This area covers 2671 km^2 with more than 2.4 million inhabitants in 2014 according to Statistics Netherlands. ECGs recordings from the ambulance monitors/defibrillators or automated external defibrillators are used to determine whether VT/VF occurred. Further information about OHCA cases is collected from ambulance dispatch to hospital discharge or until death based on the Utstein template for uniform reporting of data from OHCA (10). Information on drug use by OHCA cases is obtained from the patient's community pharmacists. Detailed information on the ARREST registry is described elsewhere (3).

The PHARMO Database Network is a population-based network of electronic healthcare databases combining data from different primary and secondary healthcare settings in the Netherlands, including community pharmacies and hospitals. It provides detailed information on hospital discharge diagnoses and drug dispensing information obtained from community pharmacies including date, dose, and duration. More than 4 million (25%) inhabitants are registered in this database. Clinical diagnoses are recorded according to The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) (11).

Case and control definitions

In this case-control study, cases were patients with VT/VF-OHCA during the period July 2005–December 2011. Patients with OHCA were excluded when non-cardiac causes were documented and/or

only asystole (without VT/VF) was found in ECG recordings. All ECG recordings were analyzed by using the software Code Stat Reviewer 7.0, Physio-Control Redmond, Washington, USA. AMI status for patients with VT/VF-OHCA was determined according to ECG recordings, enzymatic findings, and/or cardiovascular procedures (percutaneous transluminal coronary angioplasty and/or stenting), as reported in the hospital charts. Controls were age/sex-matched individuals without OHCA at the index date, drawn from the PHARMO Database Network. Up to 5 controls were drawn per case.

Exposures

The use of selective COX-2 inhibitors or conventional NSAIDs in cases and controls was evaluated. We used the Anatomical Therapeutic Chemical (ATC) Classification system for conventional NSAIDs (ATC-codes M01AA, M01AB, M01AC M01AE, M01AG, M01AX) and selective COX-2 inhibitors (M01AH) (**Supplementary, Table S1**). Patients were considered as current users if the index date fell between the dispensing date of any NSAIDs and the theoretical end date of a dispensing. If any NSAID was discontinued within 3 months prior to the index date, they were considered as recent users. Subjects were considered as past users when NSAID use was discontinued more than 3 months prior to the index date, while those who did not receive any NSAIDs during the defined observation time window were classified as nonusers. A patient who was prescribed both conventional NSAIDs and selective COX-2 inhibitors at different time windows was classified as a user of a conventional NSAID or selective COX-2 inhibitor (whichever was closest to the index date). We allowed for a ≤30 days gap between the end date of the previous dispensing to assume continuous exposure anticipating carry-over effects and non-adherence to the medications. The duration of current use at the index date was then classified into 2 categories: either <183 days (<6 months), or 183-365 days (6-12 months) before the index date.

Potential confounders

Current use of class I or III antiarrhythmic drugs (C01B, C07AA07) or non-antiarrhythmic class 1 or 2 QTc-prolonging drugs (12) were evaluated as potential confounders (**Supplementary, Table S2** and **S3**). Several other medications were also taken into account within the 6 months period before the index date,

including cardiovascular drugs (antithrombotic agents (ATC-code B01A), cardiac glycosides (C01A), organic nitrates (C01DA), anti-hypertensive drugs (C02), diuretics (C03), beta-adrenoceptors blockers (C07), calcium-antagonists (C08), agents acting on the renin-angiotensin system (C09), and/or statins (C10AA)); anti-diabetic drugs (insulins and analogues (A10A), and/or blood glucose lowering drugs (A10B)), and at least two drugs for obstructive pulmonary disease (R03).

Data-analyses

Chi-square (X^2) test and t-test were used to compare baseline characteristics of cases and controls. Odds ratios (ORs) and 95% of confidence interval (95% CI) for the association between selective COX-2 inhibitors or conventional NSAIDs and VT/VF-OHCA were estimated by conditional logistic regression analysis. Adjusted ORs were calculated with adjustment for all potential confounders. We also stratified our analyses for the duration of current NSAID use, age, and sex and performed separate regression analyses within different strata. All statistical analyses were performed using IBM Statistic SPSS 23 and p-values of <0.05 were considered statistically significant. We performed a power calculation using the PS Power and Sample Size program which takes a matched case-control study design into consideration (13). With the number of cases (n=2,483) and controls (n=10,441) available and a percentage of conventional NSAID use in controls of 2.5%, we were able to detect an odds ratio from 1.38 as statistically significant with a power of 80% and an α of 0.05. For selective COX-2 inhibitors, with a percentage of 0.3% in controls, we could detect an odds ratio from 1.9 as statistically significant. In the subgroup analyses of VT/VF patients in the context of AMI (994 cases and 4,171 controls), these odds ratios were 1.62 and 2.54, respectively.

RESULTS

Characteristics

We identified 2,483 cases and 10,441 controls during the 79-months observation period. Their baseline characteristics are shown in **Table 1**. The mean age was 65.5 years for both groups, whereas 77.5% of cases and 77.4% of controls were male. Cases were more likely to receive antiarrhythmic or non-

antiarrhythmic QTc-prolonging drugs, cardiovascular drugs, anti-diabetic drugs, and obstructive pulmonary disease drugs compared to controls.

Among cases, 40.0% and 21.6% had AMI and non-AMI, respectively. In the remaining 38.3%, AMI status could not be established, because they died before hospital admission.

Table 1 Baseline characteristics of the cases and controls

Variables	Cases (n=2,483)	Controls (n=10,441)	p-value
Age, mean (years ± sd)	65.49 ± 14.48	65.47 ± 14.32	NA
Sex, n (%)			
Women	560 (22.6)	2,354 (22.5)	NA
Co-medication(s), n (%)			
Antiarrhythmic drugs[1]	45 (1.8)	36 (0.3)	<0.001*
Non-antiarrhythmic QTc-prolonging drugs[1]	231 (9.3)	639 (6.1)	<0.001*
Drugs used within 6 months prior to the index date, n (%)			
Cardiovascular drugs[2]	1,601 (64.5)	5,258 (50.4)	<0.001*
Anti-diabetic drugs[3]	394 (15.9)	1,115 (10.7)	<0.001*
Obstructive pulmonary disease drugs[4]	144 (5.8)	92 (0.9)	<0.001*

Cases: patients with out-of-hospital cardiac arrest with documented ventricular tachycardia/ventricular fibrillation. Controls: age/sex/index date-matched non-cardiac arrest patients.

Abbreviations: NA = Not Applicable

[1]Concomitant current use of class I and III antiarrhythmic or non-antiarrhythmic drugs with (possible) risk of QT prolongation at the index date, [2]Use of any following drugs: antithrombotic agents, cardiac glycosides, organic nitrates, anti-hypertensive, diuretics, beta-adrenoceptors blockers, calcium-antagonists, agents acting on the renin-angiotensin system, and/or statins, [3]Use of antidiabetic drugs: insulin and/or oral anti-diabetics, [4]Use of at least 2 drugs for obstructive pulmonary diseases

*statistically significant ($p<0.05$)

Risk of VT/VF-OHCA for NSAID users

Current use of selective COX-2 inhibitors was not associated with an increased risk of VT/VF-OHCA compared to nonuse (adjusted OR 1.11; CI 95%, 0.79-1.56), neither was recent or past use. Similarly, neither current nor past use of conventional NSAIDs were associated with an increased risk of VT/VF-OHCA compared to nonuse (adjusted OR 0.97; CI95%, 0.86-1.10 and adjusted OR 0.94; CI95%, 0.87-1.02, respectively) (**Table 2**).

Table 2 Odds ratios of out-of-hospital cardiac arrest with documented ventricular tachycardia/ ventricular fibrillation for users of conventional NSAIDs and selective COX-2 inhibitors with nonusers as the reference group

Exposure	Cases (n = 2,483)	Controls (n = 10,441)	Crude OR (95% CI)	Adjusted OR[Ŧ] (95% CI)
Nonuse, n (%)	2,066 (83.2)	8,085 (77.4)	1	1
Current use, n (%)				
Conventional NSAIDs	63 (2.5)	266 (2.5)	0.98 (0.87-1.12)	0.97 (0.86-1.10)
Selective COX-2 inhibitors	12 (0.5)	32 (0.3)	1.10 (0.78-1.55)	1.11 (0.79-1.56)
Recent use, n (%)				
Conventional NSAIDs	194 (7.8)	1,195(11.4)	0.92 (0.87-0.98)*	0.92 (0.86-0.98)*
Selective COX-2 inhibitors	14 (0.6)	70 (0.7)	0.96 (0.75-1.22)	0.97 (0.76-1.23)
Past use, n (%)				
Conventional NSAIDs	126 (5.1)	760 (7.3)	0.93 (0.86-1.00)	0.94 (0.87-1.02)
Selective COX-2 inhibitors	8 (0.3)	33 (0.3)	0.99 (0.70-1.41)	1.01 (0.71-1.43)

Abbreviations: CI = Confidence Interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio

[Ŧ]adjusted for antiarrhythmic drugs, non-antiarrhythmic QT-prolonging drugs, cardiovascular drugs, antidiabetic drugs, and obstructive pulmonary diseases drugs

*statistically significant ($p<0.05$)

When we stratified our analyses according to AMI status, we found that both selective COX-2 inhibitors and conventional NSAIDs had a similar non-elevated risk of VT/VF-OHCA compared to nonuse for both cases with or without AMI (**Table 3** and **4**).

Differences in the duration of NSAID use, age, and sex and the association between current NSAID use and the risk of VT/VF-OHCA

Differences in the duration of NSAID use, age, and sex were not associated with the different risks of VT/VF-OHCA for either selective COX-2 inhibitor or conventional NSAID use compared to nonuse. The risk was similar for selective COX-2 inhibitors and conventional NSAIDs (**Table 5, 6,** and **7**).

Table 3 Odds ratios of out-of-hospital cardiac arrest with documented ventricular tachycardia/ ventricular fibrillation in the context of acute myocardial infarction for users of conventional NSAIDs and selective COX-2 inhibitors with nonusers as the reference group.

Exposure	Cases (n = 994)	Controls (n = 4,171)	Crude OR (95% CI)	Adjusted OR[Ŧ] (95% CI)
Nonuse, n (%)	822 (82.7)	3,247 (77.8)	1	1
Current use, n (%)				
Conventional NSAIDs	26 (2.6)	103 (2.5)	1.00 (0.82-1.22)	0.99 (0.81-1.21)
Selective COX-2 inhibitors	2 (0.2)	11 (0.3)	0.94 (0.50-1.74)	0.92 (0.50-1.71)
Recent use, n (%)				
Conventional NSAIDs	88 (8.9)	472 (11.3)	0.95 (0.86-1.05)	0.94 (0.85-1.04)
Selective COX-2 inhibitors	5 (0.5)	21 (0.5)	0.99 (0.64-1.53)	1.00 (0.64-1.54)
Past use, n (%)				
Conventional NSAIDs	47 (4.7)	307 (7.4)	0.92 (0.81-1.04)	0.93 (0.82-1.05)
Selective COX-2 inhibitors	4 (0.4)	10 (0.2)	1.13 (0.62-2.06)	1.13 (0.62-2.08)

Abbreviations: CI = Confidence Interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio

[Ŧ]adjusted for antiarrhythmic drugs, non-antiarrhythmic QT-prolonging drugs, cardiovascular drugs, antidiabetic drugs, and obstructive pulmonary diseases drugs

Table 4 Odds ratios of out-of-hospital cardiac arrest with documented ventricular tachycardia/ ventricular fibrillation without acute myocardial infarction for users of conventional NSAIDs and selective COX-2 inhibitors with nonusers as the reference group.

Exposure	Cases (n = 537)	Controls (n = 2,262)	Crude OR (95% CI)	Adjusted OR[Ŧ] (95% CI)
Nonuse, n (%)	455 (84.7)	1,747 (77.2)	1	1
Current use, n (%)				
Conventional NSAIDs	13 (2.4)	59 (2.6)	0.96 (0.74-1.26)	0.94 0.72-1.23)
Selective COX-2 inhibitors	3 (0.6)	11 (0.5)	1.00 (0.55-1.82)	1.06 (0.58-1.93)
Recent use, n (%)				
Conventional NSAIDs	38 (7.1)	248 (11.0)	0.91 (0.79-1.05)	0.90 0.78-1.04)
Selective COX-2 inhibitors	1 (0.2)	15 (0.7)	0.84 (0.49-1.46)	0.87 (0.50-1.51)
Past use, n (%)				
Conventional NSAIDs	26 (4.8)	178 (7.9)	0.91 (0.77-1.07)	0.92 (0.79-1.09)
Selective COX-2 inhibitors	1 (0.2)	4 (0.2)	0.98 (0.36-2.66)	1.11 (0.41-3.01)

Abbreviations: CI = Confidence Interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio

[Ŧ]adjusted for antiarrhythmic drugs, non-antiarrhythmic QT-prolonging drugs, cardiovascular drugs, antidiabetic drugs, and obstructive pulmonary diseases drugs

Table 5 Odds ratios of out-of-hospital cardiac arrest with documented ventricular tachycardia/ ventricular fibrillation for current users of NSAIDs stratified by the duration of drug exposure

< 182 days (<6 months)	**Cases (n = 2,119)**	**Controls (n = 8,308)**	**Crude OR (95% CI)**	**Adjusted OR[Ŧ] (95% CI)**
Nonuse, n (%)	2,066 (97.5)	8,085 (97.3)	1	1
Conventional NSAIDs, n (%)	47 (2.2)	206 (2.5)	1.12 (0.81-1.54)	1.25 (0.89-1.74)
Selective COX-2 inhibitors, n (%)	6 (0.3)	17 (0.2)	0.73 (0.29-1.84)	0.67 (0.26-1.72)
182 -365 days (6-12 months)	**Cases (n = 2,088)**	**Controls (n = 8,160)**	**Crude OR (95% CI)**	**Adjusted OR[Ŧ] (95% CI)**
Nonuse, n (%)	2,066 (98.9)	8,085 (99.1)	1	1
Conventional NSAIDs, n (%)	16 (0.8)	60 (0.7)	0.96 (0.55-1.67)	1.05 (0.60-1.84)
Selective COX-2 inhibitors, n (%)	6 (0.3)	15 (0.2)	0.64 (0.25-1.65)	0.58 (0.22-1.52)

Abbreviations: CI = Confidence Interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio

[Ŧ]adjusted for antiarrhythmic drugs, non-antiarrhythmic QT-prolonging drugs, cardiovascular drugs, antidiabetic drugs, and obstructive pulmonary diseases drugs

Table 6 Odds ratios of out-of-hospital cardiac arrest with documented ventricular tachycardia/ ventricular fibrillation for current users of NSAIDs stratified by age groups

<65 years old	**Cases (n = 946)**	**Controls (n = 3,675)**	**Crude OR (95% CI)**	**Adjusted OR[Ŧ] (95% CI)**
Nonuse, n (%)	914 (96.6)	3,539 (96.3)	1	1
Conventional NSAIDs, n (%)	28 (3.0)	123 (3.3)	1.14 (0.75-1.72)	1.27 (0.83-1.95)
Selective COX-2 inhibitors, n (%)	4 (0.4)	13 (0.4)	0.84 (0.27-2.58)	0.80 (0.26-2.50)
≥65 years old	**Cases (n = 1,195)**	**Controls (n = 4,708)**	**Crude OR (95% CI)**	**Adjusted OR[Ŧ] (95% CI)**
Nonuse, n (%)	1,152 (96.4)	4,546 (96.6)	1	1
Conventional NSAIDs, n (%)	35 (2.9)	143 (3.0)	1.04 (0.71-1.51)	1.16 (0.78-1.71)
Selective COX-2 inhibitors, n (%)	8 (0.7)	19 (0.4)	0.60 (0.26-1.38)	0.54 (0.24-1.25)

Abbreviations: CI = Confidence Interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio

[Ŧ]adjusted for antiarrhythmic drugs, non-antiarrhythmic QT-prolonging drugs, cardiovascular drugs, antidiabetic drugs, and obstructive pulmonary diseases drugs

Table 7 Odds ratios of out-of-hospital cardiac arrest with documented ventricular tachycardia/ ventricular fibrillation for current users of NSAIDs stratified by sex

Men	**Cases (n = 1,659)**	**Controls (n = 6,504)**	**Crude OR (95% CI)**	**Adjusted OR[Ŧ] (95% CI)**
Nonuse, n (%)	1,607 (96.9)	6,304 (96.9)	1	1
Conventional NSAIDs, n (%)	44 (2.7)	179 (2.8)	1.04 (0.74-1.45)	1.13 (0.80-1.59)
Selective COX-2 inhibitors, n (%)	8 (0.5)	21 (0.3)	0.67 (0.30-1.51)	0.61 (0.27-1.38)
Women	**Cases (n = 482)**	**Controls (n = 1,879)**	**Crude OR (95% CI)**	**Adjusted OR[Ŧ] (95% CI)**
Nonuse, n (%)	459 (95.2)	1,781 (94.8)	1	1
Conventional NSAIDs, n (%)	19 (3.9)	87 (4.6)	1.18 (0.71-1.96)	1.40 (0.82-2.40)
Selective COX-2 inhibitors, n (%)	4 (0.8)	11 (0.6)	0.71 (0.23-2.24)	0.65 (0.20-2.08)

Abbreviations: CI = Confidence Interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio

[Ŧ]adjusted for antiarrhythmic drugs, non-antiarrhythmic QT-prolonging drugs, cardiovascular drugs, antidiabetic drugs, and obstructive pulmonary diseases drugs

DISCUSSION

Risk of VT/VF-OHCA for NSAID users

In this observational study, we found that both selective COX-2 inhibitors and conventional NSAIDs were not associated with a higher risk of VT/VF-OHCA compared to nonuse. Also, when VT/VF-OHCA was stratified to AMI status, no association was found. Similarly, a population-based study from the Danish Cardiac Arrest Registry demonstrated that selective COX-2 inhibitors were not associated with an increased risk of OHCA. In contrast, that study showed an increased OHCA risk during the use of conventional NSAIDs, particularly diclofenac and ibuprofen (14). We identified several factors that might contribute to this disagreement including differences in the study design, exposure, and outcome. First, the Danish study was a case-time-control study among patients aged 10 years or older. This study design is intended to lower the risk of confounding by indication, by eliminating the potential confounding effect of characteristics that remain stable over time. In contrast, our study was a case-control study among patients in all age groups. We tackled confounding by indication by stratification for the presence/absence of AMI and standard multivariate adjustment for potential confounders which were time-varying and constant over time. A previous study has shown that these two study designs can cause considerable differences in study results

(15). Second, the results of the Danish study might be influenced by changes in physician's behavior towards the prescribing of rofecoxib after media attention on its cardiovascular risks in the early 2000s. In our study, such influence was not possible as our data collection started in 2005, while rofecoxib was withdrawn from the market in 2004. Finally, in the Danish Cardiac Arrest Registry, the cause of cardiac arrest is not registered. Instead, a presumed cardiac cause of cardiac arrest is classified using discharge diagnoses from the Danish Patient Registry, and death certificates from the National Causes of Death Registry. The cardiac arrests of presumed cardiac cause represent about 75% of all OHCA recorded (14). In contrast, the present study included only OHCA cases with documented VT/VF in an effort to limit the risk of misclassification by excluding non-cardiac causes of OHCA, e.g., pulmonary embolism, stroke, ruptured aneurysm (3). Moreover, the inclusion criterion of documented VT/VF was consistent with previous reports on cardiac electrophysiological effects of NSAIDs, and our aim to establish whether NSAID use is associated with increased risk of cardiac arrhythmia and OHCA.

Currently, no studies assessing the relations between NSAIDs and VT/VF-OHCA stratified by duration of NSAID use, age, or sex. Our study indicated that the risk of VT/VF-OHCA for either conventional NSAIDs or selective COX-2 inhibitors was similar for different durations of use, age, and sex. A recent meta-analysis of observational studies mentioned that the effect of duration of NSAID use on the association between NSAIDs and the cardiovascular hazard such as AMI is inconsistent. A longer duration of naproxen use was associated with a higher risk of AMI, but such an association was not found for rofecoxib, celecoxib, ibuprofen, and diclofenac (16).

Strengths and Limitations

This study has several strengths. First, information bias of the outcome is unlikely since VT/VF-OHCA was determined by the presence of VT/VF on the ECG recordings. Second, confounding by indication was less likely as we also stratified our analyses to VT/VF-OHCA cases according to AMI status. Finally, inclusion bias is minimal because all OHCA cases with the involvement of emergency medical services are included, and the ARREST region covers one contiguous region of the Netherlands, including both urban and rural areas. Hence, this study is representative of OHCA cases for the inhabitants of the Netherlands.

Several limitations should be acknowledged. First, as the information on drug use was collected from pharmacy dispensing records, we had no direct measure of medication adherence. Also, we had no information on whether NSAIDs were prescribed as regular or needed medication. Thus, we are not sure about the actual intake. Second, this study is a subject to misclassification of the exposure because information on over-the-counter (OTC) NSAID use is not recorded in these databases. A previous observational study indicated that 30% of the population of the Netherlands took OTC NSAIDs (17), including diclofenac, naproxen, and ibuprofen, which have ranked among the most commonly issued NSAIDs for the last 5 years (2011-2015) (18). However, the use of OTC NSAID in the Netherlands was not statistically different between cases and controls as demonstrated in our previous study (19). Moreover, a sensitivity analysis study on OTC NSAIDs indicated that when the overall prevalence of OTC use is <35%, missing information on OTC use in a study might not invalidate its findings (20). Third, we had no information on several important risk factors for cardiovascular diseases such as lifestyle (alcohol use, smoking, physical activities), body mass index, a history of cardiovascular diseases, or familial history of cardiovascular diseases. These confounding factors are possibly unequally distributed between cases and controls. Hence, the baseline risk of cardiovascular diseases might differ between cases and controls. Finally, based on the number of cases and controls available, we did not have enough power to detect relatively weak associations between selective COX-2 inhibitors and VT/VF-OHCA (below 1.9). The power may not have been an important issue for conventional NSAID use because the estimated risk was about 1 (OR 0.97, 95%CI; 0.86-1.10).

CONCLUSION

Selective COX-2 inhibitors and conventional NSAIDs were not associated with an increased risk of VT/VF-OHCA. Both among patients with AMI and among those without, these drugs did not increase the risk of VT/VF-OHCA compared to nonuse. Differences in the duration of use, age, and sex were not associated with the differences in risk of VT/VF-OHCA associated with selective COX-2 inhibitors and conventional NSAIDs.

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SUPPLEMENTARY

Table S1 Non-steroidal Anti-inflammatory Drugs according to Anatomical Therapeutic Chemical (ATC) Classification System

No	Group of drug	ATC code
1	Conventional NSAIDs	
	Butylpyrazolidines	M01AA
	Acetic acid derivatives and related substances	M01AB
	Oxicams	M01AC
	Propionic acid derivatives	M01AE
	Fenamates	M01AG
	Other anti-inflammatory and anti-rheumatic agents, non-steroid	M01AX
2	Selective COX-2 inhibitors	M01AH

Table S2 Class I and III Antiarrhythmic drugs

No	Class	Drug	ATC code
1.	Class Ia	Quinidine	C01BA01
		Procainamide	C01BA02
		Disopyramide	C01BA03
		Sparteine	C01BA04
		Ajmaline	C01BA05
		Prajmaline	C01BA08
		Lorajmine	C01BA12
		Quinidine, combinations excl. psycholeptics	C01BA51
		Quinidine, combinations with psycholeptics	C01BA71
	Class Ib	Lidocaine	C01BB01
		Mexiletine	C01BB02
		Tocainide	C01BB03
		Aprindine	C01BB04
	Class Ic	Propafenone	C01BC03
		Flecainide	C01BC04
		Lorcainide	C01BC07
		Encainide	C01BC08
		Ethacrinide	C01BC09
2.	Class III	Amiodarone	C01BD01
		Bretylium tosylate	C01BD02
		Bunaftine	C01BD03
		Dofetilide	C01BD04
		Ibutilide	C01BD05
		Tedisamil	C01BD06
		Dronedarone	C01BD07
3.	Other antiarrhythmic	Moricizine	C01BG01
		Cibenzoline	C01BG07
		Vernakalant	C01BG11
		Sotalol	C07AA07

Table S3 Non-QT-prolonging drugs

No.	Risk of TdP	No.	Possible Risk of TdP
1.	Amiodarone	1.	Alfuzosin
2.	Anagrelide	2.	Apomorphine
3.	Arsenic trioxide	3.	Aripiprazole
4.	Astemizole	4.	Artenimol+piperaquine
5.	Azithromycin	5.	Asenapine
6.	Bepridil	6.	Atomoxetine
7.	Chloroquine	7.	Bedaquiline
8.	Chlorpromazine	8.	Bortezomib
9.	Cilostazol	9.	Bosutinib
10.	Ciprofloxacin	10.	Buprenorphine
11.	Cisapride	11.	Capecitabine
12.	Citalopram	12.	Ceritinib
13.	Clarithromycin	13.	Clomipramine
14.	Cocaine	14.	Clozapine
15.	Disopyramide	15.	Crizotinib
16.	Dofetilide	16.	Cyamemazine
17.	Domperidone	17.	Dabrafenib
18.	Donepezil	18.	Dasatinib
19.	Dronedarone	19.	Degarelix
20.	Droperidol	20.	Delamanid
21.	Erythromycin	21.	Desipramine
22.	Escitalopram	22.	Dexmedetomidine
23.	Flecainide	23.	Dolasetron
24.	Fluconazole	24.	Eribulin mesylate
25.	Gatifloxacin	25.	Ezogabine
26.	Grepafloxacin	26.	Famotidine
27.	Halofantrine	27.	Felbamate
28.	Haloperidol	28.	Fingolimod
29.	Ibutilide	29.	Flupentixol
30.	Levofloxacin	30.	Foscarnet
31.	Levomepromazine	31.	Gemifloxacin
32.	Levomethadyl	32.	Granisetron
33.	Mesoridazine	33.	Hydrocodone
34.	Methadone	34.	Iloperidone
35.	Moxifloxacin	35.	Imipramine
36.	Ondansetron	36.	Isradipine
37.	Oxaliplatin	37.	Lapatinib
38.	Papaverine HCl	38.	Lenvatinib
39.	Pentamidine	39.	Leuprolide
40.	Pimozide	40.	Lithium
41.	Probucol	41.	Mifepristone

Table S3 (continued)

42.	Procainamide	42.	Mirabegron
43.	Propofol	43.	Mirtazapine
44.	Quinidine	44.	Moexipril/HCTZ
45.	Roxithromycin	45.	Nicardipine
46.	Sevoflurane	46.	Nilotinib
47.	Sotalol	47.	Norfloxacin
48.	Sparfloxacin	48.	Nortriptyline
49.	Sulpiride	49.	Ofloxacin
50.	Sultopride	50.	Olanzapine
51.	Terfenadine	51.	Osimertinib
52.	Thioridazine	52.	Oxytocin
53.	Vandetanib	53.	Paliperidone
		54.	Panobinostat
		55.	Pasireotide
		56.	Pazopanib
		57.	Perflutren lipid microspheres
		58.	Pipamperone
		59.	Promethazine
		60.	Rilpivirine
		61.	Risperidone
		62.	Roxithromycin
		63.	Saquinavir
		64.	Sertindole
		65.	Sorafenib
		66.	Sunitinib
		67.	Tacrolimus
		68.	Tamoxifen
		69.	Telavancin
		70.	Telithromycin
		71.	Tetrabenazine
		72.	Tiapride
		73.	Tizanidine
		74.	Tolterodine
		75.	Toremifene
		76.	Trimipramine
		77.	Tropisetron
		78.	Vardenafil
		79.	Vemurafenib
		80.	Venlafaxine
		81.	Vorinostat
		82.	Zotepine

CHAPTER 3

RISK OF NEPHROTIC SYNDROME

FOR NON-STEROIDAL ANTI-INFLAMMATORY DRUG USERS:

A CASE-CONTROL STUDY

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ABSTRACT

Background Non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with acute kidney injury. Their association with nephrotic syndrome (NS) has not been systematically studied.

Objectives to assess the risk of NS associated with NSAID use.

Methods A matched case-control study was performed in the UK primary care database. Cases were patients with a first diagnosis of NS and controls were those without NS. NSAID exposure (grouped either based on cyclooxygenase enzyme selectivity and chemical groups) was classified as either current (use at the NS diagnosis date and the corresponding date in the control group), recent, or past use. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated using unconditional logistic regression analysis.

Results We included 2,620 cases and 10,454 controls. Compared to non-use, current use of 15-28 days and >28 days of conventional NSAIDs was associated with a higher relative risk of NS: adjusted OR 1.34 (95%CI, 1.06-1.70) and 1.42 (0.79-2.55), respectively. Also, recent use (discontinuation 1-2 months before NS diagnosis date; OR 1.55 (1.11-2.15)) and past use (discontinuation 2 months-2 years; OR 1.24 (1.07-1.43)), but not current use of <15 days (OR, 0.78 (0.46-1.31)) nor past use (discontinuation >2 years; OR, 0.96 (0.85-1.09)) were associated with a higher relative risk of NS as well as past use of selective COX-2 inhibitors (discontinuation 2 months-2 years; OR, 1.24 (0.98-1.58)). Categorization based on chemical groups showed that acetic acid derivatives (AADs) and propionic acid derivatives (PADs) were associated with a higher risk of NS.

Conclusions The use of conventional NSAIDs was associated with a higher risk of NS starting from at least 2 weeks of exposure, as well as for recent and past exposure up to 2 years before the diagnosis of NS. This higher risk appeared mainly attributable to AADs and PADs.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) can induce kidney lesions [1]. Several studies demonstrated that conventional NSAIDs were associated with a higher risk of acute kidney injury and glomerulonephritis and decreased kidney hemodynamic functions, including sodium excretion. However, these adverse effects were not consistently seen for selective cyclooxygenase (COX)-2 inhibitors [2-8]. These side effects occurred at a rate as low as 1-5% for NSAID users [9]. However, because NSAIDs are one of the most prescribed drugs and some of them are available over-the-counter, these small increased risks may translate into high absolute numbers of patients being affected, especially in those with pre-existing impaired kidney function [10].

Several case-reports indicate a potential causal relation between specific conventional NSAIDs or selective COX-2 inhibitors and NS [11-17]. The exact mechanism by which NSAIDs might cause NS is largely unknown. Inhibition of COX enzymes by NSAIDs that increases arachidonic cascade products, such as leukotrienes which may play a pathophysiological role in inflammatory processes in kidneys, in conjunction with aldosterone are thought to contribute [18, 19]. In contrast, in another case study, celecoxib was safely administered in a patient developing NS due to conventional NSAIDs [20]. A few case studies showed that indomethacin and ibuprofen improve proteinuria and edema in patients with NS [21-23].

Since a potential higher NS risk for NSAID users is uncertain, we performed a systematic observational study to asses and quantify this risk for NSAID users according to both COX enzyme selectivity and chemical groups. The impact of duration of NSAID use on this association was also studied.

METHODS

Study Design and Data Source

We carried out a matched case-control study using data from the Clinical Practice Research Datalink. This general practitioner database is the UK National Health Service observational data and

interventional research service that has been established since 1987. The database provides detailed information on demographics, drug prescriptions, clinical events, specialist referrals, and hospital admissions [24]. At the time of data extraction, information on more than 15 million patients from 720 general practitioner practices had been registered. Medical diagnoses are recorded based on the Read codes, and the drugs are recorded based on British National Formulary and product codes. The independent scientific advisory committee of the Medicines and Healthcare product Regulatory Agency (MHRA) database research approved this study (protocol number: 17_268).

Case and Control Definition

Cases were patients with a first diagnosis of NS during valid data collection from October 1989 until November 2017. NS diagnoses are entered into the database in various manners. Most of them are entered as NS only. A few NS diagnoses are entered with information on either co-morbidities or kidney biopsy (**Supplementary, Table S1**). The date of this diagnosis was the index date. Controls were patients without NS before and at the index date. Up to five controls were matched to each case by age, sex, general practitioner practice, and index date. Participants were included if they were 18 years or older and had at least one year of history in the database before the index date. Participants who were <18 years old were excluded because the causes of NS in children are different from adults like congenital disorders, genetic mutations, and certain diseases such as infections that damage kidneys [25, 26].

Exposure definition

NSAID exposure was determined according to the prescription information before the index date and was categorized as either current, recent, or past use of NSAIDs. NSAIDs were further classified by their COX selectivity or chemical groups. Current users were patients who received the last NSAID prescription within 28 days before the index date. Current use was further categorized according to the duration of use by calculating the number of days of continuous NSAID exposure before the index date, using a permissible gap of 28 days between prescriptions to determine whether the current use period was continuous or not. The duration was classified as either 1-14 days, 15-28 days, or >28 days. Those who had received the last

NSAID prescription within 29-56 days and 57 days or more before the index date were categorized as recent and past users, respectively. Past users were then divided based on the length of discontinuation before the index date, i.e., between >2 months–2 years and >2 years. Because of the limited sample size, only current use of conventional NSAIDs was categorized based on the duration of use. Patients who switched between conventional NSAIDs and selective COX-2 inhibitors were classified to the subgroup that was closest to the index date. Those who did not receive any prescriptions of NSAIDs before and at the index date were defined as nonusers. Chemical groups of NSAIDs were determined according to the Anatomical Therapeutic Chemical Classification systems, including acetic acid derivatives (AADs), propionic acid derivatives (PADs), fenamates, oxicams, coxibs (selective COX-2 inhibitors), and other NSAIDs, i.e., NSAIDs that are not classified elsewhere (**Supplementary, Table S2**). Butylpyrazolidines were excluded since this chemical group has not been longer approved for human use in the UK. Fenamates, oxicams, and other NSAIDs were then grouped as "other conventional NSAIDs" because their sample size was too low to study them separately.

Potential Confounders

We considered comorbidities associated with NS (diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, amyloidosis, and leukemia). Several factors associated with kidney toxicity were also collected including comorbidities (hypertension, chronic kidney diseases, heart failure, and chronic liver diseases), co-medications (cardiovascular drugs (angiotensin converting enzymes inhibitors, angiotensin II antagonists, beta blockers, diuretics, calcium channel blockers, and statins), systemic corticosteroids, antibiotics (aminoglycosides, sulfamethoxazole and trimethoprim, vancomycin, and ciprofloxacin), and chemotherapeutic agents), and lifestyle factors (body mass index, smoking, and alcohol abuse). Comorbidities were assessed as ever before the index date, and co-medications were evaluated during 6 months before the index date. Body mass index and lifestyle factors were defined according to the latest information with a maximum of one year allowed between the latest assessment and the index date.

Demographic and medical data of cases and controls were compared using t-test or chi-square, whichever applicable. We performed conditional logistic regression analyses to calculate odds ratios (ORs),

95% confidence intervals (95% CIs), and to adjust for confounding factors. Since the risk of NS for conventional NSAIDs was assessed separately, the matching was lost. We, therefore also performed unconditional logistic regression analyses to calculate ORs, 95%CIs, and to adjust for all confounding factors including matching variables (age, sex, the general practitioner practices, and index date). The ORs for current users of conventional NSAIDs were stratified by the duration of use. We stratified our analyses by either age or sex to assess whether the estimated risks for NSAIDs were different within these subgroups. ORs were presented if there were at least five patients exposed to NSAIDs in case or control groups. We applied multiple imputations with fully conditional specification using a total of 5 datasets to address missing values for body mass index and smoking status. All other variables in the model were used as predictors in this iterative method. All statistical analyses were performed using statistical software IBM SPSS 24 and $p<0.05$ was considered statistically significant.

Sensitivity Analysis

We performed several sensitivity analyses. First, we assessed the risk for NSAID users by including only NS diagnoses that were entered with information on kidney biopsy cases. Small sample size prevented us from assessing the ORs for current users based on the duration of use. Second, to anticipate on the delay in establishing the diagnosis of NS from the first complaints, we considered four different time windows, i.e., assuming that the index date was 3, 6, 9, or 12 months before the index date we have chosen in our study. Third, we excluded cases and controls with co-morbidities that are well-known causes of NS including diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, amyloidosis, and leukemia. Finally, we tested the applicability of our findings for hospitalized patients with NS in which the data were collected from the Hospital Episode Statistics Admitted Patient Care. It includes in- or out-patients, and accidental and emergency admissions to the National Health Services hospitals in England. About 98-99% of private or charitable hospitals are funded by the National Health Service [27, 28]. Cases were hospitalized patients with a first discharge diagnosis of NS based on the International Statistic Classification of Diseases and Related Health Problems 10th Revision (code N04). Because of the limited sample size, we presented the ORs only for conventional NSAID use.

RESULTS

Characteristics

A total of 2,620 NS cases and 10,454 matched-controls were identified from more than 27 years of data collection. The mean age (± sd) of cases and controls was 58 ± 17 and 57 ± 17 years, respectively, and 55% was female. Compared to controls, cases had a higher prevalence of comorbidities associated with either NS or kidney toxicity and co-medications associated with kidney toxicity. Most cases and controls had normal weight to obese, had no alcohol abuse (95% vs. 96 %), and were smokers (57% vs. 52%), respectively. Controls had a higher proportion of missing values on body mass index (12% vs. 8%) and smoking status (5% vs. 3%) than cases, respectively (**Table 1**).

Table 1 Baseline characteristics of patients with nephrotic syndrome and controls

Baseline characteristics	Cases (n = 2,620)	Controls (n = 10,454)
Age, [mean (year) ± sd]	58 ± 17	57 ± 17
18-64 years old, n (%)	1,579 (60)	6,316 (60)
>64 years old, n (%)	1,041 (40)	4,138 (40)
Female, n (%)	1,432 (55)	5,714 (55)
Body mass index, [mean (kg/m^2) ± sd]	28.0 ± 6.3	27.0 ± 5.4
Underweight (<18.5 kg/m^2), n (%)	57 (2)	229 (2)
Normal weight (18.5 – 24.9 kg/m^2), n (%)	783 (30)	3,278 (31)
Overweight (25.0 – 29.9 kg/m^2), n (%)	808 (31)	3,453 (33)
Obesity (>30 kg/m^2), n (%)	753 (29)	2,207 (21)
Unknown, n (%)	219 (8)	1,287 (12)
Comorbidities associated with nephrotic syndrome, n (%)		
Diabetes mellitus	629 (24)	740 (7)
Systemic lupus erythematosus	120 (5)	7 (0)
Rheumatoid arthritis	36 (1)	82 (1)
Amyloidosis	23 (1)	1 (0)
Leukemia	13 (1)	16 (0)
Comorbidities associated with kidney toxicity, n (%)		
Hypertension	1,190 (45)	2,655(25)
Chronic kidney diseases	474 (18)	188 (2)
Heart failure	204 (8)	219 (2)
Chronic liver diseases	42 (2)	70 (1)

Table 1 (continued)

Co-medications within 6 months prior to the index date, n (%)		
Cardiovascular drugs[1]	1,843 (70)	3,392 (32)
Systemic corticosteroids	413 (16)	316 (3)
Antibiotics[2]	98 (4)	93 (1)
Chemotherapeutic agents	83 (3)	87 (1)
Smoking status, n (%)		
Current	553 (21)	2,272 (22)
Ever	947 (36)	3,112 (30)
Never	1,042 (40)	4,545 (43)
Unknown	78 (3)	525 (5)
Alcohol abuse, n (%)	126 (5)	412 (4)

[1]angiotensin converting enzymes inhibitors, angiotensin II antagonists, beta-blockers, diuretics, calcium channel blockers, and statins, [2]aminoglycosides, sulfamethoxazole and trimethoprim, vancomycin, and ciprofloxacin

Of 2,620 cases, 288 (11%) NS diagnoses were entered with information on kidney biopsy. A diagnosis of membranous glomerulonephritis was shown in 78 cases. Among them, 167 cases with information on kidney biopsy received at least one NSAID prescription in which membranous glomerulonephritis was found in 50 cases. The results of kidney biopsy for NS cases are shown in **Table 2**.

Table 2 The result of kidney biopsy for sub-group (n=288) of cases with nephrotic syndrome

Kidney biopsy	**Frequency, n (%)**		
	NSAID use	**Non-NSAID use**	**Total**
Membranous glomerulonephritis	50 (30)	28 (23)	78 (27)
Focal and segmental glomerular lesions	34 (20)	35 (29)	69 (24)
Diffuse crescentic glomerulonephritis	19 (11)	12 (10)	31 (11)
Diffuse mesangio-capillary glomerulonephritis	18 (11)	7 (6)	25 (9)
Minimal change glomerulonephritis	15 (9)	13 (11)	28 (10)
Diffuse membranous glomerulonephritis	10 (6)	10 (9)	20 (7)
Diffuse mesangial proliferative glomerulonephritis	10 (6)	7 (6)	17 (6)
Minor glomerular abnormality	6 (4)	6 (5)	12 (4)
Diffuse endocapillary proliferative glomerulonephritis	3 (2)	0 (0)	3 (1)
Dense deposit diseases	1 (1)	1 (1)	2 (1)
Congenital nephrotic syndrome with focal glomerulosclerosis	1 (1)	0 (0)	1 (0)
Lipoid nephrosis	0 (0)	1 (1)	1 (0)
Other patological kidney lesions	0 (0)	1 (1)	1 (0)
Total	167 (100)	121 (100)	288 (100)

Abbreviations: NSAIDs = Non-Steroidal Anti-Inflammatory Drugs

Current use for 15-28 days and >28 days, recent use, and past use (discontinuation >2 months-2 years) of conventional NSAIDs were associated with higher risk of NS (adjusted OR 1.34 (95%CI; 1.06-1.70), 1.42 (0.79-2.55), 1.55 (1.11-2.15), and 1.24 (1.07-1.43)), respectively compared to non-use. However, the risk for current use for >28 days of conventional NSAIDs was not statistically significant. Current use for 1-14 days and past use of conventional NSAIDs (discontinuation >2 years) were not associated with a higher risk compared to non-use (**Table 3**). Although not statistically significant, compared to non-use, past use of selective COX-2 inhibitors (>2 months-2 years) was associated with higher risk (1.24 (0.98-1.58)). In contrast, current and past use (>2 years) were associated with lower risk. The number of cases with recent use was too small to evaluate this association (**Table 4**).

Table 3 Odds ratios of nephrotic syndrome for conventional NSAID[1] users

	Cases (n = 2,536)	**Controls (n = 10,168)**	**Crude OR (95% CI)**	**Adjusted OR[Ŧ] (95% CI)**
Nonuse, n (%)	1,118 (44)	5,142 (51)	1	1
Current use[ϕ], n (%)				
1-14 days	24 (1)	104 (1)	1.06 (0.68-1.66)	0.78 (0.46-1.31)
15-28 days	29 (1)	104 (1)	1.28 (0.85-1.95)	1.34 (1.06-1.70)
>28 days	21 (1)	56 (1)	1.73 (1.04-2.86)	1.42 (0.79-2.55)
Recent use, n (%)	73 (3)	182 (2)	1.85 (1.40-2.44)	1.55 (1.11-2.15)
Past use (discontinuation between >2 months–2 years), n (%)	474 (19)	1,477 (15)	1.48 (1.31-1.67)	1.24 (1.07-1.43)
Past use (discontinuation >2 years), n (%)	797 (31)	3,103 (31)	1.18 (1.07-1.31)	0.96 (0.85-1.09)

Abbreviations: CI = Confidence Interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio

[1]acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, and other NSAIDs

[ϕ]duration of use

[Ŧ]adjusted for matching variables (age, sex, general practitioners' practice, and the index date), comorbidities, co-medications, body mass index, smoking behavior, and alcohol abuse

According to the chemical groups of NSAIDs, either current, recent, or past use (>2 months–2 years) of AADs were associated with higher risk of NS (adjusted OR, 1.11 (95%CI; 0.73-1.64), 1.99 (1.28-3.10), and 1.36 (1.13-1.64)), respectively compared to non-use. The higher risk was also found for current, recent, and past use (>2 months–2 years) of propionic acid derivatives (adjusted OR 1.41 (0.90-2.20), 1.24 (0.74-2.08), and 1.14 (1.02-1.26)), respectively compared to non-use. However, the higher risks for current

use of AADs, and current and recent use of propionic acid derivatives were not statistically significant (**Table 4**).

Table 4 Odds ratios of nephrotic syndrome for NSAID users according to chemical groups and selective COX-2 inhibitors

	Cases (n = 2,620)	**Controls (n = 10,454)**	**Crude OR (95% CI)**	**Adjusted OR[Ŧ] (95% CI)**
Nonuse, n (%)	1,118 (43)	5,142 (49)	1	1
Current use, n (%)				
Acetic acid derivatives	35 (1)	139 (1)	1.16 (0.80-1.69)	1.11 (0.73-1.70)
Propionic acid derivatives	33 (1)	93 (1)	1.63 (1.09-2.44)	1.41 (0.90-2.20)
Other conventional NSAIDs[Φ]	6 (0)	32 (1)	0.86 (0.36-2.07)	0.51 (0.19-1.33)
Selective COX-2 inhibitors	8 (0)	39 (1)	0.94 (0.44-2.02)	0.40 (0.24-0.65)
Recent use, n (%)				
Acetic acid derivatives	37 (1)	89 (1)	1.91 (1.30-2.82)	1.99 (1.28-3.10)
Propionic acid derivatives	31 (1)	77 (1)	1.85 (1.21-2.82)	1.24 (0.74-2.08)
Other conventional NSAIDs[Φ]	5 (0)	16 (0)	1.44 (0.53-3.93)	1.01 (0.56-1.84)
Selective COX-2 inhibitors	4 (0)	15 (0)	NA	NA
Past use (discontinuation between >2 months–2 years), n (%)				
Acetic acid derivatives	239 (9)	700 (7)	1.57 (1.34-1.84)	1.36 (1.13-1.64)
Propionic acid derivatives	193 (7)	637 (6)	1.39 (1.17-1.66)	1.14 (1.02-1.26)
Other conventional NSAIDs[Φ]	42 (2)	140 (1)	1.38 (0.97-1.96)	1.13 (0.76-1.70)
Selective COX-2 inhibitors	37 (1)	99 (1)	1.72 (1.17-2.52)	1.24 (0.98-1.58)
Past use (discontinuation >2 years), n (%)				
Acetic acid derivatives	379 (5)	1,466 (14)	1.19 (1.04-1.35)	1.02 (0.88-1.19)
Propionic acid derivatives	347 (13)	1,368 (13)	1.17 (1.02-1.33)	0.90 (0.77-1.06)
Other conventional NSAIDs[Φ]	71 (3)	269 (3)	1.21 (0.93-1.59)	1.00 (0.74-1.35)
Selective COX-2 inhibitors	35 (1)	133 (1)	1.21 (0.83-1.77)	0.77 (0.50-1.20)

Abbreviations: CI= Confidence Interval; COX-2 = Cyclooxygenase-2; NA = Not Applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR=Odds Ratio

[Φ]oxicams, fenamates, other NSAIDs not classified elsewhere

[Ŧ]adjusted for comorbidities, co-medications, body mass index, smoking behavior, and alcohol abuse

Effect modification by age and sex

Age did not modify the risk of NS for the users of either conventional NSAIDs or selective COX-2 inhibitors compared to non-use (**Supplementary, Table S3**). Sex did not either modify the risk, except for

past users of conventional NSAIDs and selective COX-2 inhibitors. Compared to females who were non-users of any NSAIDs, females who were past users of conventional NSAIDs (>2 years) had a similar risk of NS. In contrast, females who were past users of selective COX-2 inhibitors (between >2 months – 2 years) were associated with a higher risk. For males, either past users of conventional NSAIDs (>2 years) or selective COX-2 inhibitors (>2 months – 2 years) were associated with a lower risk of NS compared to males who were no-users of any NSAIDs (**Supplementary, Table S4**)**.**

Sensitivity analyses

Our findings were similar when only cases with information on kidney biopsy were used. Recent and past use (>2 months–2 years) of conventional NSAIDs were associated with higher risk (although not statistically significant) of NS (adjusted OR 1.83 (95%CI; 0.89-3.80), 1.23 (0.85-1.78)), respectively compared to non-use. The risk for current use of conventional NSAID was not assessed according to the duration of use because of the small sample size (**Supplementary, Table S5**). In extensive sensitivity analyses for various index dates, we found similar associations between conventional NSAIDs and NS as found above. However, the higher risks were already observed during the first 2 weeks prior to the index-date (**Supplementary, Table S6-9**). Excluding cases and controls with co-morbidities that are well-known causes of NS did not change the results (**Supplementary, Table S10**). Considering only hospitalized NS patients as cases did not either change the results. For current use with duration 15-28 days, >28 days, recent use, and past use (>2 months–2 years) of conventional NSAIDs, the adjusted ORs were 1.61, (95%CI; 0.78-3.32); 1.53 (0.59-3.95), 1.52 (0.89-2.59), and 1.27 (1.00-1.61), respectively compared to non-use (**Supplementary, Table S11**).

DISCUSSION

Our study demonstrated that current use for more than 2 weeks, recent use, and past use (>2 months–2 years) of conventional NSAIDs were associated with a higher risk of NS. The higher risk seems to disappear after 2 years of discontinuation. The higher risk for conventional NSAIDs is mainly attributable to

AADs and PADs. Current and past use of selective COX-2 inhibitors were not associated with a higher risk, although small sample size hampers drawing definite conclusions.

The risk estimates shown in the main analyses were confirmed when we specified our cases only for patients with available information on kidney biopsy. Furthermore, another study showed that the validity of several diagnoses in this database is high [29]. When we varied the index date, we consistently found the same association between conventional NSAIDs and NS. These findings strengthen the suggestion of a possible causal relationship. There is an indication that the higher risk might start within 2 weeks of NSAID exposure. When we excluded well-known conditions associated with NS in both cases and controls, the estimated risks remained similar suggesting that NSAIDs are independently associated with the occurrence of NS. The higher risk for conventional NSAIDs was also demonstrated for hospitalized patients with NS. It implies that the risk of NS for conventional NSAIDs was independent of their severity.

Our findings confirmed previous studies. Case reports and case series showed that NSAIDs-associated NS occurs from the exposure durations of <1 week [30, 31] until years [17, 32, 33]. Even more, NS might develop 6 months after the discontinuation of an NSAID [34]. In a review of acute kidney diseases associated with NSAID use, it appeared that especially the propionic acid derivative, fenoprofen was associated with NS (half of the 34 cases) [35]. Our finding that current and past use (>2 years) of selective COX-2 inhibitors are not associated with a higher risk of NS risk corresponds with the safe administration of celecoxib to a patient with repeated episodes of NS induced by NSAIDs [20].

NSAID-associated NS is thought to be mediated by either the inhibition of prostaglandins synthesis or a hypersensitivity mechanism. Prostaglandins are essential for kidney hemodynamic including glomerular filtration. In NS, glomeruli are impaired by the inflammation processes that allow proteins to pass through kidney cell membranes [30, 36, 37]. Hypersensitivity mechanisms of NSAIDs for NS are caused allegedly by the shift of prostaglandin synthesis from COX to lipoxygenase paths or the release of lymphokines that increase the production of leukotrienes. Leukotrienes can activate T helper lymphocytes that ultimately affect glomerular permeability [30].

Clinical Implications

Our results demonstrated that conventional NSAIDs, especially current, recent, and past use (>2 months-2 years) of AADs (such as indomethacin, diclofenac, and ketorolac) and current, recent, and past use (>2 months-2 years) of PADs (such as ibuprofen, naproxen, and ketoprofen), and past use (>2 months-2 years) of selective COX-2 inhibitors were associated with a higher risk of NS. However, this higher relative risk that was observed in our study is relatively low. Thus, health care professionals should be more alert on the development of clinical features of NS caused by other risk factors. A patient who develops NS should be asked about the use of NSAIDs, including over-the-counter. Even though our study indicated that current and past use (>2 years) of selective COX-2 inhibitors were not associated with a higher risk, the number of subjects was too small to draw definite conclusions.

Strengths and Limitations

Our study has several strengths. The data were extracted over a long observation time, and the database contained longitudinal data of the patient's medical history and lifestyle. Many potential risk factors were available allowing us to adjust for many potential confounders. The routine collection of medical information and medication use lowers the risk of information bias.

Nonetheless, some limitations need to be acknowledged. We might encounter the delay in establishing the diagnosis from the first complaints. The index date was the date of diagnosis entered in the database, while the first complaints that bring patients seeking help might have preceded this index date. If the delay is substantial (weeks to months are not uncommon in NS), and patients take a NSAID within this period, it inadvertently attributes to misclassification of the exposure status. This might also partly explain the higher risk for recent and past use (>2 months–2 years) of conventional NSAIDs. Nevertheless, our sensitivity analyses consistently showed that the delay was unlikely to change the risk estimates. Even though most diagnoses were entered without information on kidney biopsy, the analysis among cases with kidney biopsy supported our main results. When we excluded cases and controls with well-known conditions associated with NS for sensitivity analyses, the estimated risks remained similar. The actual

NSAID use is uncertain. We had no direct measure on NSAID use because medication use is determined based on prescribing information. Information on whether NSAIDs were prescribed as a regular or needed use was not available. Furthermore, we had no information on over-the-counter NSAID use. However, only ibuprofen is available as over-the-counter NSAIDs in the UK [38, 39]. Furthermore, we expect the use is unlikely to be different between cases and controls. Therefore, misclassification of NSAID exposure is probably non-differential. We cannot either ignore the fact that the previous use of NSAID (either recent or past use) might affect the magnification risk for their following use (current or recent use, respectively). We had no information on patients being allergic. Since hypersensitivity reaction-mediated NS is suspected to be low, this misclassification problem is unlikely to influence our results. The sample size for selective COX-2 inhibitors and an individual chemical group of NSAIDs was small causing a too low power to detect statistically significant associations. Finally, the extrapolation of our results to age groups younger than 18 years old is less valid. Further studies to test the consistency of our findings may consider unmeasured potential confounders and a larger population.

In conclusion, the use of conventional NSAIDs was associated with a higher risk of NS starting from at least 2 weeks of exposure. This higher risk was also shown for recent and past exposure up to 2 years before NS diagnosis. These higher risks appeared mainly attributable to AADs and PADs. In contrast, current and past use (>2 months–2 years) of selective COX-2 inhibitors were not associated with a higher risk.

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SUPPLEMENTARY

Table S1 CPRD codes for nephrotic syndrome and the clinical events

No	Med code	Read code	Read term	Frequency, n (%)
1	2999	K01..00	NS	1972 (75)
2	2471	K01X100	NS in DM	172 (7)
3	22205	K01X411	Lupus nephritis	138 (5)
4	1803	K011.00	NS with membranous glomerulonephritis	78 (3)
5	22852	K015.00	NS, focal and segmental glomerular lesions	69 (3)
6	17365	K01B.00	NS, diffuse crescentic glomerulonephritis	31 (1)
7	29634	K013.00	NS with minimal change glomerulonephritis	28 (1)
8	21989	K019.00	NS, diffuse mesangio-capillary glomerulonephritis	25 (1)
9	27427	K01z.00	NS NOS	24 (1)
10	19316	K016.00	NS, diffuse membranous glomerulonephritis	20 (1)
11	21947	K017.00	NS, diffuse mesangial proliferative glomerulonephritis	17 (1)
12	23913	K014.00	NS, minor glomerular abnormality	12 (1)
13	47922	K01x000	NS in amyloidosis	10 (0)
14	47672	K01x400	NS in systemic lupus erythematosus	9 (0)
15	50472	K018.00	NS, diffuse endocapillary proliferative glomerulonephritis	3 (0)
16	45499	K01X111	Kimmelstiel-Wilson Disease	2 (0)
17	56987	K01A.00	NS, dense deposit disease	2 (0)
18	57926	K013.12	Steroid sensitive NS	2 (0)
19	108816	K01x.00	NS in diseases EC	2 (0)
20	40349	K013.11	Lipoid nephrosis	1 (0)
21	58750	K01x300	NS in poly-arthritis nodosa	1 (0)
22	94373	K01y.00	NS with other pathological kidney lesions	1 (0)
23	110794	K01w200	Congenital NS with focal glomerulosclerosis	1 (0)
24	63786	K01w.00	Congenital NS	0 (0)
25	72303	K01w000	Finnish NS	0 (0)
26	9840	K010.00	NS with proliferative glomerulonephritis	0 (0)
27	99201	K01x200	NS in malaria	0 (0)
28	99644	K012.00	NS + membrano-proliferative glomerulonephritis	0 (0)
29	108591	K01w100	Drash syndrome	0 (0)
30	108922	K01w112	Wilms' tumor + NS + pseudohermaphroditism	0 (0)
31	111370	K01wz00	Congenital NS NOS	0 (0)
			TOTAL	2620 (100)

CPRD = the Clinical Practice Research Datalink; DM = Diabetes Mellitus; EC = Elsewhere Classified; NOS = Not Otherwise Specified; NS = Nephrotic Syndrome

Table S2 The Anatomical Therapeutic Chemical Classification system for NSAIDs

No	NSAIDs according to COX enzyme selectivity and chemical structures	ATC codes
1	Conventional NSAIDs	
	Butylpyrazolidines	M01AA
	Acetic acid derivatives and related substances	M01AB
	Oxicams	M01AC
	Propionic acid derivatives	M01AE
	Fenamates	M01AG
	Other anti-inflammatory and anti-rheumatoid agents, non-steroid	M01AX
2	Selective COX-2 inhibitors	M01AH

Abbreviations: ATC = The Anatomical Therapeutic Chemical; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs

Table S3 Odds ratios of nephrotic syndrome for NSAID users stratified by age

18-64 years old	Cases (n = 1,579)	Controls (n = 6,316)	Crude OR (95% CI)	Adjusted OR[Ŧ] (95% CI)
Nonuse, n (%)	715 (45)	3,375 (53)	1	1
Current use, n (%)				
Conventional NSAIDs[1]	40 (3)	123 (2)	1.54 (1.07-2.13)	1.08 (0.69-1.68)
Selective COX-2 inhibitors	6 (0)	20 (0)	1.42 (0.57-3.54)	0.38 (0.21-0.70)
Recent use, n (%)				
Conventional NSAIDs[1]	47 (3)	91 (1)	2.44 (1.70-3.50)	1.59 (1.03-2.47)
Selective COX-2 inhibitors	2 (0)	5 (0)	NA	NA
Past use (discontinuation between 2 months – 2 years), n (%)				
Conventional NSAIDs[1]	300 (19)	900 (14)	1.57 (1.35-1.84)	1.13 (0.94-1.36)
Selective COX-2 inhibitors	17 (1)	25 (0)	3.21 (1.72-5.98)	1.43 (0.92-2.23)
Past use (discontinuation >2 years), n (%)				
Conventional NSAIDs[1]	443 (28)	1734 (28)	1.21 (1.06-1.38)	0.91 (0.77-1.07)
Selective COX-2 inhibitors	9 (1)	43 (1)	0.99 (0.48-2.04)	0.32 (0.13-0.80)
≥65 years old	Cases (n = 1,041)	Controls (n = 4,138)	Crude OR (95% CI)	Adjusted OR[Ŧ] (95% CI)
Nonuse, n (%)	403 (39)	1,767 (43)	1	1
Current use, n (%)				
Conventional NSAIDs[1]	34 (3)	141 (3)	1.06 (0.72-1.56)	1.02 (0.67-1.55)
Selective COX-2 inhibitors	2 (0)	19 (1)	NA	NA
Recent use, n (%)				
Conventional NSAIDs[1]	26 (3)	92 (2)	1.25 (0.80-1.96)	1.31 (0.80-2.15)
Selective COX-2 inhibitors	2 (0)	10 (0)	NA	NA
Past use (discontinuation between 2 months – 2 years), n (%)				
Conventional NSAIDs[1]	174 (17)	577 (14)	1.32 (1.08-1.62)	1.26 (1.01-1.58)
Selective COX-2 inhibitors	20 (2)	74 (2)	1.19 (0.72-1.97)	1.15 (0.67-1.98)
Past use (discontinuation >2 years), n (%)				
Conventional NSAIDs[1]	354 (34)	1,369 (33)	1.13 (0.97-1.33)	0.97 (0.81-1.16)
Selective COX-2 inhibitors	26 (3)	90 (2)	1.27 (0.81-1.99)	0.98 (0.59-1.62)

Abbreviations: CI = Confidence Interval; COX-2 = Cyclooxygenase-2; NA = Non Applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds ratio

[1]acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, and other NSAIDs

[Ŧ]adjusted for comorbidities, co-medications, body mass index, smoking, and alcohol abuse

Table S4 Odds ratios of nephrotic syndrome for NSAID users stratified by sex

Female	Cases (n = 1,432)	Controls (n = 5,714)	Crude OR (95% CI)	Adjusted OR[Ŧ] (95% CI)
Nonuse, n (%)	639 (45)	2,984 (52)	1	1
Current use, n (%)				
Conventional NSAIDs[1]	33 (2)	130 (2)	1.19 (0.80-1.75)	1.15 (0.92-1.44)
Selective COX-2 inhibitors	18 (0)	18 (0)	0.78 (0.23-2.65)	0.51 (0.27-0.97)
Recent use, n (%)				
Conventional NSAIDs[1]	40 (3)	94 (2)	1.99 (1.36-2.91)	1.80 (1.17-2.79)
Selective COX-2 inhibitors	2 (0)	2 (0)	NA	NA
Past use (discontinuation between 2 months – 2 years), n (%)				
Conventional NSAIDs[1]	240 (17)	722 (13)	1.55 (1.31-1.84)	1.35 (1.11-1.63)
Selective COX-2 inhibitors	54 (2)	54 (1)	2.08 (1.27-3.38)	1.91 (1.24-2.94)
Past use (discontinuation >2 years), n (%)				
Conventional NSAIDs[1]	433 (30)	1,654 (29)	1.22 (1.07-1.40)	1.02 (0.87-1.20)
Selective COX-2 inhibitors	56 (1)	56 (1)	1.58 (0.94-2.69)	0.98 (0.53-1.81)
Male	Cases (n = 1,188)	Controls (n = 4,740)	Crude OR (95% CI)	Adjusted OR[Ŧ] (95% CI)
Nonuse, n (%)	479 (40)	2158 (46)	1	1
Current use, n (%)				
Conventional NSAIDs[1]	41 (4)	134 (3)	1.38 (0.96-1.98)	1.07 (0.70-1.64)
Selective COX-2 inhibitors	5 (0)	21 (0)	1.07 (0.40-2.86)	0.26 (0.06-1.15)
Recent use, n (%)				
Conventional NSAIDs[1]	33 (3)	88 (2)	1.69 (1.12-2.55)	1.31 (0.79-2.18)
Selective COX-2 inhibitors	3 (0)	13 (0)	NA	NA
Past use (discontinuation between 2 months – 2 years), n (%)				
Conventional NSAIDs[1]	234 (20)	755 (16)	1.40 (1.17-1.67)	1.12 (0.91-1.39)
Selective COX-2 inhibitors	13 (1)	45 (1)	1.30 (0.70-2.43)	0.52 (0.21-1.28)
Past use (discontinuation >2 years), n (%)				
Conventional NSAIDs[1]	364 (31)	1449 (31)	1.13 (0.97-1.32)	0.90 (0.75-1.09)
Selective COX-2 inhibitors	16 (1)	77 (2)	0.94 (0.54-1.62)	0.62 (0.33-1.17)

Abbreviations: CI = Confidence Interval; COX-2 = Cyclooxygenase-2; NA = Non Applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio

[1]acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, and other NSAIDs

[Ŧ]adjusted for comorbidities, co-medications, body mass index, smoking, and alcohol abuse

Table S5 Odds ratios of nephrotic syndrome defined by kidney biopsy for conventional NSAID[1] users

	Cases (n = 279)	Controls (n = 10,168)	Crude OR (95% CI)	Adjusted OR[Ŧ] (95% CI)
Nonuse, n (%)	121 (43)	5,142 (51)	1	1
Current use, n (%)	7 (3)	264 (3)	1.13 (0.52-2.44)	1.06 (0.47-2.37)
Recent use, n (%)	10 (4)	182 (2)	2.35 (1.21-4.51)	1.83 (0.89-3.80)
Past use (discontinuation between 2 months – 2 years), n (%)	49 (18)	1,477 (15)	1.41 (1.01-1.98)	1.23 (0.85-1.78)
Past use (discontinuation >2 years), n (%)	92 (33)	3,103 (31)	1.26 (0.96-1.66)	1.09 (0.80-1.49)

Abbreviations: CI = Confidence Interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio

[1]acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, and other NSAIDs

[Ŧ]adjusted for matching variables (age, sex, the general practitioner practice, and index-date), comorbidities, co-medications, body mass index, smoking, and alcohol abuse

Table S6 Odds ratios of nephrotic syndrome for conventional NSAID users[1] 3 months before the index date

	Cases (n =2,536)	Controls (n = 10,168)	Crude OR (95% CI)	Adjusted OR[Ŧ] (95% CI)
Nonuse, n (%)	1,147 (45)	5,208 (51)	1	1
Current use[ϕ], n (%)				
1-14 days	36 (1)	96 (1)	1.70 (1.15-2.51)	1.38 (0.89-2.13)
15-28 days	29 (1)	95 (1)	1.38 (0.91-2.11)	1.24 (0.79-1.97)
>28 days	26 (1)	66 (1)	1.79 (1.13-2.82)	1.77 (1.09-2.89)
Recent use, n (%)	71 (3)	177 (2)	1.82 (1.37-2.41)	1.78 (1.31-2.43)
Past use (discontinuation between >2 months – 2 years), n (%)	445 (18)	1,504 (15)	1.34 (1.19-1.52)	1.19 (1.03-1.36)
Past use (discontinuation >2 years), n (%)	782 (31)	3,022 (30)	1.17 (1.06-1.30)	1.03 (0.92-1.15)

Abbreviations: CI = Confidence Interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio

[1]acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, and other NSAIDs

[ϕ]duration of use

[Ŧ]adjusted for matching variables (age, sex, general practitioners' practice, and the index date), comorbidities, co-medications, body mass index, smoking behavior, and alcohol abuse

Table S7 Odds ratios of nephrotic syndrome for conventional NSAID users[1] 6 months before the index date

	Cases (n =2,536)	Controls (n = 10,168)	Crude OR (95% CI)	Adjusted OR[₮] (95% CI)
Nonuse, n (%)	1,179 (46)	5,265 (52)	1	1
Current use[ϕ], n (%)				
1-14 days	37 (2)	117 (1)	1.42 (0.98-2.07)	1.32 (1.31-1.34)
15-28 days	44 (2)	123 (1)	1.61 (1.13-2.28)	1.45 (1.00-2.12)
>28 days	23 (1)	47 (1)	2.20 (1.33-3.63)	2.03 (1.17-3.52)
Recent use, n (%)	48 (2)	193 (2)	1.09 (0.79-1.51)	0.89 (0.62-1.27)
Past use (discontinuation between >2 months – 2 years), n (%)	448 (18)	1,487 (15)	1.35 (1.20-1.53)	1.22 (1.06-1.39)
Past use (discontinuation >2 years), n (%)	758 (30)	2,936 (29)	1.16 (1.05-1.28)	1.03 (0.92-1.15)

Abbreviations: CI = Confidence Interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio

[1]acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, and other NSAIDs

[ϕ]duration of use

[₮]adjusted for matching variables (age, sex, general practitioners' practice, and the index date), comorbidities, co-medications, body mass index, smoking behavior, and alcohol abuse

Table S8 Odds ratios of nephrotic syndrome for conventional NSAID users[1] 9 months before the index date

	Cases (n = 2,536)	Controls (n = 10,168)	Crude OR (95% CI)	Adjusted OR[₮] (95% CI)
Nonuse, n (%)	1,202 (47)	5,323 (52)	1	1
Current use[ϕ], n (%)				
1-14 days	35 (1)	128 (1)	1.22 (0.83-1.78)	1.16 (0.77-1.73)
15-28 days	53 (2)	113 (1)	2.09 (1.50-2.91)	2.13 (1.49-3.04)
>28 days	27 (1)	64 (1)	1.88 (1.19-2.96)	1.60 (0.97-2.62)
Recent use, n (%)	57 (2)	180 (2)	1.41 (1.04-1.91)	1.21 (0.87-1.68)
Past use (discontinuation between >2 months – 2 years), n (%)	426 (17)	1,492 (15)	1.27 (1.12-1.44)	1.15 (1.00-1.31)
Past use (discontinuation >2 years), n (%)	736 (29)	2,868 (28)	1.14 (1.03-1.27)	1.01 (0.90-1.14)

Abbreviations: CI = Confidence Interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio

[1]acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, and other NSAIDs

[ϕ]duration of use

[₮]adjusted for matching variables (age, sex, general practitioners' practice, and the index date), comorbidities, co-medications, body mass index, smoking behavior, and alcohol abuse

Table S9 Odds ratios of nephrotic syndrome for conventional NSAID users[1] 12 months before the index date

	Cases (n = 2,536)	Controls (n = 10,168)	Crude OR (95% CI)	Adjusted OR[Ŧ] (95% CI)
Nonuse, n (%)	1,215 (48)	5,413 (53)	1	1
Current use[ϕ], n (%)				
1-14 days	46 (2)	116 (1)	1.77 (1.25-2.50)	1.56 (1.07-2.27)
15-28 days	31 (1)	116 (1)	1.19 (0.80-1.78)	1.14 (0.75-1.75)
>28 days	24 (1)	55 (1)	1.94 (1.20-3.15)	1.51 (0.89-2.56)
Recent use, n (%)	62 (2)	165 (2)	1.67 (1.24-2.26)	1.51 (1.09-2.08)
Past use (discontinuation between >2 months – 2 years), n (%)	428 (17)	1,510 (15)	1.26 (1.12-1.43)	1.13 (0.99-1.29)
Past use (discontinuation >2 years), n (%)	730 (29)	2,795 (27)	1.16 (1.05-1.29)	1.04 (0.93-1.16)

Abbreviations: CI = Confidence Interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio

[1]acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, and other NSAIDs

[ϕ]duration of use

[Ŧ]adjusted for matching variables (age, sex, general practitioners' practice, and the index date), comorbidities, co-medications, body mass index, smoking behavior, and alcohol abuse

Table S10 Odds ratios of nephrotic syndrome for conventional NSAID users among those without comorbidities[1] that are well-known causes of nephrotic syndrome

	Cases (n = 1,785)	Controls (n = 9,373)	Crude OR (95% CI)	Adjusted OR[Ŧ] (95% CI)
Nonuse, n (%)	815 (46)	4,859 (52)	1	1
Current use[ϕ], n (%)				
1-14 days	18 (1)	91 (1)	1.18 (0.71-1.97)	0.91 (0.52-1.60)
15-28 days	23 (1)	99 (1)	1.39 (0.88-2.19)	1.41 (0.86-2.31)
>28 days	14 (1)	47 (1)	1.78 (0.97-3.24)	1.60 (0.83-3.10)
Recent use, n (%)	51 (3)	166 (2)	1.83 (1.33-2.53)	1.66 (1.16-2.39)
Past use (discontinuation between >2 months – 2 years), n (%)	331 (19)	1,346 (14)	1.47 (1.27-1.69)	1.29 (1.10-1.51)
Past use (discontinuation >2 years), n (%)	533 (30)	2,765 (30)	1.15 (1.02-1.29)	1.01 (0.88-1.16)

Abbreviations: CI = confidence interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio

[1]diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, amyloidosis, and leukemia

[ϕ]duration of use

[Ŧ]adjusted for matching variables (age, sex, general practitioners' practice, and the index date), comorbidities associated with kidney toxicity, co-medications, body mass index, smoking, and alcohol abuse

Table S11 Odds ratios of hospitalized patients with nephrotic syndrome for conventional NSAID[1] users

	Cases (n = 680)	Controls (n = 10,168)	Crude OR (95% CI)	Adjusted OR[₮] (95% CI)
Nonuse, n (%)	276 (41)	5,142 (51)	1	1
Current use[ϕ], n (%)				
1-14 days	6 (1)	104 (1)	1.08 (0.47-2.47)	0.83 (0.35-1.97)
15-28 days	9 (1)	104 (1)	1.61 (0.81-3.22)	1.61 (0.78-3.32)
>28 days	6 (1)	56 (1)	2.00 (0.85-4.67)	1.53 (0.59-3.95)
Recent use, n (%)	19 (3)	182 (2)	1.95 (1.19-3.17)	1.52 (0.89-2.59)
Past use (discontinuation between >2 months – 2 years), n (%)	130 (19)	1,477 (15)	1.64 (1.32-2.04)	1.27 (1.00-1.61)
Past use (discontinuation >2 years), n (%)	234 (34)	3,103 (31)	1.41 (1.17-1.68)	1.06 (0.87-1.30)

Abbreviations: CI = Confidence Interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio

[1]acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, and other NSAIDs

[ϕ]duration of use

[₮]adjusted for matching variables (age, sex, general practitioners' practice, and the index date), comorbidities, co-medications, body mass index, smoking, and alcohol abuse

CHAPTER 4

GASTROINTESTINAL TOXICITY

AMONG PATIENTS TAKING SELECTIVE COX-2 INHIBITORS OR CONVENTIONAL NSAIDS,

ALONE OR COMBINED WITH PROTON-PUMP INHIBITORS:

A CASE-CONTROL STUDY

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ABSTRACT

Background: Conventional NSAIDs increase the risk of gastrointestinal (GI) toxicity. This risk can be reduced by combining with a proton pump inhibitor (PPI) or replace it with a selective COX-2 inhibitor. In daily practice, a selective COX-2 inhibitor is sometimes combined with a PPI, but only a few studies evaluated the added value of this combination.

Purposes: To assess the risk of gastrointestinal perforation, ulcers, or bleeding (PUB) associated with the use of conventional NSAIDs with proton pump inhibitors (PPIs) and selective COX-2 inhibitors, with or without PPIs compared to conventional NSAIDs.

Methods: A case-control study was performed within conventional NSAIDs and/or selective COX-2 inhibitors users identified from the Dutch PHARMO Record Linkage System in the period 1998-2012. Cases were patients aged ≥18 years with first hospital admission for PUB. For each case, up to 4 controls were matched for age and sex at the date a case was hospitalized (the index date). Logistic regression analysis was used to calculate odds ratios (ORs).

Results: At the index date 2,634 cases and 5,074 controls were current users of conventional NSAIDs or selective COX-2 inhibitors. Compared to conventional NSAIDs, selective COX-2 inhibitors with PPIs had the lowest risk of PUB (adj. OR 0.51, 95%CI: 0.35-0.73) followed by selective COX-2 inhibitors (adj. OR 0.66, 95%CI: 0.48-0.89) and conventional NSAIDs with PPIs (adj. OR 0.79, 95%CI: 0.68-0.92). Compared to conventional NSAIDs, the risk of PUB was lower for those aged ≥75 years taking conventional NSAIDs with PPIs compared to younger patients(adj. interaction OR 0.79, 95%CI: 0.64-0.99). However, those aged ≥75 years taking selective COX-2 inhibitors, the risk was higher compared to younger patients (adj. interaction OR 1.22, 95%CI: 1.01-1.47).

Conclusions: Selective COX-2 inhibitors with PPIs, selective COX-2 inhibitors and conventional NSAIDs with PPIs were associated with lower risks of PUB compared to conventional NSAIDs. These effects were modified by age.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are extensively used to treat pain-related musculoskeletal diseases such as osteoarthritis, rheumatoid arthritis and chronic low back pain (1-3). Conventional NSAIDs inhibit the cyclooxygenase (COX) iso-enzymes, COX-1 and COX-2, while the selective COX-2 inhibitors mainly inhibit the latter (4).

Two meta-analyses of clinical trials showed that conventional NSAIDs increase the risk of gastrointestinal (GI) complications (5, 6). Although selective COX-2 inhibitors have a lower risk of GI toxicity than conventional NSAIDs, a meta-analysis of clinical trials showed that celecoxib still increases the risk of GI toxicity compared to placebo (7).

Several evidence-based strategies are implemented to lower the risk of GI adverse events when a NSAID is needed, such as the substitution of conventional NSAIDs for selective COX-2 inhibitors or co-administration of proton pump inhibitors (PPIs) with conventional NSAIDs (8-11). When conventional NSAIDs are combined with PPIs, the risk of symptomatic GI ulcers is lower than with conventional NSAIDs alone (11, 12), in particular for patients with risk factors for GI complications and long-term use (13). Furthermore, a meta-analysis of clinical trials demonstrated that the risk of upper GI toxicity for the combined treatment of a conventional NSAID and a PPI is similar for selective COX-2 inhibitors alone (14).

Another strategy to reduce GI toxicity is by combining selective COX-2 inhibitors with PPIs (15). Several studies showed that this combination is associated with a lower risk of GI adverse events compared to conventional NSAIDs (16-18) or selective COX-2 inhibitors alone (19, 20).

Compared to younger users, elderly aged ≥75 years taking ibuprofen with omeprazole showed a higher risk of recurrent ulcers (21) and a combination of celecoxib and a PPI was more beneficial to decrease the risk of GI hospitalization with celecoxib as a comparator (22). Male gender is also associated with a higher risk of GI adverse events among conventional NSAIDs users (23).

As presented above there is a large body of evidence about the GI protective strategies when patients with an increased risk of GI problems are in need of a NSAID. Still, it was shown in an observational

study that in clinical practice, >58% of NSAID users with an increased risk for GI problems do not receive a gastroprotective strategy (24). This undertreatment might be partly explained by the fact that there is no clear recommendation when to use which strategy. It is probably related to the fact that the relative effects of the different GI protective strategies are largely unknown.

There have been many studies published in which the GI safety of conventional NSAIDs or selective COX-2 inhibitors, alone or combined with a PPI were compared. However, these different GI protective strategies were never evaluated in one study together. We, therefore, conducted a study comparing the relative risks of PUB for selective COX-2 inhibitors with PPIs, selective COX-2 inhibitors alone and conventional NSAIDs with PPIs versus conventional NSAIDs alone, and to identify whether age, sex, and availability of PPIs as over-the-counter (OTC) drug modify these risk estimates.

METHODS

Data source

Data were obtained from the Dutch PHARMO Record Linkage System (PHARMO RLS) from January 1998 until December 2012. This is a population-based network of healthcare databases combining data from different healthcare settings in the Netherlands, such as the hospitalization database, out- and in-patients pharmacy, the general practitioner database, etc. More than 4 million (25%) inhabitants in the Netherlands have participated in this database. Patient's histories include detailed information about all drugs dispensed by date of dispensing, type of prescriber, dose, and duration of use, surgical procedure, discharge diagnosis, cost and other administrative information (25, 26).

Study design and population

We conducted a case-control study in subjects who had ever used conventional NSAIDs and/or selective COX-2 inhibitors. Cases were patients aged ≥18 years at first hospital admission with a primary discharge diagnosis of GI toxicity defined as PUB in the GI tract [The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) codes 531, 532 and 533]. The date of hospital admission

was defined as the index date. Potential controls were patients without any diagnoses of GI toxicity prior to and at the index date of the case to which they were matched. For each case, up to four controls were matched on year of birth and sex at the index date.

Exposure definition

All prescriptions for conventional NSAIDs, selective COX-2 inhibitors, and PPIs before the index date were identified. Exposure classification was based on the use of conventional NSAIDs [Anatomical Therapeutic Chemical (ATC) codes M01AA, M01AB, M01AC, M01AE, M01AG, or M01AX] alone or combined with PPIs (A02BC), or selective COX-2 inhibitors (M01AH) alone or combined with PPIs. Patients were classified as current users when the theoretical end date of the last prescription ended after the index date. We allowed the gap by a half duration of the previous prescription between the end date of the prescription and the start date of the following one. We included only current users of conventional NSAIDs or selective COX-2 inhibitors (without or with PPIs) in the analysis. Patients who had both conventional NSAIDs and selective COX-2 inhibitors at the index date were excluded.

Potential confounders

Potential confounders taken into account were age, sex, and concomitant drug use on the index date, including antacids (ATC-code A02A), histamine-2 receptor antagonists (A02BA), phenprocoumon (B01AA04), acenocoumarol (B01AA07), clopidogrel (B01AC04), acetylsalicylic acid (B01AC06), dipyridamole (B01AC07), prasugrel (B01AC22), glucocorticoids (H02AB), and selective serotonin reuptake inhibitors (SSRIs) (N06AB). Potential confounders measured in the year prior to the index date were a history of conventional NSAIDs, selective COX-2 inhibitors, antacid, histamine-2 receptor antagonists, or PPIs use.

Data analyses

Logistic regression was used to estimate crude and adjusted odds ratios (OR)s and 95% confidence intervals (95%CI) of the risk of PUB associated with the current use of conventional NSAIDs with PPIs, selective COX-2 inhibitors alone, or selective COX-2 inhibitors with PPIs compared to conventional NSAIDs alone. We also evaluated the interaction by age, sex, and availability of PPIs as OTC drug by entering

product terms in the model. Availability of PPIs as OTC drug was defined by the date when PPIs were first available as OTC drug in the Netherlands (February 2000). The synergy index (SI) was calculated to assess the risk and the significance of these interactions. The SI is defined as an interaction term between 2 variables. On the relative risk scale (multiplicative), this quantity measures whether the effect of both exposures together exceeds the product of the effects of the two exposures considered separately. If the SI >1, the interaction is said to be positive. In contrast, if the SI <1, the interaction is negative. A 95% confidence interval of SI is used to define the significance of the interaction. All the analyses were carried out using IBM Statistic SPSS 23 and p-values of <0.05 were considered statistically significant.

Sensitivity analysis

For our main analysis, we defined current use if the index date fell within a time period of the last prescription of conventional NSAIDs or selective COX-2 inhibitors. Patients who discontinued medication within 90 days prior to the index date were excluded. Since the gap between current and recent use was narrow, a sensitivity analysis was performed in which current users were defined as patients who discontinued medication in a time window of 90 days prior to the index date or were current users at the index date.

RESULTS

Characteristics

In the cohort, we identified 15,962 PUB cases and 62,683 age- and sex-matched controls among users of conventional NSAIDs and/or selective COX-2 inhibitors within our 15 year study period. Of those, 2,634 cases and 5,074 controls were current users of conventional NSAIDs or selective COX-2 inhibitors (with or without PPIs) at the index date. By restricting to current users, the original matching ratio was not retained. Compared to controls, cases had more comorbidities determined by the number of concomitant drug use, namely acid-lowering drugs, vitamin K antagonists, platelet aggregation inhibitors,

glucocorticoids, and SSRIs. The prevalence of drug use before the index date was also higher, e.g. selective COX-2 inhibitors and acid lowering drugs (**Table 1**).

Table 1 Baseline characteristics of cases with perforation, ulcers or bleeding (PUB) and controls exposed to current use of conventional NSAIDs or selective COX-2 inhibitors

Variables	Cases (n= 2,634)	Controls (n = 5,074)	p-value
Age, mean (year ± sd)	68.75 ± 15.6	69.28 ± 14.6	NA
Sex, n (%)			
Women	1576 (59.8)	3084 (60.8)	NA
Concomitant drug(s) use at the index date, n (%)			
Acid lowering drugs[a]	164 (6.2)	187 (3.7)	0.000*
Vitamin K antagonists [b]	399 (15.1)	244 (4.8)	0.000*
Platelet aggregation inhibitors[c]	707 (26.8)	999 (19.7)	0.000*
Glucocorticoids	188 (7.1)	234 (4.6)	0.000*
Serotonin selective re-uptake inhibitors	132 (5.0)	205 (4.0)	0.048*
History of drug(s) use, n (%)			
Conventional NSAIDs	192 (7.3)	502 (9.9)	0.000*
Selective COX-2 inhibitors	409 (15.5)	619 (12.2)	0.000*
Conventional NSAIDs + selective COX-2 inhibitors	0 (0.0)	0 (0.0)	NA
Acid lowering drugs[d]	1444 (54.8)	2432 (47.9)	0.000*

Abbreviations: COX-2 = Cyclooxygenase-2; NA = Not Applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs

[a]acid lowering drugs (antacids and H2-receptor antagonists), [b]vitamin K antagonists (phenprocoumon and acenocoumarol), [c]platelet aggregation inhibitors (clopidogrel, acetylsalicylic acid, dipyridamole, and prasugrel), [d]acid-lowering drugs (antacids, H2-receptor antagonists, and proton pump inhibitors)

*statistically significant ($p<0.05$).

Risk of PUB for current users of conventional NSAIDs or selective COX-2 inhibitors, alone or combined with PPIs

Compared to conventional NSAIDs, selective COX-2 inhibitors with PPIs were associated with a lower risk of PUB (adj. OR 0.51, 95%CI: 0.35-0.73) followed by selective COX-2 inhibitors (adj. OR 0.66, 95%CI: 0.48-0.89) and conventional NSAIDs with PPIs (adj. OR 0.79, 95%CI: 0.68-0.92) (**Table 2**). When we defined selective COX-2 inhibitors alone as a reference group, the relative risks for conventional NSAIDs with PPIs and selective COX-2 inhibitors with PPIs were not statistically different (adj. OR 0.77, 95%CI: 0.55-1.07 and adj. OR 1.21, 95%CI: 0.87-1.68, respectively) (**Supplementary, Table S1**).

Table 2 Odds ratios for perforation, ulcers or bleeding (PUB) events among current users of conventional NSAIDs or selective COX-2 inhibitors alone or combined with PPIs

Exposure	Cases (n = 2,634)	Controls (n = 5,074)	Crude OR (95% CI)	Adjusted OR[Ŧ] (95% CI)
Current use, n (%)				
Conventional NSAIDs - PPIs	1,599 (60.7)	3,013 (59.4)	1	1
Conventional NSAIDs + PPIs	775 (29.4)	1,356 (26.7)	1.08 (0.97-1.20)	0.79 (0.68-0.92)*
Selective COX-2 inhibitors - PPIs	179 (6.8)	487 (9.6)	0.69 (0.58-0.83)*	0.66 (0.48-0.89)*
Selective COX-2 inhibitors + PPIs	81 (3.1)	218 (4.3)	0.70 (0.54-0.91)*	0.51 (0.35-0.73)*

Abbreviations: CI = Confidence Interval; COX-2 = Cyclooxygenase-2; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; PPIs = Proton-Pump Inhibitors; OR = Odds Ratio

[Ŧ]Adjusted for age, sex, concomitant drugs (acid-lowering drugs, vitamin K antagonists, platelet aggregation inhibitors, glucocorticoids, and selective serotonin receptor inhibitors), and a history of drug use (conventional NSAIDs, selective COX-2 inhibitors, and acid-lowering drugs)

*statistically significant ($p<0.05$)

Effect Modification

For all age groups, our study revealed that conventional NSAIDs with PPIs, selective COX-2 inhibitors alone and selective COX-2 inhibitors with PPIs decreased the relative risk of PUB compared to conventional NSAIDs alone as we found in our main analyses. Compared to younger patients, those aged ≥75 years taking conventional NSAIDs with PPIs had a lower risk (adj. OR 0.69, 95%CI: 0.47-1.03 vs adj. OR 0.87, 95%CI: 0.73-1.04), but those aged ≥75 years taking selective COX-2 inhibitors were associated with a higher risk (adj. OR 0.88, 95%CI: 0.64-1.22 vs adj. OR 0.72, 95%CI: 0.63-0.83) with conventional NSAIDs alone as the comparator. These interactions were statistically significant (adj. interaction OR 0.79, 95%CI: 0.64-0.99 for conventional NSAIDs with PPIs and adj. interaction OR 1.22, 95%CI: 1.01-1.47 for selective COX-2 inhibitors). Even though patients aged ≥75 years taking selective COX-2 inhibitors with PPIs had a lower risk of PUB compared to younger patients (adj. OR 0.71, 95%CI: 0.53-0.97 vs adj. OR 0.85, 95%CI: 0.75-0.97), the interaction was not statistically significant (adj. interaction OR 0.84, 95%CI: 0.70-1.00) (**Table 3**).

Table 3 Effect modification of age toward the association between conventional NSAIDs or selective COX-2 inhibitors alone or combined with PPIs and the risk of perforation, ulcer, or bleeding (PUB)

Age 18-74 years	**Cases (n = 1,386)**	**Controls (n = 2,538)**	**Crude OR (95% CI)**	**Adjusted OR ǂ (95% CI)**	**Crude SI (95% CI)**	**Adjusted SI ǂ (95% CI)**
Conventional NSAIDs - PPIs, n (%)	948 (68.4)	1,820 (71.7)	1	1		
Conventional NSAIDs + PPIs, n (%)	438 (31.6)	718 (28.3)	1.17 (1.02-1.35)*	0.87 (0.73-1.04)		
Age≥75 years	**Cases (n = 988)**	**Controls (n = 1,831)**	**Crude OR (95% CI)**	**Adjusted OR ǂ (95% CI)**	0.83 (0.67-1.03)	0.79 (0.64-0.99)*
Conventional NSAIDs - PPIs, n (%)	651 (65.9)	1,193 (65.2)	1	1		
Conventional NSAIDs + PPIs, n (%)	337 (34.1)	638 (34.8)	0.97 (0.68-1.39)	0.69 (0.47-1.03)		
Age 18-74 years	**Cases (n = 1,020)**	**Controls (n = 2,075)**	**Crude OR (95% CI)**	**Adjusted OR ǂ (95% CI)**	**Crude SI (95% CI)**	**Adjusted SI ǂ (95% CI)**
Conventional NSAIDs - PPIs, n (%)	948 (92.2)	1,820 (87.7)	1	1		
Selective COX-2 inhibitors - PPIs, n (%)	72 (7.1)	255 (12.3)	0.74 (0.64-0.84)*	0.72 (0.63-0.83)*		
Age≥75 years	**Cases (n = 658)**	**Controls (n = 1,425)**	**Crude OR (95% CI)**	**Adjusted OR ǂ (95% CI)**	1.25 (1.04-1.50)	1.22 (1.01-1.47)*
Conventional NSAIDs - PPIs, n (%)	651 (85.9)	1,193 (83.7)	1	1		
Selective COX-2 inhibitors - PPIs, n (%)	107 (14.1)	232 (16.3)	0.93 (0.67-1.26)	0.88 (0.64-1.22)		

Table 3 (continued)

Age 18-74 years	**Cases (n = 994)**	**Controls (n = 1,917)**	**Crude OR (95% CI)**	**Adjusted OR ǂ (95% CI)**	**Crude SI (95% CI)**	**Adjusted SI ǂ (95% CI)**
Conventional NSAIDs - PPIs, n (%)	948 (95.4)	1,820 (94.9)	1	1		
Selective COX-2 inhibitors + PPIs, n (%)	46 (4.6)	97 (5.1)	0.97 (0.86-1.09)	0.85 (0.75-0.97)*		
Age≥75 years	**Cases (n = 686)**	**Controls (n =1,314)**	**Crude OR (95% CI)**	**Adjusted OR ǂ (95% CI)**	0.84 (0.70-1.00)*	0.84 (0.70-1.00)
Conventional NSAIDs - PPIs, n (%)	651 (94.9)	1,193 (90.8)	1	1		
Selective COX-2 inhibitors + PPIs, n (%)	35 (5.1)	121 (9.2)	0.81 (0.60-1.09)	0.71 (0.53-0.97)*		

Abbreviations: CI = Confidence Interval; COX-2 = Cyclooxygenase-2; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio; PPIs = Proton-Pump Inhibitors; SI = synergy index

ǂAdjusted for sex, concomitant drugs (acid-lowering drugs, vitamin K antagonists, platelet aggregation inhibitors, glucocorticoids, and selective serotonin receptor inhibitors), and a history of drug use (conventional NSAIDs, selective COX-2 inhibitors, and acid lowering drugs)

*statistically significant ($p<0.05$)

Table 4 Effect modification of sex toward the association between conventional NSAIDs or selective COX-2 inhibitors alone or combined with PPIs and the risk of perforation, ulcers, or bleeding (PUB)

Women	**Cases (n = 1,396)**	**Controls (n = 2,592)**	**Crude OR (95% CI)**	**Adjusted OR ŦŦ (95% CI)**	**Crude SI (95% CI)**	**Adjusted SI ŦŦ (95% CI)**
Conventional NSAIDs - PPIs, n (%)	949 (68.0)	1,757 (67.8)	1	1		
Conventional NSAIDs + PPIs, n (%)	447 (32.0)	835 (32.2)	1.22 (1.03-1.44)*	0.89 (0.72-1.08)		
Men	**Cases (n = 978)**	**Controls (n = 1,777)**	**Crude OR (95% CI)**	**Adjusted OR ŦŦ (95% CI)**	0.82 (0.66-1.01)	0.84 (0.67-1.05)
Conventional NSAIDs - PPIs, n (%)	650 (60.6)	1,256 (62.8)	1	1		
Conventional NSAIDs + PPIs, n (%)	328 (30.6)	521 (26.1)	1.00 (0.68-1.45)	0.75 (0.48-1.14)		
Women	**Cases (n = 1,069)**	**Controls (n = 2,085)**	**Crude OR (95% CI)**	**Adjusted OR ŦŦ (95% CI)**	**Crude SI (95% CI)**	**Adjusted SI ŦŦ (95% CI)**
Conventional NSAIDs - PPIs, n (%)	949 (88.8)	1,756 (70.7)	1	1		
Selective COX-2 inhibitors - PPIs, n (%)	120 (11.2)	329 (29.3)	0.85 (0.73-0.99)*	0.82 (0.69-0.96)*		
Men	**Cases (n = 709)**	**Controls (n = 1,414)**	**Crude OR (95% CI)**	**Adjusted OR ŦŦ (95% CI)**	0.97 (0.80-1.17)	0.97 (0.80-1.19)
Conventional NSAIDs - PPIs, n (%)	650 (91.7)	1,256 (88.8)	1	1		
Selective COX-2 inhibitors - PPIs, n (%)	59 (8.3)	158 (11.2)	0.82 (0.58-1.14)	0.80 (0.55-1.14)		

Table 4 (continued)

Women	**Cases (n = 1,009)**	**Controls (n = 1,920)**	**Crude OR (95% CI)**	**Adjusted OR ₮ (95% CI)**	**Crude SI (95% CI)**	**Adjusted SI ₮ (95% CI)**
Conventional NSAIDs - PPIs, n (%)	949 (94.1)	1,757 (91.5)	1	1		
Selective COX-2 inhibitors + PPIs, n (%)	60 (5.9)	163 (8.5)	0.90 (0.76-1.07)	0.77 (0.65-0.92)*		
Men	**Cases (n = 671)**	**Controls (n = 1,311)**	**Crude OR (95% CI)**	**Adjusted OR ₮ (95% CI)**	0.97 (0.80-1.19)	1.02 (0.83-1.25)
Conventional NSAIDs - PPIs, n (%)	650 (96.9)	1,256 (95.8)	1	1		
Selective COX-2 inhibitors + PPIs, n (%)	21 (3.1)	55 (4.2)	0.87 (0.61-1.27)	0.79 (0.54-1.49)		

Abbreviations: CI = Confidence Interval; COX-2 = Cyclooxygenase-2; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio; PPIs = Proton-Pump Inhibitors; SI = Synergy Index

₮Adjusted for age, concomitant drugs (acid-lowering drugs, vitamin K antagonists, platelet aggregation inhibitors, glucocorticoids, and selective serotonin receptor inhibitors), and a history of drug use (conventional NSAIDs, selective COX-2 inhibitors, and acid lowering drugs)

*statistically significant ($p<0.05$)

Table 5 Effect modification of the availability of PPIs as OTC drug toward the association between conventional NSAIDs or selective COX-2 inhibitors alone or combined with PPIs and the risk of perforation, ulcers, or bleeding (PUB)

Not available	**Cases (n = 262)**	**Controls (n = 478)**	**Crude OR (95% CI)**	**Adjusted OR ₮ (95% CI)**	**Crude SI (95% CI)**	**Adjusted SI₮ (95% CI)**
Conventional NSAIDs - PPIs, n (%)	222 (84.7)	417 (87.2)	1	1	0.87 (0.56-1.36)	0.88 (0.56-1.39)
Conventional NSAIDs + PPIs, n (%)	40 (15.3)	61 (12.8)	1.23 (0.80-1.90)	0.90 (0.57-1.42)		
Available	**Cases (n = 2,112)**	**Controls (n =3,891)**	**Crude OR (95% CI)**	**Adjusted OR ₮ (95% CI)**		
Conventional NSAIDs - PPIs, n (%)	1,377 (65.2)	2,596 (66.7)	1	1		
Conventional NSAIDs + PPIs, n (%)	735 (34.8)	1,295 (33.3)	1.07 (0.45-2.58)	0.79 (0.32-1.97)		

Abbreviations: CI = Confidence Interval; COX-2 = Cyclooxygenase-2; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio; PPIs = Proton-Pump Inhibitors; SI = Synergy Index

₮Adjusted for age, sex, concomitant drugs (acid-lowering drugs, vitamin K antagonists, platelet aggregation inhibitors, glucocorticoids, and selective serotonin receptor inhibitors), and a history of drugs use (conventional NSAIDs, selective COX-2 inhibitors, and acid-lowering drugs)

Sensitivity Analysis

In our sensitivity analysis, we defined current users as patients who discontinued the medication within 90 days prior to the index date or were current users at the index date. Selective COX-2 inhibitors with PPIs and selective COX-2 inhibitors alone decreased the relative risk of PUB by 16% (adj. OR 0.84, 95%CI: 0.62-1.13) and by 15% (adj. OR 0.85, 95%CI: 0.67-1.06), respectively, compared to conventional NSAIDs. However, these relative risks were not statistically significant. Unexpectedly, conventional NSAIDs with PPIs significantly increased the risk by 25% (adj. OR 1.25, 95%CI: 1.13-1.38) compared to conventional NSAIDs alone (**Supplementary, Table S2**).

In contrast to age, our study indicated that sex did not modify the risk of PUB for conventional NSAIDs plus PPIs or selective COX-2 inhibitors (with or without PPIs) (**Table 4**), and availability of PPIs as OTC drug did not either modify the risk of PUB for conventional NSAIDs with PPIs all compared with conventional NSAIDs alone (**Table 5**). The interaction between the availability of PPIs as OTC drug and selective COX-2 inhibitors (with or without PPIs) could not be determined because OTC PPIs have been available before the first selective COX-2 inhibitors were introduced in the Netherlands in May 2000 (27).

DISCUSSION

This study demonstrated that compared to conventional NSAIDs, conventional NSAIDs with PPIs, selective COX-2 inhibitors alone and selective COX-2 inhibitors with PPIs decreased the risk of PUB with 21%, 34%, and 49%, respectively. Furthermore, our study showed that in patients >75 years old the GI protective effect of conventional NSAIDs with PPIs and selective COX-2 inhibitors with PPIs were higher than in patients <75. However, for selective COX-2 inhibitors alone this protective effect in the older age group unexpectedly appeared less. Sex and availability of PPIs as OTC drugs did not modify the effect of these gastroprotective strategies. These results which were obtained from one study are

consistent with several earlier studies in which the different contrasts were evaluated separately. Two systematic reviews of clinical trials showed that selective COX-2 inhibitors or conventional NSAIDs with PPIs were associated with a lower risk of GI ulcers by 74% and 91%, respectively compared to conventional NSAIDs (8, 11). Several observational studies also concluded that selective COX-2 inhibitors with PPIs were associated with a 39%-64% lower risk of upper GI complications compared to conventional NSAIDs (16-18).

A meta-analysis of clinical trials also showed that the relative risk of upper GI adverse events for conventional NSAIDs with PPIs was comparable to selective COX-2 inhibitors (14). Furthermore, two clinical trials showed that the risks of GI ulcers were reduced by 8.9%-15.6% for selective COX-2 inhibitors with esomeprazole compared to selective COX-2 inhibitors alone (19, 20). Our study also indicated a decreased risk of PUB for selective COX-2 inhibitors with PPIs compared to selective COX-2 inhibitors alone. However, the association was not significant. A possible explanation for this discrepancy is that our study included a relatively small number of patients exposed to selective COX-2 inhibitors, leading to limited statistical power.

Our study showed that age modified the risk of PUB for conventional NSAIDs with PPIs and selective COX-2 inhibitors alone compared to conventional NSAIDs alone. Compared to younger adults, patients aged ≥75 years taking conventional NSAIDs with PPIs or apparently selective COX-2 inhibitors with PPIs were associated with a lower risk of PUB, but those taking selective COX-2 inhibitors alone had a higher risk with conventional NSAIDs alone as the comparator. These findings are consistent with several previous studies. A study conducted in France demonstrated that patients aged ≥ 60 years taking selective COX-2 inhibitors alone had a higher rate of GI adverse events compared to younger patients by 0.54-0.96 and 0-0.23 per 1000 patients, respectively (28). Another study done in Canada indicated that patients aged ≥75 years taking celecoxib with a PPI had a 42% lower risk of GI hospitalization compared to younger elderly. In contrast to our result for those aged ≥75 years taking conventional NSAIDs with PPIs, this Canadian study mentioned that this age group had a slightly higher

risk of GI hospitalization by 4% compared to younger patients (22). This different risk might be due to differences in study design, sample size and comparator used. It was a retrospective cohort study involving a large number of patients taking a combination of conventional NSAIDs and a PPI by almost 20000 patients. They restricted the comparator to celecoxib, while our study took into account all selective COX-2 inhibitors.

Finally, our study found that sex did not modify relative risks of PUB for all comparisons. Even though a meta-analysis mentioned the risk of serious GI complications was higher in men than women exposed to conventional NSAIDs and/or selective COX-2 inhibitors (23), a previous Dutch cohort study conducted in a similar setting showed that men and women taking these medications shared a similar risk of GI hospitalization (29).

Sensitivity Analysis

In contrast to our main analysis, the sensitivity analysis surprisingly showed conventional NSAIDs with PPIs significantly increased the relative risk of PUB by 25% compared to conventional NSAIDs alone. This finding can be explained by channeling. Patients taking conventional NSAIDs alone are likely to discontinue or switch therapy because of GI adverse events (30). Subsequently, a PPI is more likely to be added or selective COX-2 inhibitors are more likely to substitute conventional NSAIDs. It indicates that patients who discontinued conventional NSAIDs with PPIs and then switched to a more stomach protective strategy had a high risk of PUB.

Strengths and Limitations

The strength of this study is it was population-based and used a large study population of about 80,000 conventional NSAIDs and/or selective COX-2 inhibitors users for whom high-quality data on hospitalizations and drugs dispensing information were extracted over a 15-year period. The completeness and the accuracy of dispensing data in the Dutch PHARMO RLS database are high (31). By comparing the different strategies to lower risk of PUB when in need of a NSAID in one observational

study, the relative effect estimates of these strategies are a better comparison than when these contrasts were evaluated separately.

As in all case-control studies using databases, we also considered several potential biases, namely selection bias, information bias, and confounding. Selection bias is unlikely to happen because we limited our cases to first hospitalized patients for PUB. Hence, we specified our attention to a certain spectrum of disease, i.e. severe cases.

Information bias includes misclassification of exposure, outcome, and confounding. We had no direct measure of patients' adherence to medications (including the exposures) because the Dutch PHARMO RLS is a database with a dispensing record of drugs. This database neither has records on OTC drug use. The use of OTC NSAIDs might lead to misclassification (underestimation) of the exposures. However, we expected its effect on the relative risk is minimal because in the Netherlands OTC NSAIDs are commonly used for a short duration (1-7 days) (32), while the risks of GI complication are significantly increased after 84 days of conventional NSAIDs exposure, except for indomethacin (5). However, indomethacin is not available as an OTC drug in the Netherlands (27). We could not either take into account OTC PPIs use, but our analysis showed that availability of PPIs as OTC drug had no significant impact on relative risk for users of conventional NSAIDs and a PPI. With regards to the outcome, the validity of diagnoses in this database is high as shown for pneumonia and cardiovascular (CV) diseases (33, 34).

With regards to confounding, as we restricted our study into current users of conventional NSAIDs or selective COX-2 inhibitors, we minimized confounding by indication. Although we adjusted for the most relevant potential confounders such as concomitant medications and history of drug use, we had no information on the history of GI ulcers, lifestyles (smoking status and alcohol consumption), *Helicobacter pylori* infection, and body mass index which are also prognostic factors of PUB. However, the proportions of these lifestyle factors and *Helicobacter pylori* infection were equally distributed among a Dutch population with or without GI symptoms using conventional NSAIDs and/or selective

COX-2 inhibitors as shown in earlier observational studies (35-37). We also tried to minimize confounding by the history of GI ulcers by considering past use of acid lowering drugs as a proxy. In addition, in our case-control study, we were not able to estimate the absolute risks which might be estimated in a cohort study.

Clinical Implications

Even though several guidelines have been established in order to prevent GI toxicity for patients with an increased risk of GI problems during NSAID exposure, >58% of those did not receive a gastroprotective strategy (24). Our findings may help to reassure physicians in their therapeutic decision to decrease the potential GI risk. We found that the risk differences between the three strategies to lower the risk of PUB were not statistically significant, but there are some indications that the gastroprotective strategy can be based on the degree of GI risk. When the risk increases, the order to implement a preventive strategy might be a conventional NSAID plus a PPI, a selective COX-2 inhibitor alone and a selective COX-2 inhibitor plus a PPI. Obviously, the choice does not depend only on GI risk but also on potential CV problems. For the selective COX-2 inhibitors, the increased risk of CV events has been clearly shown in clinical trials. Meanwhile, this is less clear for conventional NSAIDs, although several observational studies have shown that conventional NSAIDs probably also increase the risk of CV disease (38, 39).

CONCLUSIONS

Our study demonstrated that conventional NSAIDs combined with PPIs, selective COX-2 inhibitors alone or combined with a PPI were associated with a significantly decreased risk of PUB compared to conventional NSAIDs alone. Although in the same order the gastroprotective effect appeared to increase, the differences were not statistically significant. Compared to conventional NSAIDs alone, the risk for patients aged ≥75 years taking conventional NSAIDs with PPIs was lower,

whereas for those taking selective COX-2 inhibitors alone the risk was higher than younger patients. Both sex and availability of PPIs as OTC drug did not modify the risk of PUB.

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SUPPLEMENTARY

Table S1 Odds ratios for perforation, ulcers or bleeding (PUB) events among current users of conventional NSAIDs or selective COX-2 inhibitors alone or combined with PPIs

Exposure	Cases (n = 2,634)	Controls (n = 5,074)	Crude OR (95% CI)	Adjusted OR[Ŧ] (95% CI)
Current use, n (%)				
Selective COX-2 inhibitors - PPIs	179 (6.8)	487 (9.6)	1	1
Selective COX-2 inhibitors + PPIs	81 (3.1)	218 (4.3)	1.01 (0.74-1.37)	0.77 (0.55-1.07)
Conventional NSAIDs - PPIs	1,599 (60.7)	3,013 (59.4)	1.44 (1.20-1.73)*	1.52 (1.12-2.08)*
Conventional NSAIDs + PPIs	775 (29.4)	1,356 (26.7)	1.56 (1.28-1.89)*	1.21 (0.87-1.68)

Abbreviations: CI = Confidence Interval; COX-2 = Cyclooxygenase-2; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio; PPIs = Proton-Pump Inhibitors

[Ŧ]Adjusted for age, sex, concomitant drugs (acid-lowering drugs, vitamin K antagonists, platelet aggregation inhibitors, glucocorticoids, and selective serotonin receptor inhibitors), and a history of drug use (conventional NSAIDs, selective COX-2 inhibitors, and acid-lowering drugs)

*statistically significant (p<0.05)

Table S2 Sensitivity results for odds ratios for perforation, ulcers or bleeding (PUB) events among current users of conventional NSAIDs or selective COX-2 inhibitors alone or combined with PPIs

Exposure	Cases (n = 4,823)	Controls (n = 12,888)	Crude OR (95% CI)	Adjusted OR[Ŧ] (95% CI)
Current use[(1)], n (%)				
Conventional NSAIDs - PPIs	3,181 (66.0)	9,462 (73.4)	1	1
Conventional NSAIDs + PPIs	1,260 (26.1)	2,243 (17.4)	1.67 (1.54-1.81)*	1.25 (1.13-1.38)*
Selective COX-2 inhibitors - PPIs	274 (5.7)	902 (7.0)	0.90 (0.79-1.04)	0.85 (0.67-1.06)
Selective COX-2 inhibitors + PPIs	108 (2.2)	281 (2.2)	1.14 (0.91-1.43)	0.84 (0.62-1.13)

Abbreviations: CI = Confidence Interval; COX-2 = Cyclooxygenase-2; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio; PPIs = Proton-Pump Inhibitors

[(1)]Patients who discontinued conventional NSAIDs or selective COX-2 inhibitors within 90 days prior to the index date or current use of these medications at the index date

[Ŧ]Adjusted for age, sex, concomitant drugs (acid-lowering drugs, vitamin K antagonists, platelet aggregation inhibitors, glucocorticoids, and serotonin selective reuptake inhibitors), and a history of drug use (conventional NSAIDs, selective COX-2 inhibitors, and acid-lowering drugs)

*statistically significant (p<0.05)

CHAPTER 5

CYCLOOXYGENASE SELECTIVITY AND CHEMICAL GROUPS

OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

AND THE FREQUENCY OF REPORTING HYPERSENSITIVITY REACTIONS:

A CASE/NON-CASE STUDY IN VigiBase

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ABSTRACT

Background: The reporting of hypersensitivity reactions (HSRs) among non-steroidal anti-inflammatory drugs (NSAIDs) according to cyclooxygenase (COX) selectivity and chemical groups in one study has not been published yet.

Purposes: To assess the frequency of spontaneous reporting of suspected HSRs for NSAIDs based on relative inhibitory concentration towards COX enzymes and chemical groups, including the presence/absence of sulfonamide group, in strata of 5 years after market authorization.

Methods: A case/non-case study was performed among Individual Case Safety Reports (ICSRs) with NSAIDs as suspected drugs using data from VigiBase, the WHO spontaneous reporting database. Cases were ICSRs mentioning angioedema and anaphylactic/anaphylactoid shock conditions, while non-cases were ICSRs without HSRs. NSAIDs were categorized into (1) NSAIDs with highly COX-2 selectivity (coxibs), (2) Non-coxib NSAIDs with COX-2 preference, (3) NSAIDs with poor selectivity, or (4) NSAIDs with unknown selectivity. Chemical groups were defined based on the Anatomical Therapeutic Chemical classification system and the presence/absence of a sulfonamide group. Reporting odds ratios (RORs) and 95% confidence intervals (95% CIs) were calculated using logistic regression analysis.

Results: 13,229 cases and 106,444 non-cases were identified. In the first 5 years after marketing, as suspected drugs, NSAIDs with poor selectivity and acetic acid derivatives were associated with the highest ROR of HSRs (age- and sex-adjusted ROR 2.12, 95%CI: 1.98-2.28 and ROR 2.21, 95%CI: 1.83-2.66, respectively), all compared to coxibs, and also sulfonamide NSAIDs compared to non-sulfonamide NSAIDs (age- and sex-adjusted ROR 1.38, 95%CI: 1.29-1.47). After the 1st 5 years of marketing, most of the RORs returned to approximately 1.

Conclusions: In the first 5 years after marketing, NSAIDs with poor selectivity were associated with the highest ROR of HSRs and also acetic acid derivatives all compared to coxibs. HSRs were reported more often for sulfonamide NSAIDs compared to non-sulfonamide NSAIDs.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most often reported drugs associated with adverse drug reactions (ADRs) (1, 2). This group of drugs might cause various type of hypersensitivity reactions (HSRs) and be classified into either allergic reactions or non-allergic reactions with similar symptoms, i.e., pseudoallergic (anaphylactoid reactions) (3, 4).

Both clinical trials and observational studies have shown that cyclooxygenase (COX) selectivity and chemical groups of NSAIDs were associated with differences in sensitizing capacities and hypersensitivity risks. Selective COX-2 inhibitors were associated with a lower hospitalization risk for angioedema compared to non-selective NSAIDs (5) and well tolerable for patients with angioedema and urticaria attributable to non-selective NSAIDs (6-10). A pharmacovigilance study in the Netherlands showed that among all chemical groups of NSAIDs, propionic acid derivatives (PADs) and acetic acid derivatives (AADs) were associated with a higher risk of anaphylaxis compared to non-use (11). The presence of a sulfonamide functional group in the chemical structure of NSAIDs is also suspected to affect the risk of HSRs (12).

Many studies have investigated the association between NSAIDs and risk of HSRs. These studies differed in study design and exposure definitions, and none of them evaluated the above-mentioned exposure classifications in one study. Therefore, our study was aimed to evaluate the association between NSAIDs, classified by their COX selectivity and chemical groups including the presence of a sulfonamide functional group, and HSRs as reported in VigiBase using one study design.

METHODS

Study design

We performed a case/non-case study using data from 1978 until June 2016. We nested our study among ICSRs with an NSAID as a suspected drug. Only individual NSAIDs with first market approval after 1977 were included. Information on the date of market approval for an individual NSAID was obtained from

the US Food and Drugs Administration (FDA), the European Medicines Agency (EMA), and the Pharmaceutical and Medical Devices Agency (PMDA) Japan. ICSRs with missing information on age, sex, or date of ADR occurrence were excluded.

Data sources

For our study, we used coded fields from the WHO global individual case safety report (ICSR) database, VigiBase which holds reports on suspected ADRs submitted since 1968. In 1978, VigiBase was transferred from the WHO to the Uppsala Monitoring Center (UMC) in Sweden. Recently, >150 countries are members of the WHO Program for International Drug Monitoring and contribute reports from their respective national ADR reporting system.

Information from contributing countries is heterogeneous, but several items are obligatory to include, i.e., patient demographics (age, sex, and reporting countries), ADRs (onset, duration, and causality assessment), suspected drugs (route of administration, dates of first intake and discontinuation, dosing regimen, and co-medications), and administrative data (type of report, reporters, and source). Often, there is missing information. Duplication is detected by checking of case identifiers, manual inspection of case series, and specific statistical algorithms. The reported drugs are encoded using the WHO Drug Dictionary Enhanced, which uses the WHO Anatomical Therapeutic Chemical (ATC) Classification. ADRs are encoded in the WHO Adverse Reaction Terminology (WHO-ART) and the Medical Dictionary for Regulatory Authorities (MedDRA) in parallel. The MedDRA is used to assess medical issues involving a system, organ, or etiology using its hierarchical structure or through the distinctive feature of Standardized MedDRA Queries (SMQs) (13, 14). By June 2016, >13 million ICSRs were recorded.

Case and non-case definitions

HSR cases were defined as ICSRs for angioedema and anaphylactic/anaphylactoid shock conditions using relevant SMQ codes, including 40 and 9 narrow scopes of preferred terms (PTs) MedDRA, respectively (**Supplementary, Table S1**). The narrow scope refers to most likely HSRs that give a high specificity. Non-cases were ICSRs without HSRs with an NSAID as a suspected drug. Since each NSAID-associated ICSR only

contributed once, a single ICSR with multiple ADRs was considered as a case if one of these ADRs was a HSR, but as a non-case, if none of these was a HSR.

Drugs of Interest

NSAIDs were categorized based on both COX selectivity and chemical groups. The COX selectivity was defined based on their relative inhibitory potency towards COX enzymes as the ratios of inhibitory concentration 80% (IC_{80}) against COX-2 and COX-1 enzymes (15-21). Inhibitory concentration 50% (IC_{50}) values are often used when comparing the potencies of NSAIDs against COX-1 and COX-2 with the following assumptions. The inhibitory curves should be preferably parallel, and NSAIDs produce a 50% or less reduction in prostanoid formation at therapeutic doses. However, since IC_{50} does not meet these assumptions, IC_{80} is a more valid approach to be used to compare the potency of NSAIDs (15). It includes (1) coxibs, i.e., NSAIDs based on the Anatomical Therapeutic Chemical (ATC) Classification system that inhibit both COX-2 and COX-1 with high selectivity towards COX-2 by 5 times or more, (2) non-coxib NSAIDs based on ATC classification that inhibit COX-2 and COX-1 with high selectivity towards COX-2 by 5 times or more (3) NSAIDs that inhibit both COX-2 and COX-1 with selectivity towards COX-2 enzyme <5 times (poor selectivity), and (4) NSAIDs without available information on COX inhibitory potency. Individual NSAIDs under each category were shown in **Supplementary, Table S2.** Chemical groups of NSAIDs were categorized based on the ATC classification, i.e., butylpyrazolidines, AADs, oxicams, PADs, fenamates, coxibs, and other NSAIDs, i.e., NSAIDs that are not classified elsewhere. Based on the presence of a sulfonamide functional group, NSAIDs were categorized into (1) sulfonamide NSAIDs, i.e., oxicam group, celecoxib, valdecoxib, polmacoxib, parecoxib, and nimesulide, and (2) non-sulfonamide NSAIDs, i.e., acetic acid and propionic acid derivatives, butylpyrazolidine and fenamate groups, rofecoxib, etoricoxib, lumiracoxib, nabumetone, niflumic acid, azapropazone, and proquazone. Concomitant use of two or more NSAIDs was excluded.

Data-analyses

We calculated reporting odds ratios (RORs) as a measure of disproportionality. Analogous to a case-control study, a ROR was calculated by dividing the exposure odds among cases divided by the exposure

odds in non-cases (22). To minimize the effect of under-reporting of ADRs, we considered time after market approval of a NSAID into the analyses. Even though the Weber effect is described as ADR reports that peak at the 2nd year after drug approval, other studies showed that ADR reports still increase until 5 years (23, 24). We calculated RORs in 3 strata of 5 years after market approval to ensure that time after market approval indeed contributes to ROR differences. NSAID-associated ICSRs that were reported after this period were excluded. We stratified our analyses to the most reported HSRs (urticaria, angioedema, and anaphylactic shock), age, sex, and reporting countries. Reports from the US were analyzed separately because these reports 1) were submitted by healthcare professionals (such as physicians, pharmacists, nurses, and others) as well as consumers (such as patients, family members, lawyers, and others), while from non-US countries reports were submitted mostly by healthcare professionals, 2) also come from other countries because of industry reports with head offices located in the US, and 3) contributed to the highest proportion of reports in VigiBase. Coxibs were the reference group in the analyses based on COX selectivity and chemical groups, and non-sulfonamide NSAIDs were the reference group for sulfonamide NSAIDs. If the proportion of individual NSAIDs that caused HSRs was >2%, these NSAIDs were further analyzed. Rofecoxib was used as the reference group because of having the most favorable tolerability for patients intolerant to NSAIDs (25, 26). Since rofecoxib was approved in 1999 and then withdrawn in 2004, RORs for individual NSAIDs were calculated only for 5 years after marketing. Crude and age- and sex-adjusted RORs and 95% confidence intervals (95% CIs) were determined using logistic regression analysis. The statistical package SPSS version 24 was used to perform data analyses and p-values <0.05 were considered statistically significant.

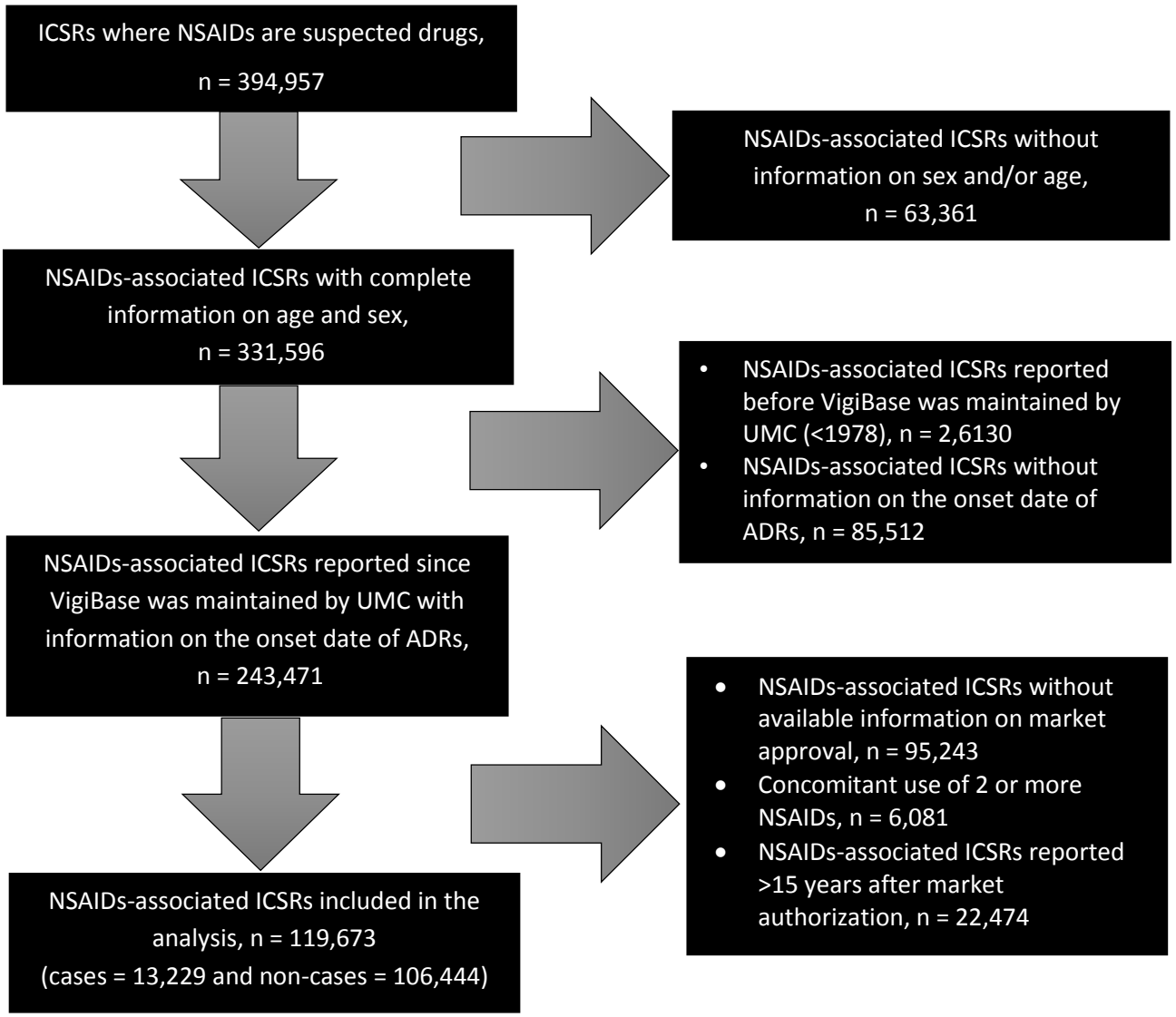
Sensitivity Analysis

In sensitivity analyses, to test the robustness of our main findings, a broad scope of PT SMQs of HSRs was used to calculate the RORs. The broad scope includes terms that are often less likely to represent the outcome of interest but gives high sensitivity including 52 and 21 broad scopes for angioedema and anaphylactic/anaphylactoid shock conditions, respectively (**Supplementary, Table S2**).

RESULTS

Characteristics

By June 2016, VigiBase contained 394,957 ICSRs where an NSAID was a suspected drug. After excluding ICSRs reported before 1978, those without information on sex, age, or onset date, NSAIDs without information on the market authorization, NSAIDs with >15 years after market approval, and concomitant use of two or more NSAIDs, 119,673 ICSRs remained, including 13,229 HSR cases and 106,444 non-HSR cases. The inclusion flow diagram is presented in **Figure 1**.



Abbreviations: ADRs = Adverse Drug Reactions; ICSRs = Individual Case Safety Reports; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; UMC = Uppsala Monitoring Center

Figure 1 Flowchart describing the inclusion of ICSRs

The mean age for the cases was lower than the non-cases (47.8 years vs. 57.8 years). Most of the cases and non-cases were <60 years old (75% vs. 52.2%) and female (69.4% vs. 64%). The most significant number of NSAID-associated ICSRs originated from the United States (US) (29.2%), followed by the United Kingdom (UK) (12.2%), Thailand (7.6%), South Korea (5.9%), and Singapore (4.9%). Among these countries, a NSAID as a suspected drug associated with HSRs was mostly found in Thailand. When ignoring the date of market authorization, NSAIDs with poor selectivity were more likely to be a suspected drug among cases (58.3%), while coxibs were more likely to be suspected drugs among non-cases (47.5%). According to chemical groups, coxibs were more likely to be suspected drugs among both cases and non-cases (27.9% and 47.5%, respectively). Also, non-sulfonamide NSAIDs were more likely to be suspected drugs among both cases and non-cases (61.4% and 62.4%, respectively). Heterogeneity in the proportion of cases and non-cases for the reporting countries and NSAIDs either according to COX selectivity and chemical groups was found ($p<0.05$). The characteristics of ICSRs are shown in **Table 1**.

Table 1 Characteristics of ICSRs where NSAIDs are a suspected drug with hypersensitivity reactions (cases) and without hypersensitivity reactions (non-cases)

Variables	Cases (n=13,229)	Non-cases (n=106,444)	p-value
Age, mean (year ± sd)	47.8 ± 17.6	57.8 ± 18.2	0.000*
Adults (<60 years old), n (%)	9,926 (75.0)	55,544 (52.2)	0.000*
Elderly (≥60 years old), n (%)	3,303 (25.0)	50,900 (47.8)	
Sex, n (%)			
Females	9,180 (69.4)	68,149 (64.0)	0.000*
Males	4,049 (30.6)	38,295 (36.0)	
Reporting NSAID use according to COX selectivity, n (%)			
Coxibs	3,689 (27.9)	50,596 (47.5)	0.000*
NSAIDs with poor selectivity	7,706 (58.3)	41.123 (38.6)	
Non-coxib NSAIDs with COX-2 preference	1,741 (13.2)	13,680 (12.9)	
Unknown potency	93 (0.7)	1,045 (1.0)	
Reporting NSAID use according to chemical groups, n (%)			
Coxibs	3,689 (27.9)	50,596 (47.5)	0.000*
Oxicams	3,006 (22.7)	20,290 (19.1)	
Acetic acid derivatives and related-substances	2,754 (20.8)	16,389 (15.4)	
Fenamates	2,427 (18.3)	6,820 (6.4)	
Propionic acid derivatives	669 (5.1)	5,405 (5.1)	
Butylpyrazolidines	132 (1.0)	1,096 (1.0)	
Other NSAIDs	552 (4.2)	5,848 (5.5)	

Table 1 (continued)

Reporting NSAID use according to the presence/ absence of sulfonamide group, n (%)			
Non-sulfonamide NSAIDs	8,124 (61.4)	66,380 (62.4)	0.033*
Sulfonamide NSAIDs	5,105 (38.6)	40,064 (37.6)	
Reporting countries, n (%)			
Thailand	3,268 (24.7)	5,812 (5.5)	0.000*
United States	2,210 (16.7)	32,779 (30.8)	
Singapore	1,496 (11.3)	4,388 (4.1)	
Great Britain	971 (7.3)	13,634 (12.8)	
South Korea	905 (6.8)	6,176 (5.8)	
Other countries	4,379 (33.1)	43,655 (41.0)	

Abbreviations: COX = Cyclooxygenase; ICSRs = Individual Case Safety Reports; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs

*statistically significant ($p<0.05$)

Within 5 years after market approval, NSAIDs with poor COX selectivity as suspected drugs were associated with the highest ROR of HSRs (age- and sex-adjusted ROR 2.12, 95%CI; 1.98-2.28) compared to coxibs. Of NSAIDs with unknown selectivity, no ICSRs were reported within 10 years after market approval (**Figure 2a** and **Supplementary, Table S3a**). As suspected drugs, of all chemical groups of NSAIDs, AADs, fenamates, and PADs were associated with the highest RORs (age- and sex-adjusted ROR 3.07, 95%CI; 2.83-3.33, ROR 2.21, 95%CI; 1.83-2.66, and ROR 1.93, 95%CI; 1.69-2.19, respectively) compared to coxibs (**Figure 2b** and **Supplementary, Table S3b**), and sulfonamide NSAIDs were associated with a higher ROR (age- and sex-adjusted ROR 1.38, 95%CI; 1.29-1.47) compared to non-sulfonamide NSAIDs **(Figure 2c** and **Supplementary, Table S3c).** After the 1st 5 years of marketing, most of the RORs returned to approximately 1. Among individual NSAIDs, tolmetin, zomepirac, and loxoprofen as suspected drugs were associated with the highest RORs (age- and sex-adjusted ROR 12.83, 95%CI; 10.53-15.64, ROR 11.26, 95%CI; 9.89-12.81, and ROR 5.73, 95%CI; 4.64-7.09, respectively) compared to rofecoxib (**Supplementary, Table S3d**).

RORs stratified by individual HSRs, reporting countries, sex, and age

The RORs of most frequently reported HSRs (urticaria, angioedema, and anaphylactic shock) were similar to the composite of all HSRs for NSAIDs either based on COX-2 selectivity, chemical groups, and

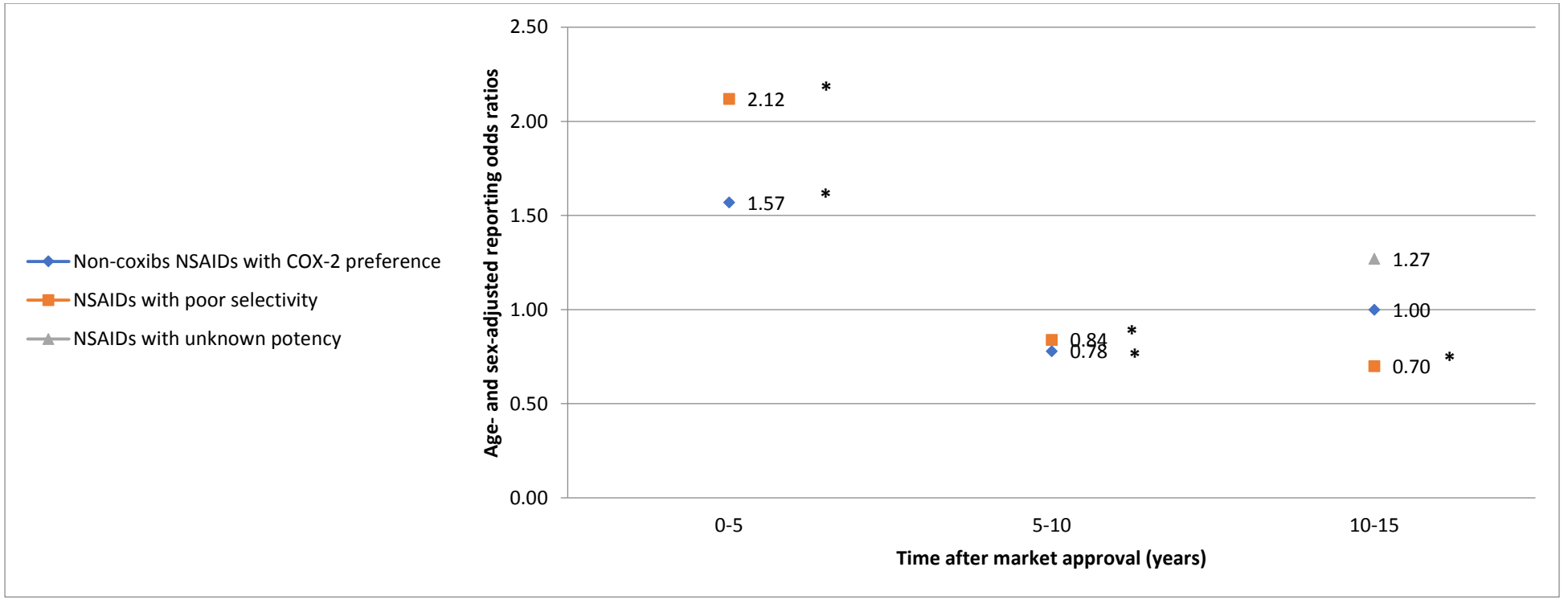
individual NSAIDs, except for ROR of an anaphylactic shock for sulfonamide NSAIDs. Within 5 years after marketing, sulfonamide NSAIDs were associated with a similar ROR of an anaphylactic shock compared to non-sulfonamide NSAIDs (**Supplementary, Table S4a-d, Table S5a-d,** and **Table S6a-d**). Different reporting countries were associated with different RORs for NSAID use based on both COX selectivity and the presence or absence of a sulfonamide group, but not on chemical groups nor individual NSAIDs. For non-US reports, non-coxib NSAIDs with COX-2 preference and NSAIDs with poor selectivity were associated with similar RORs, but for US reports, these groups were associated with higher RORs compared to coxibs. For non-US reports, sulfonamide NSAIDs were associated with a higher ROR, but for US reports, this group was associated with a similar ROR compared to non-sulfonamide NSAIDs (**Supplementary, Table S7a-d**). Finally, differences in age and sex generally were not associated with differences in the RORs (**Supplementary, Table S8a-d** and **Table S9a-d**).

Sensitivity analyses

By using a broad scope of HSRs to assess the RORs for NSAIDs, similar results were shown as the main findings (**Supplementary, Table S10a-d**).

DISCUSSION

Our results show that COX selectivity and chemical groups of NSAIDs, as well as time after market authorization, contribute to the differences in the reporting of HSRs for NSAID use. In the first 5 years after marketing, as suspected drugs, NSAIDs with poor COX selectivity were associated with the highest ROR compared to coxibs. This group was also associated with the highest ROR of urticaria and angioedema compared to coxibs. As suspected drugs, of all chemical groups, AADs, fenamates, and PADs compared to coxibs and sulfonamide NSAIDs compared to non-sulfonamide NSAIDs were associated with higher RORs. Among individual NSAIDs, tolmetin and zomepirac that belong to AADs, and loxoprofen that belongs to PADs were associated with the highest RORs compared to rofecoxib. Our sensitivity analyses supported these findings.



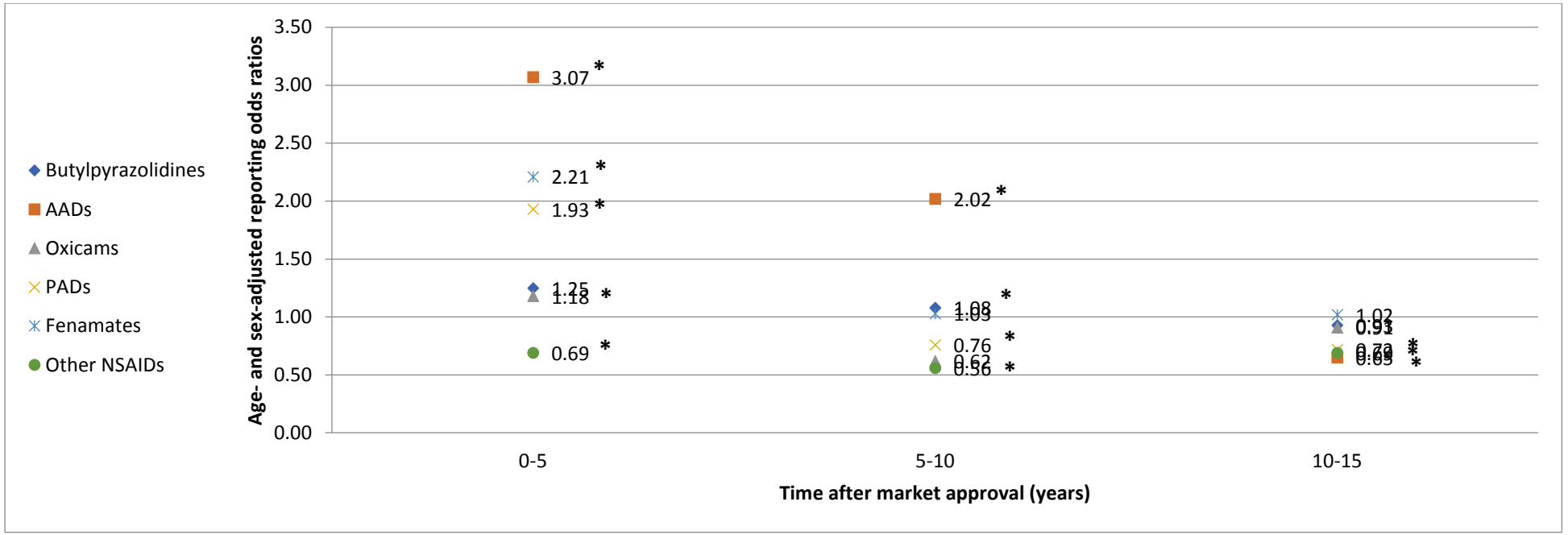
	0-5 years		5-10 years		10-15 years	
	Cases (n=4,196)	Non-Cases (n=56,477)	Cases (n=1,706)	Non-Cases (n=13,013)	Cases (n=1,804)	Non-Cases (n=12,854)
Coxibs						
Cases/non-cases, n (%)	2,226 (53.1)	40,743 (72.1)	629 (36.9)	4,257 (32.7)	715 (39.6)	4,565 (35.5)
Crude RORs/Age- and sex-adjusted RORs	1	1	1	1	1	1
NSAIDs with poor selectivity						
Cases/non-cases, n (%)	1,524 (36.3)	11,147 (19.7)	680 (39.9)	5,467 (42.0)	716 (39.7)	6,074 (47.3)
Crude RORs/Age- and sex-adjusted RORs	2.50 (2.34-2.68)*	2.12 (1.98-2.28)*	0.84 (0.75-0.95)*	0.84 (0.74-0.94)*	0.75 (0.67-0.84)*	0.70 (0.63-0.78)*

Non-coxib NSAIDs with COX-2 preference						
Cases/non-cases, n (%)	446 (10.6)	4,587 (8.1)	397 (23.3)	3,285 (25.2)	358 (19.8)	2,142 (16.7)
Crude RORs/Age- and sex-adjusted RORs	1.78 (1.60-1.98)*	1.57 (1.41-1.75)*	0.82 (0.72-0.94)*	0.78 (0.68-0.90)*	1.07 (0.93-1.22)	1.00 (0.87-1.15)
NSAIDs with unknown potency						
Cases/non-cases, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.0)	15 (0.8)	73 (0.6)
Crude RORs/Age- and sex-adjusted RORs	NA	NA	NA	NA	1.31 (0.75-2.30)	1.27 (0.72-2.24)

Abbreviations: CI = Confidence Interval; COX-2 = Cyclooxygenase-2; NA = Not Applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; RORs = Reporting Odds Ratios

*statistically significant ($p<0.05$)

Figure 2a Reporting odds ratios of hypersensitivity reactions for any NSAIDs according to cyclooxygenase selectivity with coxibs as a reference group



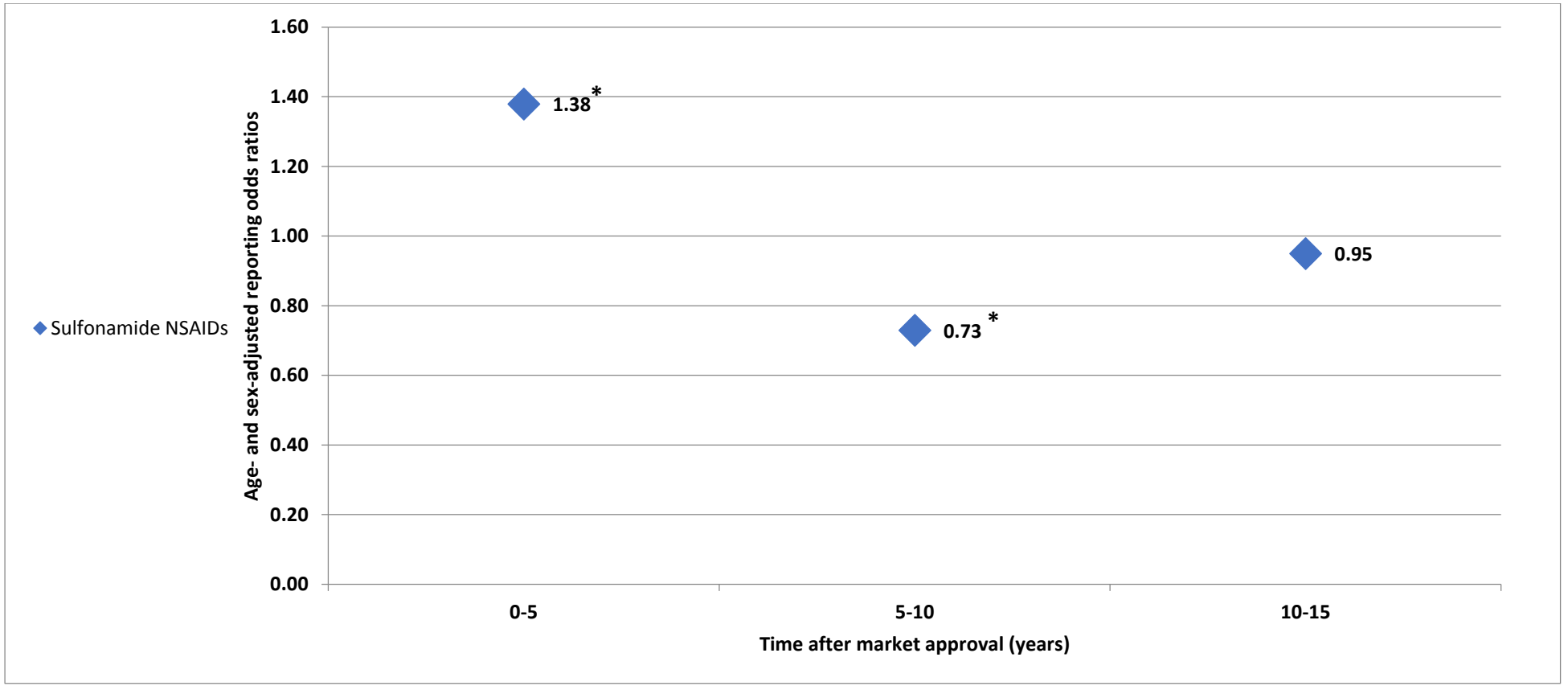
	0-5 years		5-10 years		10-15 years	
	Cases (n=4,196)	Non-cases (n=56,477)	Cases (n=1,706)	Non-cases (n=13,013)	Cases (n=1,804)	Non-cases (n=12,854)
Coxibs						
Cases/non-cases, n (%)	2,226 (53.1)	40,743 (72.1)	629 (36.9)	4,257 (32.7)	715 (39.6)	4,565 (35.5)
Crude RORs/Age- and sex-adjusted RORs	1	1	1	1	1	1
Oxicams						
Cases/non-cases, n (%)	371 (8.8)	5,270 (9.3)	347 (20.3)	4,009 (30.8)	424 (23.5)	2,983 (23.2)
Crude RORs/Age- and sex-adjusted RORs	1.29 (1.15-1.44)*	1.18 (1.05-1.32)*	0.59 (0.51-0.67)*	0.62 (0.54-0.71)*	0.91 (0.80-1.03)	0.91 (0.80-1.04)

Acetic acid derivatives						
Cases/non-cases, n (%)	1,047 (25.0)	5,299 (9.4)	236 (13.8)	852 (6.5)	333 (18.5)	3,059 (23.8)
Crude RORs/Age- and sex-adjusted RORs	3.62 (3.34-3.91)*	3.07 (2.83-3.33)*	1.88 (1.59-2.22)*	2.02 (1.70-2.39)*	0.70 (0.61-0.80)*	0.65 (0.57-0.75)*
Fenamates						
Cases/non-cases, n (%)	142 (3.4)	899 (1.6)	121 (7.1)	548 (4.2)	135 (7.5)	554 (4.3)
Crude RORs/Age- and sex-adjusted RORs	2.89 (2.41-3.47)*	2.21 (1.83-2.66)*	1.49 (1.21-1.85)*	1.03 (0.83-1.29)	1.56 (1.27-1.91)*	1.02 (0.83-1.27)
Propionic acid derivatives						
Cases/non-cases, n (%)	307 (7.3)	2,443 (4.3)	271 (15.9)	2,215 (17.0)	79 (4.4)	625 (4.9)
Crude RORs/Age- and sex-adjusted RORs	2.30 (2.03-2.61)*	1.93 (1.69-2.19)*	0.83 (0.71-0.96)*	0.76 (0.65-0.89)*	0.81 (0.63-1.03)	0.72 (0.56-0.92)*
Butylpyrazolidines						
Cases/non-cases, n (%)	56 (1.3)	698 (1.2)	21 (1.2)	114 (0.9)	10 (0.6)	58 (0.5)
Crude RORs/Age- and sex-adjusted RORs	1.47 (1.12-1.93)*	1.25 (0.95-1.65)	1.25 (0.78-2.00)	1.08 (0.67-1.75)	1.10 (0.56-2.16)	0.93 (0.47-1.83)
Others						
Cases/non-cases, n (%)	47 (1.1)	1,125 (2.0)	81 (4.7)	1,018 (7.8)	108 (6.0)	1,010 (7.9)
Crude RORs/Age- and sex-adjusted RORs	0.77 (0.57-1.03)	0.69 (0.51-0.92)*	0.54 (0.42-0.69)*	0.56 (0.44-0.71)*	0.68 (0.55-0.85)*	0.69 (0.56-0.86)*

Abbreviation: AADs = acetic acid derivatives; CI = Confidence Interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; PADs = propionic acid derivatives; RORs = Reporting Odds Ratios

*statistically significant ($p<0.05$)

Figure 2b Reporting odds ratios of hypersensitivity reactions of any NSAIDs according to chemical groups with coxibs as a reference group



	0-5 years		5-10 years		10-15 years	
	Cases (n=4,196)	Non-cases (n=56,477)	Cases (n=1,706)	Non-cases (n=13,013)	Cases (n=1,804)	Non-cases (n=12,854)
Non-sulfonamide NSAIDs						
Cases/non-cases, n (%)	2,614 (62.3)	38,860 (68.8)	1,106 (64.8)	7,145 (54.9)	1,118 (62.0)	7,422 (57.7)
Crude RORs/Age- and sex-adjusted RORs	1	1	1	1	1	1

Sulfonamide NSAIDs						
Cases/non-cases, n (%)	1,582 (37.7)	17,617 (31.2)	600 (35.2)	5,868 (45.1)	686 (38.0)	5,432 (42.3)
Crude RORs/Age- and sex-adjusted RORs	1.34 (1.25-1.43)*	1.38 (1.29-1.47)*	0.66 (0.60-0.73)*	0.73 (0.66-0.82)*	0.84 (0.76-0.93)*	0.95 (0.86-1.06)

Abbreviation: CI = Confidence Interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; RORs = Reporting Odds Ratios

*statistically significant ($p<0.05$)

Figure 2c Reporting odds ratios of hypersensitivity reactions for any NSAIDs according to the presence/absence of sulfonamide groups with non-sulfonamide NSAIDs as a reference group

Our findings are in line with previous studies. Risk of hospitalization for angioedema was higher for non-selective NSAIDs compared to selective COX-2 inhibitors (5). Celecoxib (a sulfonamide NSAID) had a higher risk of urticaria compared to rofecoxib (a non-sulfonamide NSAID), although both drugs belong to coxibs (12). Also, zomepirac was associated with a high risk of allergy and anaphylaxis compared to other NSAIDs (27, 28).

Both non-allergic and allergic mechanisms might trigger NSAID-associated HSRs. The inhibition of COX-1 enzyme alters eicosanoid biosynthesis that leads to a disruption of the arachidonic acid pathway. It induces an imbalance of prostaglandins and cysteinyl leukotriene that are responsible for the clinical features of HSRs (29, 30). The presence of an N1 heterocyclic ring and an arylamine group at the N4 position in a sulfonamide group is expected to be responsible for HSRs of sulfonamide chemotherapeutics. This structure triggers mast cells to release IgE (31, 32). However, since most sulfonamide NSAIDs do not contain this structure, the risk of HSRs probably involves other factors such as the effect of other chemical structures in sulfonamide group and the involvement of non-type I immune responses. Parent sulfonamide or its reactive metabolite can cause tissue damage or stimulate cellular or humoral immunity such as T cells to initiate an immune response towards haptenation or antigen. HSRs might also more likely occur among those with atopy (31, 33).

Several factors might also influence the reporting of ADRs next to time after marketing. First, mild ADRs such as urticaria and ADRs that are already included in the summary of product characteristics (SmPC) are less likely to be reported (34). Second, several NSAIDs have been withdrawn from the market during the observation time. Within 1982-2004, benoxaprofen, oxyphenbutazone, indoprofen, suprofen, pirprofen, fenclofenac, zomepirac, isoxicam, and rofecoxib were withdrawn due to various serious ADRs (28). Moreover, an individual NSAID is often not marketed in the same year between countries. For example, celecoxib was approved in 1998 for the US market and in 2000 for the Dutch market. Third, when the WHO International Drug Monitoring Program was launched in 1968, only 10 countries participated, but currently, VigiBase contains data from >150 countries (13, 14). Finally, an alert from regulatory authorities or media

attention on safety issues might have a direct and substantial impact on reporting and clinical practice, such as a decrease in drug prescription or utilization (35-37).

For US reports, we found differences in RORs of HSRs for sulfonamide NSAIDs compared to our primary analyses. Differences in reporting habits and ethnicity (38, 39) might explain these differences as well as NSAID sales and consumptions between countries. For example, only celecoxib among coxibs is still available in the US market (40, 41).

Strengths and Limitations

The strengths of this study are that, first, VigiBase contains a large number of spontaneous reporting data collected from national pharmacovigilance centers worldwide, representing >90% of the global population. Second, VigiBase enables to study ADRs in a realistic setting (42), such as the use of over-the-counter medications that often are not recorded in electronic health record databases. Finally, this system can detect reporting ADRs immediately following the market launch (43).

Nonetheless, we need to mention several limitations. First, pharmacovigilance data represents <10% of the actual events leading to problems in selective and under-reporting, and external validity (39, 44). Second, we cannot completely neglect that within 5 years after market authorization, ADR reports are still possibly affected by factors like new drug policies from regulatory bodies or safety issues from media. Third, the quality of reports is variable causing misclassification of exposure and outcomes such as mild ADRs are less likely to be reported as mentioned above. Finally, information on COX selectivity was not available for several NSAIDs. However, the proportion of ICSRs for this group was small for both cases and non-cases.

Due to the heterogeneity of reports and the limited clinical data associated with HSRs, especially medical history, we cannot reach definite conclusions. Nonetheless, based on the strength of the associations, supported by the consistency of the findings in our sensitivity analyses, and mechanistic considerations, we detected a possible association between either COX selectivity or chemical groups of NSAIDs, including the presence of a sulfonamide functional group and HSRs. Further

pharmacoepidemiologic studies are needed to confirm these potential associations by using conventional electronic health databases and considering several important potential risk factors. These include allergic-associated factors such as atopy, genetic profiles, positive HSRs from re-challenging NSAIDs, and familial history, as well as co-medication use such as corticosteroids and antihistamines, and comorbidities such as auto-immune disorders (e.g., rheumatoid arthritis and systemic lupus erythematosus).

It remains important to be vigilant during the initial marketing phase of a drug for all stakeholders. Health care professionals should stay aware of the benefits and risks when prescribing NSAIDs for those who are in need mainly during the 1st 5 years after market approval. Market authorization holders should report periodic safety up-date profiles of their products. Likewise, regulatory bodies should be reactive when a new signal pops-up, and pro-active to monitor for specific and unexpected signals or to follow the initial users of a drug.

CONCLUSIONS

COX selectivity and chemical groups of NSAIDs affect the risk of HSRs, including angioedema and urticaria according to spontaneous reporting data. As suspected drugs, NSAIDs with poor COX selectivity were associated with highest RORs of HSRs, as well as AADs all compared to coxibs, and sulfonamide NSAIDs compared to non-sulfonamide NSAIDs.

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reaction is drug-related is not the same in all cases. The findings of this study do not represent the opinion of either the UMC, National Pharmacovigilance Centers, or WHO.

Conflict of interest: None declared

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SUPPLEMENTARY

Table S1 Diagnoses of hypersensitivity reactions in MedDRA browser

Angioedema (SMQs code 20000024)					
No	**Narrow scope**	**Preferred Term (PT) Codes**	**No**	**Broad scope**	**Preferred Term (PT) Codes**
1.	Allergic edema	10060934	1.	Auricular swelling	10003800
2.	Angioedema	10002424	2.	Breast edema	10006294
3.	Circumoral edema	10052250	3.	Breast swelling	10006312
4.	Conjunctival edema	10010726	4.	Choking	10008589
5.	Corneal edema	10011033	5.	Choking sensation	10008590
6.	Epiglottis edema	10015029	6.	Drug cross-reactivity	10076743
7.	Eye edema	10052139	7.	Drug hypersensitivity	10058061
8.	Eye swelling	10015967	8.	Ear swelling	10018092
9.	Eyelid edema	10015993	9.	Endotracheal intubation	10067639
10.	Face edema	10016029	10.	Gastrointestinal edema	10058061
11.	Gingival edema	10049305	11.	Generalized edema	10018092
12.	Gingival swelling	10018291	12.	Genital swelling	10067639
13.	Gleich's syndrome	10066837	13.	Hypersensitivity	10020751
14.	Hereditary angioedema	10019860	14.	Laryngeal dyspnea	10052390
15.	Idiopathic angioedema	10073257	15.	Laryngeal obstruction	10059639
16.	Idiopathic urticaria	10021247	16.	Local swelling	10024770
17.	Intestinal angioedema	10076229	17.	Localized edema	10048961
18.	Laryngeal angioedema	10023845	18.	Nasal obstruction	10028748
19.	Laryngotracheal angioedema	10023893	19.	Nasal edema	10028750
20.	Limbal swelling	10070492	20.	Nipple edema	10059012
21.	Lipedema	10024558	21.	Nipple swelling	10058680
22.	Lip swelling	10024570	22.	Obstructive airways disorder	10061877
23.	Mouth swelling	10075203	23.	Edema	10030095
24.	Oculo-respiratory syndrome	10067317	24.	Edema genital	10030104
25.	Edema mouth	10030110	25.	Edema mucosal	10030111
26.	Oropharyngeal edema	10078783	26.	Edema neonatal	10061317
27.	Oropharyngeal swelling	10031118	27.	Edema peripheral	10030124
28.	Palatal edema	10056998	28.	Orbital edema	10031051
29.	Palatal swelling	10074403	29.	Penile edema	10066774
30.	Periorbital edema	10034545	30.	Penile swelling	10034319
31.	Pharyngeal edema	10034829	31.	Perinephric edema	10078818
32.	Scleral edema	10057431	32.	Peripheral edema neonatal	10049779
33.	Swelling face	10042682	33.	Peripheral swelling	10048959
34.	Swollen tongue	10042727	34.	Reversible airway obstruction	10062109
35.	Tongue edema	10043967	35.	Scrotal edema	10039755
36.	Tracheal edema	10044296	36.	Scrotal swelling	10039759
37.	Urticaria	10046735	37.	Skin edema	10058679
38.	Urticaria cholinergic	10046740	38.	Skin swelling	10053262

Table S1. (continued)

39.	Urticarial chronic	10052568	39.	Soft tissue swelling	10076991
40.	Urticarial popular	10046750	40.	Stridor	10042241
			41.	Suffocation feeling	10042444
			42.	Swelling	10042674
			43.	Throat tightness	10043528
			44.	Tracheal obstruction	10044291
			45.	Tracheostomy	10044320
			46.	Type I hypersensitivity	10045240
			47.	Upper airway obstruction	10067775
			48.	Vaginal edema	10063818
			49.	Visceral edema	10065768
			50.	Vulval edema	10047763
			51.	Vulvovaginal swelling	10071211
			52.	Wheezing	10047924
Anaphylactic/anaphylactoid shock conditions (SMQ code 20000071)					
No.	**Narrow scope**	**Preferred Term (PT) Codes**	**No.**	**Broad scope**	**Preferred Term (PT) Codes**
1.	Anaphylactic reaction	10002198	1.	Acute kidney injury	10002198
2.	Anaphylactic shock	10002199	2.	Acute pre-renal failure	10002199
3.	Anaphylactic transfusion reaction	10067113	3.	Acute respiratory failure	10067113
			4.	Anuria	10002216
4.	Anaphylactoid reaction	10002216	5.	Blood pressure immeasurable	10063119
5.	Anaphylactoid shock	10063119	6.	Cerebral hypo-perfusion	10009192
6.	Circulatory collapse	10009192	7.	Grey syndrome neonatal	10070559
7.	Distributive shock	10070559	8.	Hepatic congestion	10040560
8.	Shock	10040560	9.	Hepatojugular reflux	10040581
9.	Shock symptom	10040581	10.	Hepatorenal failure	10002198
			11.	Hypo-perfusion	10002199
			12.	Jugular vein distension	10067113
			13.	Myocardial depression	10002216
			14.	Neonatal anuria	10063119
			15.	Neonatal multi-organ failure	10009192
			16.	Organ failure	10070559
			17.	Prerenal failure	10040560
			18.	Propofol infusion syndrome Renal	10040581
			19.	failure	10002198
			20.	Renal failure neonatal	10002199
			21.	Respiratory failure	10067113

Table S2 Categorization of NSAIDs based on COX selectivity as the ratios of inhibitory concentration 80% (IC_{80}) against COX-2 and COX-1 enzymes (15-21)

No	Categories	Individual drugs
1.	Coxibs	celecoxib, rofecoxib, valdecoxib, polmacoxib, parecoxib, etoricoxib, and lumiracoxib
2.	Non-coxib NSAIDs	etodolac, meloxicam, nimesulide, loxoprofen, and zaltoprofen
3.	NSAIDs with poor selectivity	phenylbutazone, indomethacin, tolmetin, zomepirac, diclofenac, ketorolac, piroxicam, ibuprofen, naproxen, ketoprofen, fenoprofen, suprofen, flurbiprofen, oxaprozin, carprofen, mefenamic acid, tolfenamic acid, flufenamate, niflumic acid, tenidap, nabumetone, and sulindac
4.	NSAIDs without available information on COX inhibitory potency	mofebutazone, oxyphenbutazone, clofezone, kebuzone, alclofenac, bumadizone, lonazolac, fentiazac, acetamicin, difenpiramide, oxametacin, proglumetacin, ketorolac, aceclofenac, bufexamac, droxicam, lornoxicam, fenbufen, benoxaprofen, pirprofen, indoprofen, tiaprofenic acid, ibuproxam, dexibuprofen, flunoxaprofen, alminoprofen, dexketoprofen, and naproxinod

Abbreviations: COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs

Table S3a Reporting odds ratios of hypersensitivity reactions for any NSAIDs based on cyclooxygenase selectivity

0-5 years	Cases (n=4,196)	Non-cases (n=56,477)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	2,226 (53.1)	40,743 (72.1)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	1,524 (36.3)	11,147 (19.7)	2.50 (2.34-2.68)*	2.12 (1.98-2.28)*
Non-coxib NSAIDs with COX-2 preference, n (%)	446 (10.6)	4,587 (8.1)	1.78 (1.60-1.98)*	1.57 (1.41-1.75)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=1,706)	Non-cases (n=13,013)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	629 (36.9)	4,257 (32.7)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	680 (39.9)	5,467 (42.0)	0.84 (0.75-0.95)*	0.84 (0.74-0.94)*
Non-coxib NSAIDs with COX-2 preference, n (%)	397 (23.3)	3,285 (25.2)	0.82 (0.72-0.94)*	0.78 (0.68-0.90)*
Unknown potency, n (%)	0 (0.0)	4 (0.0)	NA	NA
10-15 years	Cases (n=1,804)	Non-cases (n=12,854)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	715 (39.6)	4,565 (35.5)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	716 (39.7)	6,074 (47.3)	0.75 (0.67-0.84)*	0.70 (0.63-0.78)*
Non-coxib NSAIDs with COX-2 preference, n (%)	358 (19.8)	2,142 (16.7)	1.07 (0.93-1.22)	1.00 (0.87-1.15)
Unknown potency, n (%)	15 (0.8)	73 (0.6)	1.31 (0.75-2.30)	1.27 (0.72-2.24)

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NA = Not Applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S3b Reporting odds ratios of hypersensitivity reactions for any NSAIDs based on chemical group

0-5 years	Cases (n=4,196)	Non-cases (n=56,477)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	2,226 (53.1)	40,743 (72.1)	1 (reference)	1 (reference)
Oxicams, n (%)	371 (8.8)	5,270 (9.3)	1.29 (1.15-1.44)*	1.18 (1.05-1.32)*
Acetic acid derivatives and related substances, n (%)	1,047 (25.0)	5,299 (9.4)	3.62 (3.34-3.91)*	3.07 (2.83-3.33)*
Fenamates, n (%)	142 (3.4)	899 (1.6)	2.89 (2.41-3.47)*	2.21 (1.83-2.66)*
Propionic acid derivatives, n (%)	307 (7.3)	2,443 (4.3)	2.30 (2.03-2.61)*	1.93 (1.69-2.19)*
Butylpyrazolidines, n (%)	56 (1.3)	698 (1.2)	1.47 (1.12-1.93)*	1.25 (0.95-1.65)
Others, n (%)	47 (1.1)	1,125 (2.0)	0.77 (0.57-1.03)	0.69 (0.51-0.92)*
5-10 years	Cases (n=1,706)	Non-cases (n=13,013)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	629 (36.9)	4,257 (32.7)	1 (reference)	1 (reference)
Oxicams, n (%)	347 (20.3)	4,009 (30.8)	0.59 (0.51-0.67)*	0.62 (0.54-0.71)*
Acetic acid derivatives and related substances, n (%)	236 (13.8)	852 (6.5)	1.88 (1.59-2.22)*	2.02 (1.70-2.39)*
Fenamates, n (%)	121 (7.1)	548 (4.2)	1.49 (1.21-1.85)*	1.03 (0.83-1.29)
Propionic acid derivatives, n (%)	271 (15.9)	2,215 (17.0)	0.83 (0.71-0.96)*	0.76 (0.65-0.89)*
Butylpyrazolidines, n (%)	21 (1.2)	114 (0.9)	1.25 (0.78-2.00)	1.08 (0.67-1.75)
Others, n (%)	81 (4.7)	1,018 (7.8)	0.54 (0.42-0.69)*	0.56 (0.44-0.71)*
10-15 years	Cases (n=1,804)	Non-cases (n=12,854)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	715 (39.6)	4,565 (35.5)	1 (reference)	1 (reference)
Oxicams, n (%)	424 (23.5)	2,983 (23.2)	0.91 (0.80-1.03)	0.91 (0.80-1.04)
Acetic acid derivatives and related substances, n (%)	333 (18.5)	3,059 (23.8)	0.70 (0.61-0.80)*	0.65 (0.57-0.75)*
Fenamates, n (%)	135 (7.5)	554 (4.3)	1.56 (1.27-1.91)*	1.02 (0.83-1.27)
Propionic acid derivatives, n (%)	79 (4.4)	625 (4.9)	0.81 (0.63-1.03)	0.72 (0.56-0.92)*
Butylpyrazolidines, n (%)	10 (0.6)	58 (0.5)	1.10 (0.56-2.16)	0.93 (0.47-1.83)
Others, n (%)	108 (6.0)	1,010 (7.9)	0.68 (0.55-0.85)*	0.69 (0.56-0.86)*

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S3c Reporting odds ratios of hypersensitivity reactions for any NSAIDs according to the presence/ absence of sulfonamide group

0-5 years	Cases (n=4,196)	Non-cases (n=56,477)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	2,614 (62.3)	38,860 (68.8)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	1,582 (37.7)	17,617 (31.2)	1.34 (1.25-1.43)*	1.38 (1.29-1.47)*
5-10 years	Cases (n=1,706)	Non-cases (n=13,013)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	1,106 (64.8)	7,145 (54.9)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	600 (35.2)	5,868 (45.1)	0.66 (0.60-0.73)*	0.73 (0.66-0.82)*
10-15 years	Cases (n=1,804)	Non-cases (n=12,854)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	1,118 (62.0)	7,422 (57.7)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	686 (38.0)	5,432 (42.3)	0.84 (0.76-0.93)*	0.95 (0.86-1.06)

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S3d Reporting odds ratios of hypersensitivity reactions for individual NSAIDs within 5 years after market approval

Individual NSAIDs	Cases (n=4,195)	Non-cases (n=56,455)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Rofecoxib, n (%)	839 (20.0)	26,250 (46.5)	1 (reference)	1 (reference)
Celecoxib, n (%)	1,070 (25.5)	11,405 (20.2)	2.94 (2.68-3.22)*	2.93 (2.67-3.22)*
Zomepirac, n (%)	520 (12.4)	1,102 (2.0)	14.76 (13.03-16.73)*	11.26 (9.89-12.81)*
Tolmetin, n (%)	175 (4.2)	348 (0.6)	15.73 (12.96-19.11)*	12.83 (10.53-15.64)*
Sulindac, n (%)	166 (4.0)	1,969 (3.5)	2.64 (2.22-3.14)*	2.43 (2.04-2.89)*
Piroxicam, n (%)	164 (3.9)	2,488 (4.4)	2.06 (1.74-2.45)*	1.93 (1.62-2.29)*
Mefenamic acid, n (%)	136 (3.2)	777 (1.4)	5.48 (4.51-6.65)*	4.23 (1.92-2.81)*
Meloxicam, n (%)	133 (3.2)	1,998 (3.5)	2.08 (1.73-2.52)*	1.87 (1.55-2.26)*
Etoricoxib, n (%)	132 (3.1)	1,653 (2.9)	2.50 (2.07-3.02)*	2.32 (1.92-2.81)*
Loxoprofen, n (%)	120 (2.9)	565 (1.0)	6.65 (5.39-8.19)*	5.73 (4.64-7.09)*

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S4a Reporting odds ratios of urticaria for any NSAIDs based on cyclooxygenase selectivity

0-5 years	Cases (n=1,303)	Non-cases (n=59,370)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	680 (52.2)	42,289 (71.2)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	470 (36.1)	12,201 (0.0)	2.40 (2.13-2.70)*	2.12 (1.88-2.40)*
Non-coxib NSAIDs with COX-2 preference, n (%)	153 (11.7)	4,880 (8.2)	1.95 (1.63-2.33)*	1.78 (1.49-2.13)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=448)	Non-cases (n=14,271)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	139 (31.0)	4,747 (33.3)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	208 (46.4)	5,939 (41.6)	1.20 (0.96-1.49)	1.19 (0.95-1.48)
Non-coxib NSAIDs with COX-2 preference, n (%)	101 (22.5)	3,531 (25.1)	0.96 (0.74-1.25)	0.91 (0.70-1.19)
Unknown potency, n (%)	0 (0.0)	4 (0.0)	NA	NA
10-15 years	Cases (n=458)	Non-cases (n=14,200)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	187 (40.8)	5,093 (35.9)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	182 (39.7)	6,608 (46.5)	0.75 (0.61-0.92)*	0.69 (0.56-0.85)*
Non-coxib NSAIDs with COX-2 preference, n (%)	81 (17.7)	2,419 (17.0)	0.91 (0.70-1.19)	0.85 (0.65-1.11)
Unknown potency, n (%)	8 (1.7)	80 (0.6)	2.72 (1.30-5.72)*	2.64 (1.25-5.56)*

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NA = Not Applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S4b Reporting odds ratios of urticaria for any NSAIDs based on chemical group

0-5 years	Cases (n=1,303)	Non-cases (n=59,370)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	680 (52.2)	42,289 (71.2)	1 (reference)	1 (reference)
Oxicams, n (%)	150 (11.5)	5,491 (9.2)	1.70 (1.42-2.03)*	1.59 (1.33-1.90)*
Acetic acid derivatives and related substances, n (%)	283 (21.7)	6,063 (10.2)	2.90 (2.52-3.34)*	2.56 (2.21-2.95)*
Fenamates, n (%)	68 (5.2)	973 (1.6)	4.35 (3.36-5.62)*	3.57 (2.75-4.64)*
Propionic acid derivatives, n (%)	76 (5.8)	2,674 (4.5)	1.77 (1.39-2.25)*	1.56 (1.22-1.99)*
Butylpyrazolidines, n (%)	22 (1.7)	732 (1.2)	1.87 (1.22-2.88)*	1.67 *1.09-2.58)*
Others, n (%)	24 (1.8)	1,148(1.9)	1.30 (0.86-1.96)	1.21 (0.80-1.82)
5-10 years	Cases (n=448)	Non-cases (n=14,271)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	139 (31.0)	4,747 (33.3)	1 (reference)	1 (reference)
Oxicams, n (%)	109 (24.3)	4,247 (29.8)	0.88 (0.68-1.13)	0.92 (0.71-1.19)
Acetic acid derivatives and related substances, n (%)	49 (10.9)	1,039 (7.3)	1.61 (1.16-2.25)*	1.67 (1.20-2.34)
Fenamates, n (%)	46 (10.3)	623 (4.4)	2.52 (1.79-3.56)*	1.78 (1.25-2.53)*
Propionic acid derivatives, n (%)	66 (14.7)	2,420 (17.0)	0.93 (0.69-1.25)	0.85 (0.63-1.14)
Butylpyrazolidines, n (%)	4 (0.9)	131 (0.9)	1.04 (0.38-2.86)	0.87 (0.31-2.38)
Others, n (%)	35 (7.8)	1,064 (7.5)	1.12 (0.77-1.64)	1.18 (0.81-1.72)
10-15 years	Cases (n=458)	Non-cases (n=14,200)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	187 (40.8)	5,093 (35.9)	1 (reference)	1 (reference)
Oxicams, n (%)	113 (24.7)	3,294 (23.2)	0.93 (0.74-1.19)	0.93 (0.74-1.19)
Acetic acid derivatives and related substances, n (%)	64 (14.0)	3,328 (23.4)	0.52 (0.39-0.70)*	0.49 (0.36-0.65)*
Fenamates, n (%)	46 (10.0)	643 (4.5)	1.95 (1.40-2.72)*	1.29 (0.91-1.82)
Propionic acid derivatives, n (%)	14 (3.1)	690 (4.9)	0.55 (0.32-0.96)*	0.49 (0.28-0.84)*
Butylpyrazolidines, n (%)	1 (0.2)	67 (0.5)	0.41 (0.06-2.94)	0.33 (0.05-2.41)
Others, n (%)	33 (7.2)	1,085 (7.6)	0.83 (0.57-1.21)	0.84 (0.58-1.23)

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S4c Reporting odds ratios of urticaria for any NSAIDs according to the presence/absence of sulfonamide group

0-5 years	Cases (n=1,303)	Non-cases (n=59,370)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	684 (52.5)	40,790 (68.7)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	619 (47.5)	18,580 (31.3)	1.99 (1.78-2.22)*	2.03 (1.82-2.27)*
5-10 years	Cases (n=448)	Non-cases (n=14,271)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	258 (57.6)	7,993 (56.0)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	190 (42.4)	6,278 (44.0)	0.94 (0.76-1.13)	1.05 (0.87-1.28)
10-15 years	Cases (n=458)	Non-cases (n=14,200)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	267 (58.3)	8,273 (58.3)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	191 (41.7)	5,927 (41.7)	1.00 (0.83-1.21)	1.15 (0.95-1.40)

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S4d Reporting odds ratios of urticaria for individual NSAIDs within 5 years after market approval

Individual NSAIDs	Cases (n=1,302)	Non-cases (n=59,348)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Rofecoxib, n (%)	192 (14.7)	26,897 (45.3)	1 (reference)	1 (reference)
Celecoxib, n (%)	428 (32.9)	12,047 (20.3)	4.98 (4.19-5.91)*	4.95 (4.17-5.88)*
Zomepirac, n (%)	98 (7.5)	1,524 (2.6)	9.01 (7.03-11.55)*	7.13 (5.52-9.20)*
Tolmetin, n (%)	39 (3.0)	484 (0.8)	11.29 (7.91-16.11)*	9.41 (6.57-13.48)*
Sulindac, n (%)	61 (4.7)	2,074 (3.5)	4.12 (2.08-5.52)*	3.86 (2.88-5.16)*
Piroxicam, n (%)	73 (5.6)	2,579 (4.3)	3.97 (3.02-5.21)*	3.76 (2.86-4.94)*
Mefenamic acid, n (%)	65 (5.0)	848 (1.4)	10.74 (8.04-14.34)*	8.74 (6.51-11.72)*
Meloxicam, n (%)	47 (3.6)	2,084 (3.5)	3.16 (2.29-4.36)*	2.91 (2.10-4.01)*
Etoricoxib, n (%)	16 (1.2)	1,769 (3.0)	1.27 (0.76-2.12)	1.19 (0.71-1.99)
Loxoprofen, n (%)	17 (1.3)	668 (1.1)	3.57 (2.16-5.89)*	3.14 (1.90-5.19)*

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S5a Reporting odds ratios of angioedema for any NSAIDs based on cyclooxygenase selectivity

0-5 years	Cases (n=3,708)	Non-cases (n=59,965)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	2,013 (54.3)	40,956 (71.9)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	1,301 (35.1)	11,370 (20.0)	2.33 (2.17-2.50)*	2.00 (1.85-2.15)*
Non-coxib NSAIDs with COX-2 preference, n (%)	394 (10.6)	6,639 (8.1)	1.73 (1.55-1.93)*	1.54 (1.37-1.72)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=1,436)	Non-cases (n=13,283)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	566 (39.4)	4,320 (32.5)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	531 (37.0)	5,616 (42.3)	0.72 (0.64-0.82)*	0.72 (0.63-0.81)*
Non-coxib NSAIDs with COX-2 preference, n (%)	339 (23.6)	3,343 (25.2)	0.77 (0.67-0.89)*	0.74 (0.64-0.85)*
Unknown potency, n (%)	0 (0.0)	4 (0.0)	NA	NA
10-15 years	Cases (n=1,590)	Non-cases (n=13,068)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	678 (42.6)	4,602 (35.2)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	568 (35.7)	6,222 (47.6)	0.62 (0.55-0.70)*	0.58 (0.1-0.65)*
Non-coxib NSAIDs with COX-2 preference, n (%)	329 (20.7)	2,171 (16.6)	1.03 (0.89-1.19)	0.97 (0.84-1.12)
Unknown potency, n (%)	15 (0.9)	73 (0.6)	1.40 (0.80-2.45)	1.36 (0.77-2.40)

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NA = Not Applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S5b Reporting odds ratios of angioedema for any NSAIDs based on chemical group

0-5 years	Cases (n=3,708)	Non-cases (n=59,956)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	2,013 (54.3)	40,956 (71.9)	1 (reference)	1 (reference)
Oxicams, n (%)	354 (9.5)	5,287 (9.3)	1.36 (1.21-1.53)*	1.25 (1.11-1.41)*
Acetic acid derivatives and related substances, n (%)	859 (23.2)	5,487 (9.6)	3.19 (2.93-3.47)*	2.72 (2.49-2.97)*
Fenamates, n (%)	131 (3.5)	910 (1.6)	2.93 (2.43-3.57)*	2.27 (1.87-2.75)*
Propionic acid derivatives, n (%)	255 (6.9)	2,495 (4.4)	2.08 (1.81-2.38)*	1.77 (1.54-2.03)*
Butylpyrazolidines, n (%)	49 (1.3)	705 (1.2)	1.41 (1.06-1.90)*	1.22 (0.91-1.64)
Others, n (%)	47 (1.3)	1,125 (2.0)	0.85 (0.63-1.14)	0.77 (0.57-1.03)
5-10 years	Cases (n=1,436)	Non-cases (n=13,283)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	566 (39.4)	4,320 (32.5)	1 (reference)	1 (reference)
Oxicams, n (%)	328 (22.8)	4,028 (30.3)	0.62 (0.54-0.72)*	0.66 (0.57-0.76)*
Acetic acid derivatives and related substances, n (%)	137 (9.5)	951 (7.2)	1.10 (0.90-1.34)	1.16 (0.95-1.42)
Fenamates, n (%)	101 (7.0)	568 (4.3)	1.36 (1.08-1.71)*	0.93 (0.73-1.18)
Propionic acid derivatives, n (%)	212 (14.8)	2,274 (17.1)	0.71 (0.60-0.80)*	0.65 (0.55-0.77)*
Butylpyrazolidines, n (%)	18 (1.3)	117 (0.9)	1.17 (0.71-1.94)	1.04 (0.62-1.73)
Others, n (%)	74 (5.2)	1,025 (7.7)	0.55 (0.43-0.71)*	0.57 (0.44-0.73)*
10-15 years	Cases (n=1,590)	Non-cases (n=13,068)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	678 (42.6)	4,602 (35.2)	1 (reference)	1 (reference)
Oxicams, n (%)	398 (25.0)	2,009 (23.0)	0.90 (0.79-1.03)	0.90 (0.79-1.03)
Acetic acid derivatives and related substances, n (%)	239 (15.0)	3,153 (24.1)	0.52 (0.44-0.60)*	0.48 (0.41-0.56)*
Fenamates, n (%)	115 (7.2)	574 (4.4)	1.36 (1.10-1.69)*	0.88 (0.70-1.10)
Propionic acid derivatives, n (%)	54 (3.4)	650 (5.0)	0.56 (0.42-0.75)*	0.50 (0.37-0.67)*
Butylpyrazolidines, n (%)	9 (0.6)	59 (0.5)	1.04 (0.51-2.10)	0.88 (0.43-1.78)
Others, n (%)	97 (6.1)	1,021 (7.8)	0.65 (0.52-0.81)*	0.65 (0.52-0.82)*

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S5c Reporting odds ratios of angioedema for any NSAIDs according to the presence/absence of sulfonamide group

0-5 years	Cases (n=3,708)	Non-cases (n=59,956)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	2,241 (60.4)	39,233 (68.9)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	1,467 (39.6)	17,732 (31.1)	1.45 (1.35-1.55)*	1.49 (1.39-1.59)*
5-10 years	Cases (n=1,436)	Non-cases (n=13,283)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	902 (62.8)	7,349 (55.3)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	534 (37.2)	5,934 (44.7)	0.73 (0.66-0.82)*	0.82 (0.73-0.92)*
10-15 years	Cases (n=1,590)	Non-cases (n=13,068)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	954 (60.0)	7,568 (58.1)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	636 (40.0)	5,482 (41.9)	0.92 (0.83-1.03)	1.05 (0.94-1.17)

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S5d Reporting odds ratios of angioedema for individual NSAIDs within 5 years after market approval

Individual NSAIDs	Cases (n=3,707)	Non-cases (n=56,943)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Rofecoxib, n (%)	753 (20.3)	26,336 (46.2)	1 (reference)	1 (reference)
Celecoxib, n (%)	985 (26.6)	11,490 (20.2)	3.00 (2.72-3.31)*	2.98 (2.71-3.29)*
Zomepirac, n (%)	419 (11.3)	1,203 (2.1)	12.18 (10.67-13.91)*	9.36 (8.16-10.74)*
Tolmetin, n (%)	117 (3.2)	406 (0.7)	10.08 (8.10-12.54)*	8.22 (6.59-10.26)*
Sulindac, n (%)	148 (4.0)	1,987 (3.5)	2.61 (2.17-3.13)*	2.40 (2.00-2.88)*
Piroxicam, n (%)	162 (4.4)	2,490 (4.4)	2.76 (1.91-2.71)*	2.13 (1.79-2.54)*
Mefenamic acid, n (%)	125 (3.4)	788 (1.4)	5.55 (4.53-6.79)*	4.32 (3.52-5.31)*
Meloxicam, n (%)	121 (3.3)	2,010 (3.5)	2.11 (1.73-2.57)*	1.90 (1.56-2.31)*
Etoricoxib, n (%)	118 (3.2)	1,667 (2.9)	2.48 (2.03-3.03)*	2.31 (1.89-2.82)*
Loxoprofen, n (%)	91 (2.5)	594 (1.0)	5.36 (4.25-6.76)*	4.64 (3.67-5.87)*

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S6a Reporting odds ratios of anaphylactic shock for any NSAIDs based on cyclooxygenase selectivity

0-5 years	Cases (n=122)	Non-cases (n=60,551)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	55 (45.1)	42,914 (70.9)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	51 (41.8)	12,620 (20.8)	3.15 (2.15-4.62)*	2.38 (1.61-3.53)*
Non-coxib NSAIDs with COX-2 preference, n (%)	16 (13.1)	5, 017 (8.3)	2.49 (1.43-4.35)*	2.06 (1.18-3.62)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=99)	Non-cases (n=14,620)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	30 (30.3)	4,856 (33.2)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	36 (36.4)	6,111 (41.8)	0.95 (0.59-1.55)	0.94 (0.58-1.53)
Non-coxib NSAIDs with COX-2 preference, n (%)	33 (33.3)	3,649 (25.0)	1.46 (0.89-2.41)	1.40 (0.85-2.31)
Unknown potency, n (%)	0 (0.0)	4 (0.0)	NA	NA
10-15 years	Cases (n=78)	Non-cases (n=14,580)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	20 (25.6)	5,260 (36.1)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	47 (60.3)	6,743 (46.2)	1.83 (1.09-3.10)*	1.73 (1.02-2.93)*
Non-coxib NSAIDs with COX-2 preference, n (%)	11 (14.1)	2,489 (17.1)	1.16 (0.56-2.43)	1.10 (0.53-2.32)
Unknown potency, n (%)	0 (0.0)	88 (0.6)	NA	NA

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NA = Not Applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S6b Reporting odds ratios of anaphylactic shock for any NSAIDs based on chemical group

0-5 years	Cases (n=122)	Non-cases (n=60,551)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	55 (45.1)	42,914 (70.9)	1 (reference)	1 (reference)
Oxicams, n (%)	4 (3.3)	5,637 (9.3)	0.55 (0.20-1.53)	0.49 (0.18-1.35)
Acetic acid derivatives and related substances, n (%)	26 (21.3)	6,320 (10.4)	3.21 (2.02-5.12)*	2.50 (1.55-4.03)*
Fenamates, n (%)	10 (8.2)	1,031 (1.7)	7.56 (3.85-14.89)*	5.11 (2.55-10.26)*
Propionic acid derivatives, n (%)	22 (18.0)	2,728 (4.5)	6.29 (3.83-10.33)*	4.65 (2.79-7.75)*
Butylpyrazolidines, n (%)	5 (4.1)	749 (1.2)	5.21 (2.08-13.05)*	4.01 (1.59-10.10)*
Others, n (%)	0 (0.0)	1,172 (1.9)	NA	NA
5-10 years	Cases (n=99)	Non-cases (n=14,620)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	30 (30.3)	4,856 (33.2)	1 (reference)	1 (reference)
Oxicams, n (%)	12 (12.1)	4,344 (29.7)	0.45 (0.23-0.87)*	0.46 (0.23-0.90)*
Acetic acid derivatives and related substances, n (%)	6 (6.1)	1,082 (7.4)	0.90 (0.37-2.16)	0.91 (0.38-2.20)
Fenamates, n (%)	12 (13.1)	656 (4.5)	3.21 (1.67-6.18)*	2.69 (1.37-5.28)*
Propionic acid derivatives, n (%)	34 (34.3)	2,452 (16.8)	2.24 (1.37-3.68)*	2.12 (1.29-3.48)*
Butylpyrazolidines, n (%)	3 (3.0)	132 (0.9)	3.68 (1.11-12.21)*	3.20 (0.96-10.67)
Others, n (%)	1 (1.0)	1,098 (7.5)	0.15 (0.02-1.08)	0.15 (0.02-1.11)
10-15 years	Cases (n=78)	Non-cases (n=14,580)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	20 (25.6)	5,260 (36.1)	1 (reference)	1 (reference)
Oxicams, n (%)	14 (17.9)	3,393 (23.3)	1.09 (0.55-2.15)	1.08 (0.54-2.13)
Acetic acid derivatives and related substances, n (%)	12 (15.4)	3,380 (23.2)	0.93 (0.46-1.91)	0.90 (0.44-1.84)
Fenamates, n (%)	16 (20.5)	673 (4.6)	6.25 (3.22-12.13)*	5.62 (2.77-11.38)*
Propionic acid derivatives, n (%)	12 (15.4)	692 (4.7)	4.56 (2.22-9.37)*	4.34 (2.11-8.96)*
Butylpyrazolidines, n (%)	0 (0.0)	68 (0.5)	NA	NA
Others, n (%)	4 (5.1)	1,114 (7.6)	0.94 (0.32-2.77)	0.95 (0.32-2.78)

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NA = Not Applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S6c Reporting odds ratios of anaphylactic shock for any NSAIDs according to the presence/ absence of sulfonamide group

0-5 years	Cases (n=122)	Non-cases (n=60,551)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	89 (73.0)	41,385 (68.3)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	33 (27.0)	19,166 (31.7)	0.80 (0.54-1.19)	0.85 (0.57-1.27)
5-10 years	Cases (n=99)	Non-cases (n=14,620)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	63 (63.6)	8,188 (56.0)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	36 (36.4)	6,432 (44.0)	0.73 (0.48-1.10)	0.79 (0.52-1.19)
10-15 years	Cases (n=78)	Non-cases (n=14,580)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	52 (66.7)	8,488 (58.2)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	26 (33.3)	6,092 (41.8)	0.70 (0.44-1.12)	0.77 (0.48-1.25)

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S6d Reporting odds ratios of an anaphylactic shock for individual NSAIDs within 5 years after market approval

Individual NSAIDs	Cases (n=122)	Non-cases (n=60,528)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Rofecoxib, n (%)	17 (13.9)	27,072 (44.7)	1 (reference)	1 (reference)
Celecoxib, n (%)	23 (18.9)	12,452 (20.6)	2.94 (1.57-5.51)*	2.97 (1.59-5.57)*
Zomepirac, n (%)	13 (10.7)	1,609 (2.7)	12.87 (6.24-26.54)*	8.84 (4.20-18.62)*
Tolmetin, n (%)	9 (7.4)	514 (0.8)	27.88 (12.37-62.85)*	20.47 (8.95-46.78)*
Sulindac, n (%)	4 (3.3)	2,131 (3.5)	2.99 (1.01-8.89)*	2.75 (0.92-8.19)
Piroxicam, n (%)	2 (1.6)	2,650 (4.4)	1.20 (0.28-5.21)	1.11 (0.26-4.80)
Mefenamic acid, n (%)	10 (8.2)	903 (1.5)	17.64 (8.05-38.62)*	12.83 (5.75-28.63)*
Meloxicam, n (%)	1 (0.8)	2,130 (3.5)	0.75 (0.10-5.62)	0.67 (0.09-5.01)
Etoricoxib, n (%)	4 (3.3)	1,781 (2.9)	3.58 (1.20-10.64)*	3.25 (1.09-9.67)*
Loxoprofen, n (%)	15 (12.3)	670 (1.1)	35.65 (17.73-71.69)*	28.55 (14.05-58.00)

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S7a Reporting odds ratios of hypersensitivity reactions for NSAIDs according to cyclooxygenase selectivity stratified by reporting countries

United States				
0-5 years	Cases (n=1,548)	Non-cases (n=26,846)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	621 (40.1)	21,737 (81.0)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	804 (51.9)	3,771 (14.0)	7.46 (6.68-8.33)*	6.21 (5.54-6.98)*
Non-coxib NSAIDs with COX-2 preference, n (%)	123 (7.9)	1,338 (5.0)	3.22 (2.63-3.94)*	2.90 (2.36-3.55)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=294)	Non-cases (n=2,113)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	10 (3.4)	283 (13.4)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	268 (91.2)	1,675 (79.3)	4.53 (2.38-8.62)*	4.49 (2.35-8.58)*
Non-coxib NSAIDs with COX-2 preference, n (%)	16 (5.4)	155 (7.3)	2.92 (1.29-6.59)*	2.97 (1.30-6.77)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
10-15 years	Cases (n=281)	Non-cases (n=2,861)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	7 (2.5)	139 (4.9)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	263 (93.6)	2,548 (89.1)	2.05 (0.95-4.43)	1.71 (0.79-3.71)
Non-coxib NSAIDs with COX-2 preference, n (%)	11 (3.9)	174 (6.1)	1.26 (0.47-3.32)	1.04 (0.39-2.78)
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
Non-US countries				
0-5 years	Cases (n=2,648)	Non-cases (n=29,631)	Crude ROR (95% CI)	Age-and sex-adjusted ROR (95% CI)
Coxibs, n (%)	1,605 (60.6)	19,006 (64.1)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	720 (27.2)	7,376 (24.9)	1.16 (1.05-1.27)*	1.02 (0.92-1.12)
Non-coxib NSAIDs with COX-2 preference, n (%)	323 (12.2)	3,249 (11.0)	1.18 (1.04-1.33)*	1.04 (0.92-1.18)
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA

Table S7a (continued)

5-10 years	Cases (n=1,412)	Non-cases (n=10,900)	Crude ROR (95% CI)	Age-and sex-adjusted ROR (95% CI)
Coxibs, n (%)	619 (43.8)	3,974 (36.5)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	412 (29.2)	3,792 (34.8)	0.70 (0.61-0.80)*	0.68 (0.60-0.78)*
Non-coxib NSAIDs with COX-2 preference, n (%)	381 (27.0)	3,130 (28.7)	0.78 (0.68-0.90)*	0.75 (0.65-0.86)*
Unknown potency, n (%)	0 (0.0)	4 (0.0)	NA	NA
10-15 years	Cases (n=1,523)	Non-cases (n=9,993)	Crude ROR (95% CI)	Age-and sex-adjusted ROR (95% CI)
Coxibs, n (%)	708 (46.5)	4,426 (44.3)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	453 (29.7)	3,526 (35.3)	0.80 (0.71-0.91)*	0.74 (0.65-0.84)*
Non-coxib NSAIDs with COX-2 preference, n (%)	347 (22.8)	1,968 (19.7)	1.10 (0.96-1.27)	1.04 (0.90-1.20)
Unknown potency, n (%)	15 (1.0)	73 (0.7)	1.29 (0.73-2.25)	1.25 (0.71-2.21)

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NA = Not Applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S7b Reporting odds ratios of hypersensitivity reactions for any NSAIDs based on chemical group stratified by reporting countries

United States				
0-5 years	Cases (n=1,548)	Non-cases (n=26,846)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	621 (40.1)	21,737 (81.0)	1 (reference)	1 (reference)
Oxicams, n (%)	55 (3.6)	505 (1.9)	3.81 (2.85-5.09)*	3.59 (2.68-4.81)*
Acetic acid derivatives and related substances, n (%)	719 (46.4)	2,997 (11.2)	8.40 (7.49-9.41)*	6.93 (6.15-7.80)*
Fenamates, n (%)	7 (0.5)	126 (0.5)	1.95 (0.91-4.18)	1.70 (0.79-3.66)
Propionic acid derivatives, n (%)	140 (9.0)	1,422 (5.3)	3.45 (2.85-4.17)*	2.88 (2.37-3.51)*
Butylpyrazolidines, n (%)	6 (0.4)	58 (0.2)	3.62 (1.56-8.42)*	3.01 (1.28-7.05)*
Others, n (%)	0 (0.0)	1 (0.0)	NA	NA
5-10 years	Cases (n=294)	Non-cases (n=2,113)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	10 (3.4)	283 (13.4)	1 (reference)	1 (reference)
Oxicams, n (%)	47 (16.0)	572 (27.1)	2.33 (1.16-4.67)*	2.29 (1.14-4.62)*
Acetic acid derivatives and related substances, n (%)	184 (62.6)	446 (21.1)	11.68 (6.07-22.45)*	11.27 (5.83-21.77)*
Fenamates, n (%)	7 (2.4)	51 (2.4)	3.88 (1.41-10.67)*	3.23 (1.16-9.02)*
Propionic acid derivatives, n (%)	16 (5.4)	159 (7.5)	2.85 (1.26-6.43)*	2.90 (1.28-6.59)*
Butylpyrazolidines, n (%)	0 (0.0)	12 (0.6)	NA	NA
Others, n (%)	30 (10.2)	590 (27.9)	1.44 (0.69-2.99)	1.48 (0.71-3.08)
Non-US countries				
0-5 years	Cases (n=2,648)	Non-cases (n=29,631)	Crude ROR (95% CI)	Age-and sex-adjusted ROR (95% CI)
Coxibs, n (%)	1,605 (60.6)	19,006 (64.1)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	720 (27.2)	7,376 (24.9)	1.16 (1.05-1.27)*	1.02 (0.92-1.12)
Non-coxib NSAIDs with COX-2 preference, n (%)	323 (12.2)	3,249 (11.0)	1.18 (1.04-1.33)*	1.04 (0.92-1.18)
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA

Table S7b (continued)

5-10 years	Cases (n=1,412)	Non-cases (n=10,900)	Crude ROR (95% CI)	Age-and sex-adjusted ROR (95% CI)
Coxibs, n (%)	619 (43.8)	3,974 (36.5)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	412 (29.2)	3,792 (34.8)	0.70 (0.61-0.80)*	0.68 (0.60-0.78)*
Non-coxib NSAIDs with COX-2 preference, n (%)	381 (27.0)	3,130 (28.7)	0.78 (0.68-0.90)*	0.75 (0.65-0.86)*
Unknown potency, n (%)	0 (0.0)	4 (0.0)	NA	NA
10-15 years	Cases (n=1,523)	Non-cases (n=9,993)	Crude ROR (95% CI)	Age-and sex-adjusted ROR (95% CI)
Coxibs, n (%)	708 (46.5)	4,426 (44.3)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	453 (29.7)	3,526 (35.3)	0.80 (0.71-0.91)*	0.74 (0.65-0.84)*
Non-coxib NSAIDs with COX-2 preference, n (%)	347 (22.8)	1,968 (19.7)	1.10 (0.96-1.27)	1.04 (0.90-1.20)
Unknown potency, n (%)	15 (1.0)	73 (0.7)	1.29 (0.73-2.25)	1.25 (0.71-2.21)
10-15 years	Cases (n=281)	Non-cases (n=2,861)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	7 (2.5)	139 (4.9)	1 (reference)	1 (reference)
Oxicams, n (%)	36 (12.8)	427 (14.9)	1.67 (0.73-3.85)	1.50 (0.65-3.46)
Acetic acid derivatives and related substances, n (%)	203 (72.2)	1,947 (68.1)	2.07 (0.96-4.48)	1.67 (0.77-3.63)
Fenamates, n (%)	1 (0.4)	9 (0.3)	2.21 (0.24-19.93)	1.96 (0.22-17.87)
Propionic acid derivatives, n (%)	1 (0.4)	16 (0.6)	1.24 (0.14-10.74)	1.03 (0.12-9.03)
Butylpyrazolidines, n (%)	0 (0.0)	0 (0.0)	NA	NA
Others, n (%)	33 (11.7)	323 (11.3)	2.03 (0.88-4.70)	1.90 (0.82-4.14)

Table S7b (continued)

Non-United States Countries				
0-5 years	Cases (n=2,648)	Non-cases (n=29,631)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	1,605 (60.6)	19,006 (64.1)	1 (reference)	1 (reference)
Oxicams, n (%)	316 (11.9)	4,765 (16.1)	0.79 (0.69-0.89)*	0.72 (0.63-0.82)*
Acetic acid derivatives and related substances, n (%)	328 (12.4)	2,302 (7.8)	1.69 (1.49-1.92)*	1.51 (1.33-1.72)*
Fenamates, n (%)	135 (5.1)	773 (2.6)	2.07 (1.71-2.50)*	1.57 (1.29-1.91)*
Propionic acid derivatives, n (%)	167 (6.3)	1,021 (3.4)	1.94 (1.63-2.30)*	1.65 (1.39-1.97)*
Butylpyrazolidines, n (%)	50 (1.9)	640 (2.2)	0.93 (0.69-1.24)	0.79 (0.59-1.06)
Others, n (%)	47 (1.8)	1,124 (3.8)	0.50 (0.37-0.67)*	0.45 (0.33-0.60)*
5-10 years	Cases (n=1,412)	Non-cases (n=10,900)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	619 (43.8)	3,974 (36.5)	1 (reference)	1 (reference)
Oxicams, n (%)	300 (21.2)	2,437 (31.5)	0.56 (0.49-0.65)*	0.59 (0.51-0.69)*
Acetic acid derivatives and related substances, n (%)	52 (3.7)	406 (3.7)	0.82 (0.61-1.11)	0.94 (0.69-1.27)
Fenamates, n (%)	114 (8.1)	497 (4.6)	1.47 (1.18-1.84)*	1.02 (0.81-1.28)
Propionic acid derivatives, n (%)	255 (18.1)	2,056 (18.9)	0.80 (0.68-0.93)*	0.73 (0.62-0.86)*
Butylpyrazolidines, n (%)	21 (1.5)	102 (0.9)	1.32 (0.82-2.13)	1.18 (0.73-1.91)
Others, n (%)	51 (3.6)	428 (3.9)	0.77 (0.57-1.04)	0.75 (0.55-1.02)
10-15 years	Cases (n=1,532)	Non-cases (n=9,993)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	708 (46.5)	4,426 (44.3)	1 (reference)	1 (reference)
Oxicams, n (%)	388 (25.5)	2,556 (25.6)	0.95 (0.83-1.08)	0.95 (0.83-1.09)
Acetic acid derivatives and related substances, n (%)	130 (8.5)	1,112 (11.1)	0.73 (0.60-0.89)*	0.71 (0.58-0.87)*
Fenamates, n (%)	134 (8.8)	545 (5.5)	1.54 (1.25-1.89)*	1.00 (0.81-1.24)
Propionic acid derivatives, n (%)	78 (5.1)	609 (6.1)	0.80 (0.62-1.03)	0.72 (0.56-0.92)*
Butylpyrazolidines, n (%)	10 (0.7)	58 (0.6)	1.08 (0.55-2.12)	0.92 (0.46-1.82)
Others, n (%)	75 (4.9)	687 (6.9)	0.68 (0.53-0.88)*	0.67 (0.52-0.87)*

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NA = Not Applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S7c Reporting odds ratios of hypersensitivity reactions for any NSAIDs according to the presence/ absence of sulfonamide group stratified by reporting countries

United States				
0-5 years	Cases (n=1,548)	Non-cases (n=26,846)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	1,214 (78.4)	20,711 (77.1)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	334 (21.6)	6,135 (22.9)	0.93 (0.82-1.05)	1.02 (0.90-1.16)
5-10 years	Cases (n=294)	Non-cases (n=2,113)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	237 (80.6)	1,437 (68.0)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	57 (19.4)	676 (32.0)	0.51 (0.38-0.69)*	0.51 (0.37-0.70)*
10-15 years	Cases (n=281)	Non-cases (n=2,861)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	238 (84.7)	2,294 (80.2)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	43 (15.3)	567 (19.8)	0.73 (0.52-1.02)	0.82 (0.58-1.15)
Non-United States Countries				
0-5 years	Cases (n=2,648)	Non-cases (n=29,631)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	1,400 (52.9)	18,149 (61.3)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	1,248 (47.1)	11,482 (38.7)	1.41 (1.30-1.53)*	1.42 (1.31-1.54)*
5-10 years	Cases (n=1,412)	Non-cases (n=10,900)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	869 (61.5)	5,708 (52.4)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	543 (38.5)	5,192 (47.6)	0.69 (0.61-0.77)*	0.78 (0.70-0.88)*
10-15 years	Cases (n=1,532)	Non-cases (n=9,993)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	880 (57.8)	5,128 (51.3)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	643 (42.2)	4,865 (48.7)	0.77 (0.69-0.86)*	0.88 (0.79-0.99)*

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S7d Reporting odds ratios of hypersensitivity reactions for individual NSAIDs within 5 years after market approval stratified by reporting countries

United States				
Individual NSAIDs	Cases (n=1,548)	Non-cases (n=26,846)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Rofecoxib, n (%)	342 (22.1)	16,106 (60.0)	1 (reference)	1 (reference)
Celecoxib, n (%)	260 (16.8)	5,517 (20.6)	2.22 (1.88-2.62)*	2.21 (1.87-2.60)*
Zomepirac, n (%)	405 (26.2)	805 (3.0)	23.69 (20.18-27.82)*	18.09 (15.26-21.44)*
Tolmetin, n (%)	134 (8.7)	233 (0.9)	27.08 (21.35-34.36)*	22.85 (17.92-29.14)*
Sulindac, n (%)	71 (4.6)	843 (3.1)	3.97 (3.04-5.17)*	3.68 (2.82-4.80)*
Piroxicam, n (%)	47 (3.0)	411 (1.5)	5.39 (3.91-7.42)*	5.19 (3.76-7.15)*
Mefenamic acid, n (%)	1 (0.1)	7 (0.0)	6.73 (0.83-54.83)	4.10 (0.94-34.05)
Meloxicam, n (%)	8 (0.5)	94 (0.4)	4.01 (1.93-8.32)*	3.62 (1.74-7.52)*
Etoricoxib, n (%)	0 (0.0)	1 (0.0)	NA	NA
Loxoprofen, n (%)	0 (0.0)	9 (0.0)	NA	NA
Non-US countries				
Individual NSAIDs	Cases (n=2,647)	Non-cases (n=29,609)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Rofecoxib, n (%)	497 (18.8)	10,144 (34.3)	1 (reference)	1 (reference)
Celecoxib, n (%)	810 (30.6)	5,888 (19.9)	2.81 (2.50-3.15)*	2.78 (2.48-3.13)*
Zomepirac, n (%)	115 (4.3)	297 (1.0)	7.90 (6.26-9.98)*	6.55 (5.16-8.30)*
Tolmetin, n (%)	41 (1.5)	115 (0.4)	7.28 (5.04-10.51)*	5.68 (2.91-8.25)*
Sulindac, n (%)	95 (3.6)	1,126 (3.8)	1.72 (1.37-2.16)*	1.57 (1.25-1.98)*
Piroxicam, n (%)	117 (4.4)	2,077 (7.0)	1.15 (0.94-1.41)	1.06 (0.86-1.30)
Mefenamic acid, n (%)	135 (5.1)	770 (2.6)	3.58 (2.92-4.39)*	2.71 (2.20-3.34)*
Meloxicam, n (%)	125 (4.7)	1,904 (6.4)	1.34 (1.10-1.64)*	1.19 (0.97-1.46)
Etoricoxib, n (%)	132 (5.0)	1,652 (5.6)	1.63 (1.34-1.99)*	1.49 (1.22-1.82)*
Loxoprofen, n (%)	120 (4.5)	556 (1.9)	4.41 (2.55-5.47)*	3.73 (2.99-4.64)*

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NA = Not Applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S8a Reporting odds ratios of hypersensitivity reactions for any NSAIDs based on cyclooxygenase selectivity stratified by age

<60 years old				
0-5 years	Cases (n=2,589)	Non-cases (n=24,514)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	1,125 (43.5)	16,358 (66.7)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	1,153 (44.5)	5,860 (23.9)	2.86 (2.62-3.12)*	2.85 (2.61-3.11)*
Non-coxib NSAIDs with COX-2 preference, n (%)	311 (12.0)	2,296 (9.4)	1.97 (1.72-2.25)*	1.92 (1.68-2.20)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=1,240)	Non-cases (n=6,771)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	460 (37.1)	2,271 (33.5)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	480 (38.7)	2,718 (40.1)	0.87 (0.76-1.00)	0.88 (0.77-1.01)
Non-coxib NSAIDs with COX-2 preference, n (%)	300 (24.2)	1,779 (26.3)	0.83 (0.71-0.98)*	0.84 (0.71-0.98)*
Unknown potency, n (%)	0 (0.0)	3 (0.0)	NA	NA
10-15 years	Cases (n=1,324)	Non-cases (n=7,079)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	500 (37.8)	2,395 (33.8)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	549 (41.5)	3,404 (48.1)	0.77 (0.68-0.88)*	0.78 (0.68-0.89)*
Non-coxib NSAIDs with COX-2 preference, n (%)	264 (19.9)	1,239 (17.5)	1.02 (0.87-1.20)	1.02 (0.86-1.20)
Unknown potency, n (%)	11 (0.8)	41 (0.6)	1.29 (0.66-2.52)	1.32 (0.67-2.58)

Table S8a (continued)

≥60 years old				
0-5 years	Cases (n=1,607)	Non-cases (n=31,963)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	1,101 (68.5)	24,385 (76.3)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	371 (23.1)	5,287 (16.5)	1.55 (1.38-1.76)*	1.54 (1.37-1.74)*
Non-coxib NSAIDs with COX-2 preference, n (%)	135 (8.4)	2,291 (7.2)	1.31 (1.09-1.57)*	1.30 (1.08-1.56)*
Unknown potency, n (%)	0 ().0)	0 (0.0)	NA	NA
5-10 years	Cases (n=466)	Non-cases (n=6,242)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	169 (36.3)	1,986 (31.8)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	200 (42.9)	2,749 (44.0)	0.86 (0.69-1.06)	0.86 (0.69-1.06)
Non-coxib NSAIDs with COX-2 preference, n (%)	97 (20.8)	1,506 (24.1)	0.76 (0.58-0.98)*	0.76 (0.59-0.99)*
Unknown potency, n (%)	0 (0.0)	1 (0.0)	NA	NA
10-15 years	Cases (n=480)	Non-cases (n=5,775)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	215 (44.8)	2,170 (37.6)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	167 (34.8)	2,670 (46.2)	0.63 (0.51-0.78)*	0.64 (0.52-0.79)*
Non-coxib NSAIDs with COX-2 preference, n (%)	94 (19.6)	903 (15.6)	1.05 (0.82-1.36)	1.06 (0.82-1.36)
Unknown potency, n (%)	4 (0.8)	32 (0.6)	1.26 (0.44-3.60)	1.27 (0.44-3.61)

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NA = Not Applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S8b Reporting odds ratios of hypersensitivity reactions for any NSAIDs based on chemical group stratified by age

<60 years old				
0-5 years	Cases (n=2,589)	Non-cases (n=24,514)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	1,125 (43.5)	16,358 (66.7)	1 (reference)	1 (reference)
Oxicams, n (%)	245 (9.5)	2,491 (10.2)	1.43 (1.24-1.65)*	1.40 (1.21-1.62)*
Acetic acid derivatives and related substances, n (%)	810 (31.3)	2,789 (11.4)	4.22 (3.83-4.66)*	4.16 (3.76-4.59)*
Fenamates, n (%)	109 (4.2)	502 (2.0)	3.16 (2.55-3.92)*	3.04 (2.45-3.78)*
Propionic acid derivatives, n (%)	224 (8.7)	1,428 (5.8)	2.28 (1.96-2.66)*	2.36 (2.02-2.75)*
Butylpyrazolidines, n (%)	44 (1.7)	399 (1.6)	1.60 (1.17-2.20)*	1.64 (1.19-2.25)*
Others, n (%)	32 (1.2)	547 (2.2)	0.85 (0.59-1.22)	0.84 (0.59-1.21)
5-10 years	Cases (n=1,240)	Non-cases (n=6,771)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	460 (37.1)	2,271 (33.5)	1 (reference)	1 (reference)
Oxicams, n (%)	228 (18.4)	1,879 (27.8)	0.60 (0.51-0.71)*	0.61 (0.51-0.72)*
Acetic acid derivatives and related substances, n (%)	177 (14.3)	343 (5.1)	2.55 (2.07-3.13)*	2.59 (2.22-3.19)*
Fenamates, n (%)	107 (8.6)	388 (5.7)	1.36 (1.08-1.72)*	1.33 (1.05-1.69)*
Propionic acid derivatives, n (%)	207 (16.7)	1,310 (19.3)	0.78 (0.65-0.93)*	0.79 (0.66-0.94)*
Butylpyrazolidines, n (%)	11 (0.9)	88 (1.3)	0.62 (0.33-1.16)	0.66 (0.35-1.25)
Others, n (%)	50 (4.0)	492 (7.3)	0.50 (0.37-0.68)*	0.50 (0.37-0.68)*
10-15 years	Cases (n=1,324)	Non-cases (n=7,079)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	500 (37.8)	2,395 (33.8)	1 (reference)	1 (reference)
Oxicams, n (%)	316 (23.9)	1,548 (21.9)	0.98 (0.84-1.14)	0.98 (0.84-1.15)
Acetic acid derivatives and related substances, n (%)	259 (19.6)	1,702 (24.0)	0.73 (0.62-0.86)*	0.74 (0.63-0.87)*
Fenamates, n (%)	128 (9.7)	481 (6.8)	1.28 (1.03-1.58)*	1.24 (1.00-1.55)*
Propionic acid derivatives, n (%)	58 (4.4)	411 (5.8)	0.68 (0.51-0.91)*	0.68 (0.51-0.91)*
Butylpyrazolidines, n (%)	8 (0.6)	48 (0.7)	0.80 (0.38-1.70)	0.84 (0.39-1.79)
Others, n (%)	55 (4.2)	494 (7.0)	0.53 (0.40-0.72)*	0.53 (0.40-0.71)*

Table S8b (continued)

≥ 60 years old				
0-5 years	Cases (n=1,607)	Non-cases (n=31,936)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	1,101 (68.5)	24,385 (76.3)	1 (reference)	1 (reference)
Oxicams, n (%)	126 (7.8)	2,779 (8.7)	1.00 (0.83-1.21)	1.00 (0.83-1.21)
Acetic acid derivatives and related substances, n (%)	237 (14.7)	2,510 (7.9)	2.09 (1.81-2.42)*	2.07 (1.79-2.40)*
Fenamates, n (%)	33 (2.1)	397 (1.2)	1.84 (1.28-2.64)*	1.79 (1.25-2.57)*
Propionic acid derivatives, n (%)	83 (5.2)	1,015 (3.2)	1.81 (1.44-2.28)*	1.81 (1.43-2.28)*
Butylpyrazolidines, n (%)	12 (0.7)	299 (0.9)	0.89 (0.50-1.59)	0.90 (0.50-1.61)
Others, n (%)	15 (0.9)	578 (1.8)	0.58 (0.34-0.96)*	0.57 (0.34-0.95)*
5-10 years	Cases (n=466)	Non-cases (n=6,242)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	169 (36.3)	1,986 (31.8)	1 (reference)	1 (reference)
Oxicams, n (%)	119 (25.5)	2,130 (34.1)	0.66 (0.52-0.84)*	0.66 (0.52-0.84)*
Acetic acid derivatives and related substances, n (%)	59 (12.7)	509 (8.2)	1.36 (1.00-1.86)	1.36 (1.00-1.86)
Fenamates, n (%)	14 (3.0)	160 (2.6)	1.03 (0.58-1.82)	1.03 (0.58-1.81)
Propionic acid derivatives, n (%)	64 (13.7)	905 (14.5)	0.83 (0.62-1.12)	0.84 (0.63-1.14)
Butylpyrazolidines, n (%)	10 (2.1)	26 (0.4)	4.52 (2.14-9.53)*	4.55 (2.16-9.61)*
Others, n (%)	31 (6.7)	526 (8.4)	0.69 (0.47-1.03)	0.69 (0.46-1.02)
10-15 years	Cases (n=480)	Non-cases (n=5,775)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	215 (44.8)	2,170 (37.6)	1 (reference)	1 (reference)
Oxicams, n (%)	108 (22.5)	1,435 (24.8)	0.76 (0.60-0.97)*	0.77 (0.60-0.97)*
Acetic acid derivatives and related substances, n (%)	74 (15.4)	1,357 (23.5)	0.55 (0.42-0.72)*	0.56 (0.43-0.74)*
Fenamates, n (%)	7 (1.5)	73 (1.3)	0.97 (0.44-2.13)	0.98 (0.45-2.16)
Propionic acid derivatives, n (%)	21 (4.4)	214 (3.7)	0.99 (0.62-1.58)	1.01 (0.63-1.61)
Butylpyrazolidines, n (%)	2 (0.4)	10 (0.2)	2.02 (0.44-9.27)	2.01 (0.44-9.25)
Others, n (%)	53 (11.0)	516 (8.9)	1.04 (0.76-1.42)	1.04 (0.76-1.43)

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S8c Reporting odds ratios of hypersensitivity reactions for any NSAIDs according to the presence/ absence of sulfonamide group stratified by age group

<60 years old				
0-5 years	Cases (n=2,589)	Non-cases (n=24,514)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	1,749 (67.6)	17,418 (71.1)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	840 (32.4)	7,096 (28.9)	1.18 (1.08-1.29)*	1.14 (1.05-1.24)*
5-10 years	Cases (n=1,240)	Non-cases (n=6,771)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	844 (68.1)	3,978 (58.8)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	396 (31.9)	2,793 (41.2)	0.67 (0.59-0.76)*	0.67 (0.59-0.77)*
10-15 years	Cases (n=1,324)	Non-cases (n=7,079)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	865 (65.3)	4,539 (64.1)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	459 (34.7)	2,540 (35.9)	0.95 (0.84-1.07)	0.95 (0.84-1.07)
≥60 years old				
0-5 years	Cases (n=1,607)	Non-cases (n=31,963)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	865 (53.8)	21,442 (67.1)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	742 (46.2)	10.521 (32.9)	1.75 (1.58-1.93)*	1.75 (1.58-1.93)*
5-10 years	Cases (n=466)	Non-cases (n=6,242)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	262 (56.2)	3,167 (50.7)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	204 (43.8)	3,075 (49.3)	0.80 (0.66-0.97)*	0.80 (0.66-0.97)*
10-15 years	Cases (n=480)	Non-cases (n=5,775)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	253 (52.7)	2,883 (49.9)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	227 (47.3)	2,892 (50.1)	0.89 (0.74-1.08)	0.89 (0.74-1.07)

Abbreviations: CI = confidence interval; COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant ($p<0.05$)

Table S8d Reporting odds ratios of hypersensitivity reactions for individual NSAIDs within 5 years after market approval stratified by age group

<60 years old				
Individual NSAIDs	Cases (n=2,588)	Non-cases (n=24,499)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Rofecoxib, n (%)	425 (16.4)	10,699 (43.7)	1 (reference)	1 (reference)
Celecoxib, n (%)	496 (19.2)	4,095 (16.7)	3.05 (2.67-3.49)*	2.93 (2.56-3.36)*
Zomepirac, n (%)	450 (17.4)	809 (3.3)	14.00 (12.05-16.28)*	13.78 (11.85-16.03)*
Tolmetin, n (%)	141 (5.4)	236 (1.0)	15.04 (11.95-18.93)*	15.05 (11.94-18.96)*
Sulindac, n (%)	99 (3.8)	833 (3.4)	2.99 (2.38-3.77)*	2.84 (2.26-3.58)*
Piroxicam, n (%)	103 (4.0)	1,102 (4.5)	2.35 (1.88-2.94)*	2.29 (1.83-2.87)*
Mefenamic acid, n (%)	107 (4.1)	441 (1.8)	6.11 (4.84-7.71)*	5.79 (4.59-7.32)*
Meloxicam, n (%)	99 (3.8)	1,003 (4.1)	2.49 (1.98-3.12)*	2.37 (1.88-2.97)*
Etoricoxib, n (%)	83 (3.2)	781 (3.2)	2.68 (2.09-3.42)*	2.61 (2.04-3.33)*
Loxoprofen, n (%)	89 (3.4)	306 (1.2)	7.32 (5.67-9.45)*	7.26 (5.62-9.38)*
≥ 60 years old				
Individual NSAIDs	Cases (n=1,607)	Non-cases (n=31,956)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Rofecoxib, n (%)	414 (25.8)	15,551 (48.7)	1 (reference)	1 (reference)
Celecoxib, n (%)	574 (35.7)	7,310 (22.9)	2.95 (2.59-3.36)*	2.94 (2.58-3.34)*
Zomepirac, n (%)	70 (4.4)	293 (0.9)	8.97 (6.79 (11.86)*	9.00 (6.81-11.89)*
Tolmetin, n (%)	34 (2.1)	112 (0.4)	11.40 (7.67-16.94)*	11.51 (7.74-17.12)*
Sulindac, n (%)	67 (4.2)	1,136 (3.6)	2.22 (1.70-2.89)*	2.19 (1.68-2.85)*
Piroxicam, n (%)	61 (3.8)	1,386 (4.3)	1.65 (1.26-2.18)*	1.65 (1.26-2.18)*
Mefenamic acid, n (%)	29 (1.8)	226 (1.1)	3.24 (2.19-4.80)*	3.15 (2.13-4.66)*
Meloxicam, n (%)	34 (2.1)	995 (3.1)	1.28 (0.90-1.83)	1.28 (0.90-1.83)
Etoricoxib, n (%)	49 (3.0)	872 (2.7)	2.11 (1.56-2.86)*	2.14 (1.58-2.89)*
Loxoprofen, n (%)	31 (1.9)	259 (0.8)	4.50 (3.06-6.61)*	4.59 (3.12-6.75)*

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S9a Reporting odds ratios of hypersensitivity reactions for any NSAIDs based on cyclooxygenase selectivity stratified by sex

Females				
0-5 years	Cases (n=2,734)	Non-cases (n=36,460)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	1,508 (55.2)	26,022 (71.4)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	935 (34.2)	7,348 (20.2)	2.20 (2.02-2.39)*	1.87 (1.71-2.04)*
Non-coxib NSAIDs with COX-2 preference, n (%)	291 (10.6)	3,090 (8.5)	1.63 (1.43-1.85)*	1.44 (1.26-1.65)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=1,019)	Non-cases (n=8,449)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	413 (40.5)	2,814 (33.3)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	357 (35.0)	3,595 (42.5)	0.68 (0.58-0.79)*	0.68 (0.58-0.79)*
Non-coxib NSAIDs with COX-2 preference, n (%)	249 (24.4)	2,038 (24.1)	0.83 (0.70-0.98)*	0.78 (0.66-0.92)*
Unknown potency, n (%)	0 (0.0)	2 (0.0)	NA	NA
10-15 years	Cases (n=1,130)	Non-cases (n=8,463)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	508 (45.0)	3,123 (36.9)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	375 (33.2)	3,853 (45.5)	0.60 (0.52-0.69)*	0.53 (0.46-0.61)*
Non-coxib NSAIDs with COX-2 preference, n (%)	238 (21.1)	1,441 (17.0)	1.02 (0.86-1.20)	0.94 (0.79-1.11)
Unknown potency, n (%)	9 (0.8)	46 (0.5)	1.20 (0.59-2.47)	1.14 (0.55-2.35)

Table S9a (continued)

Males				
0-5 years	Cases (n=974)	Non-cases (n=20,505)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	505 (51.8)	14,934 (72.8)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	366 (37.6)	4,022 (19.6)	2.69 (2.34-3.09)*	2.39 (2.07-2.76)*
Non-coxib NSAIDs with COX-2 preference, n (%)	103 (10.6)	1,549 (7.6)	1.97 (1.58-2.45)*	1.84 (1.48-2.29)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=417)	Non-cases (n=4,834)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	153 (36.7)	1,506 (31.2)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	174 (41.7)	2,021 (41.8)	0.85 (0.68-1.06)	0.82 (0.65-1.03)
Non-coxib NSAIDs with COX-2 preference, n (%)	90 (21.6)	1,305 (27.0)	0.68 (0.52-0.89)*	0.66 (0.50-0.86)*
Unknown potency, n (%)	0 (0.0)	2 (0.0)	NA	NA
10-15 years	Cases (n=460)	Non-cases (n=4,605)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	170 (37.0)	1,479 (32.1)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	193 (42.0)	2,369 (51.4)	0.71 (0.57-0.88)*	0.70 (0.56-0.87)*
Non-coxib NSAIDs with COX-2 preference, n (%)	91 (19.8)	730 (15.9)	1.09 (0.83-1.42)	1.04 (0.79-1.37)
Unknown potency, n (%)	6 (1.3)	27 (0.6)	1.93 (0.79-4.75)	1.91 (0.77-4.72)

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NA = Not Applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S9b Reporting odds ratios of hypersensitivity reactions for any NSAIDs based on chemical group stratified by sex

Females				
0-5 years	Cases (n=2,734)	Non-cases (n=36,460)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	1,508 (55.2)	26,022 (71.4)	1 (reference)	1 (reference)
Oxicams, n (%)	272 (9.9)	2,477 (9.5)	1.35 (1.18-1.54)*	1.24 (1.08-1.41)*
Acetic acid derivatives and related substances, n (%)	603 (22.1)	2,687 (10.1)	2.82 (2.55-3.12)*	2.40 (2.16-2.66)*
Fenamates, n (%)	112 (4.1)	641 (1.8)	3.02 (2.45-3.71)*	2.36 (1.91-2.91)*
Propionic acid derivatives, n (%)	169 (6.2)	1,468 (4.0)	1.99 (1.68-2.35)*	1.67 (1.41-1.98)*
Butylpyrazolidines, n (%)	33 (1.2)	414 (1.1)	1.38 (0.96-1.97)	1.15 (0.80-1.65)
Others, n (%)	37 (1.4)	751 (2.1)	0.85 (0.61-1.19)	0.78 (0.56-1.09)
5-10 years	Cases (n=1,019)	Non-cases (n=8,449)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	413 (40.5)	2,814 (33.3)	1 (reference)	1 (reference)
Oxicams, n (%)	237 (23.3)	2,531 (30.0)	0.64 (0.54-0.76)*	0.68 (0.58-0.81)*
Acetic acid derivatives and related substances, n (%)	87 (8.5)	605 (7.2)	0.98 (0.77-1.26)	1.03 (0.80-1.33)
Fenamates, n (%)	69 (6.8)	413 (4.9)	1.14 (0.87-1.50)	0.79 (0.59-1.05)
Propionic acid derivatives, n (%)	146 (14.3)	1,336 (15.8)	0.75 (0.61-0.91)*	0.65 (0.53-0.80)*
Butylpyrazolidines, n (%)	9 (0.9)	54 (0.6)	1.14 (0.56-2.32)	0.97 (0.47-1.99)
Others, n (%)	58 (5.7)	696 (8.2)	0.57 (0.43-0.76)*	0.60 (0.45-0.81)*
10-15 years	Cases (n=1,130)	Non-cases (n=8,463)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	508 (45.0)	3,123 (36.9)	1 (reference)	1 (reference)
Oxicams, n (%)	285 (25.2)	1,919 (22.7)	0.91 (0.78-1.07)	0.89 (0.76-1.04)
Acetic acid derivatives and related substances, n (%)	149 (13.2)	1,862 (22.0)	0.49 (0.41-0.60)*	0.43 (0.35-0.53)*
Fenamates, n (%)	79 (7.0)	434 (5.1)	1.12 (0.87-1.45)	0.69 (0.52-0.90)*
Propionic acid derivatives, n (%)	34 (3.0)	409 (4.8)	0.51 (0.36-0.73)*	0.44 (0.30-0.63)*
Butylpyrazolidines, n (%)	5 (0.4)	30 (0.4)	1.03 (0.40-2.65)	0.84 (0.32-2.21)
Others, n (%)	70 (6.2)	686 (8.1)	0.63 (0.48-0.82)*	0.62 (0.47-0.81)*

Table S9b (continued)

Males				
0-5 years	Cases (n=974)	Non-cases (n=20,505)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	505 (51.8)	14,934 (72.8)	1 (reference)	1 (reference)
Oxicams, n (%)	82 (8.4)	1,810 (8.8)	1.34 (1.06-1.70)*	1.28 (1.01-1.62)*
Acetic acid derivatives and related substances, n (%)	256 (26.3)	1,800 (8.8)	4.21 (3.59-4.93)*	3.80 (3.23-4.46)*
Fenamates, n (%)	19 (2.0)	269 (1.3)	2.09 (1.30-3.35)*	1.78 (1.10-1.87)*
Propionic acid derivatives, n (%)	86 (8.8)	1,027 (5.0)	2.48 (1.95-3.14)*	2.09 (1.64-2.66)*
Butylpyrazolidines, n (%)	16 (1.6)	291 (1.4)	1.63 (0.98-2.71)	1.43 (0.86-2.39)
Others, n (%)	10 (1.0)	374 (1.8)	0.79 (0.42-1.49)	0.73 (0.39-1.38)
5-10 years	Cases (n=417)	Non-cases (n=4,834)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	153 (36.7)	1,506 (31.2)	1 (reference)	1 (reference)
Oxicams, n (%)	91 (2.18)	1,497 (31.0)	0.60 (0.46-0.78)*	0.60 (0.46-0.79)*
Acetic acid derivatives and related substances, n (%)	50 (12.0)	346 (7.2)	1.42 (1.01-2.00)*	1.46 (1.04-2.06)*
Fenamates, n (%)	32 (7.7)	155 (3.2)	2.03 (1.34-3.08)*	1.45 (0.94-2.22)
Propionic acid derivatives, n (%)	66 (15.8)	938 (19.4)	0.69 (0.51-0.94)*	0.66 (0.48-0.89)*
Butylpyrazolidines, n (%)	9 (2.2)	63 (1.3)	1.41 (0.69-2.88)	1.13 (0.55-2.34)
Others, n (%)	16 (3.8)	329 (6.8)	0.48 (0.28-0.81)*	0.48 (0.28-0.81)*
10-15 years	Cases (n=460)	Non-cases (n=4,605)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	170 (37.0)	1,479 (32.1)	1 (reference)	1 (reference)
Oxicams, n (%)	113 (24.6)	1,090 (23.7)	0.90 (0.70-1.16)	0.93 (0.72-1.20)
Acetic acid derivatives and related substances, n (%)	90 (19.6)	1,291 (28.0)	0.61 (0.47-0.79)*	0.59 (0.45-0.78)*
Fenamates, n (%)	36 (7.8)	140 (3.0)	2.24 (1.50-3.34)*	1.72 (1.14-2.59)*
Propionic acid derivatives, n (%)	20 (4.3)	241 (5.2)	0.72 (0.45-1.17)	0.65 (0.40-1.06)
Butylpyrazolidines, n (%)	4 (0.9)	29 (0.6)	1.20 (0.42-2.46)	0.98 (0.34-2.83)
Others, n (%)	27 (5.9)	335 (7.3)	0.70 (0.46-1.07)	0.74 (0.49-1.14)

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S9c Reporting odds ratios of hypersensitivity reactions for any NSAIDs according to the presence/ absence of sulfonamide group stratified by sex

Females				
0-5 years	Cases (n=2,734)	Non-cases (n=36,460)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	1,659 (60.7)	24,659 (67.6)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	1,075 (39.3)	11,801 (32.4)	1.35 (1.25-1.47)*	1.40 (1.29-1.52)*
5-10 years	Cases (n=1,019)	Non-cases (n=8,449)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	633 (62.1)	4, 686 (55.5)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	386 (37.9)	3,763 (44.5)	0.76 (0.66-0.87)*	0.87 (0.76-0.99)*
10-15 years	Cases (n=1,130)	Non-cases (n=8,463)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	672 (59.5)	4,796 (56.7)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	3,667 (43.3)	3,667 (43.3)	0.89 (0.79-1.01)	1.03 (0.91-1.18)
Males				
0-5 years	Cases (n=974)	Non-cases (n=20,505)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	582 (59.8)	14,574 (71.1)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	392 (40.2)	5,931 (28.9)	1.66 (1.45-1.89)*	1.75 (1.54-2.00)*
5-10 years	Cases (n=417)	Non-cases (n=4,834)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	269 (64.5)	2,663 (55.1)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	148 (35.5)	2,171 (44.9)	0.68 (0.55-0.83)*	0.71 (0.58-0.88)*
10-15 years	Cases (n=460)	Non-cases (n=4,605)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	282 (61.3)	2,790 (60.6)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	178 (38.7)	1,815 (39.4)	0.97 (0.80-1.18)	1.08 (0.89-1.32)

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S9d Reporting odds ratios of hypersensitivity reactions for individual NSAIDs within 5 years after market approval stratified by sex

Females				
Individual NSAIDs	Cases (n=2,733)	Non-cases (n=36,449)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Rofecoxib, n (%)	594 (21.7)	16,323 (44.8)	1 (reference)	1 (reference)
Celecoxib, n (%)	709 (25.9)	7,729 (21.2)	2.52 (2.25-2.82)*	2.53 (2.26-2.84)*
Zomepirac, n (%)	295 (10.8)	758 (2.1)	10.70 (9.14-12.52)*	7.96 (6.76-9.37)*
Tolmetin, n (%)	78 (2.9)	246 (0.7)	8.71 (6.67-11.39)*	6.92 (5.28-9.08)*
Sulindac, n (%)	104 (3.8)	1,393 (3.8)	2.05 (1.65-2.54)*	1.92 (1.54-2.38)*
Piroxicam, n (%)	120 (4.4)	1,607 (4.4)	2.05 (1.68-2.51)*	1.92 (1.57-2.36)*
Mefenamic acid, n (%)	106 (3.9)	562 (1.5)	5.18 (4.15-6.48)*	4.11 (3.28-5.16)*
Meloxicam, n (%)	99 (3.6)	1,353 (3.7)	2.01 (1.61-2.51)*	1.82 (1.46-2.27)*
Etoricoxib, n (%)	93 (3.4)	1,039 (2.8)	2.46 (1.96-3.09)*	2.25 (1.79-2.82)*
Loxoprofen, n (%)	59 (2.2)	357 (1.0)	4.54 (3.41-6.05)*	3.78 (2.82-5.05)*
Males				
Individual NSAIDs	Cases (n=974)	Non-cases (n=20,494)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Rofecoxib, n (%)	159 (16.3)	10,013 (48.9)	1 (reference)	1 (reference)
Celecoxib, n (%)	276 (28.3)	3,761 (18.3)	4.62 (3.79-5.64)*	4.77 (3.91-5.82)*
Zomepirac, n (%)	124 (12.7)	445 (2.2)	17.55 (13.62-22.61)*	14.51 (11.19-18.80)*
Tolmetin, n (%)	39 (4.0)	160 (0.8)	15.35 (10.46-22.52)*	12.93 (8.77-19.05)*
Sulindac, n (%)	44 (4.5)	594 (2.9)	4.67 (3.31-6.58)*	4.57 (3.24-6.45)*
Piroxicam, n (%)	42 (4.3)	883 (4.3)	3.00 (2.12-4.24)*	2.89 (2.04-4.09)*
Mefenamic acid, n (%)	19 (2.0)	226 (1.1)	5.29 (3.23-8.67)*	4.52 (2.75-7.43)*
Meloxicam, n (%)	22 (2.3)	657 (3.2)	2.11 (1.34-3.32)*	2.02 (1.28-3.18)*
Etoricoxib, n (%)	25 (2.6)	628 (3.1)	2.51 (1.63-3.85)*	2.45 (1.59-3.77)*
Loxoprofen, n (%)	32 (3.3)	237 (1.2)	8.50 (5.69-12.70)*	7.75 (5.18-11.60)*

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

*statistically significant ($p<0.05$)

Table S10a Reporting odds ratios of hypersensitivity reactions using broad scope definition for any NSAIDs based on cyclooxygenase selectivity

0-5 years	Cases[Ŧ] (n=6,088)	Non-cases (n=54,585)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	3,622 (59.5)	39,347 (72.1)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	1,929 (31.7)	10,742 (19.7)	1.95 (1.84-2.07)*	1.69 (1.59-1.80)*
Non-coxib NSAIDs with COX-2 preference, n (%)	537 (8.8)	4,496 (8.2)	1.30 (1.18-1.43)*	1.16 (1.06-1.28)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=2,146)	Non-cases (n=12,573)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	804 (37.5)	4,082 (32.5)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	828 (38.6)	5,319 (42.3)	0.79 (0.71-0.88)*	0.79 (0.71-0.88)*
Non-coxib NSAIDs with COX-2 preference, n (%)	514 (24.0)	3,168 (25.2)	0.82 (0.73-0.93)*	0.80 (0.71-0.90)*
Unknown potency, n (%)	0 (0.0)	4 (0.0)	NA	NA
10-15 years	Cases (n=2,144)	Non-cases (n=12,514)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	846 (39.5)	4,434 (35.4)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	844 (39.4)	5,946 (47.5)	0.74 (0.67-0.83)*	0.70 (0.63-0.78)*
Non-coxib NSAIDs with COX-2 preference, n (%)	435 (20.3)	2,065 (16.5)	1.10 (0.97-1.25)	1.05 (0.92-1.19)
Unknown potency, n (%)	19 (0.9)	69 (0.6)	1.44 (0.86-2.41)	1.41 (0.84-2.37)

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NA = Not Applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

[Ŧ]broad scopes include all possible terms that are often less likely to represent the outcome of interest but give high sensitivity for the case of interest,

*statistically significant ($p<0.05$)

Table S10b Reporting odds ratios of hypersensitivity reactions using broad scope definition for any NSAIDs based on chemical group

0-5 years	Cases (n=6,088)	Non-cases (n=54,585)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	3,622 (59.5)	39,347 (72.1)	1 (reference)	1 (reference)
Oxicams, n (%)	527 (8.7)	5,114 (9.4)	1.12 (1.02-1.23)*	1.03 (0.94-1.14)
Acetic acid derivatives and related substances, n (%)	1,223 (20.1)	5,123 (9.4)	2.59 (2.42-2.78)*	2.24 (2.08-2.41)*
Fenamates, n (%)	157 (2.6)	884 (1.6)	1.93 (1.62-2.29)*	1.52 (1.27-1.81)*
Propionic acid derivatives, n (%)	406 (6.7)	2,344 (4.3)	1.88 (1.68-2.10)*	1.62 (1.44-1.81)*
Butylpyrazolidines, n (%)	94 (1.5)	660 (1.2)	1.55 (1.24-1.93)*	1.34 (1.08-1.68)*
Others, n (%)	59 (1.0)	1,113 (2.0)	0.58 (0.44-0.75)*	0.52 (0.40-0.68)*
5-10 years	Cases (n=2,146)	Non-cases (n=12,573)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	804 (37.5)	4,082 (32.5)	1 (reference)	1 (reference)
Oxicams, n (%)	460 (21.4)	3,896 (31.0)	0.60 (0.53-0.68)*	0.63 (0.56-0.71)*
Acetic acid derivatives and related substances, n (%)	256 (11.9)	832 (6.6)	1.56 (1.33-1.83)*	1.67 (1.42-1.96)*
Fenamates, n (%)	131 (6.1)	538 (4.3)	1.24 (1.01-1.52)*	0.89 (0.72-1.10)
Propionic acid derivatives, n (%)	361 (16.8)	2,125 (16.9)	0.86 (0.75-0.99)*	0.81 (0.70-0.93)*
Butylpyrazolidines, n (%)	25 (1.2)	110 (0.9)	1.15 (0.74-1.79)	1.04 (0.67-1.63)
Others, n (%)	109 (5.1)	990 (7.9)	0.56 (0.45-0.69)*	0.57 (0.46-0.71)*
10-15 years	Cases (n=2,144)	Non-cases (n=12,514)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Coxibs, n (%)	846 (39.5)	4,434 (35.4)	1 (reference)	1 (reference)
Oxicams, n (%)	524 (24.4)	2,883 (23.0)	0.95 (0.85-1.07)	0.96 (0.85-1.08)
Acetic acid derivatives and related substances, n (%)	380 (17.7)	3,012 (24.1)	0.66 (0.58-0.75)*	0.63 (0.55-0.72)*
Fenamates, n (%)	148 (6.9)	541 (4.3)	1.43 (1.18-1.74)*	0.98 (0.80-1.20)
Propionic acid derivatives, n (%)	100 (4.7)	604 (4.8)	0.87 (0.69-1.09)	0.79 (0.63-0.99)*
Butylpyrazolidines, n (%)	12 (0.6)	56 (0.4)	1.12 (0.60-2.10)	0.97 (0.51-1.82)
Others, n (%)	134 (6.3)	984 (7.9)	0.71 (0.59-0.87)*	0.72 (0.59-0.88)*

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

[Ŧ]broad scopes include all possible terms that are often less likely to represent the outcome of interest but give high sensitivity for the case of interest,

*statistically significant ($p<0.05$)

Table S10c Reporting odds ratios of hypersensitivity reactions using broad scope definition for any NSAIDs according to the presence/absence of sulfonamide group

0-5 years	Cases (n=6,088)	Non-cases (n=54,585)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	3,935 (64.6)	37,539 (68.8)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	2,153 (35.4)	17,046 (31.2)	1.21 (1.14-1.27)*	1.23 (1.17-1.30)*
5-10 years	Cases (n=2,146)	Non-cases (n=12,573)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	1,387 (64.6)	6,864 (54.6)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	759 (35.4)	5,709 (45.4)	0.66 (0.60-0.72)*	0.72 (0.65-0.79)*
10-15 years	Cases (n=2,144)	Non-cases (n=12,514)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	1,300 (60.6)	7,240 (57.9)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	844 (39.4)	5,274 (42.1)	0.89 (0.81-0.98)*	1.00 (0.91-1.10)

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

[Ŧ]broad scopes include all possible terms that are often less likely to represent the outcome of interest but give high sensitivity for the case of interest,

*statistically significant ($p<0.05$)

Table S10d Reporting odds ratios of hypersensitivity reactions using broad scope definition for individual NSAIDs within 5 years after market approval

Individual NSAIDs	Cases (n=6,087)	Non-cases (n=54,563)	Crude ROR (95% CI)	Age- and sex-adjusted ROR (95% CI)
Rofecoxib, n (%)	1,750 (28.7)	25,339 (46.4)	1 (reference)	1 (reference)
Celecoxib, n (%)	1,442 (23.7)	11,033 (20.2)	1.89 (1.76-2.04)*	1.89 (1.75-2.03)*
Zomepirac, n (%)	602 (9.9)	1,020 (1.9)	8.55 (7.64-9.56)*	6.69 (5.96-7.51)*
Tolmetin, n (%)	194 (3.2)	329 (0.6)	8.54 (7.10-10.26)*	7.10 (5.89-8.56)*
Sulindac, n (%)	205 (3.4)	1,930 (3.5)	1.54 (1.32-1.79)*	1.42 (1.22-1.66)*
Piroxicam, n (%)	276 (4.5)	2,376 (4.4)	1.68 (1.47-1.92)*	1.58 (1.38-1.81)*
Mefenamic acid, n (%)	151 (2.5)	762 (1.4)	2.87 (2.39-3.44)*	2.27 (1.89-2.73)*
Meloxicam, n (%)	155 (2.5)	1,976 (3.6)	1.14 (0.96-1.35)	1.03 (0.87-1.22)
Etoricoxib, n (%)	182 (3.0)	1,603 (2.9)	1.64 (1.40-1.93)*	1.54 (1.31-1.81)*
Loxoprofen, n (%)	153 (2.5)	532 (1.0)	4.16 (3.46-5.02)*	3.66 (3.03-4.42)*

Abbreviations: CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; ROR = Reporting Odds Ratio

[Ŧ]broad scopes include all possible terms that are often less likely to represent the outcome of interest but give high sensitivity for the case of interest,

*statistically significant ($p<0.05$)

CHAPTER 6

NON-STEROIDAL ANTI-INFLAMMATORY DRUG USE AND

THE RISK OF REVISION OF LOWER JOINT REPLACEMENT SURGERY:

A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Background The effect of non-steroidal anti-inflammatory drugs (NSAIDs) on bone-implant contact has not been established. Furthermore, few studies assessed the impact of NSAIDs on revision risk of lower joint replacement (LJR) surgery.

Purposes To assess the revision risk of LJR surgery (either hip or knee replacements) associated with the use of NSAIDs compared to non-use.

Methods A retrospective cohort study was conducted in the UK primary health care database among patients aged ≥40 years with primary LJR surgery from January 2000-December 2018. NSAIDs (either conventional NSAIDs and selective COX-2 inhibitors) as exposures and potential confounders were assessed as time-dependent variables. Patients were followed until either date of revision surgery, lost to follow-up, or end of the study. Cox-proportional hazard with time-dependent covariate analysis was used to estimate hazard ratios (HRs), and 95% confidence intervals (95% CIs).

Results 155,490 patients with primary LJR surgery were identified. At the cohort entry, of them, 26,946 (17.3%) and 4,646 (3.0%) were prescribed conventional NSAIDs and selective COX-2 inhibitors, respectively and 123,898 (79.7%) were non-users. During follow-up, 3,354 (2.16%) patients underwent a revision surgery. Compared to non-use, current use for <1 month, 3-6 months, 6-12 months, and >12 months of conventional NSAIDs were associated with a higher risk of revision (adj. HR 2.48 (95%CI; 2.07-2.96), 1.51 (1.16-1.96), 1.67 (1.27-2.20), and 2.08 (1.69-2.56), respectively). Compared to non-use, current use for <1 month, 1-3 month(s), 3-6 months, and >12 months of selective COX-2 inhibitors were also associated with a higher risk (adj. HR 2.85 (1.87-4.34), 1.17 (0.69-1.98), 1.20 (0.62-2.32), 2.07 (1.29-3.30), respectively). Likewise, recent and past use of either conventional NSAIDs or selective COX-2 inhibitors were associated with a higher risk compared to non-use.

Conclusion Compared to non-use, current use of conventional NSAIDs and selective COX-2 inhibitors for all durations of use, except for current use for 1-3 month(s) and 6-12 months, respectively was associated with a higher risk of revision of LJR. A higher risk lasted for >3 months after discontinuation.

INTRODUCTION

In the United Kingdom (UK), numbers of primary surgery for hip replacement and knee replacement increased by two and three times during 1991-2015, respectively. These numbers are predicted to increase by nine and 27 times in 2035 (1). The incidence of revision surgery for these lower joint replacements (LJRs) was more than doubled and tripled, respectively in the period of 1991 to 2000 (2), and patients who undergo these surgeries become younger (3).

Non-steroidal anti-inflammatory drugs (NSAIDs) have been known to be able to affect bone metabolism. These drugs are associated with an increased risk of fracture, and subsequent adverse events, including non-union and second fracture (4-7), and joint replacement (8). NSAIDs can also potentiate the risk of implant-related adverse events such as a revision of hip replacement surgery (9). However, several studies showed that NSAID use did not affect acetabular cup migration after hip replacement, marginal bone level around dental implants (10, 11), nor the risk of early aseptic loosening of cemented hip replacement (12, 13).

An association between NSAID use and implant-related adverse events is uncertain. Furthermore, limited studies evaluated the risk of revision surgery for a primary LJR related to NSAID use. We aimed to assess the association between NSAIDs and the risk of revision of LJR surgery, i.e., hip and knee replacements compared to non-use, and to assess the effect of duration of use on this association.

METHODS

Data source and Setting

We conducted a retrospective cohort study in the UK Clinical Practice Research Datalink (CPRD). The data was collected from January 2000–December 2018. This general practitioner (GP) database contains patient's information on demographics, clinical events, tests, diagnoses, therapies, lifestyles, and referrals to secondary health care services. It links to other data sources including hospital data, disease-

specific cohorts (such as cancer registration data and cardiovascular disease registry), national mortality records, and deprivation database. Over 6.9% of the UK population has been registered in this database with an average duration of follow-up of 5.1 years. More than 15 million patients from 720 GP practices have been recorded (14). This study has been approved by The Independent Scientific Advisory Committee of the Medicine and Health Product Regulatory Agency (MHRS) database research under the protocol number 19_016.

Study Population

We identified all patients who underwent a primary LJR surgery (either hip or knee replacements) within the study period that was determined based on CPRD Read Codes (**Supplementary, Table S1**). The date when a patient underwent the primary surgery was the cohort entry (the index date). We limited our cohort to surgeries that were most likely elective and fulfilling the following additional criteria; they should be ≥40 years old, had no history of rheumatoid arthritis, had no records of hip or knee fractures within 3 months, and had been registered in the database for at least 1 year before the cohort entry. All patients were followed from the cohort entry until the revision date of LJR surgery, end of the study, or lost to follow-up including moving out of the practice area, whichever came first.

Exposures

Exposure for this study was NSAID use during observation time that was retrieved based on both the British National Formulary codes and product codes. NSAID users were those who received at least one NSAID prescription following the cohort entry until the end of follow-up. The follow-up periods were categorized as either current, recent, or past use. Current use was a single or a continuous prescription of any NSAID during follow-up plus a 3-week period following the theoretical end date to anticipate the carry-over effect (15). A gap of 3-weeks or less between the theoretical end date of a prescription and the start of the following prescription was allowed to anticipate poor adherence to medication. Recent use was a period up to 90 days following current use, whereas past use were periods following recent use. A new prescription of any NSAID following either recent or past use was considered as current use again. A period

from the primary surgery until the first prescription of any NSAIDs during follow-up was categorized as "non-use". Non-users were also those without any NSAID prescriptions during the entire follow-up period. NSAIDs were categorized as either conventional NSAIDs or selective COX-2 inhibitors according to the Anatomical Therapeutic Chemical Classification system (M01A) (**Supplementary, Table S2**). For each NSAID prescription, the prescribed quantity and written dosage instruction were used to estimate the duration of use. It was calculated from prescription quantity divided by daily dosage instruction plus 3 weeks following the theoretical end date of this prescription. If this information was missing, we used a fixed duration of 30 days as duration. We assumed NSAIDs were taken as regular-use. Duration of use was classified as either ≤1 month, 1-3 month(s), 3-6 months, 6-12 months, or >12 months.

Outcome of Interest

Outcome of interest was revision surgery of LJR defined according to CPRD Read Codes (**Supplementary, Table S3**). We excluded patients who had revision surgery within 3 weeks following the primary LJR, as a minimum duration of NSAID use to affect bone remodeling radiologically and clinically after a bone- or joint-associated surgical procedure (16). It is also likely that the revision surgery occurring within this period is due to a technical failure during the primary surgery.

Potential confounders

We considered several potential confounders associated with implant-bone contact and bone metabolism including age, sex, GP practice, body mass index (BMI), lifestyle factors (smoking and alcohol abuse), and affected joint. We also took into account medication use (NSAID use before the primary surgery, bisphosphonates, calcium and vitamin D supplementation, hormone replacement therapy (HRT), selective oestrogen receptor modulating (SERM) drugs, oral anti-diabetic agents, proton-pump inhibitors, anti-arrhythmic drugs, anticonvulsants, antidepressants, anti-Parkinson's drugs, thiazide diuretics, anxiolytics/hypnotics, statins, oral corticosteroids, non-opioid non-NSAID analgesics, opioids, and beta blockers), morbidities (fractures, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, congestive heart failure, ischemic heart diseases, cerebrovascular diseases, chronic obstructive pulmonary

diseases (COPD), diabetes mellitus (DM), asthma, hypertension, hyperlipidemia, and atrial fibrillation). At cohort entry, medication use was assessed in the previous 6 months, except for NSAIDs, as ever before. Morbidities were assessed as ever before the cohort entry. All these potential confounders were up-dated in each 90-days period during follow-up as time-varying variables if one episode for NSAID use or non-use lasted for >90 days. BMI was defined based on the latest available record before the end of follow-up. Because of limited follow-up information, lifestyle factors were determined only at cohort entry as a time-fixed confounder as well as sex.

Data-analyses

For exposed and non-exposed groups, age and BMI were presented as both mean and proportions. Remaining categorical variables (sex, affected joints, medication use, morbidities, and lifestyles factors) were presented as proportions. The exposures and potential confounders (except for sex, BMI, and lifestyle factors) were analyzed in a time-dependent manner. Patients with missing values on BMI were dropped, leaving only complete cases for the analyses. The hazard ratios (HRs) of revision surgery of LJR for NSAIDs were estimated by using Cox proportional hazard analysis with time-dependent covariates. All potential confounders were considered to calculate adjusted HRs. We only presented the HRs if there were at least 5 events within each exposure. Analyses were performed using statistical software Stata/Special Edition (SE) version 14.1 for Windows.

Sensitivity Analyses

A sensitivity analysis was performed to capture early implant-bone loosening as the main indication for the revision surgery (12). If analgesics fail to treat complaints in the affected joint, a revision surgery as a standard treatment for end-stage joint diseases will be performed. Hence, protopathic bias may occur. To evaluate this potential bias, we considered 6 months before the revision surgery as the beginning of implant-bone loosening (which was the date of the outcome).

RESULTS

Characteristics

We included 155,490 patients who underwent primary LJR surgery, including 85,420 hip replacements (54.9%) and 70,070 knee replacements (45.1%) in 19 years of observation time. At cohort entry, 26,946 (17.3%) and 4,646 (3.0%) of them were the users of conventional NSAIDs and selective COX-2 inhibitors, respectively, and 123,898 (79.7%) were non-users. Most of them were >65 years old, female, overweight and obese, and current and ever smoking. Mean age for users of conventional NSAIDs and selective COX-2 inhibitors was lower compared to non-users (67.5 and 68.7 vs. 70.6 years old, respectively). They often were prescribed NSAIDs before the primary surgery, HRTs, SERMs, proton pump inhibitors, diuretic thiazides, non-opioids non-NSAID analgesics, or opioids, but were less likely to have diseases. However, non-users more often were prescribed oral anti-diabetics, antiarrhythmic drugs, anti-Parkinson drugs, beta-blockers, and statins. Non-users were more likely to have morbidities (fractures, inflammatory bowel diseases, congestive heart failure, ischemic heart diseases, cardiovascular diseases, COPD, asthma, hypertension, hyperlipidemia, atrial fibrillation, and DM), and alcohol abuse (**Table 1**). Median follow-up for conventional NSAIDs and selective COX-2 inhibitors was longer than for non-users (6.71 and 7.72 vs. 4.48 years), respectively. Among all subjects, 3,354 patients (2.16%) underwent revision surgery of hip (1.13%) or knee (1.03%).

Revision risk of LJR surgery for NSAID use

For conventional NSAIDs, current use for <1 month, 3-6 months, 6-12 months, and >12 months, recent use, and past use were associated with a higher risk of revision of LJR (adj. HR 2.48 (95%CI: 2.07-2.96), 1.51 (1.16-1.96), 1.67 (1.27-2.20), 2.08 (1.69-2.56), 1.38 (1.19-1.62), and 1.20 (1.10-1.31), respectively) compared to non-use. In contrast, current use for 1-3 month(s) was associated with a similar risk compared to non-use (**Table 2**). For selective COX-2 inhibitors, a higher risk was also found for current use for <1 month, 1-3 month(s), 3-6 months, and >12 months, recent use, and past use (adj. HR 2.85 (1.87-4.34), 1.17 (0.69-1.98), 1.20 (0.62-2.32), 2.07 (1.29-3.30), 1.98 (1.41-2.77), and 1.10 (0.91-1.33),

respectively) compared to non-use. However, current use for 6-12 months was associated with a similar risk compared to non-use (**Table 3**).

Table 1 Baseline characteristics of the study population at cohort entry

Characteristics	Conventional NSAID use n = 26,946	Selective COX-2 inhibitor use n = 4,646	Non-use n = 123,898
Median follow-up time [IQR], years	6.71 [3.34-10.15]	7.72 [3.97-11.26]	4.48 [1.75-8.04]
Age			
Mean age (years ± sd)	67.5 ± 9.7	68.7 ± 10.0	70.6 ± 10.7
40-65 years, n (%)	11,150 (41.4)	1,720 (37.0)	38,225 (30.9)
>65 years, n (%)	15,796 (58.6)	2,926 (63.0)	85,673 (69.1)
Sex, n (%)			
Male	11,030 (40.9)	1,568 (33.7)	50,090 (40.4)
Female	15,916 (59.1)	3,078 (66.3)	73,808 (59.6)
Body mass index			
Mean body mass index (kg/m^2 ± sd)	29.15 ± 5.46	28.79 ± 5.40	28.31 ± 5.37
Underweight, n (%)	183 (0.7)	30 (0.6)	1,820 (1.5)
Normal, n (%)	5,278 (19.6)	1,011 (21.8)	29,702 (24.0)
Overweight, n (%)	9,534 (35.4)	1,612 (34.7)	43,940 (35.5)
Obese, n (%)	9.517 (35.3)	1,509 (32.5)	38,627 (31.2)
Unknown, n (%)	2,434 (9.0)	484 (10.4)	9,809 (7.9)
Affected joint, n (%)			
Hip	14,412 (53.5)	2,445 (52.6)	68,563 (55.3)
Knee	12,534 (46.5)	2,201 (47.4)	55,335 (44.7)
Medication use within 6 months prior to the cohort entry, n (%)			
Past use NSAIDs*	3,993 (14.8)	566 (12.2)	0 (0.0)
Bisphosphonates	1,089 (4.0)	258 (5.6)	6,793 (5.5)
Calcium/Vitamin D	1,803 (6.7)	425 (9.1)	10,644 (8.6)
Hormone replacement therapy	1,163 (4.3)	266 (5.7)	2,771 (2.2)
Selective estrogen receptor modulating drugs	221 (0.8)	37 (0.8)	639 (0.5)
Oral anti-diabetics	1,434 (5.3)	220 (4.7)	9,015 (7.3)
Proton-pump inhibitors	9,255 (34.3)	1,562 (33.6)	37,606 (30.4)
Antiarrhythmics	281 (1.0)	57 (1.2)	1,982 (1.6)
Anticonvulsants-anxiolytics-hypnotics	1,972 (6.4)	464 (10.0)	7,876 (6.4)
Antidepressants	4,972 (18.5)	1,080 (23.2)	21,698 (17.5)
Anti-Parkinson drugs	208 (0.8)	43 (0.9)	1,264 (1.0)
Thiazide diuretics	6,016 (22.3)	1,097 (23.6)	25,430 (20.5)
Oral corticosteroid	1,239 (4.6)	319 (6.9)	6,958 (5.6)
Non-opioid non-NSAID analgesics	17,468 (64.8)	3,159 (68.0)	67,895 (54.8)
Opioids	10,859 (40.3)	2,278 (49.0)	34,440 (27.8)

Table 1 (continued)

Statins	6,700 (24.9)	1,010 (21.7)	39,069 (31.5)
Beta blockers	3,988 (14.8)	745 (16.0)	21,718 (17.5)
Morbidities prior to and at the index date, n (%)			
Fractures**	6,404 (23.8)	1,077 (23.2)	37,943 (30.6)
Rheumatoid arthritis	321 (1.2)	71 (1.5)	1,803 (1.5)
Osteoarthritis	20,056 (67.1)	3,507 (75.5)	83,190 (67.1)
Inflammatory bowel diseases	303 (1.1)	70 (1.5)	2,062 (1.7)
Congestive heart failure	378 (1.4)	69 (1.5)	3,905 (3.2)
Ischemic heart diseases	2,416 (9.0)	434 (9.3)	16,824 (13.6)
Cerebrovascular diseases	1,121 (4.2)	218 (4.7)	9,532 (7.7)
Chronic obstructive pulmonary diseases	823 (3.1)	160 (3.4)	6,659 (5.4)
Diabetes mellitus type II	2,235 (8.3)	340 (7.3)	13,791 (11.1)
Asthma	3,210 (11.9)	575 (12.4)	17,022 (13.7)
Hypertension	11,663 (43.3)	1,991 (42.9)	59,774 (48.2)
Hyperlipidemia	3,484 (12.9)	561 (12.1)	18,818 (15.2)
Atrial fibrillation	712 (2.6)	125 (2.7)	8,473 (6.8)
Smoking status, n (%)			
Current	3,651 (13.5)	655 (14.1)	15,369 (12.4)
Ever	9,687 (35.9)	1,590 (34.2)	49,160 (39.7)
Never	12,487 (46.3)	2,122 (45.7)	55,530 (44.8)
Unknown	1,121 (4.2)	279 (6.0)	3,839 (3.1)
Alcohol abuse, n (%)	1,116 (4.1)	168 (3.6)	6,566 (5.3)

Abbreviations: COX = Cyclooxygenase; IQR = Interquartile Range; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs

*before cohort entry

**up to 3 months before cohort entry

Based on affected joints, a higher risk of revision of hip replacement was also associated with current use for all durations of use, recent use, and past use of conventional NSAIDs compared to non-use (**Table 4**). A higher risk of revision of knee replacement was also found for current use of conventional NSAIDs for all durations of use, except for 1-3 month(s) compared to non-use as shown in the main analyses. Current use for 1-3 month(s) was associated with a not significant lower risk of revision by adj. HR 0.87 (95%CI: 0.61-1.25) (**Table 5**). A higher risk of revision of hip replacement was also found for current use for all durations of use, and recent use of selective COX-2 inhibitors compared to non-use (**Table 6**). A higher risk of revision of knee replacement was found for current use for all durations of use, recent use, and past use of selective COX-2 inhibitors compared to non-use (**Table 7**).

Table 2 Hazard ratios of the revision surgery of lower joint replacements for conventional NSAID users compared to non-users

Exposure	Events/Person-Years	Incidence rate per 10,000 person-years	Crude HR (95% CI)	Adjusted HR[Ŧ] (95% CI)
Non-use	1,440/458,913	31.4	1	1
Current use[Θ]				
Up to 1 month	151/14,226	106.1	3.13 (2.64-3.70)*	2.48 (2.07-2.96)*
1 month – 3 months	76/15,978	47.6	1.39 (1.11-1.75)*	1.03 (0.81-1.31)
3 – 6 months	62/8,732	71.0	1.97 (1.53-2.55)*	1.51 (1.16-1.96)*
6 – 12 months	55/7,912	69.5	2.16 (1.65-2.84)*	1.67 (1.27-2.20)*
>12 months	103/11,654	88.4	2.85 (2.33-3.49)*	2.08 (1.69-2.56)*
Recent use	205/36,449	56.2	1.74 (1.51-2.02)*	1.38 (1.19-1.62)*
Past use	1,029/262,010	39.3	1.29 (1.19-1.41)*	1.20 (1.10-1.31)*

Abbreviations: CI = Confidence Intervals; HR = Hazard Ratio; NSAID = Non-Steroidal Anti-Inflammatory Drugs

[Θ]duration of use

[Ŧ]adjusted for age, sex, general practitioner practice, affected joint, a history of fracture, body mass index, lifestyles (smoking status and alcohol abuse), medication use (past use NSAIDs, bisphosphonates, calcium/vitamin D supplements, hormone replacement therapy, selective estrogen receptor modulators, oral anti-diabetic agents, proton pump inhibitors, anti-arrhythmic, anticonvulsants/anxiolytics/hypnotics, antidepressants, anti-Parkinson drugs, thiazide diuretics, oral corticosteroids, non-opioid non-NSAID analgesics, opioids, beta-blockers, and statins), and morbidities (rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, congestive heart failure, ischemic heart diseases, cerebrovascular diseases, chronic obstructive pulmonary diseases, asthma, hyperlipidemia, atrial fibrillation, hypertension, and diabetes mellitus).

*statistically significant ($p<0.05$)

Sensitivity Analysis

In this sensitivity analysis, we assumed that aseptic loosening as a major indication of revision surgery of LJR occurred 6 months earlier than the entered date of the revision surgery. We found a higher risk of revision surgery of LJR for current use for all durations of use and recent use of either conventional NSAIDs or selective COX-2 inhibitors compared to non-use. Both past use of conventional NSAIDs and selective COX-2 inhibitors were associated with a similar risk of revision surgery compared to non-use (**Supplementary, Table S4** and **Table S5).**

Table 3 Hazard ratios of the revision surgery of lower joint replacements for selective COX-2 inhibitor users compared to non-users

Exposure	Events/Person-Years	Incidence rate per 10,000 person-years	Crude HR (95% CI)	Adjusted HR[Ŧ] (95% CI)
Non-use	1,440/458,913	31.4	1	1
Current use[Θ]				
Up to 1 month	23/1,891	121.6	3.52 (2.33 -5.32)*	2.85 (1.87-4.34)*
1 month – 3 months	15/2,796	53.7	1.56 (0.94-2.60)	1.17 (0.69-1.98)
3 – 6 months	10/1,650	60.6	1.67 (0.90-3.13)	1.20 (0.62-2.32)
6 – 12 months	8/1,614	49.6	1.53 (0.76-3.07)	1.05 (0.50-2.21)
>12 months	18/1,998	90.1	2.89 (1.81-4.60)*	2.07 (1.29-3.30)*
Recent use	37/4,498	82.3	2.51 (1.81-3.47)*	1.98 (1.41-2.77)*
Past use	122/33,392	36.5	1.21 (1.00-1.45)	1.10 (0.91-1.33)

Abbreviations: CI = Confidence Intervals; COX = Cyclooxygenase; HR = Hazard Ratio

[Θ]duration of use

[Ŧ]adjusted for age, sex, general practitioner practice, affected joint, a history of fracture, body mass index, lifestyles (smoking status and alcohol abuse), medication use (past use NSAIDs, bisphosphonates, calcium/vitamin D supplements, hormone replacement therapy, selective estrogen receptor modulators, oral anti-diabetic agents, proton pump inhibitors, anti-arrhythmic, anticonvulsants/anxiolytics/hypnotics, antidepressants, anti-Parkinson drugs, thiazide diuretics, oral corticosteroids, non-opioid non-NSAID analgesics, opioids, beta-blockers, and statins), and morbidities (rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, congestive heart failure, ischemic heart diseases, cerebrovascular diseases, chronic obstructive pulmonary diseases, asthma, hyperlipidemia, atrial fibrillation, hypertension, and diabetes mellitus).

*statistically significant ($p<0.05$)

DISCUSSION

Revision risk of LJR surgery for NSAID users

Our study indicated that both conventional NSAIDs and selective COX-2 inhibitors had a higher risk of revision of LJR compared to non-use, except for current use for 1-3 month(s) of conventional NSAIDs and for 6-12 months of selective COX-2 inhibitors. This higher risk lasted >3 months after discontinuation of the drugs. Our sensitivity analyses showed that current use for all durations of use of these drugs was associated with a higher risk of revision. However, this higher risk lasted only up to 3 months of discontinuation of these drugs.

Table 4 Hazard ratios of the revision surgery of hip replacements for conventional NSAID users compared to non-users

Exposure	Events/Person-Years	Incidence rate per 10,000 person-years	Crude HR (95% CI)	Adjusted HR[Ŧ] (95% CI)
Non-use	786/256,808	30.6	1	1
Current use[Θ]				
Up to 1 month	92/6,764	136.0	3.94 (3.27-4.89)*	3.16 (2.51-3.97)*
1 month – 3 months	42/7,371	57.0	1.59 (1.17-2.17)*	1.19 (0.85-1.65)
3 – 6 months	31/4,014	77.2	1.97 (1.37-2.83)*	1.55 (1.07-2.24)*
6 – 12 months	28/3,518	79.6	2.65 (1.81-3.87)*	2.01 (1.36-2.97)*
>12 months	43/5,097	84.4	3.03 (2.22-4.13)*	2.20 (1.60-3.02)*
Recent use	93/17,913	51.9	1.64 (1.32-2.03)*	1.30 (1.04-1.63)*
Past use	528/135,205	39.1	1.34 (1.19-1.52)*	1.23 (1.09-1.40)*

Abbreviations: CI = confidence intervals; HR = hazard ratio; NSAID = non-steroidal anti-inflammatory drugs

[Θ]duration of use

[Ŧ]adjusted for age, sex, general practitioner practice, year of primary surgery, a history of fracture, body mass index, lifestyles (smoking status, and alcohol abuse), medication use (bisphosphonates, calcium/vitamin D supplements, hormone replacement therapy, selective estrogen receptor modulators, oral anti-diabetic agents, proton pump inhibitors, anti-arrhythmic, anticonvulsants/anxiolytics/hypnotics, antidepressants, anti-Parkinson drugs, thiazide diuretics, oral corticosteroids, non-opioid non-NSAID analgesics, opioids, and statins), and morbidities (rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, congestive heart failure, ischemic heart diseases, cerebrovascular diseases, chronic obstructive pulmonary diseases, and diabetes mellitus).

*statistically significant ($p<0.05$)

Previous studies that were performed to investigate the revision risk of hip replacement for NSAID use supported our findings on this revision risk of LJR surgery. A randomized clinical trial demonstrated that for ibuprofen users, a revision risk of prosthetic fixation for total hip arthroplasty was higher than in the placebo group (17). Furthermore, a case-control study showed that the early revision risk of total hip replacement increased for NSAIDs compared to non-use (9). As the main indication for the revision surgery (12), aseptic non-union after surgical fixation of humeral diaphyseal fracture was also found higher for NSAIDs as shown in an observational study (18).

Table 5 Hazard ratios of the revision surgery of knee replacements for conventional NSAID users compared to non-users

Exposure	Events/Person-Years	Incidence rate per 10,000 person-years	Crude HR (95% CI)	Adjusted HR[Ŧ] (95% CI)
Non-use	654/202,105	32.4	1	1
Current use[Θ]				
Up to 1 month	59/7,462	79.1	2.31 (1.77-3.02)*	1.82 (1.37-2.41)*
1 month – 3 months	34/8,606	39.5	1.18 (0.83-1.66)	0.87 (0.61-1.25)
3 – 6 months	31/4,718	65.7	2.03 (1.41-2.91)*	1.51 (1.04-2.20)*
6 – 12 months	27/4,393	61.5	1.76 (1.19-2.59)*	1.40 (0.95-2.06)
>12 months	60/6,557	91.5	2.59 (1.98-3.37)*	1.91 (1.45-2.51)*
Recent use	112/18,536	60.4	1.77 (1.45-2.16)*	1.42 (1.15-1.75)*
Past use	501/126,805	39.5	2.22 (1.08-1.38)*	1.16 (1.02-1.31)*

Abbreviations: CI = Confidence Intervals; HR = Hazard Ratio; NSAID = Non-Steroidal Anti-Inflammatory Drugs

[Θ]duration of use

[Ŧ]adjusted for age, sex, general practitioner practice, a history of fracture, body mass index, lifestyles (smoking status and alcohol abuse), medication use (past use NSAIDs, bisphosphonates, calcium/vitamin D supplements, hormone replacement therapy, selective estrogen receptor modulators, oral anti-diabetic agents, proton pump inhibitors, anti-arrhythmic, anticonvulsants/anxiolytics/hypnotics, antidepressants, anti-Parkinson drugs, thiazide diuretics, oral corticosteroids, non-opioid non-NSAID analgesics, opioids, beta-blockers, and statins), and morbidities (rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, congestive heart failure, ischemic heart diseases, cerebrovascular diseases, chronic obstructive pulmonary diseases, asthma, hyperlipidemia, atrial fibrillation, hypertension, and diabetes mellitus).

*statistically significant ($p<0.05$)

Potential Clinical Implication

Our findings indicated a potential adverse effect of the use of either conventional NSAIDs or selective COX-2 inhibitors on the revision of LJR surgery. However, this finding should be interpreted carefully due to a possible non-causal association between NSAIDs and revision surgery. NSAIDs might be prescribed to reduce the pain that possibly occurs after the primary surgery. The pain after surgery might be related to loosening of the hip or knee replacement. The longer patients experience the pain, the longer conventional NSAIDs or selective COX-2 inhibitors will be used. When NSAIDs or other analgesics are not longer effective, revision surgery will be ultimately performed. This alternative explanation is supported by the fact that the users of conventional NSAIDs and selective COX-2 inhibitors were also more likely to be

prescribed analgesics such as opioids and non-opioid non-NSAID analgesics compared to non-users of NSAIDs.

Table 6 Hazard ratios of the revision surgery of hip replacements for selective COX-2 inhibitor users compared to non-users

Exposure	Events/Person-Years	Incidence rate per 10,000 person-years	Crude HR (95% CI)	Adjusted HR[Ŧ] (95% CI)
Non-use	786/256,808	30.6	1	1
Current use[Θ]				
Up to 1 month	14/899	155.8	4.38 (2.58-7.43)*	3.53 (2.03-6.12)*
1 month – 3 months	8/1,293	61.9	1.75 (0.87-3.51)	1.26 (0.60-2.66)
3 – 6 months	3/764	39.3	NA	NA
6 – 12 months	5/725	69.0	2.30 (0.95-5.54)	1.45 (0.54-3.88)
>12 months	5/882	56.7	2.04 (0.85-4.92)	1.51 (0.62-3.66)
Recent use	18/2,215	81.3	2.50 (1.56-3.98)*	2.02 (1.25-3.28)*
Past use	57/17,572	32.4	1.12 (0.85-1.47)	1.02 (0.77-1.35)

Abbreviations: CI = Confidence Intervals; COX = Cyclooxygenase; HR = Hazard Ratio; NA = Not-Applicable

[Θ]duration of use

[Ŧ]adjusted for age, sex, general practitioner practice, a history of fracture, body mass index, lifestyles (smoking status and alcohol abuse), medication use (past use NSAIDs, bisphosphonates, calcium/vitamin D supplements, hormone replacement therapy, selective estrogen receptor modulators, oral anti-diabetic agents, proton pump inhibitors, anti-arrhythmic, anticonvulsants/anxiolytics/hypnotics, antidepressants, anti-Parkinson drugs, thiazide diuretics, oral corticosteroids, non-opioid non-NSAID analgesics, opioids, beta-blockers, and statins), and morbidities (rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, congestive heart failure, ischemic heart diseases, cerebrovascular diseases, chronic obstructive pulmonary diseases, asthma, hyperlipidemia, atrial fibrillation, hypertension, and diabetes mellitus).

*statistically significant ($p<0.05$)

Strengths and Limitations

We identified several strengths in this study. First, we included a large sample size from CPRD data that represents the UK population. Second, information on exposures, outcomes, and potential confounders are routinely collected in CPRD database, regardless of research questions which will minimize potential recall bias. Routine data collection also enables us to analyze timing patterns precisely. Finally, CPRD database contains patient information on demographics, drug prescriptions, morbidities, and

especially lifestyles factors that are not common to be found in other electronic health care databases. Thus, we could adjust for many potential confounders.

Table 7 Hazard ratios of the revision surgery of knee replacements for selective COX-2 inhibitor users compared to non-users

Exposure	Events/Person-Years	Incidence rate per 10,000 person-years	Crude HR (95% CI)	Adjusted HR[Ŧ] (95% CI)
Non-use	654/202,105	32.4	1	1
Current use[Θ]				
Up to 1 month	9/992	90.7	2.65 (1.37-5.11)*	2.19 (1.13-4.23)*
1 month – 3 months	7/1,502	46.6	1.36 (0.65-2.86)	1.07 (0.51-2.26)
3 – 6 months	7/887	78.9	2.37 (1.12-4.99)*	1.59 (0.71-3.59)
6 – 12 months	3/890	33.7	NA	NA
>12 months	13/1,116	116.5	3.26 (1.88-5.65)*	2.21 (1.28-3.86)*
Recent use	19/2,283	83.2	2.42 (1.53-2.81)*	1.19 (1.18-3.03)*
Past use	65/15,820	41.1	1.27 (0.98-1.64)	1.17 (0.90-1.53)

Abbreviations: CI = confidence intervals; COX = Cyclooxygenase; HR = hazard ratio; NA = not applicable

[Θ]duration of use

[Ŧ]adjusted for age, sex, general practitioner practice, a history of fracture, body mass index, lifestyles (smoking status and alcohol abuse), medication use (past use NSAIDs, bisphosphonates, calcium/vitamin D supplements, hormone replacement therapy, selective estrogen receptor modulators, oral anti-diabetic agents, proton pump inhibitors, anti-arrhythmic, anticonvulsants/anxiolytics/hypnotics, antidepressants, anti-Parkinson drugs, thiazide diuretics, oral corticosteroids, non-opioid non-NSAID analgesics, opioids, beta-blockers, and statins), and morbidities (rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, congestive heart failure, ischemic heart diseases, cerebrovascular diseases, chronic obstructive pulmonary diseases, asthma, hyperlipidemia, atrial fibrillation, hypertension, and diabetes mellitus).

*statistically significant ($p<0.05$)

Nonetheless, several limitations were identified. First, the main limitation is that NSAID probably were mostly prescribed to treat pain. Pain can be a marker of loosening of a hip or knee replacement leading to revision surgery. The more pain obviously will lead to a higher chance of revision surgery. Second, our study had a relatively short duration of follow-up. The revision surgery is more likely to occur within a wide duration of time, i.e., between 10 and 20 years (19) and only <20% of this revision surgery was performed within <2 years after the primary surgery (12). In our study, the median follow-up after the primary surgery was relatively short, i.e., between 4-7 years. Third, information on both the primary and

revision surgeries were retrieved from the GP data. We cannot rule out possibilities that the surgery codes from the hospital data were not transferred to the GP data nor the date of the surgery was entered in the GP data later than the actual date. However, we expect this misclassification is non-differential between exposed and non-exposed groups. Furthermore, our previous study showed that applying GP data from the UK CPRD database to study the revision risk of LJR surgery for statin users yielded similar results compared to employing the Danish database that links to hospital data (20). Fourth, the revision surgery represented an implant failure. This revision might be conditional to surgical or technical contexts that we did not consider in this study, including technical surgery and types of fixation (either cemented, non-cemented, or hybrid). Third, we have no information on the actual NSAID use and medication adherence because medication use in the CPRD database is based on drug prescription data. Information on NSAIDs prescribed by specialists and NSAID use after primary surgery in the hospital setting, including NSAIDs that were prescribed for home-use right after hospital discharge were not available. Furthermore, over-the-counter NSAID use was not either recorded. However, ibuprofen is the only NSAIDs available for over-the-counter medication in the UK (21, 22). Thus, we expect misclassification of the exposure is not differential between exposed and non-exposed groups.

CONCLUSIONS

Both conventional NSAIDs and selective COX-2 inhibitors were associated with a higher risk of revision of LJR surgery compared to non-use, except for current use for 1-3 month(s) of conventional NSAIDs and for 6-12 months of selective COX-2 inhibitors. Furthermore, this higher risk lasted for >3 months after discontinuation of these drugs.

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SUPPLEMENTARY

Table S1 CPRD medical codes for primary TJR surgery

Total Hip Replacement	
Med code	**Read term**
394	Total prosthetic replacement of hip joint NOS
2224	THR - Total prosthetic replacement of hip joint using cement
5481	Total prosthetic replacement of hip joint using cement
2734	THR - Other total prosthetic replacement of hip joint
9762	Other total prosthetic replacement of hip joint
1092	Hip joint operations
33439	Primary total prosthetic replacement of hip joint NEC
7288	Hemiarthroplasty of head of femur NEC
589	THR - Total prosthetic replacement hip joint without cement
18442	Total prosthetic replacement of hip joint not using cement
9070	Prosthetic hemiarthroplasty of head of femur using cement
6681	Austin - Moore hemiarthroplasty of hip joint using cement
10856	Primary cemented total hip replacement
18004	Thompson hemiarthroplasty of hip joint using cement
10011	Other arthroplasty of hip joint
16671	Charnley total replacement of hip joint using cement
11846	Hip joint operations NOS
28468	Exeter total replacement of hip joint using cement
29573	Other prosthetic hemiarthroplasty of hip
2226	Prosthetic cemented hemiarthroplasty of hip NOS
47483	Primary uncemented total hip replacement
17860	Arthroplasty of hip joint using cement
25300	Other specified operations on hip joint
38001	Total prosthetic replacement of hip joint using cement OS
12847	Prosthetic cemented hemiarthroplasty of hip
12287	Austin Moore hemiarthroplasty of hip joint not using cement
15049	Other specified other prosthetic hemiarthroplasty of hip
9739	Thompson hemiarthroplasty of hip joint not using cement
10348	Primary hybrid total replacement of hip joint NEC
47812	Total prosthetic replacement of hip joint using cement NOS
28808	Primary prosthetic hemiarthroplasty of hip NEC
7171	Prosthetic hemiarthroplasty head of femur not using cement
41116	Primary cemented hemiarthroplasty of hip
27448	Other prosthetic hemiarthroplasty of hip NOS
37631	Other specified total prosthetic replacement of hip joint
29977	Stanmore total replacement of hip joint using cement
38347	Total prosthetic replacement hip joint not using cement NOS
38332	Furlong total replacement of hip joint using cement

Table S1 (continued)

43460	Prosthetic uncemented hemiarthroplasty of hip
52714	Charnley cemented total hip replacement
6013	Muller total replacement of hip joint using cement
18818	Other arthroplasty of head of femur
36590	Howse total replacement of hip joint using cement
47735	Furlong total replacement of hip joint not using cement
47482	Primary uncemented hemiarthroplasty of hip
48955	Hastings hemiarthroplasty of hip joint using cement
71351	Aufranc total replacement of hip joint using cement
28022	Arthroplasty of head of femur using cement
21366	Bateman hemiarthroplasty of hip joint not using cement
30019	Other replacement of head of femur
61099	Monk hemiarthroplasty of hip joint using cement
34911	Prosthetic cemented replacement of head of femur
58651	Arthroplasty of head of femur not using cement
34997	McKee total replacement of hip joint using cement
47715	Monk total replacement of hip joint using cement
10341	Total prosthetic replacement hip joint not using cement OS
34383	Prosthetic uncemented hemiarthroplasty of hip NOS
62092	Turner total replacement of hip joint using cement
55207	Primary hybrid total replacement of hip joint NEC
50091	Austin Moore hemiarthroplasty of hip joint not using cement
18865	Prosthetic replacement head of femur - no cement
52901	Freeman total replacement of hip joint using cement
62249	Monk hemiarthroplasty of hip joint not using cement
66139	Farrer total replacement of hip joint using cement
56215	Ilch total replacement of hip joint using cement
73951	Ring total replacement of hip joint not using cement
62046	Other specified prosthetic uncemented hemiarthroplasty hip
51519	Monk total replacement of hip joint not using cement
53109	Freeman total replacement of hip joint not using cement
94273	Pretoria total replacement of hip joint using cement
96435	Lord total replacement of hip joint not using cement
96760	Brown hemiarthroplasty of hip joint not using cement

Table S1 (continued)

Total Knee Replacement:	
Med code	Read term
5362	TKR -Total prosthetic replacement of knee joint using cement
3414	Total prosthetic replacement of knee joint using cement
673	Other total prosthetic replacement of knee joint NOS
3973	TKR - Other total prosthetic replacement of knee joint
8555	Other total prosthetic replacement of knee joint
28048	Primary total knee replacement NEC
20746	Primary cemented total knee replacement
17471	Total prosthetic replacement of knee joint not using cement
9877	TKR - Total prosthetic replacement knee joint without cement
94310	Uni-compartmental knee replacement NOS
10406	Other arthroplasty of knee joint
11225	Cemented uni-compartmental knee replacement
10372	Total prosthetic replacement of knee joint using cement OS
31977	Arthroplasty of knee joint using cement
8006	Total prosthetic replacement of knee joint using cement NOS
36343	Primary cemented uni-compartmental knee replacement
49053	Primary uncemented total knee replacement
9817	Uncemented uni-compartmental knee replacement
58612	Total prosthetic replacement knee joint not using cement NOS
54343	Primary uncemented uni-compartmental knee replacement
37979	Other total prosthetic replacement of knee joint OS
55470	Hybrid uni-compartmental knee replacement
47764	Arthroplasty of knee joint not using cement
50829	Total prosthetic replacement knee joint not using cement OS
37950	Primary hybrid uni-compartmental knee replacement
61687	Attenborough total replacement of knee joint using cement
101346	Prosthetic arthroplasty of the patellofemoral joint
46475	Charnley total replacement of knee joint using cement
93344	Anametric total replacement of knee joint using cement
44775	Denham total replacement of knee joint using cement
54860	Freeman total replacement of knee joint using cement
55991	Sheehan total replacement of knee joint using cement
44926	Stanmore total replacement of knee joint using cement
63086	Uci total replacement of knee joint using cement
83544	Primary hybrid total knee replacement NEC
47301	Polycentric total replacement of knee joint using cement
49813	Deane total replacement of knee joint using cement
92246	Liverpool total replacement of knee joint using cement
49716	Swanson total replacement of knee joint using cement
63802	Geomedic total replacement of knee joint using cement

Table S1 (continued)

66707	Herbert total replacement of knee joint using cement
71456	Cavendish total replacement of knee joint using cement
99912	Manchester total replacement of knee joint using cement
101522	Ilch total replacement of knee joint using cement
101810	Wallidus hinge arthroplasty of knee joint using cement
70507	Shiers total replacement of knee joint using cement
103334	Autophor arthroplasty of knee joint using cement

Abbreviations: CPRD = the Clinical Practice Research Datalink; NEC = Non-Elsewhere Classified; NOS = Not Otherwise Specified; OS = Otherwise Specified; THR = Total Hip Replacement; TKR = Total Knee Replacement

Table S2 Non-steroidal anti-inflammatory drugs based on the Anatomical Therapeutic Classification system

ATC codes	Chemical subgroup
M01A	Anti-inflammatory and anti-rheumatoid products, non-steroid
M01AA	Butylpyrazolidines
M01AB	Acetic acid derivatives and related substances
M01AC	Oxicams
M01AE	Propionic acid derivatives
M01AG	Fenamates
M01AH	Coxibs
M01AX	Other anti-inflammatory and anti-rheumatoid agents, non-steroids

Table S3 CPRD medical codes for THR/TKR revision surgery

Med code	Read term
2032	Revision of total prosthetic replacement of hip joint NEC
8895	Revision cemented total hip replacement
11847	Revision of total knee replacement NEC
10553	Revision cemented total knee replacement
27660	Revision of prosthetic hemiarthroplasty of hip NEC
29101	Revision uncemented total hip replacement
38942	Revision cemented hemiarthroplasty of hip
41370	Attention to total hip replacement NEC
68002	Revision one component total prosthetic replacement hip joint NEC
41545	Revision uncemented total knee replacement
41184	Revision uncemented hemiarthroplasty of hip
36700	Removal previous cemented total prosthetic replacement hip joint
31843	Conversion to cemented total hip replacement
48220	Conversion to total prosthetic replacement of hip joint NEC
54756	Attention to total knee replacement NEC
86014	Revision hybrid prosthetic replace hip joint cement acetabular comp
55662	Revision of hybrid total hip replacement NEC
73031	Revision one component total prosthetic replace knee joint NEC
87850	Revision one component total prosthetic replace knee joint cement
41693	Removal of prosthetic knee joint
93224	Revision one component total prosthetic replace hip joint cement
62757	Conversion to total knee replacement NEC
48815	Removal previous total prosthetic replacement knee joint NEC
62133	Conversion to hybrid total hip replacement NEC
59060	Removal previous uncemented total prosthetic replacement hip joint
38740	Removal previous cemented total prosthetic replacement knee
38791	Conversion from previous total pros replace hip joint NEC
50624	Conversion to uncemented total hip replacement
67778	Conversion from cemented total hip replacement
65585	Attention to prosthetic hemiarthroplasty of hip NEC
69999	Conversion to cemented total knee replacement
31930	Conversion to cemented hemiarthroplasty of hip
42259	Revision hybrid total knee replacement NEC
93613	Revision one component total prosthetic replace knee joint, not cement
97534	Revision hybrid prosthetic replacement hip joint cement NEC
93122	Revision one component total prosthetic replace hip joint, not cement
64483	Removal of prosthetic hip joint
66363	Revision of hybrid total hip replacement NEC
71947	Conversion from uncemented hemiarthroplasty of hip
58980	Revision cemented uni-compartmental knee replacement
98004	Revision hybrid prosthetic replacement hip joint cemented femoral compartmental

Table S3 (continued)

65481	Conversion to prosthetic hemiarthroplasty of hip NEC
41820	Conversion from total knee replacement NEC
61288	Revision uncemented uni-compartmental knee replacement
67306	Conversion from hybrid total prosthetic hip joint replace NEC
41489	Conversion to uncemented hemiarthroplasty of hip
67352	Conversion from previous hemiarthroplasty of hip NEC
73075	Conversion from cemented total knee replacement
47223	Attention to hybrid total knee replacement NEC
38073	Revision hybrid uni-compartmental knee replacement
97176	Conversion to hybrid total hip replacement NEC
99651	Conversion from hybrid total prosthetic hip joint replace NEC
43789	Conversion from cemented hemiarthroplasty of hip
97341	Conversion from uncemented total knee replacement
93435	Conversion to hybrid total knee replacement NEC
97400	Conversion from cemented uni-compartmental knee replacement
100089	Revision hybrid prosthetic replacement knee joint using cement

Abbreviations: CPRD = the Clinical Practice Research Datalink; NEC = Non-Elsewhere Classified; THR = Total Hip Replacement; TKR = Total Knee Replacement

Table S4 Hazard ratios of the revision surgery of lower joint replacements that were assumed to occur 6 months earlier than the actual date of revision surgery for conventional NSAID users compared to non-users

Exposure	Events**/Person-Years	Incidence rate per 10,000 person-years	Crude HR (95% CI)	Adjusted HR[Ŧ] (95% CI)
Non-use	1,260/458,235	27.5	1	1
Current use[Θ]				
Up to 1 month	139/14,183	98.0	2.02 (1.62-2.53)*	1.64 (1.29-2.07)*
1 month – 3 months	84/15,922	52.8	2.49 (2.05-3.02)*	1.85 (1.51-2.27)*
3 – 6 months	55/8,697	63.2	2.86 (2.25-3.64)*	2.23 (1.74-2.86)*
6 – 12 months	60/7,878	76.2	3.04 (2.39-3.86)*	2.33 (1.83-2.98)*
>12 months	85/11,607	73.2	2.61 (2.10-3.25)*	1.88 (1.50-2.36)*
Recent use	212/36,345	58.3	1.97 (1.71-2.28)*	1.55 (1.33-1.81)*
Past use	880/261,535	33.6	1.17 (1.07-1.28)*	1.08 (0.98-1.19)

Abbreviations: CI = Confidence Intervals; HR = Hazard Ratio; NSAID = Non-Steroidal Anti-Inflammatory Drugs

[Θ]duration of use

[Ŧ]adjusted for age, sex, general practitioner practice, affected joint, year of primary surgery, a history of fracture, body mass index, lifestyles (smoking status, and alcohol abuse), medication use (bisphosphonates, calcium/vitamin D supplements, hormone replacement therapy, selective oestrogen receptor modulators, oral anti-diabetic agents, proton pump inhibitors, anti-arrhythmic, anticonvulsants/anxiolytics/hypnotics, antidepressants, anti-Parkinson drugs, thiazide diuretics, oral corticosteroids, non-opioid non-NSAID analgesics, opioids, and statins), and morbidities (rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, congestive heart failure, ischemic heart diseases, cerebrovascular diseases, chronic obstructive pulmonary diseases, and diabetes mellitus).

*statistically significant ($p<0.05$)

**implant bone loosening as the main indication of revision surgery was assumed to occur 6 months prior to the actual date of revision surgery

Table S5 Hazard ratios of the revision surgery of lower joint replacements that were assumed to occur 6 months earlier than the actual date of revision surgery for selective COX-2 inhibitor users compared to non-users

Exposure	Events/Person-Years	Incidence rate per 10,000 person-years	Crude HR (95% CI)	Adjusted HR[Ŧ] (95% CI)
Non-use	1,260/458,235	27.5	1	1
Current use[ϴ]				
Up to 1 month	20/1,886	106.1	2.45 (1.42-4.23)*	1.86 (1.05-3.29)*
1 month – 3 months	132,786	46.7	2.39 (1.52-3.76)*	1.60 (0.98-1.19)
3 – 6 months	13/1,645	79.0	2.51 (1.42-4.43)*	2.00 (1.13-3.53)*
6 – 12 months	101,609	62.1	2.45 (1.39-4.33)*	1.95 (1.10-3.45)*
>12 months	13/1,990	65.3	2.27 (1.31-3.92)*	1.64 (0.95-2.84)
Recent use	20/44,485	44.6	1.49 (0.96-2.32)	1.25 (0.80-1.95)
Past use	104/33,336	31.2	1.09 (0.89-1.33)	1.01 (0.82-1.25)

Abbreviations: CI = Confidence Intervals; HR = Hazard Ratio; NSAID = Non-Steroidal Anti-Inflammatory Drugs

[ϴ]duration of use

[Ŧ]adjusted for age, sex, general practitioner practice, affected joint, year of primary surgery, a history of fracture, body mass index, lifestyles (smoking status, and alcohol abuse), medication use (bisphosphonates, calcium/vitamin D supplements, hormone replacement therapy, selective oestrogen receptor modulators, oral anti-diabetic agents, proton pump inhibitors, anti-arrhythmic, anticonvulsants/anxiolytics/hypnotics, antidepressants, anti-Parkinson drugs, thiazide diuretics, oral corticosteroids, non-opioid non-NSAID analgesics, opioids, and statins), and morbidities (rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, congestive heart failure, ischemic heart diseases, cerebrovascular diseases, chronic obstructive pulmonary diseases, and diabetes mellitus).

*statistically significant ($p<0.05$)

**implant bone loosening as the main indication of revision surgery was assumed to occur 6 months prior to the actual date of revision surgery

CHAPTER 7

RISK OF MYOCARDIAL INFARCTION ASSOCIATED

WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUG USE:

IMPACT OF ADDITIONAL CONFOUNDING CONTROL FOR VARIABLES

COLLECTED FROM SELF-REPORTED DATA

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ABSTRACT

Background: 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.

Purposes: 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 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 2,974 controls. Among cases, 11 (1.1%) and 185 (19.1%) were exposed to selective COX-2 inhibitors and conventional NSAIDs, respectively. Compared to nonuse, 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 minimally changed the risk estimates (adjusted OR 1.08, 95% CI: 0.53-2.22 and 0.89, 95% CI: 0.73-1.09, respectively).

Conclusions: 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.

INTRODUCTION

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- 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, 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 first, 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 nonuse. Second, to evaluate the effect of integrating OTC NSAID use collected from patient's report to pharmacy record on this association.

METHODS

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 one 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 (**Supplementary, 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, hypercholesterolemia 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.

Ethical approval

The Medical Ethics Committee of the University Medical Center Utrecht, The Netherlands has approved this study and written informed consent was obtained from participants.

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 (± one years) at the index date.

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), i.e., 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. Nonusers 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 two months before the index date from both a pharmacy dispensing and OTC medications, whereas nonusers 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 analyze the risk of AMI. Since we had no information about NSAID use more than two 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).

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 three 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 ischemic 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.

Data-analyses

Characteristics of cases and controls were compared using a t-test or a $\chi 2$-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 **Supplementary, Table S2**. Missing values were handled by multiple imputation methods with fully conditional specification using five sets of the dataset. 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%.

RESULTS

A total of 45,981 eligible patients were identified in the Dutch PHARMO Database Network for UCP study including 4,843 AMI cases and 41,138 non-cases. The median number of controls per case was 11. Of cases, 2,372 patients were dispensed anti-hypertensive drugs, 1,302 patients had hypercholesterolemia, and other 1,169 patients had both. We excluded 5,797 patients (12.61%) as either they were concomitant or past users of selective COX-2 inhibitors or conventional NSAIDs leaving 4,106 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, 4,536 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 2,974 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 regards 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.

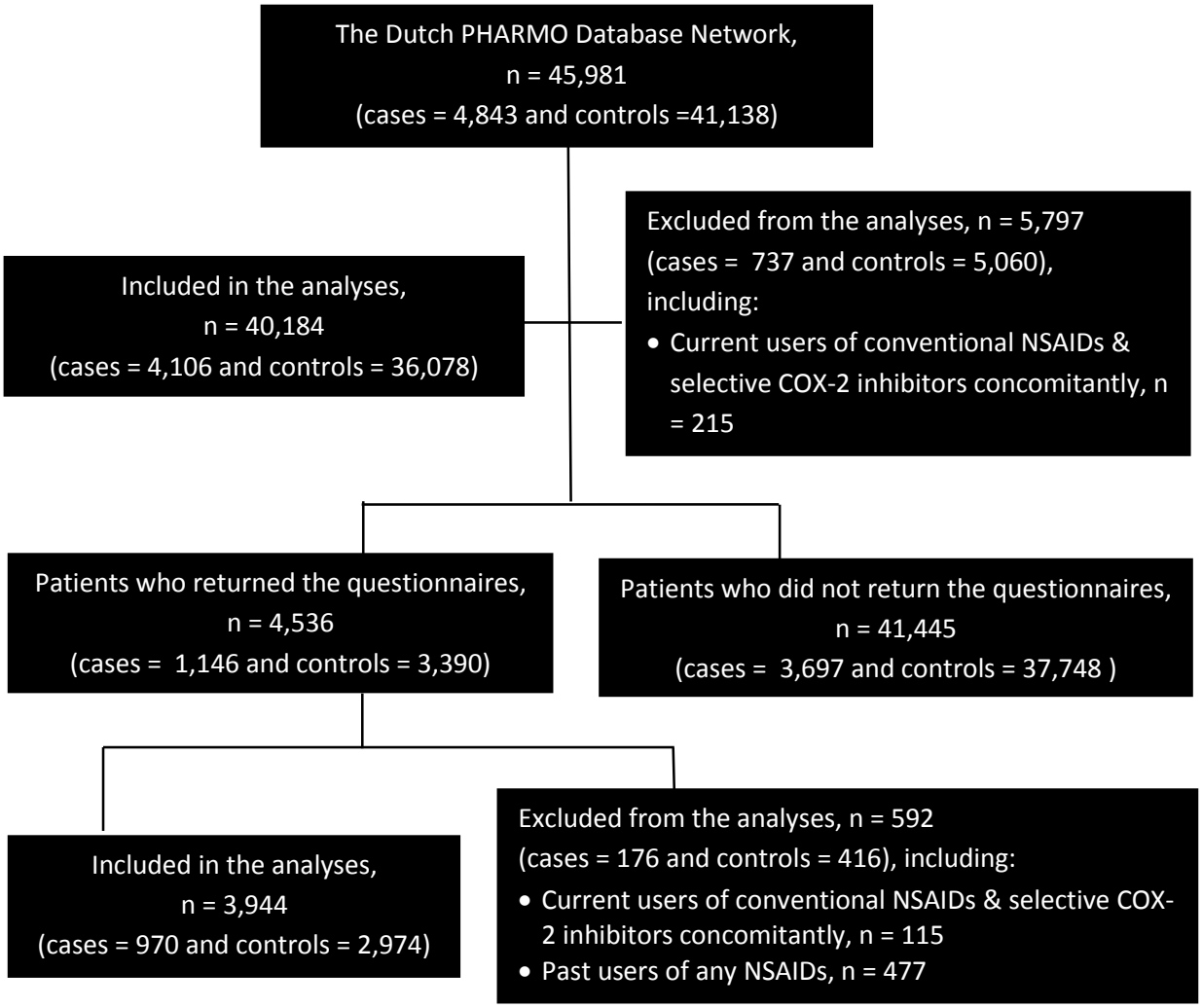

Fig 1. Flowchart of study

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 (**Supplementary, Table S3**).

Table 1 Characteristics of the study population based on data sources

Variables	PHARMO database†			Patient's reports		
	Cases (n=4,106)	Controls (n=36,078)	p-value	Cases (n=970)	Controls (n=2,974)	p-value
Age, mean (year ± sd)	66.58 ± 11.72	66.00 ± 11.39	0.002*	63.65 ± 10.30	63.31 ± 9.28	0.341
Male, n (%)	2,720 (66.2)	22,665 (62.8)	0.000*	723 (74.5)	2,211 (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	1,061 (25.8)	11,609 (32.2)	0.000*	113 (11.6)	476 (16.0)	0.001*
Beta blockers	1,611 (39.2)	14,547 (40.3)	0.179	339 (34.9)	990 (33.3)	0.342
Calcium channel blockers	982 (23.9)	6,906 (19.1)	0.000*	215 (22.2)	637 (21.4)	0.624
ACE inhibitors	813 (19.8)	9,211 (25.5)	0.000*	190 (19.6)	718 (24.1)	0.003*
ATII receptor antagonists	300 (7.3)	3,394 (9.4)	0.000*	104 (10.7)	404 (13.6)	0.021*
Cholesterol lowering drugs	917 (22.3)	9.436 (26.2)	0.000*	298 (30.7)	727 (24.4)	0.000*
Vitamin K antagonists	242 (5.9)	2,436 (6.8)	0.037*	137 (14.1)	320 (10.8)	0.004*
Platelet aggregation inhibitors	1,228 (29.9)	9,503 (26.3)	0.000*	244 (25.2)	475 (16.0)	0.000*
Anti-diabetic agents, n (%)						
Insulin	572 (13.9)	4,359 (12.1)	0.001*	86 (8.9)	178 (6.0)	0.002*
Oral anti-diabetic agents	423 (10.3)	3,384 (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)	1,151 (38.7)	
Nonsmoker	-	-		437 (45.1)	1,361 (45.8)	
Unknown	-	-		44 (4.5)	144 (4.8)	
Exercise level (hours per week), n (%)						
>4	-	-	-	411 (42.4)	1,308 (44.0)	0.357
≤4	-	-		450 (46.4)	1,362 (45.8)	
No-exercise	-	-		97 (10.0)	256 (8.6)	
Unknown	-	-		12 (1.2)	48 (1.6)	

Table 1 (continued)

Alcohol use (glass per day), n (%)						
>2	-	-	-	62 (6.4)	252 (8.5)	0.173
1-2	-	-		258 (26.6)	743 (25.0)	
<1	-	-		349 (36.0)	1,100 (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*	1,164 (28.3)	5,159 (14.3)	0.000*
Stroke	50 (5.2)	162 (5.4)	0.726	308 (7.5)	1,986 (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)	
Stroke, n (%)						
Yes	-	-	-	317 (32.7)	935 (31.4)	0.455
Unknown	-	-		33 (3.4)	98 (3.3)	

Abbreviations: ACE = Angiotensin Converting Enzyme; ATII = Angiotensin II antagonist ; COX = Cyclooxygenase; NSAIDs = Non-steroidal Anti-inflammatory Drugs

[†]patients in pharmacy records regardless of the completion of questionnaires,

*statistically significant ($p<0.05$)

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 nonuse 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 nonuse **(Table 2)**.

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 = 4,106)	Controls (n = 36,078)	Crude OR (95% CI)	Adj. OR[1] (95% CI)	Adj. OR[2] (95% CI)
Nonuse, n (%)	3,327 (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)	6,180 (17.1)	1.00 (0.92-1.09)	0.98 (0.90-1.07)	0.98 (0.94-1.03)

Abbreviations: Adj. = Adjusted; CI= confidence interval; COX = Cyclooxygenase; NSAIDs=Non-Steroidal Anti-Inflammatory Drugs; OR=Odds ratio

[1]Adjusted for age, sex, the index-date, co-medications, and a history of cardiovascular diseases routinely collected in pharmacy records, [2]Adjusted for [1] plus body mass index, lifestyles and familial history of cardiovascular diseases collected from patient's reports

*statistically significant ($p<0.05$)

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 nonuse 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)**.

Risks of AMI and the impact of additional confounding control for variables stratified based on age and sex

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 nonuse for adults, but a similar risk for the elderly. Selective COX-2 inhibitors were also associated with a higher risk compared to nonuse 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 **(Table 4** and **5).**

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

Exposures from pharmacy records	**Cases (n = 970)**	**Controls (n = 2,974)**	**Crude OR (95% CI)**	**Adj. OR[1] (95% CI)**	**Adj. OR[2] (95% CI)**	**Adj. OR[3] (95% CI)**
Nonuse, n (%)	821 (84.6)	2,432 (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	**Cases (n = 970)**	**Controls (n = 2,974)**	**Crude OR (95% CI)**	**Adj. OR[1] (95% CI)**	**Adj. OR[2] (95% CI)**	**Adj. OR[3] (95% CI)**
Nonuse, n (%)	774 (79.8)	2,336 (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)

Abbreviations: Adj. = Adjusted; CI= confidence interval; COX = Cyclooxygenase; NSAIDs=Non-Steroidal Anti-Inflammatory Drugs; OR=Odds ratio

[1]Adjusted for age, sex, the index-date, co-medications, and a history of cardiovascular diseases routinely collected in pharmacy records, [2]Adjusted for [1] plus body mass index, lifestyles and familial history of cardiovascular diseases collected from patient's reports, [3]Adjusted for [2] 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[1] (95% CI)	Adj. SI[1] (95% CI)	Adj. OR[2] (95% CI)	Adj. SI[2] (95% CI)
18-64 years old								
Nonuse, n (%)	1,379 (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)	
				1.29 (0.76-2.19)		1.32 (0.77-2.25)		1.16 (0.74-1.81)
≥65 years old								
Nonuse, n (%)	1,948 (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 years old								
Nonuse, n (%)	1,379 (81.6)	12,302 (79.9)	1		1		1	
Conventional NSAIDs, n (%)	288 (17.1)	2,912 (18.9)	0.88 (0.77-1.01)		0.86 (0.75-0.99)*		0.86 (0.75-0.99)*	
				1.26 (1.06-1.50)*		1.26 (1.06-1.50)*		0.86 (0.75-0.98)*
≥65 years old								
Nonuse, n (%)	1,948 (80.6)	17,084 (82.6)	1		1		1	
Conventional NSAIDs, n (%)	413 (17.1)	3,268 (15.8)	1.11 (0.99-1.24)		1.08 (0.96-1.21)		1.08 (0.96-1.21)	

Abbreviations: Adj. = Adjusted; CI= confidence interval; COX = Cyclooxygenase; NSAIDs=Non-Steroidal Anti-Inflammatory Drugs; OR=Odds ratio; SI=synergy index

[1]Adjusted for sex, index-date, co-medications, lifestyle factors, and a history of cardiovascular diseases routinely collected in pharmacy records, [2] Adjusted for [1] plus body mass index, lifestyles and familial history of cardiovascular diseases collected from patient's reports

*statistically significant ($p<0.05$)

Table 5 Odds ratios for acute myocardial infarction among total participants regardless of 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[1] (95% CI)	Adj. SI[1] (95% CI)	Adj. OR[2] (95% CI)	Adj. SI[2] (95% CI)
Female								
Nonuse, n (%)	1,063 (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)*	
				0.63 (0.38-1.02)		0.65 (0.40-1.06)		0.65 (0.39-1.06)
Male								
Nonuse, n (%)	2,264 (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								
Nonuse, n (%)	1,063 (76.7)	10,648 (79.4)	1		1		1	
Conventional NSAIDs, n (%)	278 (20.1)	2,505 (18.7)	1.12 (0.97-1.28)		1.06 (0.92-1.22)		1.06 (0.92-1.22)	
				0.86 (0.72-1.02)		0.88 (0.73-1.05)		0.88 (0.73-1.05)
Male								
Nonuse, n (%)	2,264 (83.2)	18,738 (82.7)	1		1		1	
Conventional NSAIDs, n (%)	423 (15.6)	3,675 (16.2)	0.95 (0.85-1.06)		0.93 (0.83-1.04)		0.93 (0.83-1.04)	

Abbreviations; Adj. = Adjusted; CI = Confidence Interval; COX = Cyclooxygenase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds Ratio; SI = Synergy Index

[1]Adjusted for age, index-date, co-medications, lifestyle factors, and a history of cardiovascular diseases routinely collected in pharmacy records, [2]Adjusted for [1] 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 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 3 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 is 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, the information is unlikely valid (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 is not recommended as a single instrument to collect information (23, 26).

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 hypercholesterolemia or those who had died because of complication from first AMI. Hence, extrapolation of our findings to patients with first AMI without hypertension and/or hypercholesterolemia 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).

CONCLUSION

Additional adjustment for potential confounders collected from patient's reports and complementing the 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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SUPPLEMENTARY

Supplementary 1. Questionnaire (translated to English from Dutch)

QUESTIONNAIRE

This research is made possible by

Remarks:

To fill out the list, you usually need only tick the box for your reply. Sometimes there are lines which you can write your answer. Most of the questions relate only to your medical history 1-2 months before a specific date. This date is for you “INDEXDT”.

General Questions

1. What is your date of birth? …. - …. – 19.. (dd-mm-yyyy)
2. What is your sex?
    - Man
    - Woman
3. How tall are you (in centimeter)? ….cm
4. How much do you weight (in kilograms)? ….kg

   How much you do you weighted on ”INDEXDT”? ….kg
5. What is your nationality?
    - Dutch
    - Non-Dutch, namely ….
6. To what race do you belong to?
    - White
    - Black
    - Asia
    - Other, namely …..

To what race does your father belong to?

- White
- Black
- Asia
- Other, namely …..

To what race does your mother belong to?

- White
- Black
- Asia
- Other, namely …..

Heart and Vascular diseases

7. Have you ever had any complaints of the heart under the care of your doctor or specialist?
    - Yes
    - No

   If yes, what symptoms of diseases? …..

   And from when? ….-19../….-20.. (mm/yyyy)
8. Have you ever had a heart attack?
    - Yes
    - No

   If yes, in which year? At about 19../20..

9. Have you ever had a stroke (cerebral hemorrhage, stroke, hemiplegia)?
    - Yes
    - No

   If yes, in which year? At about 19../20..
10. Has your father ever had a heart attack?
    - Yes
    - No

   If yes, how old was your father when it occurred? My father was about …. years old.
11. Has your mother ever had a heart attack?
    - Yes
    - No

   If yes, how old was your mother when it occurred? My mother was about …. years old.
12. Has your father ever had a stroke?
    - Yes
    - No

   If yes, how old was your father when it occurred? My father was about …. years old.
13. Has your mother ever had a stroke?
    - Yes
    - No

   If yes, how old was your mother when it occurred? My mother was about …. years old.

Hypertension

14. Have you ever been diagnosed to have a high blood pressure by a doctor?
    - Yes
    - No (go to question 17)

   If yes, when was the first time? Approximately in the year 19../20..
15. Did you use a diet for high blood pressure at the ”INDEXDT”?
    - Yes
    - No

   If yes, what diet?....
16. Did you use anti-hypertensive drugs at the ”INDEXDT”?
    - Yes
    - No

   If yes, since when? Since 19../20..

If yes, what drugs you use at the ”INDEXDT”?

1. …..
2. …..
3. I don’t remember

Cholesterol

17. Have you ever been diagnosed to have high blood cholesterol by a doctor?
    - Yes
    - No (go to question 20)

    If yes, when was the first time? Approximately in the year 19../20..

18. Did you use a diet for high blood cholesterol at the ”INDEXDT”?
    - Yes
    - No

    If yes, what diet?....

19. Did you use cholesterol-lowering drugs at the ”INDEXDT”?
    - Yes
    - No

    If yes, since when? Since 19../20..

    If yes, what drugs you use at the ”INDEXDT”?

    1. …..
    2. …..
    3. I don’t remember

Diabetes

20. Do you have diabetes?
    - Yes
    - No (go to question 22)

    If yes, from what age do you have? From my first year ….

21. Did you use this at the ”INDEXDT”?
    - Diet
    - Drugs

    If yes, what one?....

    1. …..
    2. …..
    - Injection

If yes, what one?....

1. …..
2. …..
   - Nothing

Other diseases

22. Have you ever been diagnosed with these diseases by a doctor? (cross out what is not applicable)
    - Asthma: Yes/No
    - Bronchitis: Yes/No
    - Emphysema: Yes/No
    - Cancer: Yes/No

Other medications

23. Did you use other medications at the ”INDEXDT”?
    - Yes
    - No (go to question 22)

If yes, which one?

1. …..
2. …..
3. I don’t remember

Smoking

24. Do you smoke cigarettes at the ”INDEXDT”?
    - Yes, I smoked an average one or more cigarette per month (go to question 26)
    - Yes, but I smoked less than one cigarette per month (go to question 28)
    - No, I smoked before the ”INDEXDT”, but I don’t smoke cigarettes anymore (go to question 25)
    - No, I have never smoked (go to question 32)
25. How many cigarettes did you smoke on average per day before the ”INDEXDT”? (1 pack of tobacco, 40 cigarettes)
    - I smoked on average …. cigarettes/day
    - I smoked occasionally, but less than 1 cigarette/day

Go to question 27

26. How many cigarettes did you smoke on average per day at the ”INDEXDT”? (1 pack of tobacco, 40 cigarettes)
    - I smoked on average …. cigarettes/day
    - I smoked occasionally, but less than 1 cigarette/day
27. Do you smoke cigarette mostly with or without the filter before or at the ”INDEXDT”?
    - With filter
    - Without filter

28. At what age did you begin to smoke cigarettes? ….year
29. Do you sometimes stop smoking in the period between you started to smoke cigarettes and the ”INDEXDT”?
    - Yes, in total I don’t smoke for …. Years
    - No
30. Do you smoke cigarettes or to use pipe before or at the ”INDEXDT”?
    - Yes
    - No
31. If you have stopped smoking at the ”INDEXDT”, how old were you when you stopped? ….years old.
32. How many hours per day on average are you in a smoky room to the ”INDEXDT”? ….hours/day.

Alcohol

33. Do you drink alcohol to the ”INDEXDT”?
    - No, never
    - No, I have stopped before the ”INDEXDT”
    - Occasionally, but less than 1 glass/week
    - Yes, I drink: (multiple answers is possible)
        i. Beer : …. glasses/week
        ii. Wine : …. glasses/week
        iii. Sherry, port, vermouth, advocaat, bessenjenever, etc. : …. glasses/week
        iv. Strong alcohol (wine brandy, jenever, liquor, whiskey, etc.) : …. glasses/week

Physical Activity

34. With regards to exercise, which group you share your work to the ”INDEXDT”?
    - Mainly sitting
    - Sitting, standing, sometimes running
    - Ongoing with physical stress
    - Hard physical work
    - Not applicable
35. Which group do you share your activity in your free time to the ”INDEXDT” with regards to exercise?
    - Little exercise
    - Exercise for at least 4 hours per week
    - Regular exercise
    - Regular heavy exercise

36. How often are you sweaty and/or out of breath during exercise before the ”INDEXDT”?
    - Never
    - ….times

Questions 37-39 are intended for female participants

37. How old were you when you had first menstruation? ….years old
38. How was your period before the ”INDEXDT”?
    - Regularly
    - Irregularly
    - Not applicable due to pregnancy
    - Not applicable due to menopause: age at menopause ceased ….years old
    - Not applicable due to surgery
39. Do you have children
    - Yes
    - No

    If yes, how many children do you have? I have …. children

    How old were you when your first child was born? When I was ….years old

Do you want to see the list again to go through if you have answered all the questions?

You can return this questionnaire and consent form (signed) in the enclosed reply envelope (no stamp required)

THANK YOU FOR YOUR COOPERATION

Approval after information

Signed:…….. (name), born:…….. (birth date)

Authorized the lead investigator from Utrecht University and Erasmus University Rotterdam:

- To examine the cellular material that was sent to hereditary characteristics that may determine the reactions of people on antihypertensive drugs
    - Yes
    - No
- To request further information from the general practitioners for this study
    - Yes
    - No

  Is yes, the name and address of my doctor are

  …….
- To keep the material that was sent for future research on genetic characteristics and the reaction of people on drugs, i.e., heart and vascular diseases
    - Yes
    - No
- To be contacted for a possible follow-up study in the future
    - Yes
    - No
- I declare to be fully informed about the purpose of the investigation
- I voluntarily participate in this study
- I am aware that it is not possible to request personal results
- I am aware that my doctor pharmacist will inform my participation in the study
- I may withdraw myself from the study at any time

……., ……..

Signature Date

Would you please that you have answered all the questions?

Table S2 Statistical models used and potential confounders adjusted for in each analysis

Participants	Data sources for NSAID use	Statistical models	Potential confounders for adjustment		
			1	2	3
Total population from pharmacy records regardless of the completion of the questionnaires	Pharmacy records	Unconditional logistic regression	Age, sex, the index-date, co-medications, and a history of CV diseases[†]	Age, sex, the index-date, co-medications, co-medications, a history of CV diseases[†]	
				plus BMI, lifestyle factors (smoking status, exercise level, and alcohol use), and familial history of CV diseases[‡]	
Restricted to patients from pharmacy records who returned the questionnaires	Pharmacy records	Unconditional logistic regression	Age, sex, the index-date, co-medications, a history of CV diseases[†]	Age, sex, the index-date, co-medications, a history of CV diseases[†]	Age, sex, the index date[†]
					co-medications, a history of CV diseases[§]
				plus BMI, lifestyle factors (smoking status, exercise level, and alcohol use), and familial history of CV diseases[‡]	plus BMI, lifestyle (smoking status, exercise level, and alcohol use), and familial history of CV diseases[‡]
	Pharmacy records plus patient's reports	Unconditional logistic regression	Age, sex, the index-date, co-medications, a history of CV diseases[†]	Age, sex, the index-date, co-medications, a history of CV diseases[†]	Age, sex, the index date[†]
					co-medications, a history of CV diseases[§]
				plus BMI, lifestyle factors (smoking status, exercise level, and alcohol use), and familial history of CV diseases[‡]	plus BMI, lifestyle (smoking status, exercise level, and alcohol use), and familial history of CV diseases[‡]

Abbreviations: BMI = Body Mass Index; CV = cardiovascular; NSAIDs=Non-Steroidal Anti-Inflammatory Drugs

[†]information was collected from pharmacy records;

[‡]information was collected from patient's reports;

[§]information from pharmacy records was complemented with patient's reports

Table S3 Characteristics of the study population that returned the questionnaire according to data sources

Variable	PHARMO database[†]			Patient's reports		
	Cases (n=970)	Controls (n=2,974)	*p*-value	Cases (n=970)	Controls (n=2,974)	*p*-value
Age, mean (year ± sd)	63.65 ± 10.30	63.31 ± 9.28	0.341	63.65 ± 10.30	63.31 ± 9.28	0.341
Male, n (%)	723 (74.5)	2,211 (74.3)	0.905	723 (74.5)	2,211 (74.3)	0.905
Body Mass Index, n (%)	-	-	-	194 (20.0)	521 (17.5)	0.135
>30 (kg/m^2)	-	-		32 (3.3)	153 (5.1)	
Unknown						
Co-medications						
Cardiovascular drugs, n (%)						
Diuretics[**]	196 (20.2)	846 (28.4)	0.000*	113 (11.6)	476 (16.0)	0.001*
Beta blockers[**]	382 (39.4)	1,290 (43.4)	0.029*	339 (34.9)	990 (33.3)	0.342
Calcium channel blockers[**]	225 (23.2)	590 (19.8)	0.025*	215 (22.2)	637 (21.4)	0.624
ACE inhibitors[**]	191 (19.7)	867 (29.2)	0.000*	190 (19.6)	718 (24.1)	0.003*
ATII receptor antagonists[**]	78 (8.0)	317 (10.7)	0.018*	104 (10.7)	404 (13.6)	0.021*
Cholesterol lowering drugs[**]	247 (25.5)	960 (32.3)	0.000*	298 (30.7)	727 (24.4)	0.000*
Vitamin K antagonists[**]	47 (4.8)	165 (5.5)	0.399	137 (14.1)	320 (10.8)	0.004*
Platelet aggregation inhibitors[**]	286 (29.5)	810 (27.2)	0.175	244 (25.2)	475 (16.0)	0.000*
Anti-diabetic agents, n (%)						
Insulin	85 (8.8)	306 (10.3)	0.167	86 (8.9)	178 (6.0)	0.002*
Oral anti-diabetic agents[**]	45 (4.6)	172 (5.8)	0.175	77 (7.9)	249 (8.4)	0.670
Lifestyle factors						
Smoking status, n (%)						
Current smokers	-	-	-	131 (13.5)	318 (10.7)	0.056
Past smokers	-	-		358 (36.9)	1,151 (38.7)	
Nonsmoker	-	-		437 (45.1)	1,361 (45.8)	
Unknown	-	-		44 (4.5)	144 (4.8)	

Table S3 (continued)

Exercise level (hours per week), n (%)						
>4	-	-	-	411 (42.4)	1,308 (44.0)	0.357
≤4	-	-		450 (46.4)	1,362 (45.8)	
No-exercise	-	-		97 (10.0)	256 (8.6)	
Unknown	-	-		12 (1.2)	48 (1.6)	
Alcohol use (glass per day), n (%)						
>2	-	-	-	62 (6.4)	252 (8.5)	0.173
1-2	-	-		258 (26.6)	743 (25.0)	
≤1	-	-		349 (36.0)	1,100 (37.0)	
Non-drinker	-	-		121 (12.5)	358 (12.0)	
Unknown	-	-		180 (18.6)	521 (17.5)	
A history of cardiovascular diseases						
Coronary artery diseases (angina & myocardial infarction), n (%) **						
Yes	1,164 (28.3)	5,159 (14.3)	0.000*	831 (85.7)	462 (15.5)	0.000*
Unknown	-	-	-	9 (0.9)	41 (1.4)	
Stroke, n (%) **						
Yes	308 (7.5)	1,986 (5.5)	0.000*	295 (30.4)	304 (10.2)	0.000*
Unknown	-	-	-	10 (1.0)	35 (1.2)	

Table S3 (continued)

Familial history of cardiovascular diseases						
Myocardial infarction, n (%)						
Yes	-	-	-	321 (33.1)	902 (30.3)	0.110
Unknown	-	-		26 (2.7)	84 (2.8)	
Stroke, n (%)						
Yes	-	-	-	317 (32.7)	935 (31.4)	0.455
Unknown	-	-		33 (3.4)	98 (3.3)	

Abbreviations: ACE = Angiotensin Converting Enzyme; ATII = Angiotensin II antagonist ; COX = Cyclooxygenase; NSAIDs = Non-steroidal Anti-inflammatory Drugs

[†]restricted to patients in pharmacy records who returned the questionnaires

*statistically significant ($p<0.05$) between cases and controls

[**]statistically significant ($p<0.05$) between pharmacy records data on patients who returned the questionnaires and patient's reports data

CHAPTER 8

GENERAL DISCUSSION

SCOPE OF THESIS

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective and used extensively as anti-inflammatory and analgesic drugs. Cyclooxygenase (COX) enzymes that are expressed in many different organ tissues are inhibited by NSAIDs to varying degrees. Consequently, the production of chemical products mediated by these enzymes that are responsible for physiological properties is hampered and may cause various adverse drug reactions (ADRs) (1-5). Their ratio of inhibitory concentration towards COX-1 and COX-2 enzymes is often used to compare their biochemical selectivity (6). Most ADRs associated with NSAIDs are related to their relative inhibition to COX-1 and COX-2 enzymes and to specific chemical structures (7, 8).

Therefore, this thesis aims to assess the adverse outcomes of NSAID use in various human body systems, i.e., cardiovascular (CV), renal, gastrointestinal (GI), immune, and musculoskeletal systems, and to investigate the impact of COX selectivity and chemical structure on the occurrence of these ADRs. We performed systematic observational studies using several electronic health care databases. In this chapter, we discuss these associations from a clinical perspective and address methodological issues related to these studies. Strengths and limitations of observational studies using electronic health care databases, potential clinical implications of the findings, and suggestions for future research are also presented.

MAIN FINDINGS

Adverse drug reactions in the cardiovascular and renal systems

Selective COX-2 inhibitors nor conventional NSAIDs were associated with an increased risk of ventricular tachycardia/ventricular fibrillation-documented out-of-hospital cardiac arrest (VT/VF-OHCA) compared to non-use (**Chapter 2**). Stratification of VT/VF-OHCA cases based on the occurrence of acute myocardial infarction (AMI) as a cause of VT/VF-OHCA yielded similar results. An increased risk of AMI was found for users of selective COX-2 inhibitors, but not for conventional NSAIDs compared to non-users

among patients who were dispensed anti-hypertensive drugs and/or had hypercholesterolemia (**Chapter 7**).

Current use for 2-4 weeks and >4 weeks of conventional NSAIDs was associated with a higher relative risk of a diagnosis of nephrotic syndrome (NS) by 34% and 42%, respectively compared to non-use (**Chapter 3**). This increased relative risk remained after discontinuation of conventional NSAID exposure between 1 month–2 years before the date of NS diagnosis by 24-55%. This increased risk appeared to be mainly attributable to the acetic acid derivative (AAD) and propionic acid derivative (PAD) groups. After 2 years of discontinuation, this increased risk disappeared. Even though not statistically significant, past use of selective COX-2 inhibitors (>2 months-2 years) was associated with a higher risk (OR 1.24 (0.98-1.58)) compared to non-use. In contrast, current and past use (>2 years) were associated with a lower risk compared to non-use. The number of cases for recent use was too small to evaluate this association.

Adverse drug reactions in the gastrointestinal system

Compared to conventional NSAIDs alone, selective COX-2 inhibitors combined with proton pump inhibitors (PPIs) were associated with a 49% lower relative risk of perforation, ulcers, and bleeding (PUB) in the gastrointestinal tract, followed by selective COX-2 inhibitors alone (34% lower relative risk), and conventional NSAIDs with PPIs (21% lower relative risk) (**Chapter 4**). The risk of PUB for either conventional NSAIDs combined with PPIs or selective COX-2 inhibitors combined with PPIs was not statistically different compared to selective COX-2 inhibitors alone.

Adverse drug reactions in the immune system

Conventional NSAIDs with poor COX enzyme selectivity were associated with the highest reporting odds ratio (ROR) of hypersensitivity reactions (HSRs), including urticaria, angioedema, anaphylactic shock, anaphylactic reactions, anaphylactoid shock, and anaphylactoid reactions (ROR 2.12) compared to coxibs during the first 5 years after marketing authorization (**Chapter 5**). According to their chemical groups, NSAIDs belonging to the group of AADs (such as indomethacin and diclofenac), fenamates (such as

mefenamic acid and flufenamic acid), and PADs (such as ibuprofen and naproxen) were associated with higher RORs (3.07, 2.21, and 1.93, respectively) compared to coxibs. Finally, NSAIDs containing a sulfonamide functional group were associated with a higher reporting (ROR 1.38) compared to NSAIDs without a sulfonamide functional group.

Adverse drug reactions in the musculoskeletal system

Both conventional NSAIDs and selective COX-2 inhibitors were associated with a higher risk of revision surgery of lower joint replacements (LJRs) (**Chapter 6**). Compared to non-use, current use for <1 month, 3-6 months, 6-12 months, and >12 months, recent use, and past use of conventional NSAIDs were associated with higher risk of revision (adj. HR 2.48 (95%CI; 2.07-2.96), 1.51 (1.16-1.96), 1.67 (1.27-2.20), 2.08 (1.69-2.56), 1.38 (1.19-1.62), and 1.20 (1.10-1.31), respectively). Compared to non-use, current use for <1 month, 1-3 month(s), 3-6 months, and >12 months, recent use, and past use of selective COX-2 inhibitors were also associated with higher risk (adj. HR 2.85 (1.87-4.34), 1.17 (0.69-1.98), 1.20 (0.62-2.32), 2.07 (1.29-3.30), 1.98 (1.41-2.77), 1.10 (0.91-1.33), respectively). In contrast, current use for 1-3 month(s) of conventional NSAIDs or for 6-12 months for selective COX-2 inhibitors was associated a with similar risk compared to non-use.

All studies on the adverse drug reactions

Our studies demonstrated that depending on their COX selectivity, NSAIDs were associated with an increased risk of NS, TJRs, HSRs, and AMI, but not of VT/VF-OHCA. A combination of selective COX-2 inhibitors with PPIs had the lowest risk of PUB in the GI tract. Apparently, all these adverse events are influenced by chemical groups of NSAIDs. The potential adverse events of NSAID use in various human body systems that were obtained from our study are summarized in **Table 8.1.**

Table 8.1 Summary of possible adverse events of non-steroidal anti-inflammatory drugs in various human body systems

Non-steroidal Anti-inflammatory Drugs	Adverse events					
	Cardiovascular System		Renal System	Gastrointestinal System	Immune System	Musculoskeletal System
	VT-VF/ OHCA	Acute myocardial infarction	Nephrotic syndrome	Perforation, ulcers, bleeding	Hypersensitivity reactions	Revision LJR surgery
Non-NSAID use	Ref.	Ref.	Ref.			Ref.
Inhibitory potency towards COX enzymes						
Conventional NSAIDs alone	=	=	+	Ref.		+
+ PPIs				-		
Selective COX-2 inhibitors alone	=	+	=	--		+
+ PPIs				---		
Ratios of inhibitory concentration 80% (IC_{80}) against COX-2 and COX-1 enzymes						
Coxibs (selective COX-2 inhibitors)					Ref.	
NSAIDs with poor COX selectivity					++	
Non-coxib NSAIDs with COX-2 preference					+	
NSAIDs with unknown COX inhibitory potency					NA	
Chemical Groups based on ATC Classification System						
Coxibs (selective COX-2 inhibitors)			=		Ref.	
Acetic acid derivatives			+		++++	
Propionic acid derivatives			+		++	
Fenamates			=		+++	
Oxicams					+	
Other NSAIDs					-	
Butylphyrazolidine			NA		=	

Table 8.1 (continued)

Sulfonamide functional group						
Absence					Ref.	
Presence					+	

Abbreviations: ATC = Anatomical Therapeutic Chemical; COX = Cyclooxygenase; IC = Inhibitory Concentration; LJR = Lower Joint Replacement; NA = Not Applicable; NSAIDs= Non-Steroidal Anti-Inflammatory Drugs; PPIs = Proton-Pump Inhibitors; Ref. = Reference Group; VT/VF-OHCA = Ventricular Tachycardia/Ventricular Fibrillation-Out of Hospital Cardiac Arrest

= = similar risk

+ = high risk

- = low risk

The quantity of (+) or (-) indicates the rank

NEW INSIGHTS INTO SAFETY of NSAIDs

Many studies have shown that NSAIDs are associated with many adverse events in various human body systems. Most adverse events associated with NSAID are found in the GI system. These drugs, especially conventional NSAIDs increase the relative risk of dyspepsia on average by about 36% compared to non-users (9). In the cardio-renal system, NSAIDs, particularly selective COX-2 inhibitors also increase thrombotic risks such as AMI and stroke (1, 2). Likewise, they increase blood pressure and stimulate atrial fibrillation and congestive heart failure. NSAID use could also lead to either acute or chronic renal failure. Many forms of renal failure/effects have been identified such as renal papillary necrosis, acute interstitial nephritis, hyperkalemia, and sodium and water retention (3, 10, 11). After antibiotics, NSAIDs are the major causes of drug-induced HSRs including urticaria, angioedema, and anaphylaxis (12, 13). However, limited evidence is available that shows a potential association between NSAID use and bone healing. NSAIDs have shown to be associated with an increased risk of non-union following a fracture (14) and the prevention of bone formation in acetabular fractures (15).

To the best of our knowledge, our studies on the risk of VT/VF-OHCA and NS for NSAIDs were the first systematic observational studies that quantified these risks. Previous case series and case reports indicated that conventional NSAIDs might increase NS risk. In those studies, the duration of use varied from <1 week until years prior to the occurrence of NS (16-23). Furthermore, a diagnosis of NS might still occur up to 6 months after discontinuation of any NSAIDs (21). The groups of AADs and PADs, as well as oxicams, were frequently linked to NS as reported in many case reports (16, 18, 19, 23-27).

Our findings demonstrated that both selective COX-2 inhibitors and conventional NSAIDs were not associated with an increased risk of VT/VF-OHCA. However, selective COX-2 inhibitors were associated with a higher risk of AMI. Even though a previous study also demonstrated that selective COX-2 inhibitors were not associated with an increased risk of OHCA, the risk increased during conventional NSAID use. Some factors might explain these differences, such as study design, the way of adjustment for confounders, the definition of VT/VF-OHCA, and physician's attitude towards the prescription of NSAIDs (28-31). In our case-control study, OHCA cases were defined according to the presence of VT/VF on electrocardiography

recordings and confounders were adjusted for by standard multivariable regression. Our study was unlikely to be affected by the physician's prescribing behavior towards rofecoxib since our observation time started after rofecoxib was withdrawn from the market. Two systematic reviews and meta-analysis of clinical trials also showed that selective COX-2 inhibitors were associated with an increased risk of CV adverse events including AMI compared to placebo. A systematic review of observational studies also showed that selective COX-2 inhibitors were associated with an increased risk of CV events (32-35).

Traditionally, supplementing a gastroprotective agent has been considered as the gold standard to minimize GI risk for high-risk patients taking NSAIDs (36). Indeed, there have been many studies assessing different strategies to minimize this risk, but all these studies were conducted separately. We assessed different GI protective strategies for NSAID use in one study. The use of selective COX-2 inhibitors with PPIs, selective COX-2 inhibitors alone, or conventional NSAIDs with PPIs were associated with a lower risk of GI toxicities compared to conventional NSAIDs alone (37-41). A previous study also showed that the risk of upper GI adverse events for conventional NSAIDs with PPIs was comparable to selective COX-2 inhibitors alone (42). Likewise, previous clinical trials indicated that the risks of GI ulcers for selective COX-2 inhibitors combined with PPIs were lower compared to selective COX-2 inhibitors alone (43, 44).

Even though many studies have investigated the association between NSAIDs and HSR risk, our study differed in design and data source aspects. We applied a case/non-case study to detect a signal for HSRs for NSAIDs containing a sulfonamide functional group. Other than the Anatomical Chemical Therapeutic Classification system, we defined NSAIDs based on the presence/absence of a sulfonamide functional group and the ratio of inhibitory concentration 80% against COX-2 and COX-1 enzymes. Findings from previous studies that separately assessed this association were in line with our findings on the increased HSR risk for NSAIDs. Previous studies showed that conventional NSAIDs were associated with a higher risk of hospitalization for angioedema compared to selective COX-2 inhibitors (coxibs) (45). A sulfonamide NSAID, celecoxib also had a higher risk of urticaria compared to a non-sulfonamide NSAID (rofecoxib), although both drugs belong to the coxib group (8). Likewise, zomepirac (AAD group) was associated with a higher risk of allergy and anaphylaxis compared to any other individual NSAIDs (46, 47).

A higher proportion of a revision risk of prosthetic fixation for total hip arthroplasty was shown in the ibuprofen group compared to the placebo group as demonstrated in a clinical trial (48). A case-control study also indicated that the risk of early revision of total hip replacement increased for NSAIDs compared to non-use (49). Furthermore, aseptic loosening as the primary indication for the revision surgery (30) was found high for NSAID users undergoing a fixation surgery of humeral diaphyseal fracture. Another observational study showed that NSAIDs were associated with an increased risk of aseptic non-union after surgical fixation of this fracture (50).

METHODOLOGICAL ISSUES IN OBSERVATIONAL STUDIES

During the past decades, electronic health care databases have become an important source for pharmacoepidemiologic research on the assessment of drug safety profiles. The observational studies in this thesis utilize data from various population-based databases including the Dutch PHARMO Database Network (**Chapter 2, 4,** and **7**), the Utrecht Cardiovascular Pharmacogenetics (UCP) registry **(Chapter 7),** and the AmsteRdam REsuscitation STudy (ARREST) registry from the Netherlands **(Chapter 2)**, and the Clinical Practice Research Datalink (CPRD) from the United Kingdom (UK) **(Chapter 3** and **6).**

For our study in **Chapter 5,** we used VigiBase, a spontaneous report database for ADRs. This WHO individual case safety report database contains spontaneous reports of ADRs reported from pharmacovigilance centers of >150 member countries of the WHO Program for the International Drug Monitoring representing >90% of the global population. Each country submits ADR reports from their respective national ADR reporting systems (51-55).

Conducting pharmacoepidemiologic studies using routine electronic health care databases has advantages. **First,** recall bias is unlikely to occur. Since data is routinely and prospectively collected in a standardized way, information is more likely to be accurate and not susceptible to patient's recall ability. The data are recorded independently to research questions limiting the chance of differential misclassification of exposure, potential confounders, and outcomes. If the information on morbidities is not

available, medication use might be applied as a proxy. Patients that are followed for long periods allows studying rare events and long-term effects (56). **Second,** the validity of diagnoses and completeness of data are high. For instance, the diagnosis of AMI in the Dutch PHARMO Database Network has a high sensitivity, and positive predictive value (57-60) and clinical information in the CPRD is valid for many clinical research questions (61). In the ARREST registry, VT/VF events are determined by electrocardiography recordings from automated external defibrillators or ambulance monitors with the involvement of emergency medical services (62). **Finally,** a crucial benefit of employing population-based health care databases is external validity. The findings in the databases often are representative of the population in general and include many relevant patient subgroups that can be investigated. Obviously, this depends on applied in- and exclusion criteria (56, 59, 63).

Nonetheless, several limitations in performing observational studies should be cautiously considered to assess the validity of findings. **The first** potential problem is information bias due to misclassification of exposure, outcomes, and confounders. If the information on drug use is collected from pharmacy dispensing records (such as the Dutch PHARMO Database Network) or GP prescribing data (such as the CPRD), the actual drug use (medication adherence) is unknown (**Chapter 2-4** and **6**). It is sometimes unknown whether drugs are prescribed for as needed or for regular use. This is, for instance, the case for NSAID use. When drugs are considered to be used regularly while in reality, the use it as needed, drug exposure will be overestimated. Information on over-the-counter (OTC) medication use is missing in most pharmacoepidemiological databases since they are based on prescribing or dispensing information leading to misclassification of exposure (**Chapter 2-4,** and **6**). However, the estimated risks of specific adverse events associated with NSAID use are unlikely to be hampered if NSAID prescriptions are reimbursed (64). Time-related bias might occur for specific outcomes when the diagnoses for an administrative purpose are entered later in the database than the date when the diagnoses were made. Also, for several conditions such as NS diagnosis, there might be a patient delay to visit a physician after the start of the first symptoms of the syndrome (e.g., edema). In **Chapter 3** and **6**, the delay in establishing the diagnosis of NS or revision LJR surgery might inadvertently misclassify NSAID exposure in relation to the new occurrence of NS or aseptic loosening preceding the revision surgery. To test the robustness of our findings, we evaluated

either more loose or strict inclusion or exclusion criteria on study populations (**Chapter 3** and **5)** and used different time windows in defining the exposure or in the date of diagnosis **(Chapter 3, 4,** and **6)**.

The second potential problem is selection bias. In **Chapter 7,** this bias might occur, because, among the total population, cases are more likely to participate in the study than controls by returning the questionnaire. Indeed, we found discrepancies in characteristics between the total population and responders with regards to age, sex, and baseline risks of AMI, including the proportion of the exposure. Characteristics of responders were also different from non-responders as shown in our previous study. Females were less likely to participate, as well as the elderly (65). Selection bias is a major issue in studies using spontaneous reporting databases due to selective reporting. Therefore, the findings from these databases should be considered hypothesis generating (signal detection) needing further investigation (66).

The third potential problem is confounding. Some electronic health care databases (including the Dutch PHARMO Database Network, the ARREST registry, and the VigiBase) do not record several important risk factors for specific outcomes such as body mass index, lifestyle factors, genetic profile, and history of diseases. Even though several risk factors are available in some databases (the CPRD and the UCP registry), they are often incompletely recorded. These confounding factors might unevenly be distributed between comparison groups leading to different baseline risks. The internal validity in observational studies is threatened by these unmeasured and/or inadequately measured confounders. Ultimately, risk estimates might become less accurate.

To reduce the effect of unmeasured confounders, patient's reports might be utilized to collect information on potential risk factors that are not recorded in the databases (67). Interestingly, we found that obtaining additional information from the patient's reports by a questionnaire did not lead to different results (**Chapter 7)**. It might be an indication that either information collected from patient's report is inaccurately measured, or the measured confounders have a relatively minor impact, or are already adjusted for by proxy (captured by recorded information) (67). The first possible explanation is unlikely since our previous study showed that lifestyle factors collected from patient's reports were associated with an increased risk of AMI (68). Our results support earlier studies on the impact of lifestyle factors such as

smoking behavior and alcohol consumption on the association between drug use and specific adverse events. Several observational studies showed that the risk estimates of fracture for the use of drugs affecting the nervous system or the risk of joint revision for statin use were not changed when lifestyle factors were taken into account compared to when these factors were neglected (69-71). Employing questionnaires to collect information has several drawbacks. The reports are influenced by the timing of data collection and by the level of detail asked for. Often, patient's reports have a low concordance with other data sources, such as pharmacy records (56). Patients might conceal information because of social or medical values or if one comparison group recalls information more accurately than another group (56, 72). These discrepancies were also demonstrated in several previous studies (73-75).

Several methods such as matching (**Chapter 2-4,** and **7**), multivariable adjustment (**Chapter 2-6** and **7**), stratification (**Chapter 2-6,** and **7**), restriction (**Chapter 2-6** and **7**), or using an active comparator design (**Chapter 4** and **5**) were applied to reduce confounding bias in our studies. When comparing the effects of two or more active therapies under the assumption of equal effectiveness and safety profiles, the predictors of outcomes are less likely to be imbalanced or to cause confounding (56). Nevertheless, residual confounding due to unmeasured, unavailable, or unknown confounders might remain. For example, atopy is an independent predictor for hypersensitivity-associated outcomes such as NS and HSRs and could not be taken into account in the studies on this topic.

Finally, chance findings because of small sample sizes were often a limitation, especially for selective COX-2 inhibitors and individual chemical groups of NSAIDs, in either primary (**Chapter 2-4,** and **6**) or stratified analyses (**Chapter 2-4,** and **7**). These low sample sizes reduce the power to detect small significant associations.

POTENTIAL CLINICAL IMPLICATIONS, CONCLUSIONS & FUTURE STUDIES

Our findings may help physicians to make their therapeutic decision to minimize potential adverse events for those who need a NSAID. Physicians should be more sensitive to the increased risk of NS and HSRs for conventional NSAID use, particularly for the AAD and PAD groups. Even though our study showed that neither selective COX-2 inhibitors nor conventional NSAIDs increased the risks of VT/VF-OHCA, selective COX-2 inhibitors were still associated with a high risk of AMI.

Several guidelines have been established to minimize GI toxicity during NSAID use such as the standards of the Dutch General Practitioners Association (the Nederlands Huisartsen Genootschap), the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), and the American College of Gastroenterology for patients with low CV risk (76-78), but only <20% of patients received a preventive strategy (79). The level of GI risk can be considered to choose the proper gastroprotective strategy. When the risk increases, the sequence to implement a preventive strategy might be started with a conventional NSAID combined with a PPI, followed by a selective COX-2 inhibitor alone, and ultimately a selective COX-2 inhibitor combined with a PPI. Physicians should choose an individual NSAID in which the benefits outweigh the risks. A NSAID should be selected at the lowest effective dose for the shortest possible period that has the lowest risk of adverse events (80). Physicians also need to carefully identify patients with a pre-existing risk, such as older patients, previous joint replacements, an allergic history, and CV diseases. Awareness of potential adverse events is clearly important, both for physicians and pharmacists, when prescribing and dispensing NSAIDs to patients. They need to educate their patients about these potential adverse events. Given the findings on the increased adverse events of NSAIDs in our study, patients with pre-existing conditions should also be more careful to take NSAIDs as self-medication since several NSAIDs are available OTC.

Many adverse outcomes from NSAID use and their mechanism of actions have been studied. We demonstrated that in addition to the relative inhibitory potency of COX enzymes based on the IC_{80} and their chemical groups, the adverse event of HSRs for NSAID use is also influenced by the presence of a sulfonamide functional group. Even though many in vitro studies have elucidated the biological mechanism

of a sulfonamide functional group of antibiotics on HSRs, similar studies might be still needed for NSAIDs because the mechanism on the occurrence of HSRs caused by a sulfonamide functional group for antibiotic use seems to be different compared to NSAIDs (81). Furthermore, since our conclusion was derived from a spontaneous reporting database, to confirm and quantify this association, there is a need to study this association using routine electronic health care databases. Adjustment for lifestyle factors collected from patient's reports did not have a major impact on the association between NSAIDs and the risk of AMI. Nonetheless, it remains important to collect information on potential confounders as complete and accurate as possible. Finally, more studies are needed to evaluate the safety of OTC NSAIDs. Especially, because of the use of OTC NSAIDs in daily practice might be outside of the strict dose and duration of use instructions on the label. In many electronic databases, this information is not routinely recorded and in spontaneous reporting databases, prescribed and OTC NSAIDs are commonly not distinguished. Therefore, prospective studies are needed in which information on OTC NSAID use and adverse events are collected. One way to do that is to systematically record in spontaneous adverse event reporting systems whether the NSAID was on prescription or OTC. Also, by interviewing patients on OTC NSAID use and possible adverse events such information can become newly available. However, these approaches will be hampered by selective reporting and recall bias, respectively.

In conclusion, depending on their COX-2 selectivity, NSAID use increases the risk of NS, HSRs, LJRs, and AMI but not VT/VF-OHCA. Prolonged use of NSAIDs seems to escalate these potential increased risks. A combination of selective COX-2 inhibitors and PPIs has the lowest risk of PUB, followed by selective COX-2 inhibitors alone, and conventional NSAIDs with PPIs compared to conventional NSAIDs alone.

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APPENDICES

APPENDIX A

SUMMARY

APPENDIX A1

SUMMARY IN ENGLISH

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat condition with pain, inflammation, and/or fever. These drugs inhibit cyclooxygenase (COX) enzymes, i.e., COX-1 and COX-2. The COX-1 is responsible for physiological processes, and COX-2 is formed as a response towards external stimulations. The relative inhibitory potency towards COX enzymes and the chemical groups of NSAIDs, including the presence or absence of a sulfonamide functional group seem to contribute to the adverse events of these drugs that vary from mild to severe and life-threatening conditions. Even though many studies have been performed to investigate the adverse events of NSAID use, still much is unknown and need further investigation.

In **Chapter 2**, we evaluated the association between the use of COX-2 inhibitors or conventional NSAIDs and the risk of Ventricular Tachycardia/Ventricular Fibrillation (VT/VF-OHCA). The age- and sex-matched case-control study was performed by collecting information for VT/VF-OHCA cases from the AmsteRdam REsuscitation STudy (ARREST) registry data, an ongoing Dutch registry of resuscitation attempts and for the control group from the Dutch PHARMO Network Database, an ongoing registry of dispensing records of community pharmacies over the period 2005 to 2011. Our findings showed that either current use of selective COX-2 inhibitors or conventional NSAIDs were not associated with an increased risk of VT/VF-OHCA (Odd Ratio (OR) 1.11, 95%CI: 0.79-1.56 and OR 0.97, 0.86-1.10), respectively compared to nonuse). Stratification for VT/VF-OHCA with the presence or absence of Acute Myocardial Infarction (AMI) did not change these results.

The increased risk of nephrotic syndrome (NS) diagnosis for NSAID use is inconclusive. In **Chapter 3,** we performed a systematic observational study to assess the association between the risk of NS diagnosis and NSAID use according to their COX enzyme selectivity and chemical groups. The duration of NSAID use was also studied. We evaluated this association in an age-, sex-, general practitioner practice-, and index-date matched case-control study. This population-based study was performed in the Clinical Practice Research Datalink (CPRD), i.e., a general practitioner database in the UK from 1989 to 2017. Our findings indicated that conventional NSAID use, mainly attributable to the acetic acid derivative (AAD) and propionic acid derivative (PAD) groups, is associated with an increased risk of NS diagnosis starting from 2 weeks of

exposure. Current use with duration 15-28 and >28 days of conventional NSAIDs was associated with an increased risk of NS diagnosis: adjusted OR 1.34 (95%CI, 1.06-1.70) and 1.42 (0.79-2.55), respectively. Recent use (discontinuation 1-2 months before the index date) and past use (discontinuation 2 months-2 years) of conventional NSAIDs were also associated with an increased risk of NS diagnosis by 55% (adjusted OR 1.55, 95%CI; 1.11-2.15) and 24% (1.24; 1.07-1.43), respectively. These increased risks seem to disappear after 2 years of discontinuation. In contrast, selective COX-2 inhibitors did not seem to increase the risk of NS diagnosis.

No studies evaluated gastrointestinal toxicity (i.e., perforation, ulcers, bleeding (PUB)) for NSAID use by comparing the use of selective COX-2 inhibitors either alone or combined with proton pump inhibitors (PPIs), and conventional NSAIDs with PPIs compared to conventional NSAIDs alone in one study. Hence, in **Chapter 4,** we compared the risk of PUB among these strategies in a case-control study using data from the Dutch PHARMO Network Database from 1998 to 2012. We found that selective COX-2 inhibitors with PPIs had the lowest risk (adjusted OR 0.51, 95%CI: 0.35-0.73), followed by selective COX-2 inhibitors alone (adjusted OR 0.66, 95%CI: 0.48-0.89), and conventional NSAIDs with PPIs (adjusted OR 0.79, 95%CI: 0.68-0.92) compared to conventional NSAIDs alone.

In **Chapter 5,** we evaluated the differences in relative inhibitory potency towards COX enzymes and chemical groups of NSAIDs, including the presence or absence of a sulfonamide functional group in their chemical structures on the reporting risk of hypersensitivity reactions (HSRs). This case/non-case study was conducted in a spontaneous case safety report database, the VigiBase in strata of 5 years after market authorization using data collected from 1978 until 2016. Within 5 years after market approval, NSAIDs with poor COX selectivity were associated with the highest reporting odds ratios (ROR) of HSRs (age- and sex-adjusted ROR 2.12, 95%CI; 1.98-2.28) compared to coxibs. AAD, fenamate, and PAD groups belonging to NSAIDs were associated with the highest RORs (age- and sex-adjusted ROR 3.07, 95%CI; 2.83-3.33, ROR 2.21, 1.83-2.66, and ROR 1.93, 1.69-2.19), respectively all compared to coxibs. Sulfonamide NSAIDs were also associated with a higher ROR (age- and sex-adjusted ROR 1.38, 95%CI; 1.29-1.47) compared to non-sulfonamide NSAIDs**.** After the 1st five years of marketing, most of the RORs returned to approximately 1.

The association between NSAID use and bone implant-related adverse events is uncertain. Furthermore, a limited number of studies evaluated the risk of revision of lower joint replacement (LJR) surgery for NSAID users (either conventional NSAIDs or selective COX-2 inhibitors). Thus, in **Chapter 6**, we studied the association between NSAIDs and the risk of revision surgery. A retrospective cohort study was conducted in the CPRD database from 2000-2018 among patients who underwent primary LJR surgery, either hip replacement or knee replacement. Compared to non-use, current use for <1 month, 3-6 months, 6-12 months, and >12 months of conventional NSAIDs were associated with higher risk of revision surgery (adjusted Hazard Ratio (HR) 2.48 (95%CI; 2.07-2.96), 1.51 (1.16-1.96), 1.67 (1.27-2.20), and 2.08 (1.69-2.56), respectively). Compared to non-use, current use for <1 month, 1-3 month(s), 3-6 months, and >12 months of selective COX-2 inhibitors were also associated with higher risk (adjusted HR 2.85 (1.87-4.34), 1.17 (0.69-1.98), 1.20 (0.62-2.32), and 2.07 (1.29-3.30), respectively). A higher risk was also found for recent and past use of these drugs. However, current use for 1-3 month(s) of conventional NSAIDs and for 6-12 months for selective COX-2 inhibitors was associated with a similar risk compared to non-use.

Chapter 7 described some methodological issues in observational studies on the adverse events of NSAID use using electronic health care databases. Because several important risk factors are not routinely recorded in these databases, many studies on the association between NSAIDs and specific outcomes often do not take into account these factors. Hence, the risk estimates might be biased by confounding. These risk factors include over-the-counter of NSAID use, comorbidities, lifestyle factors, body mass index, and familial history of diseases. Therefore, in this chapter, we assessed the impact of additional information collected from patient's reports by means of questionnaires on the estimated risks of AMI for NSAID users. We performed an age- and sex-matched case-control study in the Utrecht Cardiovascular Pharmacogenetics (UCP) registry, a nested cohort of adults patients taking anti-hypertensive drugs and/or with hypercholesterolemia, collected from the Dutch PHARMO Network Database from 1986-2005. For responders with information on NSAID use that was strictly retrieved from pharmacy records, after adjustment for potential confounders collected only from pharmacy records, neither selective COX-2 inhibitors nor conventional NSAIDs were associated with an increased risk of AMI compared to nonuse

(adjusted OR 1.00, 95% CI: 0.46-2.17 and adjusted OR 0.81, 95% CI: 0.66-1.00, respectively). The estimated risks for these drug classes were not changed after being additionally adjusted for potential confounders collected from patient's reports. Incorporating information on co-medications and history of cardiovascular diseases from patient's reports to pharmacy records did not either change the risk estimates. Including information on NSAID use from patient's reports into pharmacy records did not seem to change the ORs for all adjustment models.

In **Chapter 8,** we discussed the findings of this thesis in light of the current knowledge on the safety of NSAIDs. We also discussed some issues associated with these observational studies by using electronic health care databases, including the strengths and limitations. Implications for clinical practices were provided and new research questions and potential improvements in future studies were highlighted.

APPENDIX A2

NEDERLANDSE SAMENVATTING

Non-Steroidal Anti-Inflammatory Drugs (NSAID's) worden veel gebruikt om aandoeningen met pijn, ontsteking en/of koorts te behandelen. Deze geneesmiddelen remmen cyclooxygenase (COX) enzymen, d.w.z. COX-1 en COX-2. COX-1 is verantwoordelijk voor fysiologische processen en COX-2 wordt gevormd als een reactie op externe prikkels. De relatieve mate van remming van COX-enzymen en de chemische groepen van NSAID's, inclusief de aan- of afwezigheid van een functionele sulfonamidegroep, lijken bij te dragen aan de bijwerkingen van deze geneesmiddelen die variëren van milde tot ernstige en levensbedreigende aandoeningen. Hoewel veel studies zijn uitgevoerd om de bijwerkingen van het gebruik van NSAID's te onderzoeken, is er nog veel onbekend en moet verder onderzoek gedaan worden.

In **hoofdstuk 2** is het verband tussen het gebruik van COX-2-remmers of conventionele NSAID's en het risico op ventriculaire tachycardie/ventrikel fibrilleren (VT/VF-OHCA) onderzocht. In deze op leeftijd en geslacht gematchte case-controle studie werd informatie van VT/VF-OHCA-gevallen uit de AmsteRdam REsuscitation STudy (ARREST) gebruikt, dit is een doorlopend Nederlands register van reanimatiepogingen. Voor de controlegroep werden geneesmiddelaflevergegevens in de periode 2005 tot 2011 van het Nederlandse PHARMO databasenetwerk gebruikt. Onze bevindingen lieten zien dat het gebruik van selectieve COX-2-remmers of conventionele NSAID’s geen verband hadden met een verhoogd risico op VT / VF-OHCA (Odds Ratio (OR) 1,11, 95% BI: 0,79-1,56 en OR 0,97, 0,86-1,10), respectievelijk vergeleken met niet-gebruik. Stratificatie voor VT/VF-OHCA met de aan- of afwezigheid van acuut myocardinfarct (AMI) veranderde deze resultaten niet.

In **hoofdstuk 3** hebben we een observationeel onderzoek uitgevoerd om het verband tussen het risico van nefrotisch syndroom (NS) en NSAID-gebruik vast te stellen op basis van hun COX-enzymselectiviteit en aan- of afwezigheid van bepaalde chemische groepen. De duur van het gebruik van NSAID's werd ook onderzocht. We hebben deze associatie onderzocht in een case-controle studie gematcht op leeftijd, geslacht, huisartsenpraktijk en indexdatum. Deze studie werd uitgevoerd in de Clinical Practice Research Datalink (CPRD), een huisartsendatabase in het Verenigd Koninkrijk van 1989 tot 2017. Conventioneel NSAID-gebruik, voornamelijk NSAIDs met azijnzuurderivaat (AAD) en propionzuurderivaat (PAD) -groepen, werd geassocieerd met een verhoogd risico op NS vanaf 2 weken blootstelling. Huidig

gebruik met duur 15-28 en >28 dagen van conventionele NSAID's werd geassocieerd met een verhoogd risico op NS: respectievelijk gecorrigeerde OR 1,34 (95% BI, 1,06-1,70) en 1,42 (0,79-2,55). Recent gebruik (stopzetting 1-2 maanden vóór de indexdatum) en gebruik in het verleden (2 maanden-2 jaar geleden gestopt) van conventionele NSAID's werden ook geassocieerd met een verhoogd risico op NS met 55% (aangepaste OR 1,55, 95% BI; 1,11 -2,15) en 24% (1,24; 1,07-1,43), respectievelijk. Deze verhoogde risico's lijken te verdwijnen 2 jaar na stoppen.

In **hoofdstuk 4** werd het risico van gastrointestinale toxiciteit (perforatie, ulceratie, bloeding (PUB)) in verband met verschillende NSAIDs vergeleken in een case-controle studie met gegevens uit de Nederlandse PHARMO Network-database van 1998 tot 2012. In vergelijking met conventionele NSAIDs, was het gebruik van selectieve COX-2-remmers met PPI's geassocieerd met het laagste risico op PUB (gecorrigeerd OR 0,51, 95% BI: 0,35-0,73), gevolgd door selectieve COX-2-remmers alleen (gecorrigeerd OR 0,66, 95% BI: 0,48-0,89) en conventionele NSAID's met PPI's (gecorrigeerd OR 0,79, 95% BI: 0,68- 0.92.

In **hoofdstuk 5** werden meldingen van overgevoeligheidsreacties (HSR's) vergeleken tussen NSAIDs op basis van relatieve remming van Cox2/Cox1 enzymen en chemische groepen van NSAID's, inclusief de aanwezigheid of afwezigheid van een functionele sulfonamidegroep. Deze case/non-case study werd uitgevoerd in een database met spontane meldingen van bijwerkingen (VigiBase) in strata van 5 jaar na markttoelating met behulp van gegevens verzameld van 1978 tot 2016. Binnen 5 jaar na toelating op de markt werden NSAID's zonder COX-selectiviteit geassocieerd met de hoogste rapportage odds ratio's (ROR) van HSR's (leeftijd en geslacht gecorrigeerde ROR 2,12, 95% BI; 1,98-2,28) in vergelijking met coxibs. AAD-, fenamaat- en PAD-groepen behorende tot NSAID's werden geassocieerd met de hoogste ROR's (leeftijd en geslacht gecorrigeerde ROR 3,07, 95% BI; 2,83-3,33, ROR 2,21, 1,83-2,66 en ROR 1,93, 1,69-2,19), respectievelijk alle vergeleken met coxibs. Sulfonamide NSAID's werden ook geassocieerd met een hogere ROR (leeftijd en geslacht gecorrigeerde ROR 1,38, 95% BI; 1,29-1,47) in vergelijking met niet-sulfonamide NSAID's. Vijf jaar na markttoelating keerden de meeste ROR's terug naar ongeveer 1.

Het verband tussen het gebruik van NSAID's en bijwerkingen gerelateerd aan botimplantaten is onduidelijk. Een beperkt aantal studies heeft het risico van revisie van implantaten voor vervanging van

lagere gewrichten (LJR) door NSAID-gebruik (conventionele NSAID's of selectieve COX-2-remmers) onderzocht. In **hoofdstuk 6** werd de associatie tussen NSAID's en het risico op revisiechirurgie bestudeerd. Een retrospectief cohortonderzoek werd uitgevoerd in de CPRD-database vanaf 2000-2018 bij patiënten die primaire LJR-chirurgie ondergingen, hetzij heupprothese of knievervanging. Vergeleken met niet-gebruik, werd het huidige gebruik gedurende <1 maand, 3-6 maanden, 6-12 maanden en> 12 maanden van conventionele NSAID's geassocieerd met een hoger risico op revisiechirurgie (aangepaste Hazard Ratio (HR) 2,48 (95% BI) ; 2,07-2,96), 1,51 (1,16-1,96), 1,67 (1,27-2,20) en 2,08 (1,69-2,56), respectievelijk). Vergeleken met niet-gebruik, werd huidig gebruik voor <1 maand, 1-3 maand (en), 3-6 maanden en> 12 maanden van selectieve COX-2-remmers ook geassocieerd met een hoger risico (aangepast HR 2,85 (1,87-4,34)), 1,17 (0,69-1,98), 1,20 (0,62-2,32) en 2,07 (1,29-3,30), respectievelijk). Een hoger risico werd ook gevonden voor recent en gebruik in het verleden van deze medicijnen. Het huidige gebruik gedurende 1-3 maanden van conventionele NSAID's en gedurende 6-12 maanden voor selectieve COX-2-remmers werd geassocieerd met een vergelijkbaar risico in vergelijking met niet-gebruik.

Hoofdstuk 7 beschreef enkele methodologische kwesties in observationele studies naar de bijwerkingen van NSAID-gebruik met behulp van elektronische gezondheidszorgdatabases. Omdat verschillende belangrijke risicofactoren niet routinematig in deze databases worden vastgelegd, wordt in veel studies naar de associatie tussen NSAID's en specifieke uitkomsten vaak geen rekening gehouden met deze factoren. Daarom kunnen de risico-schattingen vertekend zijn door confounding. Deze risicofactoren omvatten comorbiditeiten, leefstijlfactoren, body mass index en familiegeschiedenis van ziekten. Daarnaast mist er informatie over aflevering van geneesmiddelen zonder recept in elektronische gezondheidszorgdatabases. In dit hoofdstuk is de impact van gebruik van aanvullende informatie uit vragenlijsten die zijn ingevuld door de patiënt bestudeerd op de geschatte risico's van AMI door NSAID-gebruik. Binnen het Utrecht Cardiovascular Pharmacogenetics (UCP) register werd een gematchte case-controle studie uitgevoerd, genest binnen een cohort van volwassen patiënten die antihypertensiva gebruiken en/of hypercholesterolemie hebben. Voor respondenten met informatie over het gebruik van NSAID’s alleen op basis van apotheekgegevens, werden na correctie voor potentiële confounders alleen op basis van apotheekgegevens, noch selectieve COX-2-remmers noch conventionele NSAID's geassocieerd

met een verhoogd risico op AMI in vergelijking met niet-gebruik (gecorrigeerd OR 1,00 , 95% BI: 0,46-2,17 en gecorrigeerd OR 0,81, 95% BI: 0,66-1,00, respectievelijk). De geschatte risico's veranderden niet nadat ze additioneel waren gecorrigeerd voor potentiële confounders op basis van informatie uit vragenlijsten. Het meenemen van informatie over co-medicatie en de geschiedenis van hart- en vaatziekten uit vragenlijsten veranderde de risicoschattingen ook niet. Het meenemen van informatie over het gebruik van NSAID's uit vragenlijsten had ook geen impact op de OR's.

In **hoofdstuk 8** zijn de bevindingen van dit proefschrift besproken in het licht van de huidige kennis over de veiligheid van NSAID's. Sterke en zwakke punten van de uitgevoerde observationele studies met behulp van elektronische gezondheidsdatabases zijn besproken. Tot slot zijn de implicaties voor de klinische praktijk beschreven en zijn suggesties gedaan voor nieuwe onderzoeksvragen en mogelijke verbeteringen van toekomstige studies.

APPENDIX A3

RINGKASAN BAHASA INDONESIA

Obat anti inflamasi non-steroid (AINS) banyak digunakan untuk mengatasi keluhan nyeri, radang, dan/atau demam. Obat ini menghambat enzim *cyclooxygenase* (COX), yaitu COX-1 dan COX-2. Enzim COX-1 berperan pada proses fisiologis tubuh, sementara enzim COX-2 dibentuk sebagai respon terhadap rangsangan dari luar. Penghambatan relatif terhadap enzim COX dan struktur kimia dari obat AINS ini, termasuk terdapat atau tidaknya gugus fungsional sulfonamid diduga berperan pada munculnya efek samping obat AINS. Efek samping ini bervariasi mulai dari kondisi yang ringan sampai yang serius dan bahkan mengancam jiwa. Meskipun sudah banyak penelitian tentang efek samping dari penggunaan obat AINS, ternyata masih banyak efek samping yang belum diketahui atau perlu diteliti lebih lanjut.

Di **BAB 2,** kami mempelajari hubungan antara risiko henti jantung akibat VT/VF-OHCA pada pengguna penghambat selektif enzim COX-2 atau AINS tradisional. Penelitian kasus-kontrol dengan kesesuaian berdasarkan umur dan jenis kelamin ini dilakukan dengan menggunakan informasi dari *ARREST registry,* yaitu sebuah pangkalan data berisi percobaan tindakan resusitasi terhadap kasus henti jantung yang terjadi di luar rumah sakit di Provinsi Belanda Utara. Pangkalan data ini dibuat untuk memperoleh informasi tentang kasus henti jantung. Sementara itu, informasi untuk kelompok kontrol diperoleh dari *the Dutch PHARMO Network Database,* sebuah pangkalan data terkait keluarnya obat (*drug dispensing*) dari apotek untuk masyarakat umum (*community pharmacies*) (bukan pasien rumah sakit), dari tahun 2005 sampai 2011. Hasil penelitian kami menunjukkan bahwa pengguna saat ini (*current users*) penghambat selektif COX-2 dan AINS tradisional tidak berhubungan dengan peningkatan risiko VT/VF-OHCA dengan OR masing-masing 1,11, (95%CI: 0,79-1,56) dan 0,97 (0,86-1,10) dibandingkan dengan kelompok bukan pengguna AINS. Analisis berdasarkan ada dan tidaknya kejadian infark miokard akut (IMA) pada kasus VT/VF-OHCA tidak mengubah kesimpulan penelitian ini.

Pengingkatan risiko sindrom nefrotik (SN) pada pengguna obat AINS belum dapat disimpulkan secara pasti. Di **BAB 3,** kami kemudian melakukan penelitian observasional sistematis untuk mengetahui hubungan antara risiko terjadinya SN pada pengguna AINS berdasarkan potensinya sebagai penghambat relatif enzim COX dan struktur kimianya, termasuk durasi penggunaannya. Penelitian ini dilakukan pada populasi di Inggris dari tahun 1989 sampai 2017 dengan menggunakan data dari CPRD, yaitu sebuah

pangkalan data elektronik dokter umum. Penelitian kasus-kontrol ini berdasarkan kesesuaian umur, jenis kelamin, tempat praktek dokter, dan tanggal diagnosis SN. Hasil penelitian kami menunjukkan bahwa pengguna AINS tradisional saat ini terutama yang mengandung gugus asam asetat atau asam propionat selama paling tidak 2 minggu meningkatkan risiko terjadinya SN. Pengguna saat ini AINS tradisional dengan durasi 15-28 dan >28 hari berhubungan dengan peningkatan risiko diagnosis SN yaitu masing-masing OR 1,34 (95%CI, 1,06-1,70) dan 1,42 (0,79-2,55) dibandingkan dengan kelompok bukan pengguna. Pengguna AINS tradisional yang telah berhenti antara 1-2 bulan dan antara 2 bulan-2 tahun sebelum tanggal diagnosis SN ternyata juga masih memiliki peningkatan risiko terjadinya SN masing-masing sebesar 55% (OR 1,55, 95%CI; 1,11-2,15) and 24% (1,24; 1,07-1,43) dibandingkan dengan kelompok bukan pengguna. Peningkatan risiko ini tampaknya tidak terjadi lagi setelah penghentian AINS tradisional selama lebih dari 2 tahun. Sementara itu, pengguna saat ini penghambat selektif COX-2 tampaknya tidak berhubungan dengan peningkatan risiko terjadinya SN dibandingkan dengan kelompok bukan pengguna.

Sampai saat ini belum ada penelitian yang membandingkan tingkat toksisitas pada saluran pencernaan berupa risiko perforasi, perlukaan, dan perdarahan di saluran cerna dari penghambat selektif COX-2 dan AINS tradisional, baik tunggal maupun ketika dikombinasikan dengan obat penghambat pompa proton (P3) di dalam satu penelitian. Di **BAB 4** kami membandingkan risiko tadi dari berbagai strategi tadi pada sebuah studi kasus-kontrol menggunakan pangkalan data elektronik *the Dutch PHARMO Network Database* dari tahun 1998 sampai 2012. Pengguna saat ini penghambat selektif COX-2 dikombinasikan dengan P3 memiliki risiko efek samping terendah (OR 0,51, 95%CI: 0,35-0,73), diikuti dengan penghambat selektif COX-2 saja (OR 0,66: 0,48-0,89), dan terakhir AINS tradisional yang dikombinasikan dengan P3 (OR 0,79: 0,68-0,92) dibandingkan dengan penggunaan AINS tradisional saja.

Di **BAB 5** kami meneliti perbedaan potensi penghambatan terhadap enzim COX dan struktur kimia dari obat-obat AINS, termasuk ada atau tidaknya gugus fungsional sulfonamid dari struktur kimia AINS terhadap risiko terjadinya reaksi hipersensitif. Studi kasus/non-kasus ini dilakukan dengan menggunakan data dari VigiBase, yaitu pangkalan data laporan spontan kasus keamanan penggunaan obat dari Januari 1978 sampai Juni 2016 per 5 tahun setelah otorisasi pasar. AINS yang kurang selektif dalam menghambat

enzim COX berhubungan dengan peningkatan tertinggi reaksi hipersensitif yaitu sebesar 2,12 kali lipat (ROR 2,12, 95%CI; 1,98-2,28) dibandingkan dengan coxibs setelah disesuaikan dengan perbedaan umur dan jenis kelamin dalam periode 5 tahun pertama setelah otorisasi pasar. Dari seluruh kelompok kimia AINS, derivat asam asetat, fenamat, dan derivat asam propionat berhubungan dengan peningkatan tertinggi reaksi hipersensitif (masing-masing ROR 3,07; 2,83-3,33, ROR 2,20; 1,83-2,66, dan ROR 1,93; 1,69-2,19) dibandingkan dengan coxibs setelah disesuaikan dengan perbedaan umur dan jenis kelamin. AINS yang mengandung gugus sulfonamid berhubungan dengan rasio reaksi hipersensitif lebih tinggi yaitu sebesar 38% (ROR 1,38; 1,29-1,47) dibandingkan dengan AINS yang tidak memiliki gugus sulfonamid setelah disesuaikan dengan perbedaan umur dan jenis kelamin. Setelah 5 tahun pertama otorisasi pasar, sebagian besar rasio reaksi hipersensitif kembali ke 1.

Hubungan antara penggunaan AINS dengan efek samping yang berhubungan dengan implant pada tulang masih belum dapat disimpulkan secara pasti. Lebih jauh lagi, penelitian yang mengkaji risiko bedah koreksi pada penggantian sendi bagian bawah pada pengguna AINS masih sedikit. Jadi, di **BAB 6,** kami meneliti risiko bedah koreksi untuk penggantian sendi bagian bawah, yaitu sendi panggul dan lutut pada pengguna AINS (baik AINS tradisional maupun penghambat COX-2 selektif) dibandingkan dengan kelompok bukan pengguna. Penelitian *retrospective cohort* ini dilakukan dengan menggunakan pangkalan data CPRD dari tahun 2000 sampai 2018 pada kelompok pasien-pasien yang pernah menjalani penggantian sendi panggul atau lutut. Dibandingkan dengan kelompok bukan pengguna AINS, pengguna saat ini selama <1 bulan, 3-6 bulan, 6-12 bulan, dan >12 bulan dari AINS tradisional berhubungan dengan peningkatan risiko koreksi dengan HR masing-masing 2,48 (95%CI; 2,07-2,96), 1,51 (1,16-1,96), 1,67 (1,27-2,20), dan 2,08 (1,69-2,56). Dibandingkan dengan kelompok bukan pengguna AINS, pengguna saat ini selama <1 bulan, 1-3 bulan, 3-6 bulan, dan >12 bulan dari penghambat COX-2 selektif juga berhubungan dengan peningkatan risiko koreksi dengan HR masing-masing 2,85 (1,87-4,34), 1,17 (0,69-1,98), 1,20 (0,62-2,32), dan 2.07 (1,29-3,30). Peningkatan risiko ini juga ditemukan pada pengguna dari obat ini yang telah berhenti selama 3 bulan atau lebih. Sebaliknya, pengguna saat ini AINS tradisional selama <1 bulan dan penghambat COX-2 selektif selama 6-12 bulan berhubungan dengan risiko pembedahan koreksi yang sama dengan kelompok bukan pengguna AINS.

BAB 7 menyajikan pendekatan metodologi pada penelitian tentang efek samping penggunaan AINS dengan menggunakan pangkalan elektronik data kesehatan. Karena beberapa faktor risiko penting yang terkait penyakit tidak secara rutin dicatat di dalam pangkalan data ini, kami menemukan banyak penelitian yang mengkaji efek samping penggunaan AINS tanpa mempertimbangkan beberapa faktor risiko penting yang terkait, seperti penggunaan obat AINS yang dijual bebas, penyakit penyerta, gaya hidup, indeks masa tubuh, dan riwayat penyakit keluarga. Hal ini berakibat perkiraan risiko efek sampingnya menjadi kurang akurat. Jadi, di bab ini, kami meneliti bagaimana pengaruh tambahan informasi yang diperoleh dari laporan pasien dengan menggunakan kuisioner tentang perkiraan risiko penyakit IMA pada pengguna AINS saat ini. Kami melakukan penelitian kasus-kontrol dengan kesesuaian berdasarkan umur, jenis kelamin, tempat praktek dokter, dan tahun terdiagnosisnya IMA pada orang dewasa yang menggunakan paling tidak satu obat anti hipertensi dan/atau memiliki kadar kolesterol darah di atas normal. Data untuk penelitian diperoleh dari UCP *registry,* yaitu populasi penelitian yang diperoleh dari *the Dutch PHARMO Network Database* dari tahun 1986 sampai 2005. Pada mereka yang mengembalikan kuisioner dengan informasi penggunaan AINS terbatas hanya dari data farmasi, penghambat COX-2 selektif dan AINS tradisional tidak berhubungan dengan peningkatan risiko IMA setelah disesuaikan dengan variabel pengganggu yang diperoleh dari data farmasi, masing-masing sebesar OR 1,00 (0,46-2,17) dan 0,81 (0,66-1,00). Perkiraan risiko AMI untuk obat AINS ini tidak berubah setelah disesuaikan dengan penambahan variabel yang diperoleh dari laporan pasien. Menggabungkan informasi penggunaan obat dan riwayat penyakit jantung dari laporan pasien ke data farmasi juga tidak merubah perkiraan risiko untuk penyakit IMA. Memasukkan informasi tentang penggunaan AINS (termasuk dari penggunaan obat bebas AINS) dari laporan pasien ke data farmasi tampaknya juga tidak merubah perhitungan OR pada seluruh model analisis.

Akhirnya, di **BAB 8** kami mendiskusikan hasil penelitian di buku tesis ini dengan mempertimbangkan pengetahuan terbaru tentang keamanan penggunaan obat-obat AINS. Kami juga mendiskusikan beberapa hal terkait penelitian observasional dengan menggunakan pangkalan data kesehatan elektronik, termasuk kekuatan dan kelemahannya. Kemudian, kami menyajikan kemungkinan penerapan hasil penelitian ini pada praktek klinik dan potensi penelitian selanjutnya.

APPENDIX B

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آمين

"It always seems impossible until it has been done".

– Nelson Mandela

APPENDIX C

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APPENDIX D

LIST OF PUBLICATIONS

Publications related to this thesis

1. **Bakhriansyah M**, Souverein PC, van de Hoogen M, de Boer A, Klungel OH. Risk of nephrotic syndrome for non-steroidal anti-inflammatory drug users: a case-control study. *Clinical Journal of the American Society of Nephrology.* 2019. August 7.
2. **Bakhriansyah M**, Meyboom RH, Souverein PC, de Boer A, Klungel OH. Cyclooxygenase selectivity and chemical groups of non-steroidal anti-inflammatory drugs and the frequency of reporting hypersensitivity reactions: a case/non-case study in VigiBase. *Fundamental and Clinical Pharmacology.* 2019. March 12.
3. **Bakhriansyah M**, Souverein PC, de Boer A, Klungel OH. Risk of myocardial infarction associated with non-steroidal anti-inflammatory drug use: impact of additional confounding control for variables collected from self-reported data. *Journal of Clinical Pharmacy and Therapeutics*. 2019. March 11.
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1. Kusumawardhani DA, Husein AN, **Bakhriansyah M**. Hubungan kejadian *premenstrual syndrome* (PMS) dengan kejadian insomnia pada mahasiswa Fakultas Kedokteran Universitas Lambung Mangkurat Banjarmasin: Kajian pada mahasiswa Program Studi Pendidikan Dokter (PSPD) angkatan 2010-2012. *Berkala Kedokteran.* 2016. June 3. 10(1): 89-99.
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Abstracts

1. Risk of nephrotic syndrome for non-steroidal anti-inflammatory drug users: a case-control study. **Bakhriansyah M***, Souverein PC, van de Hoogen M, de Boer A, Klungel OH.
    a. Poster presentation at the ISPE 12th Asian Conference on Pharmacoepidemiology (ACPE), 11-13 October 2019, Kyoto, Japan.
    b. Poster presentation at the International Conference on Pharmacoepidemiology (ICPE), Mid-Year Meeting, 6-9 April 2019, Rome, Italy.
2. Cyclooxygenase selectivity and chemical groups of non-steroidal anti-inflammatory drugs and the frequency of reporting hypersensitivity reactions: a case/non-case study in VigiBase.
    a. **Bakhriansyah M,** Meyboom RH, Souverein PC, de Boer A, Klungel OH***.** Poster presentation at the 18th Annual Meeting International Society of Pharmacovigilance (ISoP), 11-14 November 2018, Geneva, Switzerland.
    b. **Bakhriansyah M***, Meyboom RH, Souverein PC, de Boer A, Klungel OH. Poster presentation at the 2nd Biennial Utrecht Institute for Pharmaceutical Sciences (UIPS) symposium, 26 October 2018, Utrecht, the Netherlands.
    c. **Bakhriansyah M,** Meyboom RH, Souverein PC, de Boer A, Klungel OH. Poster presentation at the 34th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE), 22-26 August 2018, Prague, Czech Republic.
3. Non-steroidal anti-inflammatory drugs and the risk of out-of-hospital cardiac arrest: a case-control study. **Bakhriansyah M***, Souverein PC, de Boer A, Klungel OH, Blom MT, Tan HL. Oral presentation at the 33rd International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE), 26-30 August 2017, Montreal, Canada.
4. Risk of myocardial infarction associated with non-steroidal anti-inflammatory drug use: impact of additional confounding control for variables collected from self-reported data. **Bakhriansyah M***, Souverein PC, de Boer A, Klungel OH.
    a. Poster presentation at the 33rd International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE), 26-30 August 2017, Montreal, Canada.

b. Oral presentation at the International Conference on Pharmacoepidemiology (ICPE), Mid-Year Meeting, 1-4 April 2017, London, the United Kingdom.

5. Gastrointestinal toxicity among patients taking selective COX-2 inhibitors or conventional NSAIDs alone or combined with proton-pump inhibitors: a case-control study. **Bakhriansyah M***, Souverein PC, de Boer A, Klungel OH.

   a. Poster presentation at the 1st Annual Utrecht Institute for Pharmaceutical Sciences (UIPS) symposium, 28 October 2016, Utrecht, the Netherlands

   b. Poster presentation at the 32nd International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE), 25-28 August 2016, Dublin, Ireland.

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APPENDIX E

ABOUT THE AUTHOR

Mohammad Bakhriansyah was born in Amuntai, a small city remotely located in the Province of South Kalimantan, Indonesia. He earned his medical doctor degree at the School of Medicine, Lambung Mangkurat University, Banjarmasin, Indonesia. Before his medical internship, he was accepted as a lecturer in the same university. Shortly after he graduated, he continued his education in the Basic and Biomedical Sciences with a specialization in pharmacology at Gadjah Mada University, Yogyakarta, Indonesia. He obtained a master degree with his thesis about herbal medicine for breast cancer from bio-molecular perspectives. During his master research, he was extensively exposed to cyclooxygenase enzymes as a treatment target. Later on, non-steroidal anti-inflammatory drugs that inhibit these enzymes became his interest for his Ph.D. projects. Since he realized he should improve his didactic skills, he took a master program in medical education at Sydney University, Australia. By the end of 2013, he became a Ph.D. candidate at the Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, the Netherlands with financial support from the Ministry of Research, Technology, and Higher Education of Indonesia (Kementerian Riset, Teknologi, dan Pendidikan Tinggi) through the Riset-PRO platform. His thesis is titled ***"SAFETY PROFILE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN CLINICAL PRACTICE: New Insights from Electronic Health Care and Spontaneous Reporting Databases".*** During his Ph.D. internship, in 2016 he was involved as a trainer in the European Education and Training Program (Eu2P). In 2017, he was granted a master degree in Epidemiology with a specialization in pharmacoepidemiology from the Julius Center, University Medical Center, Utrecht University.