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Non-steroidal anti-inflammatory drugs and the risk of out-of-hospital cardiac arrest: a case–control study

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

Methods and results A case–control study was conducted among 2483 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 five 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 (CIs) were calculated by conditional logistic regression analysis. 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 with non-use. Stratification for VT/VF-OHCA with presence/absence of acute myocardial infarction did not change these results.

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

Keywords Non-steroidal anti-inflammatory drugs • Conventional NSAIDs • Selective COX-2 inhibitors • Out-of-hospital cardiac arrest • Ventricular tachycardia • Ventricular fibrillation

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] Non-steroidal anti-inflammatory

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What's new?

- Non-steroidal anti-inflammatory drugs (NSAIDs), particularly selective COX-2 inhibitors are associated with a higher risk of cardiovascular adverse events such as myocardial infarction (MI) (fatal and non-fatal), stroke, and heart failure. However, no studies investigated the effect of NSAIDs on the risk of out-of-hospital cardiac arrest with documented ventricular tachycardia/ventricular fibrillation (VT/VF-OHCA).
- Our study demonstrated that neither exposure to selective COX-2 inhibitors nor conventional NSAIDs are associated with an increased risk of VT/VF-OHCA, including VT/VF-OHCA cases with acute MI.

drugs 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. Out-of-hospital cardiac arrest cases were obtained from ARREST and age/sex/index date-matched non-OHCA controls were selected from 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. Electrocardiogram (ECG) 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 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 analysed by using the software Code Stat Reviewer 7.0, Physio-Control, Redmond, WA, USA. Acute myocardial infarction 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 five 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 material online, *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 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 non-users. 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 two 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 material online, *Tables 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)];

Table 1 Baseline characteristics of the cases and controls

Variables	Cases (n = 2483), n (%)	Controls (n = 10 441), n (%)	P-value
Age (years), mean ± SD	65.49 ± 14.48	65.47 ± 14.32	NA
Sex, n (%)			
Men	1923 (77.4)	8087 (77.5)	NA
Women	560 (22.6)	2354 (22.5)	
Co-medication(s), n (%)			
Antiarrhythmic drugs[a]	45 (1.8)	36 (0.3)	<0.001*
Non-antiarrhythmic QTc-prolonging drugs[a]	231 (9.3)	639 (6.1)	<0.001*
Drugs used within 6 months prior to the index date, n (%)			
Cardiovascular drugs[b]	1601 (64.5)	5258 (50.4)	<0.001*
Anti-diabetic drugs[c]	394 (15.9)	1115 (10.7)	<0.001*
Obstructive pulmonary disease drugs[d]	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.
NA, not applicable; SD, standard deviation.
[a]Concomitant current use of Classes I and III antiarrhythmic or non-antiarrhythmic drugs with (possible) risk of QT prolongation at the index date.
[b]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.
[c]Use of anti-diabetic drugs: insulin and/or oral anti-diabetics.
[d]Use of at least two drugs for obstructive pulmonary diseases.
*P-value <0.05.

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

The χ^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 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 programme which takes a matched case–control study design into consideration.[13] With the number of cases (n = 2483) and controls (n = 10441) available and a percentage of conventional NSAID use in controls of 2.5%, we were able to detect an OR 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 OR from 1.9 as statistically significant. In the subgroup analyses of VT/VF patients in the context of AMI (994 cases and 4171 controls), these ORs were 1.62 and 2.54, respectively.

Results

Characteristics

We identified 2483 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 with 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.

Risk of out-of-hospital cardiac arrest with documented ventricular tachycardia/ventricular fibrillation for non-steroidal anti-inflammatory drug users

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

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 non-use for both cases with or without AMI (*Tables 3* and *4*).

Differences in duration of non-steroidal anti-inflammatory drug use, age, and sex and the association between current non-steroidal anti-inflammatory drug use and the risk of out-of-hospital cardiac arrest with documented ventricular tachycardia/ventricular fibrillation

Differences in the duration of NSAID use, age, and sex were not associated with the different risks of VT/VF-OHCA for either selective

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 non-users as reference group

Exposures	Cases (2483)	Controls (10 441)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Non-use, *n* (%)	2066 (83.2)	8085 (77.4)	Ref	Ref
Current use				
Conventional NSAIDs, *n* (%)	63 (2.5)	266 (2.5)	0.98 (0.87–1.12)	0.97 (0.86–1.10)
Selective COX-2 inhibitors, *n* (%)	12 (0.5)	32 (0.3)	1.10 (0.78–1.55)	1.11 (0.79–1.56)
Recent use				
Conventional NSAIDs, *n* (%)	194 (7.8)	1195 (11.4)	0.92 (0.87–0.98)*	0.92 (0.86–0.98)*
Selective COX-2 inhibitors, *n* (%)	14 (0.6)	70 (0.7)	0.96 (0.75–1.22)	0.97 (0.76–1.23)
Past use				
Conventional NSAIDs, *n* (%)	126 (5.1)	760 (7.3)	0.93 (0.86–1.00)	0.94 (0.87–1.02)
Selective COX-2 inhibitors, *n* (%)	8 (0.3)	33 (0.3)	0.99 (0.70–1.41)	1.01 (0.71–1.43)

CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio.
[a]Adjusted for antiarrhythmic drugs, non-antiarrhythmic QT-prolonging drugs, cardiovascular drugs, anti-diabetic drugs, and obstructive pulmonary diseases drugs.
*P-value <0.05.

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 non-users as reference group

Exposures	Cases (994)	Controls (4171)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Non-use, *n* (%)	822 (82.7)	3247 (77.8)	Ref	Ref
Current use				
Conventional NSAIDs, *n* (%)	26 (2.6)	103 (2.5)	1.00 (0.82–1.22)	0.99 (0.81–1.21)
Selective COX-2 inhibitors, *n* (%)	2 (0.2)	11 (0.3)	0.94 (0.50–1.74)	0.92 (0.50–1.71)
Recent use				
Conventional NSAIDs, *n* (%)	88 (8.9)	472 (11.3)	0.95 (0.86–1.05)	0.94 (0.85–1.04)
Selective COX-2 inhibitors, *n* (%)	5 (0.5)	21 (0.5)	0.99 (0.64–1.53)	1.00 (0.64–1.54)
Past use				
Conventional NSAIDs, *n* (%)	47 (4.7)	307 (7.4)	0.92 (0.81–1.04)	0.93 (0.82–1.05)
Selective COX-2 inhibitors, *n* (%)	4 (0.4)	10 (0.2)	1.13 (0.62–2.06)	1.13 (0.62–2.08)

CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio.
[a]Adjusted for antiarrhythmic drugs, non-antiarrhythmic QT-prolonging drugs, cardiovascular drugs, anti-diabetic drugs, and obstructive pulmonary diseases drugs.

COX-2 inhibitor or conventional NSAID use compared with non-use. The risk was similar for selective COX-2 inhibitors and conventional NSAIDs (*Tables 5–7*).

Discussion

Risk of out-of-hospital cardiac arrest with documented ventricular tachycardia/ventricular fibrillation for non-steroidal anti-inflammatory drug 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 with non-use. 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 behaviour towards the prescribing of rofecoxib after media attention on its

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 non-users as reference group

Exposures	Cases (537)	Controls (2262)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Non-use, *n* (%)	455 (84.7)	1747 (77.2)	Ref	Ref
Current use				
Conventional NSAIDs, *n* (%)	13 (2.4)	59 (2.6)	0.96 (0.74–1.26)	0.94 (0.72–1.23)
Selective COX-2 inhibitors, *n* (%)	3 (0.6)	11 (0.5)	1.00 (0.55–1.82)	1.06 (0.58–1.93)
Recent use				
Conventional NSAIDs, *n* (%)	38 (7.1)	248 (11.0)	0.91 (0.79–1.05)	0.90 (0.78–1.04)
Selective COX-2 inhibitors, *n* (%)	1 (0.2)	15 (0.7)	0.84 (0.49–1.46)	0.87 (0.50–1.51)
Past use				
Conventional NSAIDs, *n* (%)	26 (4.8)	178 (7.9)	0.91 (0.77–1.07)	0.92 (0.79–1.09)
Selective COX-2 inhibitors, *n* (%)	1 (0.2)	4 (0.2)	0.98 (0.36–2.66)	1.11 (0.41–3.01)

CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio.
[a]Adjusted for antiarrhythmic drugs, non-antiarrhythmic QT-prolonging drugs, cardiovascular drugs, anti-diabetic 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

Exposures	Cases	Controls	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
<182 days (<6 months)				
Non-use, *n* (%)	2066 (97.5)	8085 (97.3)	Ref	Ref
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)				
Non-use, *n* (%)	2066 (98.9)	8085 (99.1)	Ref	Ref
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)

CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio.
[a]Adjusted for antiarrhythmic drugs, non-antiarrhythmic QT-prolonging drugs, cardiovascular drugs, anti-diabetic 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

Exposures	Cases	Controls	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
<65 years old				
Non-use, *n* (%)	914 (96.6)	3539 (96.3)	Ref	Ref
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				
Non-use, *n* (%)	1152 (96.4)	4546 (96.6)	Ref	Ref
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)

CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio.
[a]Adjusted for antiarrhythmic drugs, non-antiarrhythmic QT-prolonging drugs, cardiovascular drugs, anti-diabetic 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

Exposures	Cases	Controls	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Men				
Non-use, *n* (%)	1607 (96.9)	6304 (96.9)	Ref	Ref
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				
Non-use, *n* (%)	459 (95.2)	1781 (94.8)	Ref	Ref
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)

CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio.
[a]Adjusted for antiarrhythmic drugs, non-antiarrhythmic QT-prolonging drugs, cardiovascular drugs, anti-diabetic drugs, and obstructive pulmonary diseases drugs.

cardiovascular risks in the early 2000s. In our study, such influence was not possible as our data collection started in 2005, whereas 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, and 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 both conventional NSAIDs and selective COX-2 inhibitors were 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 (EMS) 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 (2011–15).[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).

Conclusions

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 with non-use. 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.

Supplementary material

Supplementary material is available at *Europace* online.

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Corrigendum

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Correction to: Non-steroidal anti-inflammatory drugs and the risk of out-of-hospital cardiac arrest: a case–control study [*Europace* doi:10.1093/europace/euy180]

In the original version of this paper, there was a typing error in the 'What's new?' section: in the first bullet-point 'without' was written where 'with' should have been written. This has now been corrected in print and online.

The authors apologise for the error.