PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2014
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3617

ORIGINAL REPORT

Risk of nonfatal acute myocardial infarction associated with non-steroidal antiinflammatory drugs, non-narcotic analgesics and other drugs used in osteoarthritis: a nested case-control study†

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ABSTRACT

Purpose The purpose of this study is to estimate the risk of nonfatal acute myocardial infarction (AMI) associated with traditional NSAIDs (tNSAIDs), non-narcotic analgesics (paracetamol and metamizole), and symptomatic slow-acting drugs in osteoarthritis (SYSADOAs) overall and in different subgroups of patients.

Methods We performed a nested case-control study using a Primary Care Database (Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria), over the study period, 2001–2007. We included patients aged 40–90 years, with nonfatal AMI and randomly selected controls matched for age, sex and calendar year. Exposure to drugs was assessed within a 30-day window before the index date.

Results We did not find an association with nonfatal AMI in patients at low-intermediate background cardiovascular risk (odds ratio = 0.92; 95% confidence interval: 0.76–1.12), whereas there was a moderate significant association among those at high risk (1.28; 1.06–1.54) or when tNSAIDs were used for longer than 365 days (1.43; 1.12–1.82). The greatest risk occurred when these two conditions were combined (1.80; 1.26–2.58). The risk varied across individual tNSAIDs, with ibuprofen (0.95; 0.78–1.16) in the lower and aceclofenac (1.59; 1.15–2.19) in the upper part of the range. Low-dose aspirin did not modify the risk profile showed by any of the individual tNSAIDs examined. Paracetamol (0.84; 0.74–0.95), metamizole (1.06; 0.87–1.29) and SYSADOAs (0.68; 0.47–0.99) were not associated with an increased risk overall or in any subgroup of patients.

Conclusions The risk of nonfatal AMI varied with individual tNSAIDs, duration of treatment and background cardiovascular risk. Paracetamol, metamizole and SYSADOAs did not increase the risk in any of the conditions examined. Copyright © 2014 John Wiley & Sons, Ltd.

KEY WORDS—NSAIDs; paracetamol; analgesics; osteoarthritis; myocardial infarction; adverse drug reaction; pharmacoepidemiology

Received 26 November 2013; Revised 24 February 2014; Accepted 27 February 2014

INTRODUCTION

Despite the huge amount of information currently available on the risk of acute myocardial infarction (AMI) associated with traditional NSAIDs (tNSAIDs),[1–3] there are still some uncertainties in three topics that need to be clarified[2]: (i) the duration effect; (ii) the effect of background cardiovascular (CV) risk; and (iii) the effect of the concomitant use of low-dose aspirin. Also, as the AMI risk seems to vary across individual tNSAIDs, it is important to provide data by each drug. In particular, Bueno *et al.*[4] have reported recently a threefold increased risk of AMI associated with aceclofenac, the third most widely used tNSAID in Spain, a worrisome result that needs further evaluation.

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†Statement about previous postings and presentations: due to the regulatory implications of the present study, the main results on tNSAIDs were presented to the Committee on Safety of Medicines for Human Use of the Spanish Agency for Medicines and Medical Devices (AEMPS). Also, this information was shared, under strict confidential measures, with the members of the Pharmacovigilance and Risk Assessment Committee of the European Medicines Agency.

On the other hand, the concerns about the CV safety of tNSAIDs may deter physicians from prescribing them in patients at high CV background risk and prefer to use either painkillers such as paracetamol (acetaminophen) and metamizole (dypirone), or agents authorised in some countries for the symptomatic treatment of osteoarthritis [the so-called symptomatic slow-acting drugs for osteoarthritis (SYSADOAs)], on the assumption that they are safer agents than tNSAIDs for the CV system. However, the empirical evidence is either lacking or not supportive of such an assumption. For instance, Hinz *et al*.[5,6] reported that both paracetamol and metamizole, in experimental conditions, exert a relevant inhibition of peripheral COX-2 and suggest that both drugs may increase the CV risk in a similar way as tNSAIDs.[7] To the best of our knowledge, only two epidemiologic studies have been published so far, assessing the association of paracetamol with AMI, showing contradictory results,[8,9] and none has been published with metamizole or SYSADOAs. The present study was designed to shed some light on all these unsolved questions.

SUBJECTS AND METHODS

The study was performed using *Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria* (BIFAP), a primary care database validated for pharmacoepidemiological research.[10,11] Over the study period (1 January 2001 to 31 December 2007), BIFAP included anonymised information on 2 410 942 patients. The dataset is comparable with the Spanish population with respect to its age and sex distribution.[11] Data recorded in BIFAP include demographic information, prescription details (including the exact date of prescription), clinical events, specialist referrals and results from laboratory and other exploratory tests. The International Classification of Primary Care[12] is the coding system for patient complaints and diagnoses, although this information is often entered and enriched as free text as well. Prescription data in BIFAP include product name, quantity dispensed, dosage regimens, strength and indication. These prescriptions are coded according to the Anatomical Therapeutic Chemical classification scheme.

Study design

We performed a case-control study nested in a primary cohort comprised by persons included in the period 2001–2007, aged 40 to 90 years old and with at least 1 year of registry with their general practitioner (GP). Additionally, we excluded all subjects who at the start date had a record of cancer. All cohort members were followed from start date until the date of one of the following endpoints: a case definition criteria, any of the exclusion criteria previously mentioned, 90 years of age, death and the end of the study period, whichever came first.

Selection of cases and controls

A first computer search identified all patients with a code (International Classification of Primary Care code K75) or a free-text compatible with AMI. The computer clinical records of the potential cases were then manually reviewed by at least two different researchers in order to confirm or rule out the diagnosis and set the index date. Cases were classified as probable nonfatal AMI when they had: (i) either a diagnosis of AMI (code or free text) and additional information confirming the diagnosis (i.e. positive enzymes, Q wave, revascularization procedures, new treatment with low-dose aspirin after AMI diagnosis or a hospital report), or a diagnosis of acute coronary syndrome with or without ST elevation and additional information confirming that the final diagnosis was AMI; and (ii) no death within the 30 days after the index date. GP validation was performed, via questionnaire, over a sample of probable cases ($N = 1422$) to obtain confirmation of the case status. Although the response rate was rather low (543; 38.2%), GPs confirmed 96.5% of all probable cases and then all probable cases were deemed valid for the analysis. The index date was considered the date of first signs or the date of first diagnosis, whichever occurred first. 20 000 controls frequency-matched by age (within 1 year), sex and calendar year were randomly selected from the study population using a density-based sampling method.[13,14] The random date assigned to controls in the process of selection was considered as the index date.

Exposure definition

We defined patients as 'current users' if a prescription for the drug of interest lasted until index date or ended within 30 days prior to the index date, 'past users' if the prescription ended between 31 and 365 days before the index date, 'remote users' if the prescription ended before 365 days prior the index date and 'non-users' if there was no prescription before index date (reference category). For tNSAIDs, we explored whether a narrower exposure window for current use (7 days) would change the results. Among current single users, we studied the effect of dose and duration of treatment.

DOI: 10.1002/pds

As in other databases, only drugs requiring a prescription are registered in BIFAP. Most NSAIDs are prescription-only drugs,[15] but products containing aspirin at analgesic doses are available over the counter. Instead, low-dose aspirin (containing 300 mg or less) for cardioprotection is only available by prescription. Despite some paracetamol-containing products being available over the counter, others are reimbursed by the National Health System and largely used by prescription (15.71 DDD/1000 inhabitants/day in 2006[16]). SYSADOAs (condroitin sulfate and glucosamine) and metamizole are prescription-only drugs and both widely used in Spain (7.59[16] and 2.68[17] DDD/1000 inhabitants/day, respectively).

Statistical analysis

To estimate the association between nonfatal AMI and current use of drugs of interest, we built unconditional logistic regression models and computed the specific odds ratios (ORs) and their 95% confidence intervals (95% CI) as compared with non-use. All estimates were adjusted for the matching variables (age, sex and calendar year) and a number of factors, diseases and drugs reported to be associated with AMI (see footnote in Table 1).

We studied whether the main effect of tNSAIDs on AMI was modified by the concomitant use of low-dose aspirin use and background CV risk. For the latter, we classified patients in three categories: (i) *low-risk patients*: those with no records of any atherothrombotic disease [ischaemic heart disease (IHD), peripheral arterial disease and stroke], diabetes or CV risk factors (hypertension, dyslipidemia and current smoking); (ii) *intermediate-risk patients*: those with no records of atherothrombotic disease or diabetes but with at least one CV risk factor; and (iii) *high-risk patients*: those with either a history of atherothrombotic disease or diabetes. We classified patients with diabetes in the high-risk group as it has been reported to have a risk equivalent to IHD.[17,18] We also explored separately the interaction of

Table 1. Risk of non-fatal AMI associated with NSAIDs according to recency of use, single or multiple use, dose, duration and indication. All were compared with non-use

NSAID	Cases (%) $N = 3833$	Controls (%) $N = 20\,000$	Non-adjusted* OR (95% CI)	Adjusted† OR (95% CI)
Non use	1570 (40.96)	8651 (43.25)	1 (ref.)	1 (ref.)
Recency				
Current use tNSAIDs (0–30 days)	437 (11.40)	2151 (10.76)	1.13 (1.00–1.27)	1.08 (0.95–1.24)
Current use coxibs (0–30 days)	10 (0.26)	93 (0.46)	0.60 (0.31–1.16)	0.59 (0.30–1.16)
Past use (31–365 days)	952 (24.84)	4817 (24.10)	1.09 (1.00–1.19)	1.09 (0.99–1.21)
Remote use (>365 days)	864 (22.54)	4288 (21.44)	1.11 (1.00–1.21)	1.14 (1.03–1.26)
Single versus multiple‡				
Single users	390 (10.17)	1916 (9.58)	1.13 (1.00–1.28)	1.10 (0.96–1.26)
Multiple users or switchers	47 (1.23)	235 (1.18)	1.12 (0.81–1.54)	0.97 (0.69–1.36)
Dose§,¶				
Low-medium	114 (2.97)	544 (2.72)	1.17 (0.95–1.45)	1.14 (0.91–1.42)
High	154 (4.02)	771 (3.86)	1.11 (0.92–1.33)	1.04 (0.85–1.26)
Unknown	122 (3.18)	601 (3.00)	1.13 (0.92–1.38)	1.15 (0.92–1.42)
Duration§				
<31	166 (4.33)	858 (4.29)	1.07 (0.90–1.27)	1.02 (0.85–1.23)
31–365	127 (3.31)	673 (3.36)	1.06 (0.87–1.29)	1.02 (0.82–1.26)
366+	97 (2.53)	385 (1.93)	1.42 (1.12–1.78)	1.43 (1.11–1.83)
Indication‡				
Osteoarthritis	174 (4.54)	926 (4.63)	1.06 (0.89–1.25)	1.04 (0.85–1.27)
Rheumatoid arthritis	18 (0.47)	52 (0.26)	1.93 (1.13–3.31)	1.27 (0.60–2.68)
Other	245 (6.39)	1173 (5.87)	1.15 (1.00–1.34)	1.11 (0.94–1.30)

*Model only adjusted for the matching variables (sex, age and calendar year).

†Full adjusted model: Matching variables and the following factors: number of visits, ischemic heart disease (acute myocardial infarction, other), history of cerebrovascular events (TIA, CVA), history of heart failure, chronic obstructive pulmonary disease, peripheral artery disease, diabetes (including use of glucose-lowering drugs), dyslipidemia (including use of lipid-lowering drugs), hypertension, smoking, body mass index, rheumatoid arthritis (except when the indication was studied), gout (including use of allopurinol and/or colchicine), hyperuricemia, renal failure; depression and use of the following drugs (non-use, current use, past use): metamizole, paracetamol, high-dose aspirin, low-dose aspirin, non-aspirin antiplatelet drugs, oral anticoagulants, alpha-blockers, calcium-channel, blockers, beta-blockers, ACE inhibitors, ARA, diuretics (high-ceiling, low-ceiling, K-sparing), nitrates, corticosteroids, SYSADOAs, inhaled beta agonist, antidepressant, sex hormones and acid-suppressing drugs.

‡Among current users of tNSAIDs

§Among current single users of tNSAIDs

¶Cut-off points (in milligrams): aceclofenac 150, meclofenamic acid 300, mefenamic acid 1000; niflumic acid 500, celecoxib 200, desketoprofen 50, desoxibuprofen 800, diclofenac 100, flurbiprofen 150, ibuprofen 1200, indometacine 75, ketoprofen 150, ketotorolac 10, lornoxicam 8, meloxicam 7.5, nabumetone 1000, nimesuide 100, piroxicam 10, rofecoxib 25, sulindac 200 and tenoxicam 10. Doses over the cut-off value were considered 'high'.

DOI: 10.1002/pds

tNSAIDs with individual CV risk factors. For the statistical evaluation of the effect modification, we ran the full logistic models across different categories of concerned variables and provide the OR associated with tNSAIDs as compared with non-use by each stratum. We compared the OR across strata by estimating the ratio of OR (ROR) and its 95% CI.[19,20]

Missing values for smoking, BMI and dose of individual tNSAIDs are identified in the tables as a missing category and included as such in the logistic models. We also performed multiple imputation using chained equations for the three variables building 10 imputation datasets to account for random variability.[21] The variables included in the imputation models were the same included in the full model plus the outcome variable (nonfatal AMI). However, we did not find any material difference (see Table 3 web in supplementary material) and thus results are only reported with the missing-category approach. We used STATA version 12.0 (StataCorp LP, College Station, TX, USA) for all analyses.

RESULTS

The study cohort fulfilling all selection criteria was made up of 799 371 patients who contributed 2 258 545 person-years. By computer search, we retrieved 11 809 potential cases. After individual review, 3833 were considered as valid incident cases of nonfatal AMI (Figure 1 web), yielding to an incidence of 1.70 per 1000 patient-years (2.73 and 0.94 per 1000 patient-years in men and women, respectively). As expected, cases presented a higher prevalence of CV and rheumatic diseases (Table 1 web), as well as use of CV drugs (Table 2 web).

Risks associated with tNSAIDs as a group

We did not find a significant increased risk associated with the current use of tNSAIDs as a group (OR = 1.08; 0.95–1.24) (Table 1). A narrower exposure window (7 days) did not materially change the overall results (OR = 1.03; 0.88–1.20), so we only used the 30-day window for further analyses.

Among tNSAIDs current users, we did not identify a dose effect, whereas there was a significant increased risk associated with long-term use (>1 year) (OR = 1.43; 1.11–1.83). No significant difference was found by indication (Table 1).

Effect of background CV risk

While in patients at low or intermediate background risk tNSAIDs did not show any association with AMI, results revealed a moderate positive association among those at high background CV risk (OR = 1.28; 1.06–1.54; ROR high versus low = 1.39; 1.06–1.82) (Figure 1). A greater increased risk was also observed among diabetics (OR = 1.31; 1.04–1.65; ROR = 1.31; 0.99–1.74) and suggested in patients with history of IHD, dyslipidemia and smokers (Figure 1). The strongest association with AMI was obtained in patients at high background CV risk exposed to tNSAIDs for long-term (>365 days) (OR = 1.80; 1.26–2.58). However, in high-risk population, even short-term treatments were associated with an increased AMI risk (OR = 1.32; 1.01–1.71) (Figure 2).

Risks associated with individual tNSAIDs

Aceclofenac was the only tNSAID which showed a significant increased risk (OR = 1.59; 1.15–2.19). For the rest of tNSAIDs, we did not detect any significant association, but all of them showed 95% CI which included an OR of 1.5 or over, with the exception of ibuprofen (OR = 0.95; 0.78–1.16) (Table 2).

For the three tNSAIDs more widely used (ibuprofen, diclofenac and aceclofenac), we explored the effect of dose, duration and background risk (Table 3). For ibuprofen, we did not observe an increased risk in any condition of use. For diclofenac, we observed a significant increased risk in patients with treatments longer than 365 days (OR = 1.70; 1.07–2.71) and in high-risk patients (OR = 1.51; 1.05–2.17). For aceclofenac, significant increased risks were observed for high doses (>150 mg, OR = 1.95; 1.30–2.93), for both short (OR = 1.78; 1.04–3.05) and long-term durations (OR = 1.88; 1.02–3.48) and for patients at high risk (OR = 1.86; 1.14–3.01). A duration effect was also suggested when all tNSAIDs different from diclofenac, aceclofenac and ibuprofen were grouped together (OR = 1.45; 0.97–2.17).

Effect of low-dose aspirin

The current use of low-dose aspirin was greater in cases (17.1%) than in controls (10.6%), yielding to a non-adjusted OR of 1.90 (1.72–2.10). However, when fully adjusted, the current use of low-dose aspirin showed a protective effect (OR = 0.87; 0.77–0.99) (Table 2 web). Low-dose aspirin did not significantly modify the OR of nonfatal AMI associated with tNSAIDs as a group (OR of tNSAIDs among aspirin users = 1.16; 0.83–1.62 vs OR among non-users of aspirin = 1.04; 0.89–1.21; ROR = 1.12; 0.77–1.61) nor with any of the individual tNSAIDs evaluated (Table 3).

DOI: 10.1002/pds

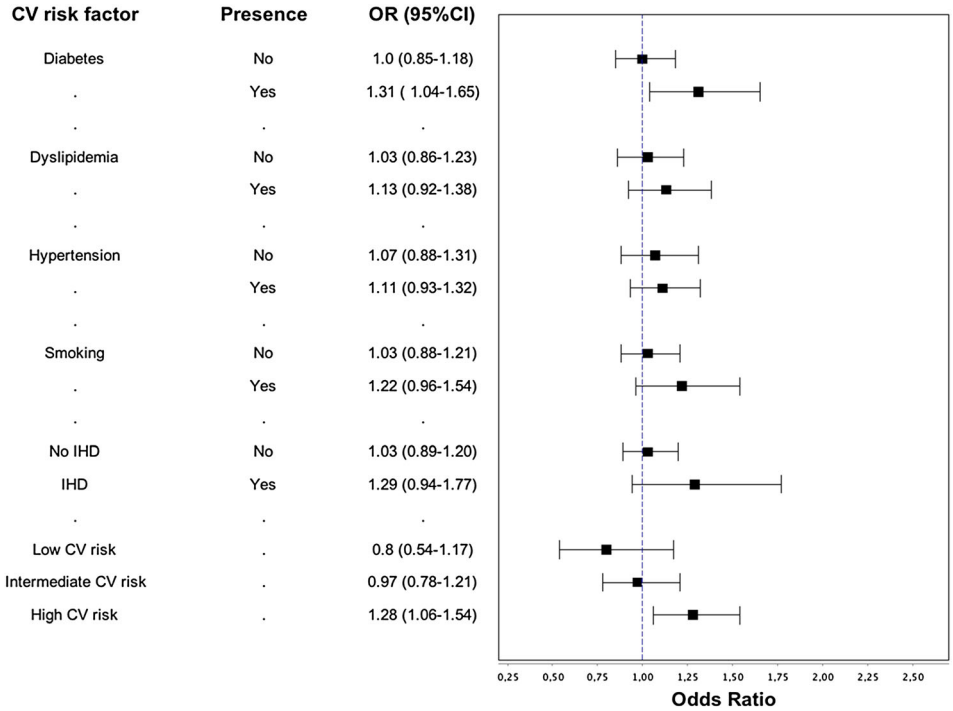

Figure 1. Risk of nonfatal AMI associated with NSAIDs by different individual risk factors and background cardiovascular risk. IHD: ischaemic heart disease. For definition of CV risk level, see methods

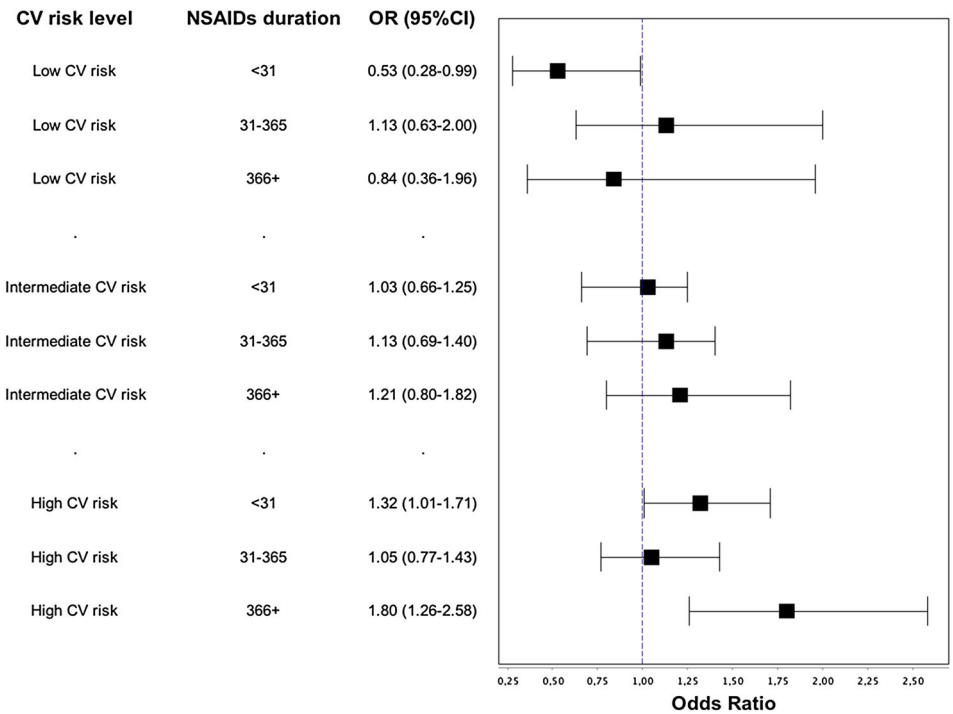

Figure 2. Risk of nonfatal AMI associated with NSAIDs by different background cardiovascular risk and duration of treatment. For definition of CV risk level, see methods

DOI: 10.1002/pds

Table 2. Risk of nonfatal AMI with the current single use of individual tNSAIDS as compared with non-use

NSAID	Cases (%) $N = 3833$	Controls (%) $N = 20\,000$	Non-adjusted* OR (95% CI)	Adjusted† OR (95%CI)
Aceclofenac	54 (1.41)	201 (1.00)	1.50 (1.11–2.04)	1.59 (1.15–2.19)
Desoxibuprofen	8 (0.21)	24 (0.12)	1.84 (0.83–4.11)	1.77 (0.77–4.07)
Dexketoprofen	14 (0.37)	51 (0.26)	1.53 (0.84–2.78)	1.36 (0.73–2.54)
Diclofenac	84 (2.20)	404 (2.00)	1.16 (0.91–1.47)	1.14 (0.88–1.47)
Ibuprofen	140 (3.65)	801 (4.00)	0.97 (0.80–1.17)	0.95 (0.78–1.16)
Indometacin	12 (0.30)	61 (0.30)	1.08 (0.58–2.02)	1.11 (0.57–2.13)
Ketorolac	8 (0.21)	38 (0.20)	1.17 (0.54–2.52)	0.90 (0.40–1.98)
Lornoxicam	9 (0.23)	27 (0.14)	1.87 (0.88–4.00)	1.54 (0.68–3.46)
Meloxicam	20 (0.50)	88 (0.44)	1.27 (0.78–2.08)	1.13 (0.67–1.91)
Naproxen	18 (0.47)	90 (0.45)	1.11 (0.67–1.85)	0.98 (0.57–1.69)
Piroxicam	16 (0.40)	100 (0.50)	0.90 (0.53–1.52)	0.87 (0.50–1.52)

Only tNSAIDs with ≥5 exposed cases are shown.
*Model only adjusted for the matching variables (sex, age and calendar year).
†Full adjusted model (Table 1).

Risk associated with non-narcotic analgesics and SYSADOAs

The use of paracetamol was not associated with an increased risk overall (OR = 0.84; 0.74–0.95) (Table 4) nor in any of the situations examined: high doses (>2000 mg/day; OR = 0.87; 0.71–1.07), long-term treatments (>365 days; OR = 0.89; 0.72–1.11) or high background CV risk (OR = 0.80; 0.67–0.94). No relevant interaction with aspirin was suggested (ROR = 1.02; 0.60–1.62) (Table 5).

For metamizole, we did not find a significant association with nonfatal AMI (OR = 1.06; 0.87–1.29) (Table 4), even when used over long-term periods (OR = 0.83; 0.54–1.28) or in high-risk populations (OR = 1.08; 0.83–1.40). However, a moderate increased risk cannot be ruled out at high doses (>1150 mg/day, OR = 1.14; 0.87–1.50). No relevant interaction with low-dose aspirin was suggested (ROR = 0.98; 0.60–1.62) (Table 5).

The use of SYSADOAs was not associated with an increased the risk of AMI overall (OR = 0.68; 0.47–0.99) (Table 4), after long-term duration (OR = 0.72; 0.34–1.55) and in high CV risk patients (OR = 0.64; 0.36–1.14) (Table 5).

DISCUSSION

The main findings of the present study are as follows: (i) the use of tNSAIDs as a group was associated with an increased risk of nonfatal AMI only when used either for long-term or in patients at high background CV risk; (ii) the risk varied across individual tNSAIDs, with aceclofenac and diclofenac showing the greatest risks, in particular when used in a high-risk population or for long-term, whereas ibuprofen did not show an increased risk in any of the conditions examined; (iii) the concomitant use of low-dose aspirin did not modify the relative risk of nonfatal AMI associated with either tNSAIDs as group or with any of the individual drugs examined; and (iv) paracetamol, metamizole and SYSADOAs were not associated with an increased risk of nonfatal AMI even in patients at high background CV risk or when used for long-term treatments.

Our study suggests that the increased risk of having a nonfatal AMI clusters on patients with a high background CV risk. Similar results were found in previous studies.[2,4,22] The interpretation of this data may be that tNSAIDs have an effect mainly when the endothelial function is already impaired, which is biologically meaningful. Nevertheless, other researchers reported similar relative risks in low-risk populations.[1,3,23–25] However, in this controversy, there is a general agreement[26,27] in recommending special caution in high-risk, as even small increases of relative risk would translate into important increases in the absolute risk.

Although the available evidence supports a dose-effect, at least for some tNSAIDs,[1,2] in our study, we did not find it either for tNSAIDs as a group or for any individual tNSAIDs analysed, with the exception of aceclofenac. As the cut-off points have varied considerably across studies, we performed a sensitivity analysis modifying the cut-off points for ibuprofen (<1800 vs ≥1800 mg) and diclofenac (<150 vs ≥150 mg or <75 vs ≥75 mg), the most widely used drugs, but we did not observe any dose-effect either for them or for tNSAIDs as a group (results not shown).

The most important predictor of an increased risk, along with the high background CV risk, was the long-term duration of treatment. Actually, we obtained the highest risks when both factors concur. Other studies have also reported increasing effects with

DOI: 10.1002/pds

Table 3. Evaluation the effect of dose, duration, background CV risk, and concomitant low-dose aspirin use with current use of most widely used NSAIDs

NSAID	Cases (%) $N = 3833$	Controls (%) $N = 20\,000$	Non-adjusted* OR (95% CI)	Adjusted† OR (95% CI)
Ibuprofen	$N = 140$	$N = 801$		
Dose (mg)				
Up to 1200	38 (1.00)	232 (1.16)	0.91 (0.64–1.30)	0.90 (0.62–1.30)
>1200	44 (1.15)	306 (1.53)	0.79 (0.57–1.09)	0.77 (0.55–1.07)
Unknown	58 (1.51)	263 (1.31)	1.22 (0.91–1.63)	1.22 (0.90–1.66)
Treatment duration				
<31 days	70 (1.83)	428 (2.14)	0.90 (0.69–1.17)	0.91 (0.69–1.19)
31–365 days	48 (1.25)	261 (1.31)	1.03 (0.75–1.40)	1.00 (0.72–1.39)
366 + days	22 (0.57)	112 (0.56)	1.10 (0.69–1.74)	1.01 (0.62–1.65)
Background CV risk				
Low/intermediate	60 (3.34)	580 (4.13)	0.89 (0.68–1.18)	0.79 (0.59–1.06)
High	80 (3.93)	221 (3.71)	1.08 (0.82–1.41)	1.13 (0.85–1.52)
Aspirin use‡				
No	108 (3.76)	689 (4.08)	0.98 (0.79–1.21)	0.94 (0.75–1.18)
Yes	21 (3.21)	90 (4.26)	0.77 (0.47–1.27)	0.70 (0.40–1.22)
Diclofenac	$N = 84$	$N = 404$		
Dose (mg)				
Up to 100	36 (0.94)	148 (0.74)	1.37 (0.94–1.98)	1.37 (0.92–2.02)
>100	28 (0.73)	144 (0.72)	1.07 (0.71–1.61)	1.03 (0.67–1.58)
Unknown	20 (0.52)	112 (0.56)	1.00 (0.61–1.60)	0.99 (0.60–1.64)
Treatment duration				
<31 days	34 (0.90)	172 (0.86)	1.09 (0.75–1.58)	1.02 (0.69–1.51)
31–365 days	23 (0.60)	142 (0.71)	0.90 (0.58–1.41)	0.93 (0.58–1.49)
366 + days	27 (0.70)	90 (0.45)	1.69 (1.09–2.61)	1.70 (1.07–2.71)
Background CV risk				
Low/intermediate	32 (1.78)	290 (2.06)	0.98 (0.68–1.43)	0.89 (0.60–1.30)
High	52 (2.56)	114 (1.92)	1.45 (1.04–2.04)	1.51 (1.05–2.17)
Aspirin use‡				
No	62 (2.16)	331 (1.96)	1.18 (0.90–1.55)	1.12 (0.83–1.51)
Yes	17 (2.60)	44 (2.08)	1.36 (0.76–2.42)	1.55 (0.82–2.95)
Aceclofenac	$N = 54$	$N = 201$		
Dose (mg)				
Up to 150	5 (0.13)	28 (0.14)	1.00 (0.39–2.61)	0.82 (0.30–2.24)
>150	36 (0.94)	104 (0.52)	1.94 (1.32–2.84)	1.95 (1.30–2.93)
Unknown	13 (0.34)	69 (0.34)	1.06 (0.58–1.92)	1.36 (0.73–2.51)
Treatment duration				
<31 days	20 (0.52)	60 (0.30)	1.85 (1.11–3.08)	1.78 (1.04–3.05)
31–365 days	20 (0.52)	89 (0.45)	1.26 (0.77–2.06)	1.30 (0.78–2.18)
366 + days	14 (0.37)	52 (0.26)	1.52 (0.84–2.76)	1.88 (1.02–3.48)
Background CV risk				
Low/intermediate	25 (1.39)	144 (1.02)	1.57 (1.02–2.43)	1.38 (0.88–2.16)
High	29 (1.43)	57 (0.96)	1.57 (1.00–2.49)	1.86 (1.14–3.01)
Aspirin use‡				
No	39 (1.36)	171 (1.01)	1.45 (1.02–2.07)	1.48 (1.02–2.16)
Yes	11 (1.68)	20 (0.95)	1.83 (0.85–3.91)	1.98 (0.83–4.70)

For dose and duration, the category of reference was non-use of NSAIDs overall. For background CV risk and aspirin use, the category of reference was non-use of NSAID within each stratum.
*Model only adjusted for the matching variables (sex, age and calendar year).
†Full adjusted model (Table 1).
‡No: non-use of low-dose aspirin; yes: current use of low-dose aspirin.

prolonged durations.[1,2] Notwithstanding, our data show that in high-risk patients, even short courses of tNSAIDs may be harmful, as other studies have reported.[2]

Ibuprofen was not associated with a significant increased risk in most situations examined. This is in contrast with the results found in clinical trials.[3] Such discrepancy may be partly explained by the fact that in clinical trials, researchers used high doses (2.400 mg/day), rarely seen in practice (in our study, just 1 in 801 users). Our study is consistent with most epidemiological studies showing that at low-moderate doses, ibuprofen does not appear to increase AMI risk.[1,2]

As of now, diclofenac has been the tNSAID most consistently identified with a higher AMI risk, with an estimated OR around 1.4.[1,2] Such an effect appeared to be present with both low and high doses,[2] though in some studies there was a clear dose gradient.[22] Our results also point out to an increased risk with

DOI: 10.1002/pds

Table 4. Risk of nonfatal AMI associated with non-narcotic analgesics and SYSADOAs*

Drugs	Cases (%) $N = 3833$	Controls (%) $N = 20\,000$	Non-adjusted† OR (95% CI)	Adjusted‡ OR (95% CI)
Paracetamol				
Non use	1532 (40.00)	7955 (39.77)	1 (ref.)	1 (ref.)
Current	552 (14.40)	2798 (14.00)	1.05 (0.94–1.18)	0.84 (0.74–0.95)
Past	1060 (27.65)	5301 (26.51)	1.05 (0.97–1.15)	0.89 (0.81–0.98)
Remote	689 (17.98)	3946 (19.73)	0.91 (0.82–1.00)	0.85 (0.77–0.95)
Metamizole				
Non use	2889 (75.37)	15 736 (78.68)	1 (ref.)	1 (ref.)
Current	154 (4.00)	655 (3.28)	1.31 (1.09–1.57)	1.06 (0.87–1.29)
Past	374 (9.76)	1605 (8.03)	1.28 (1.14–1.45)	1.15 (1.00–1.31)
Remote	416 (10.85)	2004 (10.02)	1.13 (1.01–1.27)	1.06 (0.94–1.20)
SYSADOAs*				
Non use	3675 (95.88)	19 070 (95.35)	1 (ref.)	1 (ref.)
Current	34 (0.89)	282 (1.41)	0.67 (0.48–0.94)	0.68 (0.47–0.99)
Past	61 (1.59)	283 (1.42)	1.10 (0.84–1.44)	1.19 (0.89–1.59)
Remote	63 (1.64)	365 (1.83)	0.92 (0.71–1.19)	0.91 (0.69–1.21)

*SYSADOAs includes glucosamine and condroitin sulfate.
†Model only adjusted for the matching variables (sex, age and calendar year).
‡Full adjusted model (Table 1).

diclofenac, but it was only significant in high-risk patients and in those who used it over long periods.

Aceclofenac was the only tNSAID associated with an increased risk of nonfatal AMI, confirming the results by Bueno *et al.*,[4] and the only one showing a dose-effect. Aceclofenac is greatly metabolised to diclofenac,[28] and this may partly explain the results. It is interesting to note that in three epidemiological studies performed in Spain, aceclofenac was identified as the tNSAID with the lowest risk of upper gastrointestinal bleeding.[10,29,30] Altogether, the available evidence suggests that aceclofenac behaves like a selective COX-2 inhibitor.

Our data do not support a relevant interaction between tNSAIDs and low-dose aspirin. Particularly important is the lack of evidence in this study of an interaction with ibuprofen, contrary to the data reported in experimental research[31] and suggested by an epidemiologic study.[32] However, it is consistent with other epidemiological studies that did not find evidence for such an interaction in real-life conditions of use.[22,33] Moreover, the fact that there is still an important increased risk associated with aceclofenac and diclofenac among aspirin users suggests that aspirin may not be fully effective in preventing the excess risk induced by tNSAIDs.[2]

Results obtained with paracetamol are highly reassuring, as no increased risk was observed in any of the situations examined. The marginally significant decreased risk observed in the main analysis may be the result of some overadjustment due to the complex relations between the multiple potential confounding factors included in the full model. To our knowledge, only two studies have assessed so far the association of paracetamol with AMI: Chan *et al.*[8] reported a dose-dependent increased risk of coronary events (RR = 1.56; 1.26–1.93, in those who used it >22 days/month), whereas Rosenberg *et al.*[9] found no association with AMI among men under 55 years of age, who used it daily for at least 3 months (OR = 0.7; 0.4–1.1). The heavy use of this drug in many countries (14% of the source population in our study were current users, more than the overall use of NSAIDs) demands from the scientific community a clearer position about the potential association of this drug with AMI. Our findings do not support the concerns raised by Hinz and Brune,[7] but further research is required.

For metamizole, the data do not suggest a relevant increased risk of nonfatal AMI, although at daily doses higher than 1150 mg, a moderate increased risk, similar to tNSAIDs as a group, cannot be ruled out. In our study, SYSADOAs were not associated with an increased AMI risk, even in the most susceptible patients (with high background CV risk or aspirin users). The significant risk reduction observed in some analysis merits a deeper study, but a 'healthy user effect' cannot be ruled out. Although the efficacy of SYSADOAs in osteoarthritis is a matter of controversy,[34,35] these data are, at least, reassuring.

The main strengths of our study are the following: (i) GPs are the gatekeepers of the Spanish National Health System, and all patients, including those discharged from hospitals, should visit them in order to continue treatment; therefore, the registry of important diseases can be considered almost complete; interestingly, our estimates of incidence of are similar to those found in a registry-based study[36]; (ii) GPs need to use the computer to fill in prescriptions, so

DOI: 10.1002/pds

Table 5. Risk of nonfatal AMI associated with current use of non-narcotic analgesics and SYSADOAs by dose, treatment duration, background CV risk and low-dose aspirin use

Drugs	Cases (%) $N = 3833$	Controls (%) $N = 20\,000$	Non-adjusted* RR (95% CI)	Adjusted† RR (95% CI)
Paracetamol				
Daily dose				
Up to 2000 mg	183 (4.77)	1018 (5.10)	0.96 (0.81–1.14)	0.75 (0.62–0.90)
>2000 mg	142 (3.70)	711 (3.55)	1.06 (0.88–1.29)	0.87 (0.71–1.07)
Unknown	227 (5.92)	1069 (5.34)	1.14 (0.97–1.33)	0.91 (0.77–1.08)
Treatment duration				
<31 days	198 (5.17)	1086 (5.43)	0.97 (0.82–1.14)	0.81 (0.68–0.96)
31–365 days	218 (5.69)	1107 (5.54)	1.06 (0.90–1.24)	0.84 (0.71–1.00)
366 + days	136 (3.55)	605 (3.02)	1.22 (1.00–1.49)	0.89 (0.72–1.11)
Background CV risk				
Low	51 (9.92)	469 (8.40)	1.18 (0.85–1.63)	1.11 (0.77–1.59)
Intermediate	165 (12.84)	1284 (15.16)	0.94 (0.77–1.14)	0.84 (0.68–1.03)
High	336 (16.52)	1045 (17.56)	0.92 (0.79–1.07)	0.80 (0.67–0.94)
Aspirin use‡				
No	382 (13.29)	2216 (13.13)	1.05 (0.92–1.19)	0.85 (0.74–0.98)
Yes	124 (18.96)	391 (18.50)	1.07 (0.82–1.39)	0.87 (0.65–1.18)
Metamizole				
Daily dose				
Up to 1150 mg	8 (0.21)	66 (0.33)	0.67 (0.32–1.41)	0.47 (0.22–1.02)
>1150 mg	80 (2.10)	327 (1.64)	1.37 (1.07–1.75)	1.14 (0.87–1.50)
Unknown	66 (1.72)	262 (1.31)	1.40 (1.06–1.84)	1.13 (0.84–1.51)
Treatment duration				
<31 days	69 (1.80)	265 (1.33)	1.44 (1.10–1.88)	1.25 (0.94–1.67)
31–365 days	56 (1.46)	241 (1.21)	1.30 (0.97–1.74)	0.99 (0.72–1.36)
366 + days	29 (0.76)	149 (0.75)	1.09 (0.73–1.63)	0.83 (0.54–1.28)
Background CV risk				
Low	8 (1.56)	115 (2.06)	0.77 (0.37–1.59)	0.66 (0.31–1.41)
Intermediate	43 (3.35)	281 (3.32)	1.16 (0.83–1.62)	1.08 (0.76–1.53)
High	103 (5.06)	259 (4.35)	1.22 (0.96–1.55)	1.08 (0.83–1.40)
Aspirin use‡				
No	103 (3.58)	501 (2.97)	1.30 (1.04–1.61)	1.09 (0.86–1.37)
Yes	41 (6.27)	102 (4.82)	1.44 (0.98–2.11)	1.07 (0.69–1.67)
SYSADOAs§				
Treatment duration				
<31 days	7 (0.18)	67 (0.34)	0.55 (0.25–1.19)	0.70 (0.32–1.54)
31–365 days	19 (0.50)	149 (0.75)	0.67 (0.41–1.08)	0.66 (0.40–1.09)
366 + days	8 (0.21)	66 (0.33)	0.64 (0.31–1.33)	0.72 (0.34–1.55)
Background CV risk				
Low	6 (1.17)	75 (1.34)	0.89 (0.38–2.06)	0.87 (0.36–2.11)
Intermediate	12 (0.93)	134 (1.58)	0.64 (0.35–1.17)	0.67 (0.37–1.24)
High	16 (0.79)	73 (1.23)	0.63 (0.36–1.08)	0.64 (0.36–1.14)
Aspirin use‡				
No	30 (1.04)	234 (1.39)	0.77 (0.53–1.13)	0.79 (0.53–1.18)
Yes	3 (0.46)	36 (1.70)	0.27 (0.08–0.89)	0.30 (0.09–1.03)

For dose and duration, the category of reference was non-use of NSAIDs overall. For background CV risk and aspirin use, the category of reference was nonuse of NSAID within each stratum.
*Model only adjusted for the matching variables (sex, age and calendar year).
†Full adjusted model.
‡No: non-use of low-dose aspirin; yes: current use of low-dose aspirin.
§SYSADOAs includes glucosamine and condroitin sulfate. Doses hardly differed and were not assessed.

the under-recording of prescription drugs is unlikely; (iii) controls were randomly selected from the source population, which assures representativeness of the exposure and prevents from the possibility of a selection bias; (iv) researchers were blind to drug exposure when ascertaining cases, therefore avoiding a differential misclassification; and (v) the study was shown sensitive enough to detect known risk factors of ischemic stroke (Table 1 web) ,which suggest that there should not be a major misclassification of them.

The study may have some limitations. Firstly, we did not include fatal cases, as GPs do not have a complete registry of deaths and, particularly, there is not an appropriate recording of the cause of death; however, in our view, this would have introduced a bias in the study only if NSAIDs (all except aceclofenac and diclofenac), have had an influence on survival (e.g. increasing the case-fatality rate in order to show a spurious lack of association with nonfatal AMI), which is unlikely. Additionally, an

DOI: 10.1002/pds

overview of randomised clinical trials and observational studies has suggested that NSAIDs have a more prominent effect on nonfatal AMI.[37] Secondly, over-the-counter drugs, such as analgesic aspirin, are not recorded in BIFAP, as they are not recorded in most databases; however, assuming that non-users of NSAIDs had a higher use of analgesic aspirin than NSAIDs users, the consequence would have been a spurious increased risk associated with NSAIDs, because of the protective effect of aspirin; but it is highly unlikely that this potential bias impacts selectively on diclofenac and aceclofenac which are the only tNSAIDs shown to be associated with an increased risk. Thirdly, although we adjusted for many potential confounding factors, a residual confounding cannot be ruled out. As hypertension may be acting as an intermediate variable, we excluded these factors from the models in a sensitivity analysis, as previously suggested,[2] but the main effect of tNSAIDs did not materially change (data not shown).

CONFLICT OF INTEREST

FdA received a fee as member of the scientific committee of a study conducted by Fundación Jordi Gol i Gurina (Department of Health, Government of Catalunya) aiming at assessing the CV effects of agents used in osteoarthritis; this study is funded by Bioibérica, manufacturer of glucosamine and chondroitin sulfate. Such study is being carried out by other researchers and has no connection with the present one. LAGR received unrestricted research grants from AstraZeneca and Bayer.

KEY POINTS

- The major determinants of risk of nonfatal acute myocardial infarction (AMI) associated with traditional NSAIDs (tNSAIDs) were the background cardiovascular (CV) risk and the duration of treatment.
- The risk of nonfatal AMI varied across individual tNSAIDs, with aceclofenac and diclofenac showing the greatest risks, while ibuprofen did not show any increased risk.
- The concomitant use of low-dose aspirin did not modify the relative risk of nonfatal AMI associated with either tNSAIDs as group or with any of the individual drugs examined.
- Paracetamol, metamizole and SYSADOAs were not associated with an increased risk of nonfatal AMI even in patients at high background CV risk, or when used for long-term treatments.

ETHICS STATEMENT

This study only used fully anonymised data, and the review by an Ethics Research Committee was not legally required.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the excellent collaboration of general practitioners taking part in BIFAP. BIFAP is funded by the Spanish Agency for Medicines and Medical Devices. This study was supported by a research grant from Fondo de Investigación Sanitaria—Ministerio de Ciencia e Innovación (no. PI071064).

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