***Title Page (WITH Author Details)**

TITLE PAGE

Title of the article.

Analgesic use and risk of acute coronary events in patients with osteoarthritis: a population-based nested case-control study.

Running title: Osteoarthritis drugs and coronary riskAuthors: Caridad Pontes(1,2), Josep Ramon Marsal (3,4), Josep Maria Elorza (5,6), Maria Aragón (5), Daniel Prieto-Alhambra (7,8), Rosa Morros (1,5).

Institutions at which the research was conducted:

1. Departament de Farmacologia, de Terapèutica i de Toxicologia, Universitat Autònoma de Barcelona, Barcelona (Spain).

2. Hospital de Sabadell, Institut Universitari Parc Taulí. Sabadell (Spain).

3. Unitat de Suport a la Recerca de Lleida, IDIAP Jordi Gol. Barcelona (Spain).

4. Unitat d'Epidemiologia del Servei de Cardiologia. Hospital Universitari Vall d'Hebron.

5. Institut d'Investigació d'Atenció Primària Jordi Gol (IDIAP Jordi Gol). Barcelona (Spain)

6. CAP Ripollet. Servei d'Atenció Primària Vallés Occidental. Direcció d'Atenció Primària Metropolitana Nord. Institut Català de la Salut.

7. URFOA-IMIM and RETICEF, Internal Medicine, Parc de Salut Mar-Instituto Carlos III, Barcelona, (Spain).

8. Musculoskeletal Epidemiology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford (United Kingdom).

Corresponding author:

Rosa Morros: Institut d'Investigació d'Atenció Primària Jordi Gol (IDIAP Jordi Gol) - Departament de Farmacologia, de Terapèutica i de Toxicologia, Universitat Autònoma de Barcelona, Barcelona (Spain).

Address: IDIAP Jordi Gol. Gran Via de les Corts Catalanes 587. 08007 Barcelona.

E-mail: rmorros@idiapjgol.org

Telephone number: +34 93 482 46 94

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Analgesic use and risk of acute coronary events in patients with osteoarthritis: a population-based nested case-control study.

Running title: Osteoarthritis drugs and coronary risk

Article keywords: Osteoarthritis, Myocardial Infarction, Angina Unstable, Drug therapy, electronic health records.

Key Points:

- ACE risk is high in OA patients.
- Baseline morbidity and cardiovascular risk, but not OA characteristics or extension of joint involvement, are associated to increased risk of ACE.
- Use of classical NSAIDs, and in particular of naproxene or diclofenac, is associated to increased ACE risk,.
- Exposure to opioid analgesics is associated to increased ACE risk.
- None of COX-2 selective NSAIDs, topical NSAIDs, glucosamine, chondroitin sulphate, paracetamol or metamizole were associated to increased ACE risk.

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Prior postings and presentations

The study was presented as an oral communication at the Annual Congress of the European League Against Rheumatism (EULAR) (Rome, 2015), and as a poster communication at the XXVII Congress of the Sociedad Española de Farmacología Clínica (Sevilla, 2014), and at the 12th Congress of the European Association for Clinical Pharmacology and Therapeutics (Madrid, 2015).

ABSTRACT

Purpose: Recent controversies on the safety profile of opioids and paracetamol have led to changes in clinical guidance for osteoarthritis (OA) management. We studied the existing association between the use of different OA drug therapies and the risk of acute coronary events (ACE).

Methods: A cohort of patients with clinically diagnosed OA (according to ICD10 codes) was identified in the SIDIAP database. Within the cohort, cases with incident ACE (AIM or unstable angina) between 2008 and 2012 were identified using ICD10 codes and data from hospital admission. Controls were 3 ACE-free subjects matched by sex, age (±5 years), area, and year of OA diagnosis (±2 years). Linked pharmacy dispensation data was used to assess exposure to drug therapies. Multivariable conditional logistic regression models were fitted to estimate adjusted odds ratio (OR) for ACE.

Findings: 5663 cases and 16989 controls were studied. Previous morbidity and cardiovascular risk was higher in cases than controls, with no differences in type or number of joints with OA. Multivariable adjusted analyses showed increased risks (OR(95%CI)) related to the use of diclofenac (1.16 (1.06 - 1.27)), naproxen (1.25 (1.04 - 1.48)) and opioid analgesics (1.13 (1.03 - 1.24). No significant associations were observed for COX-2 selective NSAIDs, topical NSAIDs, glucosamine, chondroitin sulphate, paracetamol or metamizole.

Implications: In patients with clinically diagnosed OA, the use of non-selective NSAIDs or opioid analgesics is associated with an increased risk of acute coronary events. These risks should be considered when selecting treatments for OA in patients with high cardiovascular risk.

INTRODUCTION

Osteoarthritis (OA) is the most prevalent rheumatic disease in the elderlyand is associated to higher mortality than that of the general population [1-6]: in a recent British study conducted in primary care, a 70% increased risk (standardized mortality ratio (95% CI) 1.71 (1.49 to 1.98)) was reported, with walking disability identified as major risk factor, together with history of diabetes, cancer and cardiovascular disease [7].

Following the description of an increased cardiovascular risk for use of selective non-steroidal antiinflammatory drugs (NSAIDs) COX-2 inhibitors in clinical trials [8,9], an excess cardiovascular risk amongst users of non-selective NSAIDs has also been reported [10]. A recent meta-analysis of 31 clinical trials concluded that various NSAIDs, both COX-2 selective and not, were associated with over 30% increased cardiovascular risk [11]. Alternative therapies such as paracetamol and opioids have also been recently related to cardiovascular, gastrointestinal and/or skeletal adverse events, leading to modifications in existing guidelines [12].

The prevalence of use of NSAIDs in the general population in Spain is over 40% [13, 14], and this figure increases further to >60% in the population with OA [15, 16]. According to the Spanish Society of Rheumatology, 10% of the Spanish population has knee pain suggestive of osteoarthritis, and 6% report hand OA. [17]. The baseline cardiovascular risk in the Mediterranean population is known to be different from that of Northern countries, but similarly modified by the use of analgesic drugs [14].

A number of risk management recommendations and interventions aimed to reduce the risks associated to NSAIDs prescription have been implemented in our region in the last decade [18]. Also, the publication of several regulatory alerts on NSAIDs safety may have varied clinical practice with regards not only to drug selection, but also to dosing and duration of treatments [13]. This may have modified the risk at the population level, since the uptake of information and interventions might have impacted risk.

To assess the risk of acute coronary events (ACE) related to the use of various drugs commonly used for the treatment of OA in our setting, we conducted a nested case-control study within a cohort of patients with clinically diagnosed OA in Catalonia. .

METHODS

Data source

We obtained data from primary care electronic medical records from the Information System for the Development of Research in Primary Care (*Sistema de Información para el Desarrollo de la Investigación en Atención Primaria* or SIDIAP) [19] which has been previously shown to be suitable for the study of cardiovascular diseases [20]. This database contains longitudinal data since 2006 on demographics, ICD-10 coded health problems, clinical visits to primary care centers and results of blood / other tests, amongst others, obtained from the computerized medical records of 274 primary care centers in Catalonia covering a population of >5,800,000 patients (>80% of the Catalan population). The billing records for pharmacy dispensation of the Catalan health system (CATSALUT) were linked to medical records, including information on product code according to the Anatomical Therapeutic Chemical classification (ATC), number of daily defined doses (DDDs) dispensed, dosage regimens, and strength of the pharmaceutical form. This pharmacy dispensing database only includes data on reimbursed drugs dispensed under prescriptions, so over-the-counter drugs could not be captured. Information on hospital admissions was obtained from the official regional database of the CATSALUT ("Conjunt Mínim Bàsic de Dades a l'Alta Hospitalària", CMBDAH), using a trusted third party deterministic linkage system to maintain data confidentiality and protection. This third party has no access to clinical information, only to codes and IDs [21]. Data from SIDIAP are always anonymized so it is not possible to re-identify individuals.

Ethical considerations

The study protocol was approved by the Independent Ethics Committee of the Institut d'Investigació Primària Jordi Gol before any data extraction.

Study population

The OA cohort included all patients registered in SIDIAP who visited any primary care professional at least twice in the previous year, who had been diagnosed with OA according to a previously validated list of ICD-10 codes [22, 23] (polyarticular: M15.0, 15.3 and 15.9, knee: M17.0-17.5, M17.9, hip M16.0-16.7, M16.9, hands: M15.1, M15.2, M18.0-18.5, M18.9, column: M47.8, M47.9, or not specified: M19.0-19.2, M19.8-19.9). Patients with a recorded history of any inflammatory arthritis were excluded.

A case-control study was nested in the OA cohort. Cases were defined as patients with a first ACE between January 2008 and December 2012, identified through a first diagnosis of acute myocardial infarction (AMI) or of unstable angina according to ICD10 codes in primary care records, and confirmed by hospital admission records. All patients with ACE previous to the OA diagnosis or January 2008 were excluded.

Controls were selected at random from the remaining ACE-free participants in the OA cohort, matched 3:1 by age (± 5 years), sex, geographical area, and year (± 2 years) since first OA diagnosis to cases. The index date for cases was the earliest of first hospital or primary care recorded diagnosis of ACE after 31st December 2007. Controls were assigned the same index date as their matched case.

Variables

Age, sex, coronary risk, toxic habits (smoking, alcohol), body mass index, hypertension (date of diagnosis, drug treatment, and the earliest blood pressure recorded value to index date), diabetes mellitus [type, date of diagnosis, organic manifestations (retinopathy, nephropathy), drug treatment and mean HbA1C in last year], dyslipidemia (date of diagnosis, drug treatment, and mean laboratory test values in last year), kidney function (MDRD in the last year estimated from laboratory test data and clinical records of the patient), co-morbidities (stroke or transient vascular accident, atrial fibrillation or flutter, mitral or aortic valve disease or rheumatic heart disease, asthma or chronic obstructive pulmonary disease, carotid or peripheral revascularization or bypass procedures, lower limb amputation, or peripheral artery disease), Charlson index, number of outpatient visits in the previous year, a combined variable of cardiovascular risk built from individual risk factors and a coronary Regicor index [24], were retrieved before the index date(Table 2). Exposure to drugs suggesting or associated to cardiovascular disease at index date were also retrieved (ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, thiazides, other diuretics, other antihypertensives, antiarrhythmics, anticoagulants, antiaggregants, nitrates, digoxin, statins, other hypolipidemic drugs, insulin, oral hypoglycemiants).

The number of different medications used and detailed information for the following ATC groups: M01AA, M01AB, M01AC, M01AE and M01AG (non-selective NSAIDs), M01AH (COX-2 selective NSAIDs), M01AX05 (glucosamine), M01AX25 (chondroitin sulphate), M02AA (NSAIDs for topical use), N02A (opioid analgesics) and N02B (other non-opioid analgesics) were also retrieved. In the main analysis, patients were considered as "exposed"

(drug users) if they had at least 3 dispensings for the same active principle. For a given exposure, 'Current users' were subjects with dispensations within 90 days prior to the index date; 'recent users' those for whom the last dispensation was between 91 and 180 days before the index date, and 'remote users' those for whom the last dispensation was before 365 days before the index date.

Defined Daily Doses (DDD)/day according to the ATC/DDD catalogue [25] were calculated for active principles using the number of packages dispensed and the time periods between dispensations. Treatment duration was derived from the time between first and last dispensation. The number of dispensations and the number of daily defined doses (DDD) dispensed per period were used to derive medication possession ratio below 80%, within 80% and 120% or above 120% of reference DDD.

Sample size

Previous data have described that the SIDIAP database included around 240,000 patients with diagnosed OA at the end of 2010 [15], with 2.1% and 2.3% having a history of AMI and angina respectively. According to published data 26, 27], the expected incidence of ACE in the Catalan population aged between 65 to 75 years is 211 women and 709 men per 100000 inhabitants, respectively. Assuming that women represent 57% of the OA population and have a similar CV risk in the OA population than in the general population, about 1000 new cases of ACE per year were expected. Based on the expected prevalence of exposure for the less frequently used OA treatments, the selection of 3 controls per case would allow, to detect increases of risk of ACE

of 1.5 or higher for exposures with prevalence of 1%, and 1.35 or higher for prevalence of 2%, with type I and II errors of 5% and 20%, respectively [28].

Statistical analysis

Baseline characteristics were contrasted for differences among cases and controls by Fisher exact test for categorical and by non-parametric test (Mann-Whitney test) for numerical data. Incidence rates of ACE in the OA cohort and 95% confidence intervals (95%CI) were estimated assuming a negative binomial distribution. Conditional logistic regression models and computed drug-specific odds ratios (ORs) and 95%CI as compared with drug-specific non-use were calculated. Two models were built for each exposure: a "crude" model matched by age, sex, and years since first OA diagnosis, and an "adjusted" multivariable model, adjusted additionally by body mass index, smoking and alcohol intake, diagnosis of high blood pressure, diabetes mellitus, dyslipidemia, heart valve disease, heart failure or ischaemic heart disease, peripheral arteriopathy or limb amputation, stroke or transient ischaemic event, asthma, chronic lung disease, degree of impairment of renal function, Charlson index, frequency of healthcare consultation, location of OA, polyarthicular OA, number of locations of OA, use of ACEi, ARA-II, antiarrhytmic drugs, anticoagulants, beta-adrenergic blocking agents, calcium channel blockers, diuretics, other antihypertensive drugs, vasodilating agents, antiplatelet agents, statins, other hypolipemiant drugs, antidiabetic drugs, and concurrent use of other drugs for OA.

The association of risks with increases or decreases of exposure was explored. The analyses were carried for all analgesics by the exposure (yes/no), including

all effects with or without significant association. No data imputation was done; for multivariable models, missing data was managed as a separate category. Non multiple comparison correction of the sample size have been done. Sensitivity analyses was made for monotherapy use (unique analgesic exposure during the study period), in order to exclude any possible interaction among the other analgesics drugs. SPSS v15 and R version 3.2.0. were used for analyses.

RESULTS

Baseline characteristics of study population

Patient disposition is shown in Figure 1.

The incidence (95%CI) of ACE (events per 10,000 patient-years) for women and men younger than 74 were 10.62 (9.89 – 11.41) and 34.97 (33.04 – 37.03), and for those 75 or older 37.19 (95%CI: 35.62 – 38.84) and 63.78 (60.51 – 67.23), respectively; incidence rate ratios by sex and age groups are shown in Figure 2. No significant effect of calendar year was observed. A significant gender by age interaction was observed for ages 85 and older, so that incidence was reduced for male subjects, but not for females.

Within the study cohort, 5,663 cases were matched to 16,989 controls. The number or location of OA involved joints did not differ between cases and controls, but polyarticular and hip location were more frequent and knee and hand OA less frequent in the cases (Table 1).

Known risk factors for cardiovascular disease were more frequent amongst cases than controls (Table 2), as was the use of cardiovascular drugs (Table 3).

Non-opioid analgesics were the most common exposures (75.4% controls and 81.3% cases), followed by non-selective NSAIDs (61.1% of controls and 64.2% cases), topical NSAIDs (36.1% controls and 39.6% cases), opioid analgesics (23.6% controls and 28.9% cases) and SYSADOAs (20.5% controls and 18.1% cases). Less than 5% of subjects were exposed to COX -2 selective NSAIDs. Combinations were frequent, including mainly NSAIDS (59% cases and 55.2%

controls), paracetamol or metamizole (36,6% cases and 35,4% controls) and opioids (28.8% cases and 23.4% controls).

Risk estimation of acute coronary events

Crude risks of ACE showed significant associations for all exposures except for aceclofenac, celecoxib and etoricoxib, and selective cox-2 inhibitors as a group; crude OR were of protective sign for glucosamine, chondroitin sulphate and SYSADOAS as a group. Adjusted models showed borderline signification for non-selective NSAIDs (p = 0.052) (Table 4), with significant dose response for cumulative, median dose, and duration of exposure (Figure 3.A.); significance was observed when the analysis was restricted to active exposures at the index date, and when restricted to NSAIDs monotherapy (Table 5). Significantly increased risks were observed for diclofenac and naproxen (Table 4).

Exposures to opioid analgesics were significantly associated to increased risk of ACE (Table 4), with dose-response trend for both cumulative and median dose, but not for duration of exposure (Table 5) (Figure 3.D.); significance was observed when restricted to exposures active at the index date (Table 5). Individual active principles within the opioid group did not show significant risks in the adjusted model (Table 4). Adjusted models did not show significant associations for COX-2 selective NSAIDs, topical NSAIDs, glucosamine, chondroitine sulphate, paracetamol nor metamizole (Table 4).

DISCUSSION

In our data, OA patients had risk scores suggestive of a high cardiovascular risk, and high incidences of ACE. In this population, the use of some non-selective NSAIDs was associated with increased adjusted risk of ACE ranging from 16% (diclofenac) to 25% (naproxen); similarly, opioids were associated with a 13% increased risk of ACE. For NSAIDs as a group and opioids as a group, associations followed a dose-response gradient, and the estimated excess risks were greater for current use when compared to previous use.

The incidence of ACE per 100,000 person-years observed in our study (222.1 for men and 462.4 for women aged 25-74 years, respectively) was greater than the comparable projected estimates in the Spanish population (77 and 263 new cases of acute myocardial infarction per 100,000 person-years in men and women, respectively) [29]; rates between 29-61 and 135-210 new cases per 100,000 person-years for female and male, respectively [30]). This fact is in line with previous reports of increased risk of ACE in the population with OA, thus identifying OA patients as a population potentially at high cardiovascular risk.

A trend for increased adjusted risk was observed for NSAIDs, supported by a significant dose-response gradient and significant risks for exposures active at the index date. This association has an accepted biological plausibility and has been previously characterized [10, 30], also in our setting [14]. Thus we consider that an increase ACE risk associated to exposure to NSAIDs as a group is plausible. Unexpectedly, the bigger risk increase was observed with naproxen, which has been often referred to be relatively safe regarding cardiovascular risk as compared to other NSAIDs [10, 14, 30]. A possible

explanation may be that widespread perception of naproxen's safety may have led to decision to prescribe naproxen to patients requiring NSAIDs who had bigger cardiovascular risk or subclinical disease, thus leading to confounding by indication or protopathic bias. Despite our adjusted model accounted for many potential confounders, we cannot discard some degree of residual confusion; more research is needed to confirm this finding.

Opioid analgesics were unexpectedly associated to an increased ACE risk that was consistent, with significant dose response and persistence of risk in current users. However, the risk could not be attributed to a single product, and both very short and very long exposures had similarly increased risks. While two previous publications have proposed a causal role of opioids in cardiovascular disease [31-33], it is possible that patients exposed to opioids as a result of sequential therapeutic decisions may constitute a different (more diseased and frail) population, as compared to patients treated with drugs used in earlier steps of the analgesic ladder, and thus may have different baseline risks for ACE. Although the multivariable model included adjustments by Charlson Index and several comorbidities, some residual degree of confounding by indication cannot be discarded, and thus a cautious interpretation of these results seems advisable.

The absence of significant associations for non-narcotic analgesics, NSAIDs for topical use and SYSADOAs were all expected, biological plausible and consistent with other studies in our setting [14]. In turn, the absence of risks for COX-2 selective inhibitors is contrary to previous publications describing an increased risk of ACE for these drugs [10, 30]. Reasons for this finding may include the success of risk-minimization strategies deployed in our setting:

health professionals are aware that they should restrict prescription of COX-2 inhibitors to low-risk patients, for short periods and only in the absence of feasible alternatives [18]; we cannot discard that the results, despite our extensive adjustment for potential confounders, might be due to residual confounding by indication due to selective prescription to low-risk subjects.

Limitations of the present study include the observational design, which precludes confirming causality of the detected associations. Also, data that is collected as a part of routine clinical care has not been individually validated for inclusion criteria (ie: OA diagnosis) not for the collection of outcomes (ACE): thus, we cannot guarantee the exhaustivity of the sample nor that all the occurring events have been identified; however, identification of both OA and cardiovascular events has been previously validated in SIDIAP through specific studies [20-23], and in that sense the results may be considered of value. Another limitation of our data source is the lack of linkage between diagnoses and prescriptions, thus we were not able to know if NSAIDs and opioids were prescribed for OA or other indication. Many factors related to differential exposure and/ or risks for ACE were included in our adjusted model, in order to control confounding, but there may be additional relevant risk factors (i ex: OA severity, metabolic syndrome and other comorbidities) not available in our dataset that may result in residual confounding. Also, our adjusted model included some independent risk factors for ACEs which are also known adverse effects of NSAIDs (i ex: hypertension and renal or heart failure), and some medications used to treat these conditions (antihypertensive drugs, diuretics) might represent intermediate variables on a causal path between exposure and outcome. In both cases, adjusting by these intermediate factors may have led to

some degree of overadjustment bias. Finally, our data source provided information on drugs dispensed through the public health system, but did not include information on dispensation through other prescription systems, nor on acquisition of analgesic drugs over the counter. Whether dispensed drugs were actually used by the subjects, and to what extent, cannot be ascertained.

The relevance of our findings should be considered from the perspective of absolute attributable risk. Unfortunately, we did not obtain prevalence of use of drugs from the full OA cohort, and prevalence of use of drugs in the case-control database could not be representative of the overall OA population. A prevalence of use for oral NSAIDs in the OA population of 0.774 was recently reported using the SIDIAP database [34]. Considering our OR adjusted estimate for NSAIDs (1.09), the resulting Absolute Attributable Risk (AAR = 100*(Prevalence of use *(OR-1))/(1+(Prevalence of use*(OR-1))) would be 6.5%. Putting this result in perspective by comparing to published data [35], the obtained AAR for NSAIDs in our exercise is smaller than the Population Attributable Risk (PAR) reported for main risk determinants, such as smoking (PAR 39%) or hypercholesterolaemia (PAR 18%), but within the same range of magnitude than that reported for diabetes (PAR 3%), a recognised and relevant clinical risk factor for cardiovascular events. As regards to other drug exposures (opioids as a whole, diclofenac or naproxen), we have not been able to obtain data from our setting for prevalences of use in OA patients.

In summary, our study has observed that, in our setting, patients with osteoarthritis represent a high-risk population for the development of acute coronary events, and the background risk of this population may be further increased by chronic exposure to non-selective NSAIDs, especially diclofenac

or naproxen. Under current conditions of use, the use of other systemic or topical NSAIDs, selective COX-2 inhibitors, non-narcotic analgesics or SYSADOAs do not represent an independent increase of ACE risk for real life (probably selected) users of these medications. A relatively novel observation of a risk increase associated with the use of opioid analgesics requires confirmation in future studies.

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AUTHOR CONTRIBUTIONS

CP and RM designed the study protocol and reviewed the statistical analysis plan, interpreted results, wrote final report and drafted the manuscript. JRM contributed to the design of the protocol, wrote the statistical plan, and did the study analysis. JME contributed to the design of the protocol and statistical plan

and did the data extraction. MA reviewed the study protocol and analysis plan and contributed to data management and final report review. DP contributed to the study design, interpretation of results and did a critical revision of the article for important intellectual content. All authors authorised the final version to be submitted.

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Conflict of interest

The authors declare that they do not have any contractual employee or financial relationship with Bioibérica S.A. representing a conflict of interest with the present report.

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FIGURE LEGENDS

Figure 1. Patient disposition.

Figure 2. ACE incidence rate ratio by gender and age group.

Footnote: Negative binomial regression.

Figure 3. Risk of ACE associated to use of drugs to treat OA and dose response analysis.

EACH INDIVIDUAL TABLE

Submitted as 5 separated files

Each individual Figure

(submitted as 3 separate files)

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TITLE PAGE

Title of the article.

~~Drug~~Analgesic use and risk of acute coronary events in patients with osteoarthritis: a population-based nested case-control study.

Running title: Osteoarthritis drugs and coronary risk

Article keywords: Osteoarthritis, Myocardial Infarction, Angina Unstable, Drug therapy, electronic health records.

Key Points:

- ACE risk is high in OA patients.
- Baseline morbidity and cardiovascular risk, but not OA characteristics or extension of joint involvement, are associated to increased risk of ACE.
- Use of classical NSAIDs, and in particular of naproxene or diclofenac, is associated to increased ACE risk,.
- Exposure to opioid analgesics is associated to increased ACE risk.
- None of COX-2 selective NSAIDs, topical NSAIDs, glucosamine, chondroitin sulphate, paracetamol or metamizole were associated to increased ACE risk.

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Prior postings and presentations

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ABSTRACT

Purpose: Recent controversies on the safety profile of opioids and paracetamol have led to changes in clinical guidance for osteoarthritis (OA) management. We studied the existing association between the use of different OA drug therapies and the risk of acute coronary events (ACE).

Methods: A cohort of patients with clinically diagnosed OA (according to ICD10 codes) was identified in the SIDIAP database. Within the cohort, cases with incident ACE (AIM or unstable angina) between 2008 and 2012 were identified using ICD10 codes and data from hospital admission. Controls were 3 ACE-free subjects matched by sex, age (±5 years), area, and year of OA diagnosis (±2 years). Linked pharmacy dispensation data was used to assess exposure to drug therapies. Multivariable conditional logistic regression models were fitted to estimate adjusted odds ratio (OR) for ACE.

Findings:~~**Results:**~~ 5663 cases and 16989 controls were studied. Previous morbidity and cardiovascular risk was higher in cases than controls, with no differences in type or number of joints with OA. Multivariable adjusted analyses showed increased risks (OR(95%CI)) related to the use of diclofenac (1.16 (1.06 - 1.27)), naproxen (1.25 (1.04 - 1.48)) and opioid analgesics (1.13 (1.03 - 1.24). No significant associations were observed for COX-2 selective NSAIDs, topical NSAIDs, glucosamine, chondroitin sulphate, paracetamol or metamizole.

Implications:~~**Conclusions:**~~ In patients with clinically diagnosed OA, the use of non-selective NSAIDs or opioid analgesics is associated with an increased risk of acute coronary events. These risks should be considered when selecting treatments for OA in patients with high cardiovascular risk.

INTRODUCTION

Osteoarthritis (OA) is the most prevalent rheumatic disease in the elderlyand is associated to higher mortality than that of the general population [1-6]: in a recent British study conducted in primary care, a 70% increased risk (standardized mortality ratio (95% CI) 1.71 (1.49 to 1.98)) was reported, with walking disability identified as major risk factor, together with history of diabetes, cancer and cardiovascular disease [7].

Following the description of an increased cardiovascular risk for use of selective non-steroidal antiinflammatory drugs (NSAIDs) COX-2 inhibitors in clinical trials [8,9], an excess cardiovascular risk amongst users of non-selective NSAIDs has also been reported [10]. A recent meta-analysis of 31 clinical trials concluded that various NSAIDs, both COX-2 selective and not, were associated with over 30% increased cardiovascular risk [11]. Alternative therapies such as paracetamol and opioids have also been recently related to cardiovascular, gastrointestinal and/or skeletal adverse events, leading to modifications in existing guidelines [12].

The prevalence of use of NSAIDs in the general population in Spain is over 40% [13, 14], and this figure increases further to >60% in the population with OA [15, 16]. According to the Spanish Society of Rheumatology, 10% of the Spanish population has knee pain suggestive of osteoarthritis, and 6% report hand OA. [17]. The baseline cardiovascular risk in the Mediterranean population is known to be different from that of Northern countries, but similarly modified by the use of analgesic drugs [14].

A number of risk management recommendations and interventions aimed to reduce the risks associated to NSAIDs prescription have been implemented in our region in the last decade [18]. Also, the publication of several regulatory alerts on NSAIDs safety may have varied clinical practice with regards not only to drug selection, but also to dosing and duration of treatments [13]. This may have modified the risk at the population level, since the uptake of information and interventions might have impacted risk.

To assess the risk of acute coronary events (ACE) related to the use of various drugs commonly used for the treatment of OA in our setting, we conducted a nested case-control study within a cohort of patients with clinically diagnosed OA in Catalonia. .

METHODS

Data source

We obtained data from primary care electronic medical records from the Information System for the Development of Research in Primary Care (*Sistema de Información para el Desarrollo de la Investigación en Atención Primaria* or SIDIAP) [19] which has been previously shown to be suitable for the study of cardiovascular diseases [20]. This database contains longitudinal data since 2006 on demographics, ICD-10 coded health problems, clinical visits to primary care centers and results of blood / other tests, amongst others, obtained from the computerized medical records of 274 primary care centers in Catalonia covering a population of >5,800,000 patients (>80% of the Catalan population). The billing records for pharmacy dispensation of the Catalan health system (CATSALUT) were linked to medical records, including information on product code according to the Anatomical Therapeutic Chemical classification (ATC), number of daily defined doses (DDDs) dispensed, dosage regimens, and strength of the pharmaceutical form. This pharmacy dispensing database only includes data on reimbursed drugs dispensed under prescriptions, so over-the-counter drugs could not be captured. Information on hospital admissions was obtained from the official regional database of the CATSALUT ("Conjunt Mínim Bàsic de Dades a l'Alta Hospitalària", CMBDAH), using a trusted third party deterministic linkage system to maintain data confidentiality and protection. This third party has no access to clinical information, only to codes and IDs [21]. Data from SIDIAP are always anonymized so it is not possible to re-identify individuals.

Ethical considerations

The study protocol was approved by the Independent ~~Ethic's~~Ethics Committee of the Institut d'Investigació Primària Jordi Gol before any data extraction.

Study population

The OA cohort included all patients registered in SIDIAP who visited any primary care professional at least twice in the previous year, who had been diagnosed with OA according to a previously validated list of ICD-10 codes [~~21,~~ 22, 23] (polyarticular: M15.0, 15.3 and 15.9, knee: M17.0-17.5, M17.9, hip M16.0-16.7, M16.9, hands: M15.1, M15.2, M18.0-18.5, M18.9, column: M47.8, M47.9, or not specified: M19.0-19.2, M19.8-19.9). Patients with a recorded history of any inflammatory arthritis were excluded.

A case-control study was nested in the OA cohort. Cases were defined as patients with a first ACE between January 2008 and December 2012, identified through a first diagnosis of acute myocardial infarction (AMI) or of unstable angina according to ICD10 codes in primary care records, and confirmed by hospital admission records. All patients with ACE previous to the OA diagnosis or January 2008 were excluded.

Controls were selected at random from the remaining ACE-free participants in the OA cohort, matched 3:1 by age (± 5 years), sex, geographical area, and year (± 2 years) since first OA diagnosis to cases. The index date for cases was the earliest of first hospital or primary care recorded diagnosis of ACE after 31st December 2007. Controls were assigned the same index date as their matched case.

Variables

Age, sex, coronary risk, toxic habits (smoking, alcohol), body mass index, hypertension (date of diagnosis, drug treatment, and the earliest blood pressure recorded value to index date), diabetes mellitus [type, date of diagnosis, organic manifestations (retinopathy, nephropathy), drug treatment and mean HbA1C in last year], dyslipidemia (date of diagnosis, drug treatment, and mean laboratory test values in last year), kidney function (MDRD in the last year estimated from laboratory test data and clinical records of the patient), co-morbidities (stroke or transient vascular accident, atrial fibrillation or flutter, mitral or aortic valve disease or rheumatic heart disease, asthma or chronic obstructive pulmonary disease, carotid or peripheral revascularization or bypass procedures, lower limb amputation, or peripheral artery disease), Charlson index, number of outpatient visits in the previous year, a combined variable of cardiovascular risk built from individual risk factors and a coronary Regicor index [24], were retrieved before the index date(Table 2). Exposure to drugs suggesting or associated to cardiovascular disease at index date were also retrieved (ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, thiazides, other diuretics, other antihypertensives, antiarrhythmics, anticoagulants, antiaggregants, nitrates, digoxin, statins, other hypolipidemic drugs, insulin, oral hypoglycemiants). ~~Data on general patient characteristics (age, sex, Body Mass Index), measures of comorbidity (Charlson index, number of medical visits in the period and number of active medications) and cardiovascular risk factors (current smoker or ex-smoker, high risk alcohol intake, hypertension; Ddiabetes Mmellitus, nephropathy or chronic kindney disease (CKD), dyslipidemia, previous cardiovascular diseases or use of antiplatelet medications, a~~

~~composite indexes (Regicor index [234], and a combined variable of cardiovascular risk built from individual risk factors (Table 2)) were retrieved.~~

The number of different medications used and detailed information for the following ATC groups: M01AA, M01AB, M01AC, M01AE and M01AG (non-selective NSAIDs), M01AH (COX-2 selective NSAIDs), M01AX05 (glucosamine), M01AX25 (~~condroitin~~chondroitin ~~S~~sulphate), M02AA (NSAIDs for topical use), N02A (opioid analgesics) and N02B (other non-opioid analgesics) were also retrieved. In the main analysis, patients were considered as "exposed" (drug users) if they had at least 3 ~~billing records~~dispensings for the same active principle. For a given exposure, 'Current users' were subjects with dispensations within 90 days prior to the index date; 'recent users' those for whom the last dispensation was between 91 and 180 days before the index date, and 'remote users' those for whom the last dispensation was before 365 days before the index date.

~~of~~ Defined Daily Doses (DDD)/day according to the ATC/DDD catalogue [2~~4~~5] were calculated for active principles using the number of packages dispensed and the time periods between dispensations. Treatment duration was derived from the time between first and last dispensation. The number of dispensations and the number of daily defined doses (DDD) dispensed per period were used to derive medication possession ratio below 80%, within 80% and 120% or above 120% of reference DDD.

Sample size

Previous data have described that the SIDIAP database included around 240,000 patients with diagnosed OA at the end of 2010 [15], with 2.1% and

2.3% having a history of AMI and angina respectively. According to published data [~~25,~~ 26, 27], the expected incidence of ACE in the Catalan population aged between 65 to 75 years is 211 women and 709 men per 100000 inhabitants, respectively. Assuming that women represent 57% of the OA population and have a similar CV risk in the OA population than in the general population, about 1000 new cases of ACE per year were expected. Based on the expected prevalence of exposure for the less frequently used OA treatments, the selection of 3 controls per case would allow, to detect increases of risk of ACE of 1.5 or higher for exposures with prevalence of 1%, and 1.35 or higher for prevalence of 2%, with type I and II errors of 5% and 20%, respectively [28~~7~~].

Statistical analysis

Baseline characteristics were contrasted for differences among cases and controls by Fisher exact test for categorical and by non-parametric test (Mann-Whitney test) for numerical data. Incidence rates of ACE in the OA cohort and 95% confidence intervals (95%CI) were estimated assuming a negative binomial distribution. Conditional logistic regression models and computed drug-specific odds ratios (ORs) and 95%CI as compared with drug-specific non-use were calculated. Two models were built for each exposure: a "crude" model matched by age, sex, and years since first OA diagnosis, and an "adjusted" multivariable model, adjusted additionally by body mass index, smoking and alcohol intake, diagnosis of high blood pressure, diabetes mellitus, dyslipidemia, heart valve disease, heart failure or ischaemic heart disease, peripheral arteriopathy or limb amputation, stroke or transient ischaemic event, asthma, chronic lung disease, degree of impairment of renal function, Charlson index, frequency of healthcare consultation, location of OA, polyarthicular OA, number

of locations of OA, use of ACEi, ARA-II, antiarrhytmic drugs, anticoagulants, beta-adrenergic blocking agents, calcium channel blockers, diuretics, other antihypertensive drugs, vasodilating agents, antiplatelet agents, statins, other hypolipemiant drugs, antidiabetic drugs, and concurrent use of other drugs for OA.

The association of risks with increases or decreases of exposure was explored. The analyses were carried for all analgesics by the exposure (yes/no), including all effects with or without significant association. ~~The association of risks with increases or decreases of exposure was explored.~~ No data imputation was done; for multivariable models, missing data was managed as a separate category. Non multiple comparison correction of the sample size have been done. Sensitivity analyses was made for monotherapy use (unique analgesic exposure during the study period), in order to exclude any possible interaction among the other analgesics drugs. ~~Sensitivity analyses included analysis restricted to current exposure and also to monotherapy use.~~ SPSS v15 and R version 3.2.0. were used for analyses.

RESULTS

Baseline characteristics of study population

Patient disposition is shown in Figure 1.

The incidence (95%CI) of ACE (events per 10,000 patient-years) for women and men younger than 74 were 10.62 (9.89 – 11.41) and 34.97 (33.04 – 37.03), and for those 75 or older 37.19 (95%CI: 35.62 – 38.84) and 63.78 (60.51 – 67.23), respectively; incidence rate ratios by sex and age groups are shown in Figure 2. No significant effect of calendar year was observed. A significant gender by age interaction was observed for ages 85 and older, so that incidence was reduced for male subjects, but not for females.

Within the study cohort, 5,663 cases were matched to 16,989 controls. The number or location of OA involved joints did not differ between cases and controls, but polyarticular and hip location were more frequent and knee and hand OA less frequent in the cases (Table 1).

Known risk factors for cardiovascular disease were more frequent amongst cases than controls (Table 2), as was the use of cardiovascular drugs (Table 3).

Non-opioid analgesics were the most common exposures (75.4% controls and 81.3% cases), followed by non-selective NSAIDs (61.1% of controls and 64.2% cases), topical NSAIDs (36.1% controls and 39.6% cases), opioid analgesics (23.6% controls and 28.9% cases) and SYSADOAs (20.5% controls and 18.1% cases). Less than 5% of subjects were exposed to COX -2 selective NSAIDs. Combinations were frequent, including mainly NSAIDS (59% cases and 55.2%

controls), paracetamol or metamizole (36,6% cases and 35,4% controls) and opioids (28.8% cases and 23.4% controls).

Risk estimation of acute coronary events

Crude risks of ACE showed significant associations for all exposures except for aceclofenac, celecoxib and etoricoxib, and selective cox-2 inhibitors as a group; crude OR were of protective sign for –glucosamine, chondroitin sulphate and SYSADOAS as a group. Adjusted models showed borderline signification for non-selective NSAIDs (p = 0.052) (Table 4), with significant dose response for cumulative, median dose, and duration of exposure (Figure 3.A.); significance was observed when the analysis was restricted to active exposures at the index date, and when restricted to NSAIDs monotherapy (Table 5). Significantly increased risks were observed for diclofenac and naproxen (Table 4).

Exposures to opioid analgesics were significantly associated to increased risk of ACE (Table 4), with dose-response trend for both cumulative and median dose, but not for duration of exposure (Table 5) (Figure 3.D.); significance was observed when restricted to exposures active at the index date (Table 5). Individual active principles within the opioid group did not show significant risks in the adjusted model (Table 4). Adjusted models did not show significant associations for COX-2 selective NSAIDs, topical NSAIDs, glucosamine, chondroitine sulphate, paracetamol nor metamizole (Table 4).

DISCUSSION

In our data, OA patients had risk scores suggestive of a high cardiovascular risk, and high incidences of ACE. In this population, the use of some non-selective NSAIDs was associated with increased adjusted risk of ACE ranging from 16% (diclofenac) to 25% (naproxen); similarly, opioids were associated with a 13% increased risk of ACE. For NSAIDs as a group and opioids as a group, associations followed a dose-response gradient, and the estimated excess risks were greater for current use when compared to previous use.

The incidence of ACE per 100,000 person-years observed in our study (222.1 for men and 462.4 for women aged 25-74 years, respectively) was greater than the comparable projected estimates in the Spanish population (77 and 263 new cases of acute myocardial infarction per 100,000 person-years in men and women, respectively) [~~28~~29]; rates between ~~-~~29-61 and 135-210 new cases per 100,000 person-years for female and male, respectively [~~29~~30]). This fact is in line with previous reports of increased risk of ACE in the population with OA, thus identifying OA patients as a population potentially at high cardiovascular risk.

A trend for increased adjusted risk was observed for NSAIDs, supported by a significant dose-response gradient and significant risks for exposures active at the index date. This association has an accepted biological plausibility and has been previously characterized [10, ~~29~~30], also in our setting [14]. Thus we consider that an increase ACE risk associated to exposure to NSAIDs as a group is plausible. Unexpectedly, the bigger risk increase was observed with naproxen, which has been often referred to be relatively safe regarding

cardiovascular risk as compared to other NSAIDs [10, 14, 2930]. A possible explanation may be that widespread perception of naproxen's safety may have led to decision to prescribe naproxen to patients requiring NSAIDs who had bigger cardiovascular risk or subclinical disease, thus leading to confounding by indication or protopathic bias. Despite our adjusted model accounted for many potential confounders, we cannot discard some degree of residual confusion; more research is needed to confirm this finding.

Opioid analgesics were unexpectedly associated to an increased ACE risk that was consistent, with significant dose response and persistence of risk in current users. However, the risk could not be attributed to a single product, and both very short and very long exposures had similarly increased risks. While two previous publications have proposed a causal role of opioids in cardiovascular disease [301--323], it is possible that patients exposed to opioids as a result of sequential therapeutic decisions may constitute a different (more diseased and frail) population, as compared to patients treated with drugs used in earlier steps of the analgesic ladder, and thus may have different baseline risks for ACE. Although the multivariable model included adjustments by Charlson Index and several comorbidities, some residual degree of confounding by indication cannot be discarded, and thus a cautious interpretation of these results seems advisable.

The absence of significant associations for non-narcotic analgesics, NSAIDs for topical use and SYSADOAs were all expected, biological plausible and consistent with other studies in our setting [14]. In turn, the absence of risks for COX-2 selective inhibitors is contrary to previous publications describing an increased risk of ACE for these drugs [10, 2930]. Reasons for this finding may

include the success of risk-minimization strategies deployed in our setting: health professionals are aware that they should restrict prescription of COX-2 inhibitors to low-risk patients, for short periods and only in the absence of feasible alternatives [18]; we cannot discard that the results, despite our extensive adjustment for potential confounders, might be due to residual confounding by indication due to selective prescription to low-risk subjects.

Limitations of the present study include the observational design, which precludes confirming causality of the detected associations. Also, data that is collected as a part of routine clinical care has not been individually validated for inclusion criteria (ie: OA diagnosis) not for the collection of outcomes (ACE): thus, we cannot guarantee the exhaustivity of the sample nor that all the occurring events have been identified; however, identification of both OA and cardiovascular events has been previously validated in SIDIAP through specific studies [20-2~~2~~3], and in that sense the results may be considered of value. Another limitation of our data source is the lack of linkage between diagnoses and prescriptions, thus we were not able to know if NSAIDs and opioids were prescribed for OA or other indication. Many factors related to differential exposure and/ or risks for ACE were included in our adjusted model, in order to control confounding, but there may be additional relevant risk factors (i ex: OA severity, metabolic syndrome and other comorbidities) not available in our dataset that may result in residual confounding. Also, our adjusted model included some independent risk factors for ACEs which are also known adverse effects of NSAIDs (i ex: hypertension and renal or heart failure), and some medications used to treat these conditions (antihypertensive drugs, diuretics) might represent intermediate variables on a causal path between exposure and

outcome. In both cases, adjusting by these intermediate factors may have led to some degree of overadjustment bias. Finally, our data source provided information on drugs dispensed through the public health system, but did not include information on dispensation through other prescription systems, nor on acquisition of analgesic drugs over the counter. Whether dispensed drugs were actually used by the subjects, and to what extent, cannot be ascertained.

The relevance of our findings should be considered from the perspective of absolute attributable risk. Unfortunately, we did not obtain prevalence of use of drugs from the full OA cohort, and prevalence of use of drugs in the case-control database could not be representative of the overall OA population. A prevalence of use for oral NSAIDs in the OA population of 0.774 was recently reported using the SIDIAP database [343]. Considering our OR adjusted estimate for NSAIDs (1.09), the resulting Absolute Attributable Risk (AAR = 100*(Prevalence of use *(OR-1))/(1+(Prevalence of use*(OR-1))) would be 6.5%. Putting this result in perspective by comparing to published data [345], the obtained AAR for NSAIDs in our exercise is smaller than the Population Attributable Risk (PAR) reported for main risk determinants, such as smoking (PAR 39%) or hypercholesterolaemia (PAR 18%), but within the same range of magnitude than that reported for diabetes (PAR 3%), a recognised and relevant clinical risk factor for cardiovascular events. As regards to other drug exposures (opioids as a whole, diclofenac or naproxen), we have not been able to obtain data from our setting for prevalences of use in OA patients.

In summary, our study has observed that, in our setting, patients with osteoarthritis represent a high-risk population for the development of acute coronary events, and the background risk of this population may be further

increased by chronic exposure to non-selective NSAIDs, especially diclofenac or naproxen. Under current conditions of use, the use of other systemic or topical NSAIDs, selective COX-2 inhibitors, non-narcotic analgesics or SYSADOAs do not represent an independent increase of ACE risk for real life (probably selected) users of these medications. A relatively novel observation of a risk increase associated with the use of opioid analgesics requires confirmation in future studies.

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AUTHOR CONTRIBUTIONS

CParidad Pontes and RMosa Morros designed the study protocol and reviewed the statistical analysis plan, interpreted results, wrote final report and drafted the manuscript. JRMosep Ramon Marsal contributed to the design of the protocol,

wrote the statistical plan, and did the study analysis. JMEosep Maria Elorza contributed to the design of the protocol and statistical plan and did the data extraction. MAaria Aragon reviewed the study protocol and analysis plan and contributed to data management and final report review. DPaniel Prieto-Alhambra and Bonaventura Bolibar contributed to the study design, interpretation of results and did a critical revision of the article for important intellectual content. All authors authorised the final version to be submitted.

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Conflict of interest

The authors declare that they do not have any contractual employee or financial relationship with Bioibérica S.A. representing a conflict of interest with the present report.

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533

FIGURE LEGENDS

Figure 1. Patient disposition.

Figure 2. ACE incidence rate ratio by gender and age group.

Footnote: Negative binomial regression.

Figure 3. Risk of ACE associated to use of drugs to treat OA and dose response analysis.

EACH INDIVIDUAL TABLE

Submitted as 5 separated files

Each individual Figure

(submitted as 3 separate files)

Table 1

Table 1. Characteristics of OA

	Cases (n=5663)	Controls (n=16989)	p-value
Years since first OA diagnosis (Mean(SD))	5.13 (5.1)	5.02 (5.08)	0.118
Number of locations of OA (Mean(SD))	1.26 (0.52)	1.27 (0.54)	0.094
Polyarticular	1478 (26.1%)	4035 (23.8%)	<0.001
Hand	827 (14.6%)	2694 (15.9%)	0.024
Hip	1008 (17.8%)	2803 (16.5%)	0.023
Knee	2457 (43.4%)	7854 (46.2%)	<0.001
Unspecified	692 (12.2%)	2144 (12.6%)	0.431
Column	661 (11.7%)	2091 (12.3%)	0.205
Single location – poliarticular	1001 (17.7%)	2642 (15.6%)	
Single location not polyarticular	3410 (60.2%)	10418 (61.3%)	
More than one location	1252 (22.1%)	3929 (23.1%)	

Table 2

Table 2. Baseline characteristics of study cases and controls.

	Cases (n=5663)	Controls (n=16989)	p-value
Age; Mean (SD)	75.8 (9.96)	75.3 (9.68)	0.001
Sex (women); N (%)	2931 (51.76%)	8793 (51.76%)	1.000
Body Mass Index; Mean (SD) *missing value [N (%)]*	30 (4.87) *[796 (14.1%)]*	29.6 (4.68) *[2889 (17.0%)]*	<0.001
BMI > 30 kg/m2; N (%) *missing value [N (%)]*	2245 (46.13%) *[796 (14.1%)]*	6061 (42.99%) *[2889 (17.0%)]*	<0.001
Charlson index; Mean (SD) Median (IQR)	1.58 (1.55) 1 (0-2)	1.02 (1.28) 1 (0-2)	<0.001
Exposure to drugs	5472 (96.63%)	15458 (90.99%)	<0.001
Number of different drugs; Mean (SD)	10.6 (5.25)	7.4 (4.35)	<0.001
Number of visits in the period; Mean (SD)	21.1 (18.55)	15.8 (14.05)	<0.001
Current smoker or ex-smoker; N (%) *missing value [N (%)]*	1172 (42.43%) *[2901 (51,23%)]*	2878 (35.25%) *[8825 (51,95%)]*	<0.001
High risk alcohol intake; N (%) *missing value [N (%)]*	91 (2.18%) *[1492 (26,35%)]*	298 (2.46%) [*4854 (28,57%)]*	0.317
Hypertension	4105 (72.49%)	10669 (62.8%)	<0.001
Years since diagnosis; Mean (SD)	8.2 (6.45)	7.8 (6.03)	0.001
SBP last year; Mean (SD) *missing value [N (%)]*	138.3 (15.24) *[1193 (21,06%)]*	136 (13.79) *[4687 (27,6%)]*	<0.001
DBP last year; Mean (SD) *missing value [N (%)]*	74.3 (8.74) *[1233 (21,77%)]*	74.8 (8.18) *[4744 (27,9%)]*	<0.001
Diabetes mellitus	2042 (36.06%)	3548 (20.88%)	<0.001
Years since diagnosis; Mean (SD)	8.4 (6.78)	7.2 (5.8)	<0.001
HbA1c last year; Mean (SD) *missing value [N (%)]*	7.5 (1.4) *[558 (27,32%)]*	7.1 (1.2) *[906 (25,53%)]*	<0.001
Diabetic retinopathy	213 (10.43%)	209 (5.89%)	<0.001
Nephropaty or CKD	300 (14.69%)	369 (10.4%)	<0.001
Dyslipidemia	2793 (49.32%)	7414 (43.64%)	<0.001

Years since diagnosis; Mean (SD)	7.3 (5.37)	7.2 (5.18)	0.151
Total Cholesterol last year; Mean (SD) *missing value [N (%)]*	190.2 (38.7) *[1416 (50,69%)]*	187.8 (35.3) *[4963 (66,94%)]*	0.152
LDL Cholesterol last year; Mean (SD) *missing value [N (%)]*	113.2 (34.02) *[1416 (50,69%)]*	109.7 (30.8) *[4963 (66,94%)]*	0.009
Atrial fibrillation or flutter	593 (10.47%)	1384 (8.15%)	<0.001
Valvular disease	453 (8%)	862 (5.07%)	<0.001
Cerebrovascular disease	200 (3.53%)	452 (2.66%)	0.001
Peripheral arteriopathy	352 (6.22%)	417 (2.45%)	<0.001
Low limb amputation	41 (0.72%)	29 (0.17%)	<0.001
Previous revascularization procedure	11 (0.19%)	18 (0.11%)	0.108
Ischaemic heart disease@	1340 (23.66%)	1082(6.37%)	<0.001
Asthma	284 (5.02%)	765 (4.5%)	0.112
Chronic Obstructive Pulmonary Disease	694 (12.25%)	1664 (9.79%)	<0.001
REGICOR score*; Mean (SD) missing value [N (%)]	7.3 (4.99) *[3718 (65,65%)]*	5.8 (4.13) *[11565 (68,07%)]*	<0.001
High cardiovascular risk~	2836 (50.08%)	2376 (13.99%)	<0.001
Moderate cardiovascular risk~	1897 (33.5%)	7498 (44.13%)	
Low cardiovascular risk~	930 (16.42%)	7115 (41.88%)	

*SBP: systolic blood pressure; DBP: Diastolic blood pressure; @other than AMI or unstable angina; *Value closer to the index date; ~ High CV risk: presence of at least one of: diabetes mellitus with retinopathy and/or nephropathy/chronic renal failure; chronic use of nitrates and antiplatelet drugs and/or previous ischemic heart disease and/or coronary revascularization; previous stroke or transient vascular cerebral event; previous peripheral arteriopathy or low limb amputation. Moderate CV risk: absence of high risk criteria and presence of at least one of: diabetes mellitus; active smoker; high*

blood pressure and dyslipidemia. Low CV risk: Absence of criteria for moderate or high risk.

Table 3

Table 3. Use of cardiovascular drugs.

	Cases (n=5663)	Controls (n=16989)	p-value
Drugs active on renin-angiotensin	3598 (63.54%)	7912 (46.57%)	<0.001
Antiarhitmics	194 (3.43%)	291 (1.71%)	<0.001
Cardiotonic glycosides	255 (4.5%)	520 (3.06%)	<0.001
Anticoagulants	595 (10.51%)	1317 (7.75%)	<0.001
Beta-adrenergic blockers	2244 (39.63%)	2005 (11.8%)	<0.001
Calcium-channel bloquers	1522 (26.88%)	2656 (15.63%)	<0.001
Loop diuretics	1354 (23.91%)	2029 (11.94%)	<0.001
Other diuretics than loop diuretics	965 (17.04%)	2435 (14.33%)	<0.001
Other antihypertensives	325 (5.74%)	624 (3.67%)	<0.001
Nitrates	2072 (36.59%)	705 (4.15%)	<0.001
Aspirin	3013 (53.21%)	3364 (19.8%)	<0.001
Other antiplatelet drugs than aspirin	1502 (26.52%)	870 (5.12%)	<0.001
HGMCoA reductase inhibitors	3128 (55.24%)	5464 (32.16%)	<0.001
Other hipolipemiant drugs	296 (5.23%)	506 (2.98%)	<0.001
Insulin and analogues	699 (12.34%)	604 (3.56%)	<0.001
Antidiabetics other than insulin	1504 (26.56%)	2575 (15.16%)	<0.001

Table 4. Risk of ACE associated to use of drugs to treat osteoarthritis

			Crude model			Adjusted model		
	Cases (n=5663)	**Controls (n=16989)**	**OR**	**95%CI**	**P value**	**OR**	**95%CI**	**P value**
Non-selective NSAIDs	**3606**	**10232**	**1.17**	**1.10-1.25**	**<0.001**	**1.09**	**1.00-1.19**	**0.052**
Ibuprofen	3091	8820	1.10	1.04-1.18	0.002	1.01	0.93-1.09	0.857
Dexketoprofen	1162	3102	1.13	1.02-1.26	0.022	0.98	0.85-1.13	0.796
Diclofenac	2355	6376	1.20	1.11-1.28	<0.001	1.16	1.06-1.27	0.001
Aceclofenac	850	2373	1.11	0.99-1.25	0.071	1.07	0.93-1.23	0.366
Naproxen	716	1889	1.27	1.11-1.46	<0.001	1.25	1.04-1.48	0.014
COX-2 selective NSAIDs	**259**	**800**	**0.97**	**0.84-1.13**	**0.731**	**0.97**	**0.80-1.16**	**0.720**
Celecoxib	185	562	1.01	0.85-1.21	0.909	0.97	0.77-1.21	0.771
Etoricoxib	113	366	0.93	0.74-1.18	0.568	1.15	0.87-1.52	0.340
SYSADOAs	**1045**	**3537**	**0.86**	**0.79-0.93**	**<0.001**	**0.96**	**0.86-1.06**	**0.402**
Glucosamine	516	1773	0.85	0.77-0.95	0.003	1.01	0.80-1.28	0.904
Chondroitin suplhate	476	1716	0.83	0.74-0.92	0.001	0.89	0.71-1.12	0.313
Topical NSAIDs	**2242**	**6134**	**1.15**	**1.08-1.23**	**<0.001**	**0.97**	**0.89-1.06**	**0.539**
Opioid analgesics	**1639**	**4004**	**1.33**	**1.24-1.43**	**<0.001**	**1.13**	**1.03-1.24**	**0.013**
Tramadol	1327	3172	1.33	1.23-1.43	<0.001	1.10	0.93-1.29	0.263
Codeine			1.21	1.08-1.35	0.001	1.03	0.88-1.20	0.745
Buprenorphin	210	419	1.47	1.18-1.83	0.001	1.16	0.87-1.54	0.317
Fentanyl	281	533	1.6	1.38-	<0.00	1.0	0.82-	0.815

			3	1.93	1	3	1.29	
Non-narcotic analgesics	**4604**	**12808**	**1.46**	**1.35-1.59**	**<0.001**	**0.99**	**0.89-1.11**	**0.872**
Paracetamol	4584	12753	0.94	0.93-0.96	<0.001	0.98	0.96-1.00	0.058
Metamizole	2274	5576	1.39	1.29-1.51	<0.001	1.01	0.91-1.12	0.871

Table 5 clean

Table 5. Risk of ACE associated to current use of NSAIDs and narcotic analgesics, with dose response analysis.

NSAIDs	Cases	Controls	Crude				Adjusted			
	n	*n*	*OR*	*Lower*	*Upper*	*p*	*OR*	*Lower*	*Upper*	*p*
No Exposure	2057	6757	*1 (Ref.)*				*1 (Ref.)*			
Exposed	3606	10232								
Exposure to combinations	3339	9372	1.19	1.11	1.27	<0.001	1.05	0.96	1.15	0.317
Monotherapy exposure	267	860	1.04	0.90	1.21	0.563	1.31	1.08	1.59	0.006
Current exposure analysis										
No current exposure			*1 (Ref.)*				*1 (Ref.)*			
Current exposure	1679	4584	1.16	1.08	1.24	<0.001	1.19	1.09	1.30	<0.005
Chronic pattern of use	636	1633	1.23	1.11	1.36	<0.001	1.27	1.12	1.45	<0.001
Cumulated Dose~	1.95 (4.70)	1.54 (3.80)	1.03	1.02	1.03	<0.001	1.03	1.02	1.04	<0.001
Mean monthly dose			1.01	1.00	1.01	<0.001	1.01	1.00	1.01	<0.001
< 80% MDD	791	2295	1.09	1.00	1.19	0.062	1.12	1.00	1.26	0.053
80 - 120% MDD	628	1683	1.17	1.06	1.30	0.002	1.22	1.07	1.38	0.002
≥ 120% MDD	260	606	1.36	1.17	1.58	<0.001	1.41	1.16	1.71	<0.001
Duration of exposure			1.00	1.00	1.00	<0.001	1.00	1.00	1.00	<0.001
≤ 3 months	6	18	1.02	0.40	2.58	0.966	0.80	0.25	2.53	0.7028
4 - 12 months	35	105	1.07	0.73	1.57	0.734	0.90	0.55	1.46	0.669

13 - 36 months	208	618	1.06	0.90	1.25	0.485	1.00	0.81	1.23	0.990
> 36 months	1430	3843	1.17	1.09	1.26	<0.001	1.24	1.13	1.36	<0.001
Opioid Analgesics	**Cases**	**Controls**	**Crude**				**Adjusted**			
	n	*n*	*OR*	*Lower*	*Upper*	*P*	*OR*	*Lower*	*Upper*	*p*
No Exposure	4024	12985	*1 (Ref.)*				*1 (Ref.)*			
Exposed										
Exposure to combinations	1629	3982	1.33	1.24	1.43	<0.001	1.12	1.02	1.23	0.017
Monotherapy exposure	10	22	1.38	0.65	2.93	0.398	1.75	0.70	4.41	0.234
Current exposure analysis										
No current exposure	829	2273	*1 (Ref.)*				*1 (Ref.)*			
Current exposure	810	1731	1.47	1.35	1.62	<0.001	1.20	1.07	1.35	0.003
Chronic pattern of use	421	882	1.49	1.32	1.68	<0.001	1.20	1.03	1.41	0.021
Cumulated Dose~	0.67 (2.94)	0.41 (1.94)	1.04	1.03	1.06	<0.001	1.04	1.02	1.05	<0.001
Mean monthly dose			1.02	1.02	1.03	<0.001	1.01	1.01	1.02	<0.001
< 80% MDD	689	2273	1.43	1.30	1.58	<0.001	1.14	1.01	1.30	0.034
80 - 120% MDD	83	1520	1.74	1.32	2.29	<0.001	1.48	1.04	2.09	0.028
≥ 120% MDD	38	61	1.97	1.31	2.97	0.001	2.12	1.25	3.59	0.005
Duration of exposure			1.01	1.01	1.01	<0.001	1.00	1.00	1.01	0.004
≤ 3 months	45	65	2.19	1.49	3.22	<0.001	1.66	1.03	2.67	0.037
4 - 12 months	68	191	1.12	0.84	1.48	0.440	1.18	0.84	1.64	0.342

13 - 36 months	168	403	1.32	1.10	1.58	0.003	1.00	0.79	1.27	0.997
> 36 months	529	1072	1.56	1.39	1.74	<0.001	1.25	1.08	1.44	0.003

Figure

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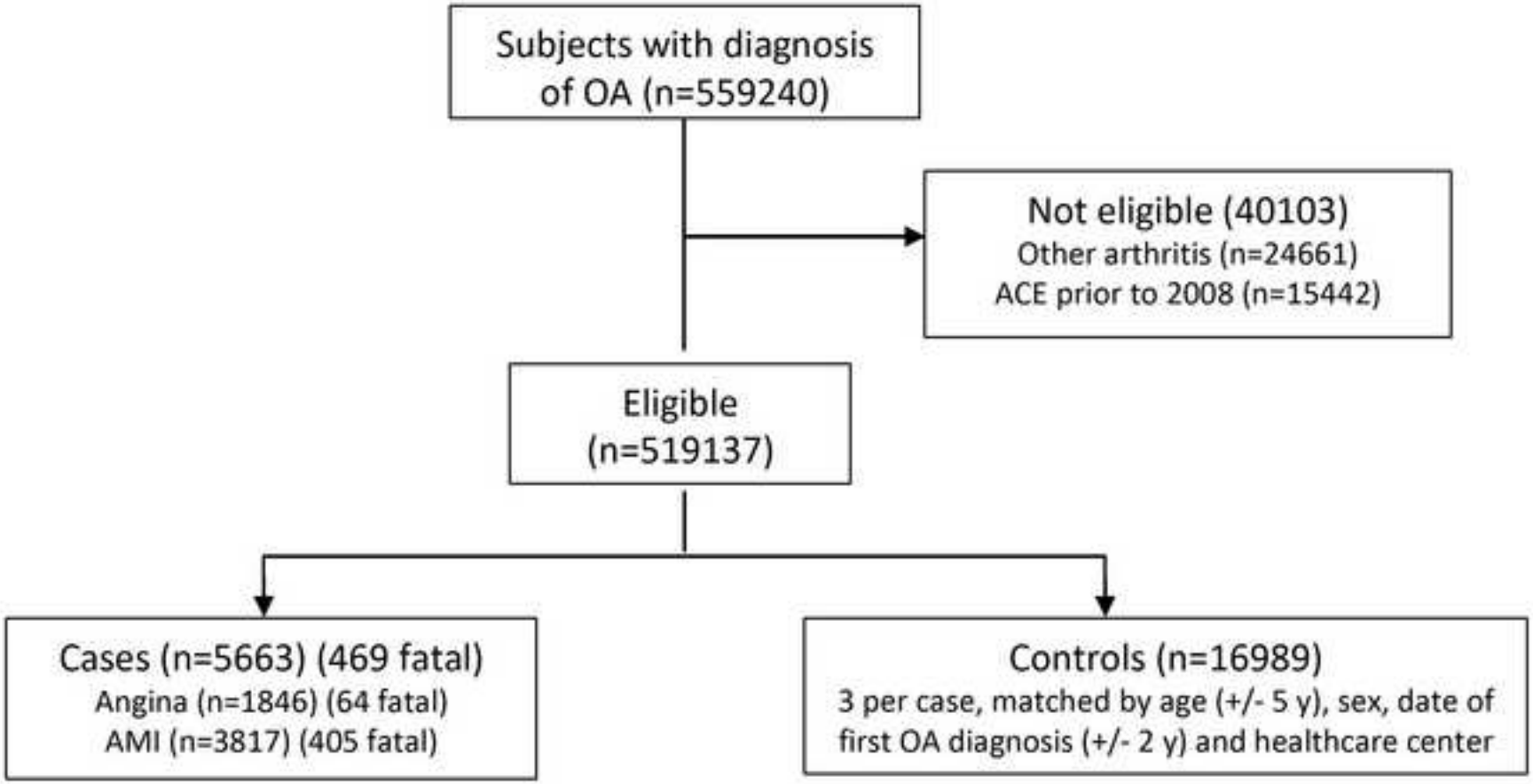

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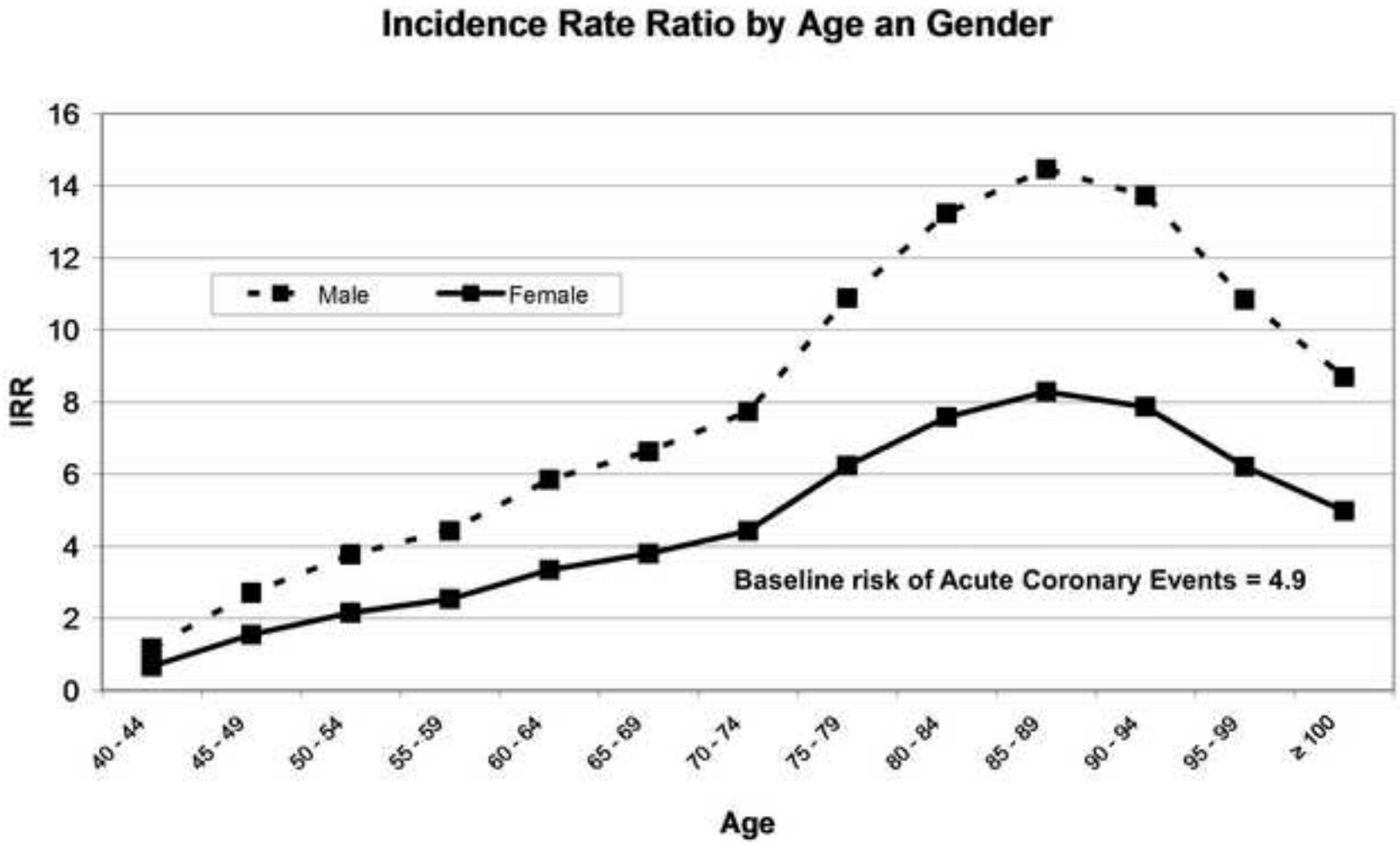

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