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ORIGINAL ARTICLE

Allopurinol use and risk of non-fatal acute myocardial infarction

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ABSTRACT

Objectives To quantify the risk of non-fatal acute myocardial infarction (AMI) among users of allopurinol.

Methods We carried out a population-based case–control study over the period 2001–2007 in patients aged 40–90 years. Patients who had prescriptions of allopurinol or an episode of AMI before the start date of follow-up were excluded from the main analysis. Allopurinol initiators were classified as current users if their last prescription ended in the 30-day window before the recorded date of AMI for cases and a random date for controls. The association between use of allopurinol and non-fatal AMI was measured through an OR and adjusted for confounding factors by an unconditional logistic regression.

Results We identified 3171 cases of non-fatal AMI and 18 525 controls. Cases had a lower prevalence of current use of allopurinol (0.82%) than controls (1.03%), yielding to an OR of 0.52 (95% CI 0.33 to 0.83). The decreased risk was driven by men (OR in men=0.44; 95% CI 0.25 to 0.76; OR in women=0.90; 0.36 to 2.23). No difference by age was observed. The effect was only observed at higher doses (300 mg or greater OR=0.30; 0.13 to 0.72; <300 mg OR=0.67; 0.37 to 1.23) and with prolonged treatments (<31 days, OR=1.12 (0.55 to 2.29); 31–180 days, OR=0.61; 0.29 to 1.29; >180 days OR=0.21; 0.08 to 0.53; p for trend=0.001). Among those with a previous AMI, allopurinol use also showed a significant reduced risk of recurrence (OR=0.16; 0.04 to 0.76).

Conclusions The present study supports the hypothesis that allopurinol is associated with a reduced risk of non-fatal AMI, which seems to be dose-dependent and duration-dependent.

INTRODUCTION

Allopurinol is the first-line urate-lowering therapy in chronic gout.[1] It acts through the inhibition of xanthine oxidase (XO), a critical enzyme that converts hypoxanthine to xanthine and xanthine into uric acid.[2] XO requires oxygen and generates, as a consequence, superoxide anions and other oxidative free radicals.[3] These products cause oxidative stress that is thought to exert harmful effects in the vasculature such as inflammation, endothelial dysfunction and progression of atherosclerosis.[3–5] Allopurinol reduces both the formation of uric acid and the production of oxidative free radicals[3] and has been recently viewed as a drug with promising cardiovascular (CV) benefits.[6] Recently, Grimaldi-Bensouda *et al*[7] found a 20% reduction in non-fatal acute myocardial infarction (AMI) in patients exposed to allopurinol, but the result did not reach statistical significance in the main analysis and had the limitation that they did not distinguish between prevalent and incident users of allopurinol. It is known that observational studies that include many prevalent users may introduce a selection bias if the risk varies with time.[8] In the present study, we tested the hypothesis that allopurinol lowers the risk of non-fatal AMI restricting the analysis to allopurinol initiators.

SUBJECTS AND METHODS

The study was performed using *Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria* (BIFAP), a Spanish primary care database which contains information from around 7% of the total Spanish population and has been validated for pharmacoepidemiological research.[9]

Study design

The data for the present study were derived from a population-based case–control study described elsewhere.[10] The source population that gave rise to cases and controls was comprised by persons enrolled in BIFAP in the period 2001–2007, aged 40–90 years old and with at least 1 year of registry with their general practitioner (GP) and without a record of cancer. Once subjects met the above-mentioned inclusion criteria, they were followed from start date until the date of one of the following endpoints: the outcome of interest, 90 years of age, a diagnosis of cancer, 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 (code K75 of International Classification of Primary Care[11]) or free-text comments compatible with AMI. The computer clinical records of all potential cases were then manually reviewed by at least two different researchers, blinded to drug exposure, in order to confirm or rule out the diagnosis and assign the index date. Cases were classified as non-fatal AMI when they had (1) either a diagnosis of AMI (code or free text) and additional information confirming the diagnosis (ie, positive enzymes, Q wave, revascularisation procedures, secondary prevention treatment pattern or a hospital report) or a diagnosis of acute coronary syndrome with or without ST segment and additional information confirming that the final diagnosis was AMI; and (2) no death within 30 days after the index date. The index date was considered the date of first signs, or the date of first diagnosis,

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whichever was recorded first. Eligible controls were randomly selected from the study population using a density-based sampling method.[12] Briefly, all persons in the study cohort were randomly assigned a date within the study period, and study cohort members with their corresponding random date occurring within their observation period were considered eligible. Then, they were frequency matched to cases by age (within 1 year), sex and calendar year and from this pool we selected a random sample of 20 000 controls. The random date assigned to controls in the process of selection was considered as index date.

In order to focus on allopurinol initiators (new users), we excluded from cases and controls those patients who had at least one prescription of allopurinol in the period before the start date of follow-up (see figure in online supplementary material). We also excluded patients with a record of AMI before the start date in order to assure that all AMI cases were first-ever events. Nonetheless, we performed a secondary analysis in those patients with a previous AMI.

Exposure definition

During the study period, allopurinol was the only urate-lowering drug available for general use in Spain. Although benzbromarone was also marketed, its potential to cause fulminant hepatitis kept this drug highly restricted,[13] which resulted in an almost negligible use (only 13 individuals among 20 000 controls). We defined the exposure to allopurinol in terms of recency of use with respect to the index date as follows: 'current users', patients with a prescription of allopurinol which ended within 30 days prior to the index date; 'recent users', patients with a prescription for allopurinol which ended between 31 and 365 days; 'past users', patients with a prescription for allopurinol which ended beyond 365 days prior to the index date and 'non-users', patients with no prescription of allopurinol before the index date.

Among current users of allopurinol, we studied the effect of dose (<300 mg and ≥300 mg) and duration of treatment (<31 days, 31–180 days, >180 days). Duration was measured in two ways: (a) using only consecutive prescriptions (when there was less than 60 days between the end of supply of one prescription and the start of the next one); and (b) since the first prescription recorded. Also, among current users we divided patients according to serum uric acid (SUA) level (≤6 mg/dL or higher according to EULAR recommended target level[1]). For this latter purpose, we retrieved the latest recorded SUA level after starting allopurinol use.

Potential confounding factors

For cases and controls, we looked for the following potential confounding factors: ischaemic heart disease, stroke, transient ischaemic accident, peripheral artery disease, heart failure, diabetes (recorded as such or when patients were using glucose-lowering drugs), rheumatoid arthritis, renal failure, gout (recorded as such), hyperuricaemia (when recorded as such, or when the latest record available of SUA was >7 mg/dL in men, or >6 mg/dL in women and, additionally, had no record of gout), dyslipidemia (recorded as such or when patients were using lipid-lowering drugs), hypertension, smoking, alcohol abuse (defined as such by the GPs), body mass index (BMI) and use of the following drugs: non-steroidal anti-inflammatory drugs, metamizole, paracetamol, corticosteroids, colchicine, alpha-blockers, calcium-channel blockers, beta-blockers, ACE inhibitors, angiotensin II receptor blockers, diuretics, nitrates, low-dose aspirin, non-aspirin antiplatelet drugs, oral anticoagulants, inhaled beta-agonist, antidepressants, acid-suppressing drugs and sexual hormones.

Statistical analysis

To estimate the association between non-fatal AMI and current use of allopurinol, we built unconditional logistic regression models and computed the specific ORs and their 95% CIs. We ran two models: (1) a non-adjusted model which included only the matching variables (age, sex and calendar year) and (2) a fully adjusted model which additionally included all potential confounding factors described above. Unless otherwise specified, all ORs given are the ones obtained with the fully adjusted model.

Missing values were identified in the tables and statistical models as a specific category. As shown in previous studies,[10 14] multiple imputation methods for smoking and BMI yielded similar results. We used STATA V.12.0 (StataCorp, College Station, Texas, USA) for all analyses.

Ethics

This study only used anonymised data and review by an ethics committee was not required. The access to the data and the protocol for this research was approved by the Spanish Agency for Medicines and Medical Devices (database owner).

RESULTS

We identified 3833 cases of non-fatal AMI and 20 000 randomly selected controls. From them, we excluded 1236 patients with antecedents of a previous AMI (553 cases and 683 controls), and subsequently 901 patients who had allopurinol prescriptions recorded before the start date (109 cases and 792 controls) (figure 1). Overall, we had 3171 incident cases of non-fatal AMI and 18 525 controls. The main characteristics of cases and controls are shown in table 1. As expected, we found an association between non-fatal AMI and known CV risk factors. Likewise, cases presented a higher exposure to drugs used for the treatment and/or prevention of CV diseases. Among controls, allopurinol initiators presented both a higher prevalence of CV risk factors and a higher proportion of use of CV drugs than non-users (see supplementary material table 1 web). The mean follow-up time since start date was similar for cases (717; SD±535 days; median=629) and controls (698; SD±524 days; median=591).

Risk of non-fatal AMI in patients with hyperuricaemia or gout

Both hyperuricaemia and gout presented a higher prevalence in cases (13.7% and 3.5%, respectively) than in controls (11.8% and 2.8%, respectively) yielding to a significant increased risk of non-fatal AMI in the crude analysis (OR hyperuricaemia=1.20; 1.08 to 1.35; OR gout=1.29; 1.05 to 1.60), but both rendered not significant after full adjustment (OR=1.00; 0.89 to 1.13 and OR=1.15; 0.88 to 1.50, respectively). When this analysis was restricted to non-users of allopurinol, the risk associated with gout increased but was still non-significant (OR=1.21; 0.91 to 1.62).

Risk of non-fatal AMI in allopurinol users

The current use of allopurinol was lower among cases (0.82%) than among controls (1.03%), yielding to an adjusted OR of 0.52 (95% CI 0.33 to 0.83). Such a reduction in risk faded out with the discontinuation of the drug (table 2).

Most current users of allopurinol were men (82%) and the decreased risk was mainly observed among men (OR=0.44;

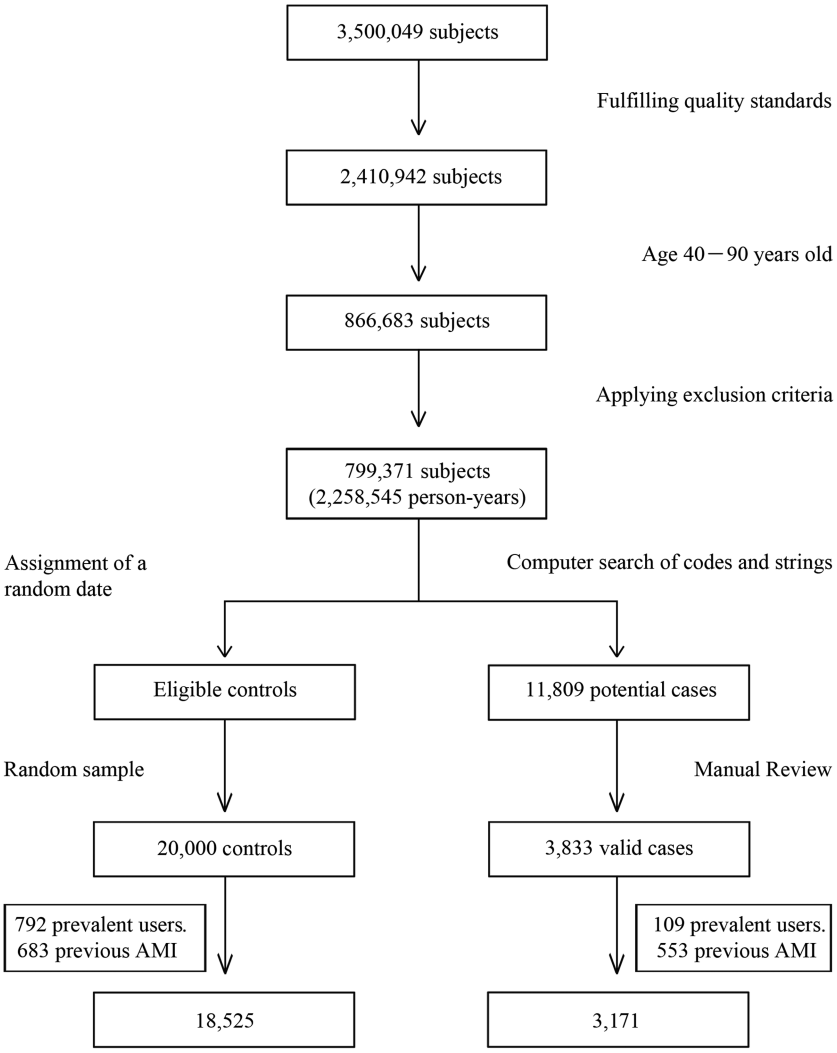

Figure 1 Flowchart of case and control selection. AMI, acute myocardial infarction.

95%: 0.25 to 0.76). In women, we did not find evidence of a decreased risk, but the precision of the estimate was low (OR=0.90; 0.36 to 2.23) (table 3). The decreased risk of non-fatal AMI was observed in both people aged 65 years or older (OR=0.51; 0.29 to 0.88) and in younger population (OR=0.41; 0.17 to 0.99) (table 3).

The decreased risk of non-fatal AMI was only shown in the subgroup who used 300 mg or greater (OR=0.30; 0.13 to 0.72), though it was not significantly different from the OR observed with lower doses (OR=0.67; 0.37 to 1.23) (p=0.13 for the comparison). A significant trend was observed with duration either with consecutive (test for trend, p=0.001) or non-consecutive prescriptions (test for trend, p=0.004) (table 2).

Risk of AMI and SUA level

SUA level within the last year before index date was available in 6447 patients (987 cases and 5460 controls). Cases presented a mean SUA level slightly higher (5.90 mg/dL; SD±1.64) than controls (5.78; SD±1.53) (p=0.017). Among allopurinol current users, 100 patients (out of 216) had a post-treatment SUA level available (10 cases and 90 controls). Of them, 52 had SUA levels 6 mg/dL or lower (5 cases and 47 controls) and 48 higher than 6 mg/dL (5 cases and 43 controls), showing no difference in the risk estimates of AMI according to SUA level (6 mg/dL or lower, OR=0.40; 0.15 to 1.07; >6 mg/dL, OR=0.41; 0.15 to 1.11).

Risk of AMI recurrence in allopurinol users

After excluding prevalent allopurinol users, we identified 1179 patients with a history of AMI. In them, the current use of allopurinol was also associated with a significant lower risk of recurrent non-fatal AMI (OR=0.16; 0.04 to 0.73) (table 4).

DISCUSSION

The results of the present study show that the use of allopurinol is associated with a significant reduction in the risk of non-fatal AMI. Such an effect was mainly apparent in men, when exposure lasted for more than 180 days and in those using doses of 300 mg or higher.

The present study confirms the protective effect suggested recently by Grimaldi-Bensouda *et al*[7] and adds to others that suggest a protective effect of allopurinol for the CV system. For instance, Luk *et al*[15] in a cohort study of hyperuricaemic patients observed that allopurinol users had a lower risk of all-cause mortality than non-users. Wei *et al*,[16] in a retrospective cohort study of patients with a recorded SUA measurement, found a HR of 0.88 (0.73 to 1.05) of any CV outcome among users of allopurinol compared with non-users. Goicoechea *et al*,[17] in a randomised clinical trial in patients with chronic renal failure found that people allocated to allopurinol exhibited a 71% reduction in the CV risk compared with patients with standard therapy. Thanassoulis *et al*[18] in a large cohort of patients with gout found a 26% reduction in all-cause mortality.

Table 1 Characteristics of cases and controls

	Cases (%) n=3171	Controls (%) n=18 525	Non-adjusted OR* (95% CI)
Characteristics			
Age mean in years (±SD)	67.17 (±12.26)	67.65 (±12.17)	NA
Men	2126 (67.05)	12 192 (65.81)	NA
Visits (n)			
1–5	565 (16.0)	4251 (17.4)	1 (ref.)
6–15	1157 (36.5)	7604 (41.1)	1.24 (1.11 to 1.39)
16–24	817 (25.8)	4050 (21.9)	1.72 (1.52 to 1.94)
25+	632 (19.9)	2620 (14.1)	2.08 (1.83 to 2.37)
History of IHD	388 (12.2)	794 (4.3)	3.23 (2.83 to 3.67)
History of TIA	52 (1.6)	327 (1.8)	0.97 (0.71 to 1.30)
History of CVA	157 (5.0)	697 (3.8)	1.36 (1.13 to 1.62)
PAD	171 (5.4)	373 (2.0)	1.66 (1.52 to 1.83)
Diabetes†	1023 (32.3)	3524 (19.0)	2.03 (1.86 to 2.20)
Dyslipidemia‡	1326 (41.8)	5698 (30.8)	1.62 (1.50 to 1.75)
Hypertension	1677 (52.9)	8343 (45.0)	1.37 (1.27 to 1.48)
Hyperuricaemia	434 (13.7)	2184 (11.8)	1.20 (1.08 to 1.35)
Gout	111 (3.5)	515 (2.8)	1.29 (1.05 to 1.60)
Smoking			
Never smoker	881 (27.8)	5839 (31.5)	1 (ref.)
Current smoker	1065 (33.6)	4764 (25.7)	1.48 (1.34 to 1.63)
Past smoker	291 (9.2)	1437 (7.8)	1.34 (1.16 to 1.55)
No record	934 (29.5)	6485 (35.0)	0.95 (0.86 to 1.05)
Renal failure	129 (4.1)	403 (2.2)	1.91 (1.56 to 2.33)
Rheumatoid arthritis	32 (1.0)	139 (0.8)	1.35 (0.92 to 1.98)
Alcohol abuse§	616 (19.4)	3523 (19.0)	1.03 (0.93 to 1.06)
BMI (kg/m^2)			
<25	373 (11.8)	2079 (11.2)	1 (ref.)
25–30	1025 (32.3)	5246 (28.3)	1.09 (0.96 to 1.24)
>30	779 (24.6)	4068 (22.0)	1.07 (0.93 to 1.22)
No record	994 (31.4)	7132 (38.5)	0.78 (0.68 to 0.88)
Drug use			
Current use of low-dose aspirin	437 (13.8)	1747 (9.4)	1.58 (1.41 to 1.77)
Alpha-blockers	99 (3.1)	520 (2.8)	1.13 (0.90 to 1.40)
Calcium-channel blockers	464 (14.6)	1800 (9.7)	1.65 (1.48 to 1.84)
Beta-blockers	285 (9.0)	1131 (6.1)	1.56 (1.36 to 1.78)
ACE inhibitors	558 (17.6)	2961 (16.0)	1.17 (1.06 to 1.29)
AII receptor blockers	341 (10.8)	1471 (7.9)	1.42 (1.26 to 1.61)
Statins	600 (18.9)	2611 (14.1)	1.48 (1.34 to 1.63)
Glucose-lowering drugs	550 (17.3)	1696 (9.2)	2.21 (1.99 to 2.45)
Nitrates	231 (7.3)	367 (2.0)	3.99 (3.36 to 4.72)
Oral anticoagulants	85 (2.7)	631 (3.4)	0.78 (0.62 to 0.98)
Diuretics—high ceiling	240 (7.6)	939 (5.1)	1.56 (1.34 to 1.80)
Diuretics—low ceiling	217 (6.8)	1606 (8.7)	0.79 (0.68 to 0.91)
Aldosterone antagonists	35 (1.1)	150 (0.8)	1.37 (0.94 to 1.98)
Colchicine	9 (0.3)	65 (0.4)	0.81 (0.40 to 1.63)

*Model adjusted only for matching variables (age, sex and calendar year). The category of reference was 'no presence of the disease' or 'non-use of the corresponding drugs'.
†Includes use of glucose-lowering drugs.
‡Includes use of lipid-lowering drugs.
§When the general practitioner recorded an excessive consumption of alcohol.
AII, angiotensin II; AMI, acute myocardial infarction; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; IHD, ischaemic heart disease; NA, not applicable; PAD, peripheral artery disease; TIA, transient ischaemic accident.

Similar finding was obtained by Dubreil *et al*[19] in allopurinol incident users compared with matched controls. Additionally, several human experimental studies have shown that allopurinol (or oxypurinol, its active metabolite) reduces circulating markers of oxidative stress and improves endothelial function,[20] actions that may help to slow the progression of atherosclerosis[5] and prevent plaque instability,[21] These actions, together with its anti-ischaemic properties[22] and its capability to regress left ventricular hypertrophy,[23] may be the underlying biological mechanisms of the protective effect of allopurinol. Contrary to this body of evidence, Kok *et al*[24] recently reported a greater risk of CV outcomes in gout patients treated with allopurinol compared with those non-treated. However, it is important to note that the outcome in this study was hospitalisation for any

Table 2 Risk of non-fatal acute myocardial infarction associated with allopurinol

	Cases (%) N=3171	Controls (%) N=18 525	Non-adjusted* OR (95% CI)	Adjusted† OR (95% CI)
Non-use	3105 (97.9)	18 171 (98.1)	1 (ref.)	1 (ref.)
Any time use	66 (2.1)	354 (2.1)	1.08 (0.83 to 1.42)	0.72 (0.52 to 0.99)
Recency (days)				
Current use (<31)	26 (0.82)	190 (1.0)	0.80 (0.52 to 1.20)	0.52 (0.33 to 0.83)
Recent use (31–365)	25 (0.79)	103 (0.56)	1.41 (0.91 to 2.19)	0.99 (0.61 to 1.61)
Past use (>365)	15 (0.47)	61 (0.33)	1.42 (0.80 to 2.51)	0.88 (0.47 to 1.65)
Allopurinol duration (consecutive prescriptions)‡ (days)				
<31	12 (0.38)	40 (0.22)	1.76 (0.92 to 3.36)	1.12 (0.55 to 2.29)
31–180	9 (0.28)	57 (0.31)	0.92 (0.46 to 1.87)	0.61 (0.29 to 1.29)
>180	5 (0.16)	93 (0.50)	0.31 (0.12 to 0.77)	0.21 (0.08 to 0.53)
				p for trend=0.001
Allopurinol duration (since first prescription)‡ (days)				
<31	4 (0.13)	13 (0.07)	1.81 (0.59 to 5.54)	0.92 (0.27 to 3.16)
31–180	9 (0.28)	53 (0.29)	1.00 (0.49 to 2.02)	0.73 (0.34 to 1.55)
>180	13 (0.41)	124 (0.67)	0.61 (0.34 to 1.08)	0.39 (0.21 to 0.73)
				p for trend=0.003
Allopurinol daily dose‡ (mg)				
<300	15 (0.47)	85 (0.46)	1.02 (0.59 to 1.79)	0.67 (0.37 to 1.23)
300+	6 (0.19)	76 (0.41)	0.46 (0.20 to 1.06)	0.30 (0.13 to 0.72)
Unknown	5 (0.16)	29 (0.16)	1.01 (0.39 to 2.59)	0.70 (0.25 to 1.96)

*Model adjusted only for the matching variables (sex, age and calendar year).
†Fully adjusted model: matching variables plus the following factors: ischaemic heart disease, cerebrovascular events (including transient ischaemic attack and stroke), peripheral artery disease, heart failure, diabetes (including use of glucose-lowering drugs), dyslipidemia (including use of lipid-lowering drugs), hyperuricaemia, gout, hypertension, smoking, rheumatoid arthritis, renal failure; and use of the following drugs: non-steroidal anti-inflammatory drugs, metamizole, paracetamol, corticosteroids, colchicine, alpha-blockers, calcium-channel blockers, beta-blockers, ACE inhibitors, angiotensin II receptor blockers, diuretics, nitrates, low-dose aspirin, non-aspirin antiplatelet drugs, oral anticoagulants, inhaled beta agonist, antidepressants, acid-suppressing drugs and sexual hormones.
‡Among current users of allopurinol.

CV disease with no specific analysis on AMI, and that 65% of patients on allopurinol used very low daily doses (100 mg or lower). Interestingly, the incidence rate of CV outcomes in patients using 300 mg or higher was half the one in patients with low doses.

Our study only used allopurinol initiators, which is a differential characteristic from the one by Grimaldi-Bensouda *et al*,[7] Allopurinol is a long-term treatment and, then, it is likely that a majority of allopurinol users are prevalent ones. Actually, in our study we excluded 958 patients who had filled prescriptions before the start of follow-up, and then considered as prevalent users (70% of allopurinol users) (57 of them also had a previous AMI). When in an observational study (either cohort or case–control) the majority of drug users are prevalent users, the study may be exposed to a selection bias when risk varies with time. For instance, if the event occurs more often at the start of treatment, prevalent users may be a less susceptible population and we observe a spurious reduction in risk associated with drug use. We minimised this bias by excluding prevalent users,[8] By definition, all patients in our study had at least 1 year of registry with the GP before starting the follow-up and the time since start date to the first prescription of allopurinol had additionally a median period of 350 days (range from 5 to 1770 days), so that we are reasonably sure that most incident users in our study were truly allopurinol initiators.

Our study suggests a dose–response, although we cannot rule out a smaller but still relevant effect with daily doses lower than 300 mg. On the other hand, we did not find a relation with SUA level, although the number of individuals with records was small. These findings are consistent with the results from George *et al*[25] who observed a clear relationship between dose of allopurinol, but not with the lowering of uric acid induced by a uricosuric agent, and the reduction of vascular oxidative stress. Also, Wei *et al*[16] found a dose dependency with a significant reduction of CV outcomes in high dose compared with low-dose allopurinol users (HR=0.63; 0.44 to 0.91). We also show a significant trend with duration, indicating that a sustained action is important to have an impact on CV outcomes.

Table 3 Risk of non-fatal acute myocardial infarction associated with current use of allopurinol compared with non-use in different subgroups

	Cases (%) N=3171	Controls (%) N=18 525	Non-adjusted* OR (95% CI)	Adjusted† OR (95% CI)
Men	N=2126 17 (0.80)	N=12 192 161 (1.3)	0.61 (0.37 to 1.00)	0.44 (0.25 to 0.76)
Women	N=1045 9 (0.86)	N=6333 29 (0.46)	1.91 (0.90 to 4.06)	0.90 (0.36 to 2.23)
<65 years	N=1286 7 (0.54)	N=7172 59 (0.82)	0.66 (0.30 to 1.45)	0.41 (0.17 to 1.00)
65+ years	N=1885 19 (1.0)	N=11 353 131 (1.2)	0.86 (0.53 to 1.40)	0.51 (0.29 to 0.88)

*Model adjusted only for the matching variables (sex, age and calendar year).
†Fully adjusted model: see footnote in table 2.

Table 4 Risk of non-fatal acute myocardial infarction (AMI) associated with hyperuricaemia, gout and allopurinol initiation in patients with a previous episode of AMI

	Cases (%) N=533	Controls (%) N=646	Non-adjusted* OR (95% CI)	Adjusted† OR (95% CI)
No hyperuricaemia/gout	432 (81.1)	522 (80.8)	1 (ref.)	1 (ref.)
Hyperuricaemia	77 (14.5)	102 (15.8)	0.87 (0.62 to 1.20)	0.83 (0.57 to 1.22)
Gout	24 (4.5)	22 (3.4)	1.49 (0.81 to 2.73)	2.00 (0.82 to 4.89)
Allopurinol initiation				
Non-use	522 (97.9)	626 (96.9)	1 (ref.)	1 (ref.)
Current use	4 (0.75)	12 (1.86)	0.49 (0.15 to 1.53)	0.16 (0.04 to 0.73)
Recent/past use	7 (1.3)	8 (1.2)	1.16 (0.41 to 3.29)	0.72 (0.19 to 2.63)

*Model adjusted only for the matching variables (sex, age and calendar year).
†Fully adjusted model: see footnote in table 2.

Both results, dose and duration effects, reinforce a causal hypothesis of the negative association found between allopurinol and non-fatal AMI. It is important to note that allopurinol use was associated with many CV risk factors (see supplementary material table 1web), thus the possibility of a 'healthy user effect' as an explanation of the protective effect can be excluded. Interestingly, we also found a negative association of allopurinol with recurrent AMI, though the numbers were small.

The use of colchicine has recently shown in a randomised clinical trial to have a protective effect in patients with stable coronary disease,[26] We included colchicine in the fully adjusted model, but we did not find a significant effect associated with this drug (OR=0.70; 0.33 to 1.47), nor did it modify the association between allopurinol and AMI. Grimaldi-Bensouda *et al*[7] did not observe either a relevant effect.

Our study also provides information on the association of hyperuricaemia and gout with non-fatal AMI. We found a statistically significant association in the crude analysis with hyperuricaemia, but disappeared after full adjustment suggesting that per se it is not a relevant cause for AMI,[27] It has been postulated that hypertension may be an 'effect' of hyperuricaemia,[28] and then it would behave as an intermediate variable rendering incorrect to adjust for it. To address this, we removed hypertension and all antihypertensive treatments from the model, but the OR associated with hyperuricaemia did not materially change (OR=1.02; 0.89 to 1.59). The available evidence is much more consistent regarding the role of gout as an independent CV risk factor,[29 30] and our results are compatible with a moderate increased risk of non-fatal AMI associated with gout.

Strengths and limitations

In addition to the 'new user' design, our study has the following strengths: (1) GPs are the gatekeepers of the Spanish National Health System and, therefore, all patients, including those discharged from hospitals, should visit them in order to continue treatment or be referred to a specialist which assures an almost complete registry of important diseases, such as gout or AMI; (2) GPs need to use the computer to fill in the prescription, so the under-recording of prescription drugs is unlikely, in particular for chronic treatments; (3) despite the study was retrospective, the gathering of the information by the GP is performed in a prospective way, which minimises the possibility of a selection bias; (4) controls were randomly sampled from the underlying population, which assures the representativeness of both drug exposures and distribution of confounding factors and (5) researchers were blind to drug exposure when ascertaining cases in order to avoid a differential misclassification of cases.

Our study has a number of limitations that should be commented. First, we did not include fatal AMI cases, as GPs in BIFAP do not have a complete registry of cause of death. Therefore, it is important to note that if allopurinol would increase the risk of fatal AMI, the protective effect on non-fatal AMI observed may have been spurious. Second, in BIFAP, as in most databases used in pharmacoepidemiological studies, there is no systematic recording of either diet or exercise, but we do not think this can fully explain the results as the percentage of obese people (BMI >30 kg/m^2) was much higher among allopurinol initiators (36%) than non-users (22%); additionally, such factors would not explain the reversal of the association when allopurinol was discontinued. Third, for some analysis the sample size was too short.

In conclusion, the present study supports the hypothesis that allopurinol use is associated with a reduced risk of non-fatal AMI, which seems to be dose-dependent and duration-dependent.

Key messages

What is known on this subject?

- Allopurinol reduces vascular oxidative stress and improves endothelial function.
- Allopurinol use in patients with hyperuricaemia or gout has been shown to be associated with a reduced risk of death.
- A recent study shows that allopurinol reduces the risk of myocardial infarction, but the result was not statistically significant and may be affected by a selection bias as most patients were presumably prevalent users of allopurinol.

What might this study add?

- The present study using only allopurinol initiators supports the hypothesis that allopurinol use reduces the risk of non-fatal acute myocardial infarction (AMI).
- The reduced risk of non-fatal AMI associated with allopurinol use is mainly observed in men and appears to be dependent on dose and duration.

How might this impact on clinical practice?

- The reduction in risk of non-fatal AMI should be counted among the cardiovascular benefits of allopurinol.

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Heart

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