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Allopurinol Use and Risk of Acute Coronary Syndrome in Gout patients: A population-based cohort study

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Competing interest

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: no support from any organization for the submitted work. PD has received fees for Advisory Board from Horizon Therapeutics. All other authors have no financial relationships with any organizations that might have an interest in the submitted work in the previous three years. No other relationships or activities that could appear to have influenced the submitted work.

Abstract

Objectives

To investigate the impact of allopurinol use on the risk of first-ever acute coronary syndrome (ACS) event in patients with gout.

Methods

Using national and regional register data, we included all patients with a gout diagnosis at primary or specialized care in Western Sweden in the period 2007-2017 (N=18,862; 67% males). Patients with prior history of coronary heart disease (CHD) were excluded. Follow-up started at the first gout diagnosis and ended at the first-ever ACS event, death, or study end. The main outcome was the risk of first-ever ACS in: 1. allopurinol users vs non-users, by defining three categories of allopurinol exposure: exposed to 100mg, >100mg, and no exposure (reference), and 2. allopurinol initiators vs long-term users (reference). Multivariable logistic regression analysis was used to calculate Odds ratios (OR) and 95% confidence intervals (CI).

Results

In Analysis 1 (N=18,862), 15.3% (N=2,892) were exposed to 100mg, 9.1% (N=1,717) to >100mg, and 75.6% (N=14,253) were not exposed. Allopurinol users were older and had more comorbidities compared to non-users. Allopurinol exposure (100mg and >100mg) was associated with significantly lower odds of first-ever ACS (OR, 0.77; 95%CI, 0.63-0.94, and OR, 0.61; 95%CI, 0.47-0.81, respectively). In Analysis 2, allopurinol initiators (N=489) had significantly higher odds of first-ever ACS compared to long-term users (N=2,916) (OR, 1.68; 95%CI, 1.03-2.75).

Conclusions

In patients with gout and without CHD, long-term allopurinol use protects against first-ever ACS compared to non-users. In contrast, allopurinol initiators, possibly having more systemic inflammation, had higher risk of first-ever ACS compared to long-term users.

What is already known on this topic

- Gout is associated with an increased risk of cardiovascular disease.
- Whether allopurinol use alters this risk is unclear and results from previous studies are conflicting.

What this study adds

- Based on real-world data, our study showed that allopurinol use protects against a first-ever acute coronary syndrome event in patients with gout and no prior history of coronary heart disease.
- Allopurinol initiators had a higher risk of a first-ever acute coronary syndrome event compared to long-term users, probably due to more systemic inflammation.

How this study may affect research, practice, or policy

- Our results provide evidence for a potential benefit of allopurinol in primary cardiovascular prevention for patients with gout.
- Physicians should be aware that recent allopurinol initiators are at higher risk of a first-ever ACS event compared to long-term users. Whether this risk decreases with the use of flare prophylaxis needs further investigation.

Introduction

Background

Cardiovascular disease (CVD) is the leading cause of death globally, with nearly half of these deaths due to ischemic heart disease (1).

Gout is the most common inflammatory arthritis, with a global prevalence ranging from less than 1% to 6.8% and rising incident rates in many countries (2). Gout patients are at increased risk of CVD, with accumulating evidence suggesting that gout is an independent cardiovascular (CV) risk factor (3-9). The mechanistic hypotheses for why gout might independently increase CV risk include hyperuricemia and systemic inflammation. Although gout has traditionally been considered an intermittent inflammatory disease, several recent studies have reported persistent inflammation even during asymptomatic periods (10, 11). Additionally, hyperuricemia itself might contribute to endothelial dysfunction (12).

The first-line treatment for gout is the urate lowering drug allopurinol (13, 14), which has well-established benefits for joint disease (15-18). It is more controversial whether allopurinol also reduces the risk of CV events, possible by reducing urate levels or by decreasing xanthine oxidase-mediated vascular oxidative stress (19).

Some observational studies reported that urate lowering therapy (ULT) reduces CV risk (20-22), whereas others did not find such benefits (23, 24). Small intervention studies have shown benefits of allopurinol on several CV manifestations, including endothelial function (25-27), blood pressure (28-30), and carotid intima-media thickness progression (29), while others have not (31-33). A previously published open-label randomized controlled trial (ALL-HEART study) in patients with ischemic heart disease did not demonstrate improvement in CV outcomes with allopurinol treatment, but gout patients were excluded (34).

Systemic inflammation itself may increase the risk for CV events both in the general population (35) and in patients with gout (36). A previous study found that the risk of CV events was temporally increased close to gout flares, suggesting that acute inflammation related to a gout flare increases the risk of CVD events for six months (36). A surrogate marker for a gout flare may be ULT initiation (37). The risk of CV events in patients initiating allopurinol compared to long-term treatment has not been previously studied.

Objectives

This study aimed to investigate the impact of allopurinol use on the risk of a first-ever acute coronary syndrome (ACS) event in patients with incident gout and no prior history of coronary heart disease (CHD) by comparing: 1) allopurinol users vs non-users (to measure of the overall effect of treatment), and 2) allopurinol initiators vs long-term users (with initiators serving as a surrogate for recent flares) at the time of ACS event.

Methods

Study design and setting

This is a population-based cohort study of patients with incident gout in Western Sweden in the period 2007-2017.

The healthcare system in Sweden is mainly public, tax-funded, and independent of the individual's insurance or financial status. The patients with gout are usually diagnosed and treated in primary health care units, and only to a lesser extent, in specialized health care units. The 10-digit personal identification number, which is unique for each individual and automatically assigned to every Swedish resident, enables linkage of data from different registers.

Ethical approval for the study was granted from the Ethical Review Board of Gothenburg, Sweden. Informed consent from the patients was not needed, as the study was based on register data.

The manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted.

Data sources

The Western Swedish Health Care Register (VEGA) contains information about all healthcare contacts at both primary and secondary healthcare in Western Sweden (approximately 1.7 million inhabitants) from 2000 onwards. All diagnoses given by physicians are registered according to the Swedish version of the International Classification of Disease (ICD) codes. Since 1997 the 10th version of ICD codes (ICD-10) is used in Sweden.

The Swedish Prescribed Drug Register (PDR) contains information about all prescribed drugs dispensed by Swedish pharmacies since July 2005, based on the Anatomical Therapeutic Chemical Classification System (ATC).

The Cause-of-death Register contains information about date and cause of death for all deceased residents since 1961.

Patients and Public Involvement

This study was based on register data. Patients or the public were not involved in the study design.

Participants

By using data from VEGA, we identified all patients aged ≥30 years in Western Sweden with first gout diagnosis after 1 January 2007 at either primary or secondary healthcare. Cases were regarded as incident, if they did not have any recorded gout diagnosis in the previous seven years. Cases with prior history of CHD or exposure to allopurinol before first gout diagnosis were excluded (Supplementary Table 1). Patients with any dispensed prescription of colchicine, febuxostat or probenecid, as well as patients with a history of hematological malignancy and/or end stage renal disease were excluded to minimize confounding (Figure 1).

Outcome of interest

The study outcome was the first-ever ACS event, defined as the first reported ICD-coded primary diagnosis of either myocardial infarction (MI) or unstable angina at discharge from an inpatient unit, or ACS as primary cause of death without prior non-fatal ACS (Supplementary Table 1). The follow-up begun on the first ICD-coded diagnosis of gout, and ended on the earliest of the outcome, emigration, death, or the end of study on 31 December 2017.

Analysis 1: users vs non-users

The exposure of interest was the prescription of allopurinol within 125 days before the end of follow-up. We considered 100 days of treatment, which allopurinol prescription in Sweden usually covers, and allowed up to 25 days of grace period. We defined three different levels of exposure based on daily dose: 100 mg daily, >100 mg, and no exposure (Figure 2, I).

Analysis 2: initiators vs long-term users

We defined two categories of exposure, allopurinol initiators and long-term users. Both categories were exposed to allopurinol at the end of follow-up, defined as having dispensed a prescription of allopurinol within 125 days before the end of follow-up. The initiators were defined as not having dispensed a prescription of allopurinol during a look-back period of 365 days and the long-term users as having continuous allopurinol treatment during the same time period (Figure 2, II). The quantity dispensed and number of days supplied from each filled

prescription were used to calculate the proportion of days on which a patient had allopurinol available (proportion of days covered [PDC]). We then defined continuous treatment as a PDC of at least 80% in the given interval (Figure 2, II).

Sensitivity analysis

To delineate the long-term effect in those on chronic allopurinol treatment from that in allopurinol initiators we also performed a sensitivity analysis excluding initiators from those exposed to allopurinol at the time of ACS event in analysis 1.

Covariates and confounders

We included comorbidities which could be possible confounders because of either the medical condition itself or its treatment (hypertension, diabetes, hyperlipidemia, obesity, renal disease, heart failure, cardiomyopathy, psoriasis, chronic obstructive pulmonary disease [COPD], alcoholism, cerebrovascular disease, atherosclerotic disease, and cancer). Comorbidities were assessed based on the presence of respective ICD-code during the follow-up period. The diagnoses of diabetes, hyperlipidemia, and obesity were further identified if they had at least one ATC-coded dispensed prescription of anti-diabetic, lipid-lowering, or anti-obesity drugs, respectively (Supplementary Table 1). Comorbidities were included in the analyses as comorbidity index based on the number of ever diagnosed comorbidities during the follow-up, 0, 1-2, 3-4, or >5.

Medication was defined as a dispensed prescription of anticoagulants, CV drugs or cortisone within six months before the end of follow-up. The category of CV drugs included vasodilator drugs, anti-hypertensive drugs, diuretics, beta-blockers, calcium antagonists, and renin-angiotensin-aldosterone (RAAS) inhibitors (Supplementary Table 1). Exposure to non-steroidal anti-inflammatory drugs (NSAIDs) or Cox-2 inhibitors were not included in the analyses, due to uncertain exposure (unknown amount sold over the counter).

Statistical methods

Continuous variables are presented as mean ± SD. Categorical variables are presented as number and percentage. Comparisons between continuous variables were performed with ANOVA and between categorical with Kruskal-Wallis test.

We performed unadjusted and adjusted logistic regression analysis to calculate Odds ratios (OR) and 95% confidence intervals (CI) for first-ever ACS event. Multivariable logistic

regression analysis was performed with adjustments for age, sex, education level, comorbidity index, and medication. The unexposed category was used as the reference group in analysis 1 and the long-term users were used as the reference group in analysis 2.

Statistical analyses were performed by using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Participants

After exclusions for age (N=423), ULT treatment before gout diagnosis (N=7,945), prior history of CHD (N=4,422), treatment with colchicine, febuxostat or probenecid (N=840), and diagnosed hematological malignancy or end stage renal disease (N=444), a total of 18,862 patients with incident gout were included in this study (67% men) (Figure 1). Of these, 41.2% (N=7,780) had at least one dispensed prescription of allopurinol and 58.8% (N=11,082) had no dispensed prescription of allopurinol during the total follow-up period (Figure 1).

Main results

Analysis 1: users vs non-users

Among the patients with incident gout included in this analysis (N=18,862), 15.3% (N=2,892) were exposed to 100 mg allopurinol, 9.1% (N=1,717) were exposed to >100 mg allopurinol, and 75.6% (N=14,253) were not exposed to allopurinol within 125 days before the end of follow-up (Table 1). The mean allopurinol dose in the group exposed to >100 mg was 260 mg in men and 246 mg in women.

Patients exposed to allopurinol were older and had more comorbidities and medication, as compared to those not exposed. No significant differences were observed between patients exposed to 100 mg and >100 mg allopurinol regarding age, comorbidity index, or medication (Table 1, Supplementary Table 2).

In the adjusted model, patients exposed to allopurinol had significantly lower odds of ACS event, compared to those not exposed (OR, 0.77; 95%CI, 0.63-0.94 for 100mg, and OR, 0.61; 95%CI, 0.47-0.81 for >100mg). Compared to low dose of allopurinol (100 mg), a higher dose (>100 mg) was associated with lower odds of ACS event, but the difference was not statistically significant (p-value for trend, 0.16). In women, exposure to > 100 mg was associated with

significantly lower odds of ACS event, whereas exposure to 100 mg did not reach statistical significance (Figure 3).

Analysis 2: initiators vs long-term users

Overall, 489 initiators and 2,916 long-term users were included in this analysis. Initiators were less likely to be treated with anticoagulants and CV drugs, but more likely to be treated with cortisone, compared to the long-term users (Table 2). Male initiators were more likely to have renal disease and COPD and less likely to have hypertension compared to male long-term users. Female initiators were more likely to have renal disease, heart failure and COPD compared to female long-term users (Supplementary Table 3).

In the adjusted multivariate logistic regression analyses, initiators had significantly higher odds of ACS events compared to long-term users, after adjustments for age, education level, comorbidity index, and medication (Figure 3).

Sensitivity analysis

After excluding allopurinol initiators (N= 489), 4,120 patients exposed to allopurinol and 14,253 patients not exposed remained. Patients exposed to allopurinol had significantly lower odds of ACS event compared to those not exposed and similar to ORs observed in Analysis 1 (OR, 0.75; 95%CI, 0.61-0.93 for those exposed to 100 mg allopurinol, and OR, 0.64; 95%CI 0.48-0.85 for those exposed to >100 mg), which is probably explained by the low number of allopurinol initiators.

Discussion

In this population-based cohort study, we studied the effect of allopurinol use on the risk of first-ever ACS event in patients with incident gout and no prior history of CHD. We found that allopurinol users at the time of the ACS event had a significantly lower risk of first-ever ACS, whereas the subgroup of recent allopurinol initiators had an increased risk, possibly reflecting recent flares and a higher contemporary level of systemic inflammation.

The first finding provide evidence for a potential benefit of allopurinol in primary CV prevention in patients with gout. Allopurinol reduces urate levels, may decrease systemic inflammation and the generation of oxidative species, and may reverse endothelial dysfunction

(38). This may explain the association between allopurinol use and the lower risk of ACS found in our study.

ULT initiation is usually started due to active gout with frequent flares and may be associated with an increased risk of gout flares during the initial period after initiation (37). A previously published study showed that gout flares were associated with a transient increase in CV events following the flares, possibly due to neutrophilic inflammation which may cause atherosclerotic plaque instability and rupture (36). This may explain the association between increased risk of ACS events and allopurinol initiation. To the best of our knowledge, this study is the first to report an increased risk of ACS event during allopurinol initiation compared to long-term allopurinol use.

Previous observational studies exploring the effect of allopurinol use on CV outcomes in patients with gout have shown conflicting results. Singh *et al* found that allopurinol use was associated with a lower risk of MI in older patients with gout (≥ 65 years) and that risk reduction was associated with the duration of treatment (39). Allopurinol use for more than 6 months to 2 years and over 2 years was associated with lower risk of MI compared to non-use, whereas allopurinol use for less than 6 months was not. In another study of Singh *et al*, current allopurinol use, defined as a new filled prescription, was associated with lower risk of MI and stroke in patients with gout and diabetes compared to previous allopurinol use (21).

In contrast, the risk of CVD did not differ significantly between the allopurinol and non-allopurinol group in a cohort of gout patients, but 69% of patients in the non-allopurinol group received an uricosuric agent (40). Lin *et al* showed that allopurinol was not associated with a lower risk of coronary artery disease (CAD) in patients with newly diagnosed gout. However, the dose-stratified analysis showed that the risk of CAD was significantly lower in higher allopurinol doses (>270 defined daily doses [DDDs]) compared to lower doses (0-90 DDDs) (41). The doses of allopurinol in our study were relatively low, but these are the doses generally used in clinical practice for gout patients in Sweden, where gout remains suboptimally managed (42, 43).

The previously published ALL-HEART study showed that allopurinol treatment does not improve CV outcomes in patients with ischemic heart disease (34). However, the study excluded patients with a history of gout, the mean urate concentration at baseline in the allopurinol group was low (0.34 mmol/L [5.7 mg/dL]), and the discontinuation rate for allopurinol was high. These differences in the selection of treated patients might explain the

divergent results between our study and ALL-HEART study, potentially reflecting different cardiovascular outcomes in patients with normouricemia and those with hyperuricemia/gout.

This study had several limitations. First, as with all observational studies, there is a risk of residual confounding. To minimize this bias, we controlled for multiple potential confounders. Second, as in other pharmacoepidemiologic studies, it was not certain that allopurinol was taken by the patients. Such misclassification of exposure is however likely to be non-differential between exposed groups and in comparison with those unexposed. Poor adherence would probably result in an underestimation of the reduced risk. Third, it was not possible to verify the indication for each allopurinol prescription, but all cases in this study had a diagnosis of gout, and cases with disorders that could indicate allopurinol use for another reason (i.e., hematological malignancy or end-stage renal disease) were excluded. Fourth, data on gout severity (i.e., tophi, erosions, urate levels) are infrequently reported in the registers and could not be adjusted for in the analyses. However, this may have had only a moderate impact on this study as we included only patients with incident gout. Fifth, in comparisons between allopurinol initiators and long-term users, the study power in the sex-stratified analyses may not have been sufficient to reach statistical significance. Finally, we were not able to adjust for smoking, body mass index, diet, exercise, over the counter NSAID use, and family history of CVD, because these data are not reported in the registers.

This study had several strengths. By excluding patients with dispensed prescription of colchicine, we were able to study the isolated effect of allopurinol on the risk of ACS. Furthermore, this study used data from large population-based registers, and the study population is representative of the general population in Sweden (44, 45). The data used were derived from both primary and secondary healthcare, covering all possible phenotypes of gout, from mild to severe disease. Gout cases and ACS events identified using validated definitions to minimize potential misclassification bias. Previous validation studies showed high validity for the diagnoses of gout and myocardial infarction in the Swedish registers (46, 47).

Conclusions

Among patients with incident gout and no prior history of CHD, allopurinol users had a significantly lower risk of a first-ever ACS event compared to non-users. This finding provides evidence for a potential benefit of allopurinol in primary CV prevention for patients with gout. However, the subgroup of recent allopurinol initiators had a higher risk of a first-ever ACS event compared to long-term users. This finding may reflect a higher risk of gout flares during

allopurinol initiation. Whether this risk is affected by the use of flare prophylaxis needs to be investigated in further studies.

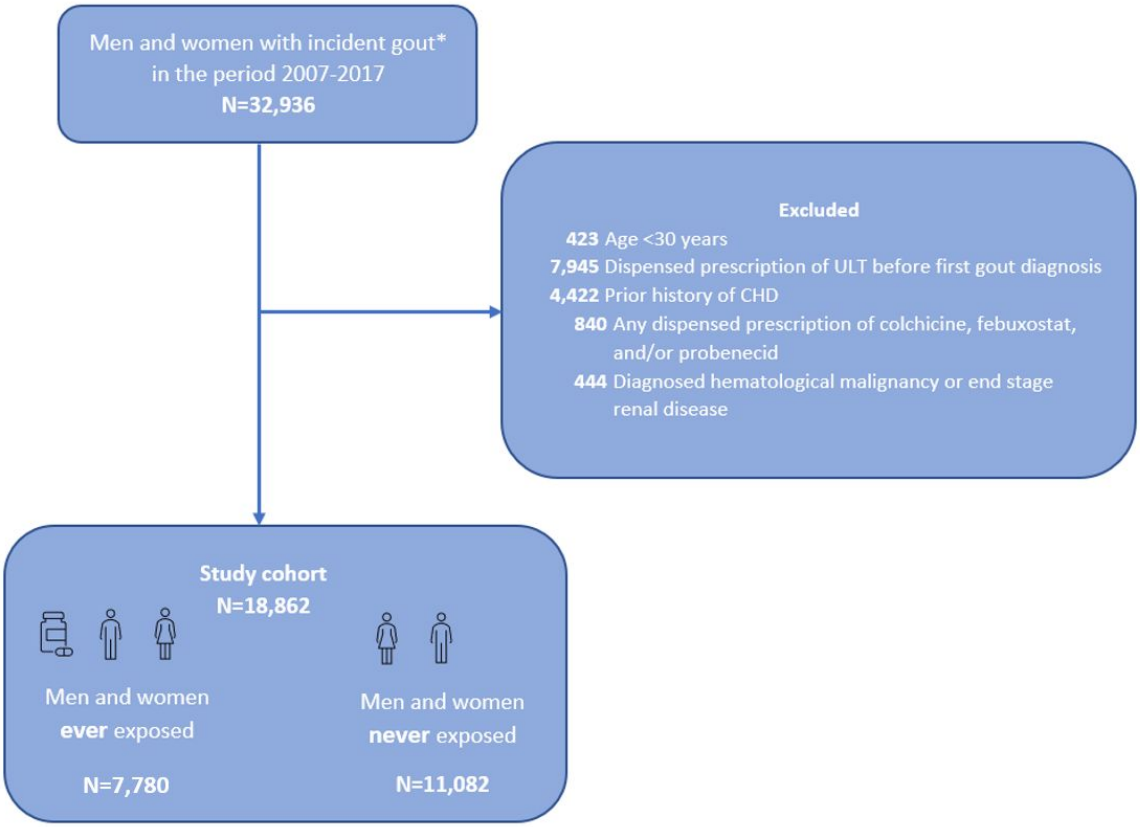

Figure 1. Design of study cohort.

*Defined as no recorded diagnosis of gout in the previous seven years.

ULT, urate lowering treatment; CHD, coronary heart disease.

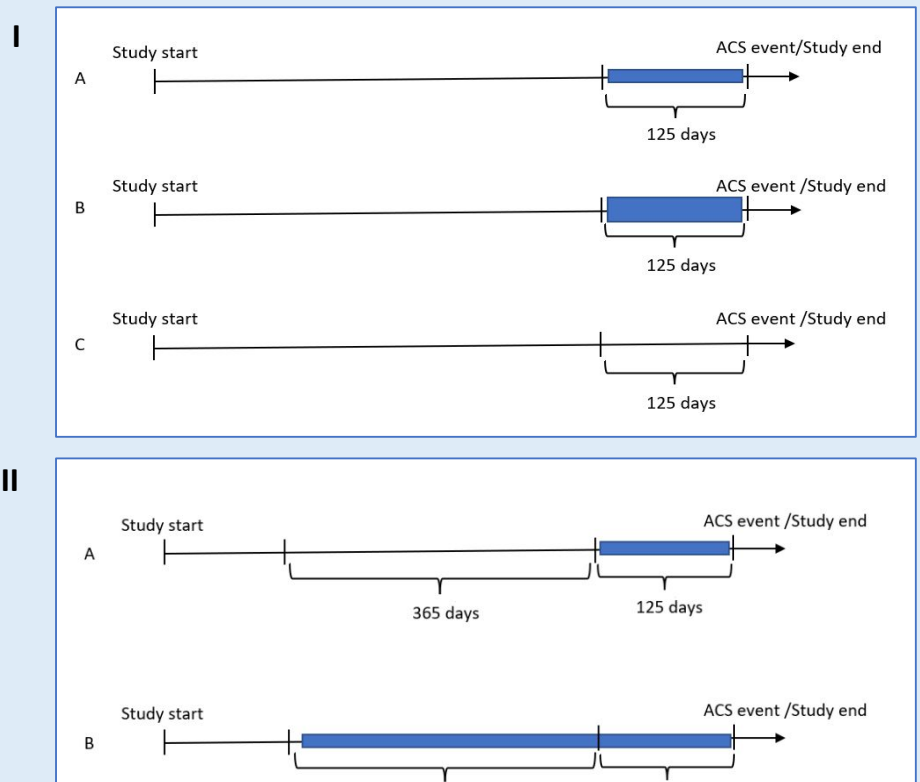

Figure 2. Study exposure of interest.

I. Analysis 1: Users vs non-users at the end of follow-up.

A. Exposure to 100mg.
B. Exposure to >100mg.
C. No exposure (reference group).

II. Analysis 2: Initiators vs long-term users.

A. Initiators, defined as having dispensed a prescription of allopurinol within 125 days before the end of follow up AND no dispensed prescription during a look-back period of 365 days.
B. Long-term users, defined as having dispensed a prescription of allopurinol within 125 days before the end of follow up AND having continuous allopurinol treatment during a look-back period of 365 days.

	ACS events, N (%)	Adjusted OR* (95%CI)
Analysis 1		
Total		
No exposure (ref.)	565 (4.0)	1
Exposure to 100mg	143 (4.9)	0.77 (0.63-0.94)
Exposure to >100mg	61 (3.6)	0.61 (0.47-0.81)
Men		
No exposure (ref.)	402 (4.3)	1
Exposure to 100mg	96 (5.0)	0.76 (0.60-0.97)
Exposure to >100mg	47 (3.7)	0.64 (0.47-0.89)
Women		
No exposure (ref.)	163 (3.4)	1
Exposure to 100mg	47 (4.9)	0.79 (0.56-1.11)
Exposure to >100mg	14 (3.3)	0.54 (0.31-0.96)
Analysis 2		
Total		
Initiators	26 (5.3)	1.68 (1.03-2.75)
Long-term users	106 (3.6)	1
Men		
Initiators	18 (5.0)	1.79 (0.99-3.24)
Long-term users	72 (3.5)	1
Women		
Initiators	8 (6.2)	1.43 (0.59-3.47)
Long-term users	34 (3.9)	1

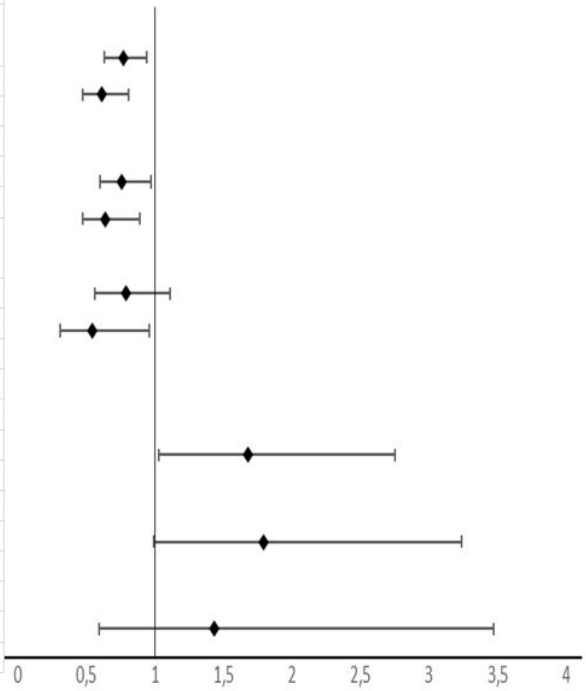

Figure 3. Association between allopurinol exposure and acute coronary syndrome (ACS) events, total and by sex.
Analysis 1: users vs non-users.
Analysis 2: allopurinol initiators vs long-term users.

*Adjusted for age, education level, comorbidity index, and medication.

Table 1. Demographic and clinical characteristics of patients with incident gout included in Analysis 1.

	Not exposed		Exposed to 100mg		Exposed to >100mg	
	Men N=9,405	Women N=4,848	Men N=1,941	Women N=951	Men N=1,287	Women N=430
Age, mean (SD), years	62.3 (14.5)	68.5 (14.7)	67.7 (13.8)	76.5 (11.6)	63.6 (13.5)	74.5 (11.3)
Follow-up, years, median (Q1, Q3)	4.1 (1.9, 6.7)	4.1 (1.9, 6.7)	4.4 (1.9, 7.0)	3.7 (1.6, 6.2)	5.0 (2.5, 7.6)	4.1 (1.9, 6.3)
Education level, years						
<9	2,901 (30.9)	1,899 (39.2)	742 (38.2)	509 (53.5)	446 (34.7)	207 (48.1)
9-12	4,275 (45.5)	1,945 (40.1)	803 (41.4)	313 (32.9)	537 (41.7)	159 (37.0)
>12	2,090 (22.2)	932 (19.2)	361 (18.6)	109 (11.5)	271 (21.1)	56 (13.0)
Comorbidity index†, N(%)						
0	2,254 (24.0)	845 (17.4)	217 (11.2)*	20 (2.1)*	1,732 (13.4)*	5 (1.2)*
1-2	3,517 (37.4)	1,877 (38.7)	600 (30.9)*	228 (24.0)*	394 (30.6)*	104 (24.2)*
3-4	2,666 (28.4)	1,527 (31.5)	709 (36.5)*	433 (45.5)*	446 (34.7)*	194 (45.1)*
≥5	968 (10.3)	599 (12.4)	415 (21.4)*	270 (28.4)*	275 (21.4)*	127 (29.5)*
Medication‡, N(%)						
Anticoagulants	2,956 (31.4)	1,630 (33.6)	917 (47.2)*	549 (57.7)*	544 (42.3)*	240 (55.8)*
CV drugs§	5,032 (53.5)	3,066 (63.2)	1,515 (78.1)*	891 (93.7)*	971 (75.4)*	404 (94.0)*
Cortisone	854 (9.1)	600 (12.4)	312 (16.1)*	217 (22.8)*	203 (15.8)*	88 (20.5)*

†Based on number of ever diagnosed comorbidities during the follow-up. Comorbidities included: hypertension, diabetes, hyperlipidemia, obesity, renal disease, heart failure, cardiomyopathy, psoriasis, chronic obstructive pulmonary disease, alcoholism, cerebrovascular disease, atherosclerotic disease, and cancer.

‡Defined as dispensed prescription within six months before the end of follow-up.

§ Drugs included: vasodilator drugs, anti-hypertensive drugs, diuretics, beta blockers, calcium antagonists, and renin-angiotensin-aldosterone inhibitors.

*p-value <0.05 compared to those not exposed.

CV, cardiovascular.

Table 2. Demographic and clinical characteristics of patients with incident gout included in Analysis 2.

	Initiators		Long-term users	
	Men N= 359	Women N= 130	Men N= 2,034	Women N= 882
Age, mean (SD), years	65.1 (14.8)	74.5 (13.3)	66.1 (13.2)	75.1 (11.0)
Follow-up, years, median (Q1, Q3)	1.3 (0.3, 5.1)	0.4 (0.2, 2.5)	5.6 (3.3, 7.8)	4.8 (2.9, 6.9)
Education level, years, N(%)				
<9	117 (32.6)	66 (50.8)	768 (37.8)	459 (52.0)
9-12	164 (45.7)	48 (36.9)	806 (39.6)	291 (33.0)
>12	71 (19.8)	12 (9.2)	417 (20.5)	119 (13.5)
Comorbidity index†, N(%)				
0	93 (25.9)	6 (4.6)	449 (22.1)	52 (5.9)
1-2	140 (39.0)	55 (42.3)	908 (44.6)	401 (45.5)
3-4	93 (25.9)	54 (41.5)	534 (26.3)	330 (37.4)
≥5	33 (9.2)	15 (11.5)	143 (7.0)	99 (11.2)
Medication‡, N(%)				
Anticoagulants	136 (37.9)*	66 (50.8)	959 (47.1)	503 (57.0)
CV drugs§	258 (71.9)*	115 (88.5)*	1,612 (79.3)	830 (94.1)
Cortisone	150 (41.8)*	65 (50.0)*	187 (9.2)	126 (14.3)

†Based on number of ever diagnosed comorbidities during the follow-up. Comorbidities included: hypertension, diabetes, hyperlipidemia, obesity, renal disease, heart failure, cardiomyopathy, psoriasis, chronic obstructive pulmonary disease, alcoholism, cerebrovascular disease, atherosclerotic disease, and cancer.

‡Defined as dispensed prescription within six months before the end of follow-up.

§ Drugs included: vasodilator drugs, anti-hypertensive drugs, diuretics, beta blockers, calcium antagonists, and renin-angiotensin-aldosterone inhibitors.

*p-value <0.05 compared to long-term users.

CV, cardiovascular.

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Data Sharing

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Supplementary Table 1. ICD and ATC codes used for the definition of gout, ACS, comorbidities, and medication.

	ICD codes	ATC codes
Gout	M10, M14.0, M14.1	
Allopurinol		M04AA01
ACS	I20.0, I21	
CHD	I20-25	
Hypertension	I10-15	
Diabetes	E10-14, O24	A10
Hyperlipidemia	E78	C10
Obesity	E66	A08
Renal disease	N00-08, N10-23	
Heart failure	I50	
Cardiomyopathy	I42	
Psoriasis	L40	
COPD	J44	
Alcoholism	Z72.1, F10	
Cerebrovascular disease	I60-69	
Atherosclerotic disease	I70-79	
Cancer	C00-43, C45-97	
Vasodilator drugs*		C01D
Antihypertensive drugs*		C02
Diuretics*		C03
Beta blockers*		C07
Calcium antagonists*		C08
RAAS inhibitors*		C09
Anticoagulants		B01AC04, B01AC06

*Included in the analyses as 'cardiovascular drugs'.

ACS, acute coronary syndrome; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; RAAS, renin-angiotensin-aldosterone system

Supplementary Table 2. Comorbidities in patients with incident gout included in Analysis 1.

	Not exposed		Exposed to 100mg		Exposed to >100mg	
Comorbidities, N (%)	Men N=9,405	Women N=4,848	Men N=1,941	Women N=951	Men N=1,287	Women N=430
Hypertension	4,147 (44.1)	2,693 (55.5)	1,214 (62.5)	801 (84.2)	753 (58.5)	368 (85.6)
Diabetes	1,172 (12.5)	784 (16.2)	347 (17.9)	252 (26.5)	215 (16.7)	132 (30.7)
Hyperlipidemia	2,321 (24.7)	1,368 (28.2)	671 (34.6)	383 (40.3)	401 (31.2)	183 (42.6)
Obesity	911 (9.7)	603 (12.4)	207 (10.7)	180 (18.9)	194 (15.1)	105 (24.4)
Renal disease	679 (7.2)	392 (8.1)	278 (14.3)	168 (17.7)	150 (11.7)	65 (15.1)
Heart failure	590 (6.3)	508 (10.5)	353 (18.2)	264 (27.8)	210 (16.3)	127 (29.5)
Cardiomyopathy	94 (1.0)	28 (0.6)	42 (2.2)	16 (1.7)	43 (3.3)	9 (2.1)
Psoriasis	324 (3.4)	213 (4.4)	61 (3.1)	39 (4.1)	53 (4.1)	16 (3.7)
COPD	408 (4.3)	367 (7.6)	131 (6.7)	104 (10.9)	67 (5.2)	42 (9.8)
Alcoholism	500 (5.3)	102 (2.1)	82 (4.2)	9 (0.9)	64 (5.0)	7 (1.6)
Cerebrovascular disease	592 (6.3)	390 (8.0)	199 (10.3)	122 (12.8)	101 (7.8)	50 (11.6)
Atherosclerotic disease	236 (2.5)	154 (3.2)	77 (4.0)	65 (6.8)	48 (3.7)	16 (3.7)
Cancer	533 (5.7)	282 (5.8)	121 (6.2)	63 (6.6)	84 (6.5)	22 (5.1)

Supplementary Table 3. Comorbidities in patients with incident gout included in Analysis 2.

	Initiators		Long-term users	
Comorbidities, N (%)	Men N= 359	Women N= 130	Men N= 2,034	Women N=882
Hypertension	205 (57.1)*	104 (80.0)	1,282 (63.0)	748 (84.8)
Diabetes	62 (17.3)	33 (25.4)	368 (18.1)	262 (29.7)
Hyperlipidemia	122 (34.0)	50 (38.5)	696 (34.2)	378 (42.9)
Obesity	43 (12.0)	32 (24.6)	264 (13.0)	183 (20.7)
Renal disease	61 (17.0)*	32 (24.6)*	263 (12.9)	126 (14.3)
Heart failure	70 (19.5)	44 (33.8)*	339 (16.7)	223 (25.3)
Cardiomyopathy	7 (1.9)	1 (0.8)	56 (2.8)	17 (1.9)
Psoriasis	20 (5.6)	7 (5.4)	72 (3.5)	38 (4.3)
COPD	31 (8.6)*	20 (15.4)*	111 (5.5)	86 (9.8)
Alcoholism	15 (4.2)	3 (2.3)	88 (4.3)	11 (1.2)
Cerebrovascular disease	36 (10.0)	19 (14.6)	181 (8.9)	104 (11.8)
Atherosclerotic disease	15 (4.2)	10 (7.7)	79 (3.9)	45 (5.1)
Cancer	23 (6.4)	9 (6.9)	122 (6.0)	43 (4.9)

*p-value <0.05 compared to long-term users

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Allopurinol Use and Risk of Acute Coronary Syndrome in Gout patients: A population-based cohort study in Sweden

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Competing interest

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Abstract

Objectives

To investigate the impact of allopurinol use on the risk of first-ever acute coronary syndrome (ACS) event in patients with gout.

Methods

Using national and regional register data, we included all patients with a gout diagnosis at primary or specialized care in Western Sweden in the period 2007-2017 (N=18,862; 67% males). Patients with prior history of coronary heart disease (CHD) were excluded. Follow-up started at the first gout diagnosis and ended at the first-ever ACS event, death, or study end. The main outcome was the risk of first-ever ACS in: 1. allopurinol users vs non-users, by defining three categories of allopurinol exposure: exposed to 100mg, >100mg, and no exposure (reference), and 2. allopurinol initiators (within 125 days) vs long-term users (reference). Multivariable logistic regression analysis was used to calculate Odds ratios (OR) and 95% confidence intervals (CI).

Results

In Analysis 1 (N=18,862), 15.3% (N=2,892) were exposed to 100mg, 9.1% (N=1,717) to >100mg, and 75.6% (N=14,253) were not exposed. Allopurinol users were older and had more comorbidities compared to non-users. Allopurinol exposure (100mg and >100mg) was associated with significantly lower odds of first-ever ACS (OR, 0.77; 95%CI, 0.63-0.94, and OR, 0.61; 95%CI, 0.47-0.81, respectively). In Analysis 2, allopurinol initiators (N=489) had significantly higher odds of first-ever ACS compared to long-term users (N=2,916) (OR, 1.68; 95%CI, 1.03-2.75).

Conclusions

In patients with gout and without CHD, long-term allopurinol use protects against first-ever ACS compared to non-users. In contrast, allopurinol initiators, possibly having more systemic inflammation, had higher risk of first-ever ACS compared to long-term users.

Strengths and limitations of this study

- This study used data from large population-based registers, minimizing selection bias.
- The data used were derived from both primary and secondary healthcare, covering all possible phenotypes of gout.
- Gout cases and ACS events identified using validated definitions, minimizing potential misclassification bias.
- Although we controlled for multiple confounders, there is still a risk of residual confounding.

Introduction

Background

Cardiovascular disease (CVD) is the leading cause of death globally, with nearly half of these deaths due to ischemic heart disease [1].

Gout is the most common inflammatory arthritis, with a global prevalence ranging from less than 1% to 6.8% and rising incident rates in many countries [2]. Gout patients are at increased risk of CVD, with accumulating evidence suggesting that gout is an independent cardiovascular (CV) risk factor [3-9]. The mechanistic hypotheses for why gout might independently increase CV risk include hyperuricemia and systemic inflammation. Although gout has traditionally been considered an intermittent inflammatory disease, several recent studies have reported persistent inflammation even during asymptomatic periods [10, 11]. Additionally, hyperuricemia itself might contribute to endothelial dysfunction [12].

The first-line treatment for gout is the urate lowering drug allopurinol [13, 14], which has well-established benefits for joint disease [15-18]. It is more controversial whether allopurinol also reduces the risk of CV events, possible by reducing urate levels or by decreasing xanthine oxidase-mediated vascular oxidative stress [19].

Some observational studies reported that urate lowering therapy (ULT) reduces CV risk [20-22], whereas others did not find such benefits [23, 24]. Small intervention studies have shown benefits of allopurinol on several CV manifestations, including endothelial function [25-27], blood pressure [28-30], and carotid intima-media thickness progression [29], while others have not [31-33]. A previously published open-label randomized controlled trial (ALL-HEART study) in patients with ischemic heart disease did not demonstrate improvement in CV outcomes with allopurinol treatment, but gout patients were excluded [34].

Systemic inflammation itself may increase the risk for CV events both in the general population [35] and in patients with gout [36]. A previous study found that the risk of CV events was temporally increased close to gout flares, suggesting that acute inflammation related to a gout flare increases the risk of CVD events for six months [36]. A surrogate marker for a gout flare may be ULT initiation [37]. The risk of CV events in patients initiating allopurinol compared to long-term treatment has not been previously studied.

Objectives

This study aimed to investigate the impact of allopurinol use on the risk of a first-ever acute coronary syndrome (ACS) event in patients with incident gout and no prior history of coronary

heart disease (CHD) by comparing: 1) allopurinol users vs non-users (to measure of the overall effect of treatment), and 2) allopurinol initiators vs long-term users (with initiators serving as a surrogate for recent flares) at the time of ACS event.

Methods

Study design and setting

This is a population-based cohort study of patients with incident gout in Western Sweden in the period 2007-2017.

The healthcare system in Sweden is mainly public, tax-funded, and independent of the individual's insurance or financial status. The patients with gout are usually diagnosed and treated in primary health care units, and only to a lesser extent, in specialized health care units. The 10-digit personal identification number, which is unique for each individual and automatically assigned to every Swedish resident, enables linkage of data from different registers.

Ethical approval for the study was granted from the Ethical Review Board of Gothenburg, Sweden. Informed consent from the patients was not needed, as the study was based on register data.

The manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted.

Data sources

The Western Swedish Health Care Register (VEGA) contains information about all healthcare contacts at both primary and secondary healthcare in Western Sweden (approximately 1.7 million inhabitants) from 2000 onwards. All diagnoses given by physicians are registered according to the Swedish version of the International Classification of Disease (ICD) codes. Since 1997 the 10th version of ICD codes (ICD-10) is used in Sweden.

The Swedish Prescribed Drug Register (PDR) contains information about all prescribed drugs dispensed by Swedish pharmacies since July 2005, based on the Anatomical Therapeutic Chemical Classification System (ATC).

The Cause-of-death Register contains information about date and cause of death for all deceased residents since 1961.

Patients and Public Involvement

This study was based on register data. Patients or the public were not involved in the study design.

Participants

By using data from VEGA, we identified all patients aged ≥30 years in Western Sweden with first gout diagnosis after 1 January 2007 at either primary or secondary healthcare. Cases were regarded as incident, if they did not have any recorded gout diagnosis in the previous seven years. Cases with prior history of CHD or exposure to allopurinol before first gout diagnosis were excluded (Supplementary Table 1). Patients with any dispensed prescription of colchicine, febuxostat or probenecid were excluded. We also excluded patients with a history of hematological malignancy and/or end stage renal disease to minimize confounding by indication (Figure 1).

Outcome of interest

The study outcome was the first-ever ACS event, defined as the first reported ICD-coded primary diagnosis of either myocardial infarction (MI) or unstable angina at discharge from an inpatient unit, or ACS as primary cause of death without prior non-fatal ACS (Supplementary Table 1). By narrowing our focus on ACS and not on other cardiovascular outcomes, we aimed to conduct a study which provides robust results regarding the relationship between allopurinol use and acute coronary events. The follow-up begun on the first ICD-coded diagnosis of gout, and ended on the earliest of the outcome, emigration, death, or the end of study on 31 December 2017.

Analysis 1: users vs non-users

The exposure of interest was the prescription of allopurinol within 125 days before the end of follow-up. We considered 100 days of treatment, which allopurinol prescription in Sweden usually covers, and allowed up to 25 days of grace period. We defined three different levels of exposure based on daily dose: 100 mg daily, >100 mg, and no exposure (Figure 2, I).

Analysis 2: initiators vs long-term users

We defined two categories of exposure, allopurinol initiators and long-term users. Both categories were exposed to allopurinol at the end of follow-up, defined as having dispensed a prescription of allopurinol within 125 days before the end of follow-up. The initiators were defined as not having dispensed a prescription of allopurinol during a look-back period of 365

days and the long-term users as having continuous allopurinol treatment during the same time period (Figure 2, II). The quantity dispensed and number of days supplied from each filled prescription were used to calculate the proportion of days on which a patient had allopurinol available (proportion of days covered [PDC]). We then defined continuous treatment as a PDC of at least 80% in the given interval (Figure 2, II).

Sensitivity analysis

To delineate the long-term effect in those on chronic allopurinol treatment from that in allopurinol initiators we also performed a sensitivity analysis excluding initiators from those exposed to allopurinol at the time of ACS event in analysis 1.

Covariates and confounders

We included comorbidities which could be possible confounders because of either the medical condition itself or its treatment (hypertension, diabetes, hyperlipidemia, obesity, renal disease, heart failure, cardiomyopathy, psoriasis, chronic obstructive pulmonary disease [COPD], alcoholism, cerebrovascular disease, atherosclerotic disease, and cancer). Comorbidities were assessed based on the presence of respective ICD-code during the follow-up period. The diagnoses of diabetes, hyperlipidemia, and obesity were further identified if they had at least one ATC-coded dispensed prescription of anti-diabetic, lipid-lowering, or anti-obesity drugs, respectively (Supplementary Table 1). Comorbidities were included in the analyses as comorbidity index based on the number of ever diagnosed comorbidities during the follow-up, 0, 1-2, 3-4, or >5.

Medication was defined as a dispensed prescription of anticoagulants, CV drugs or cortisone within six months before the end of follow-up. The category of CV drugs included vasodilator drugs, anti-hypertensive drugs, diuretics, beta-blockers, calcium antagonists, and renin-angiotensin-aldosterone (RAAS) inhibitors (Supplementary Table 1). Exposure to non-steroidal anti-inflammatory drugs (NSAIDs) or Cox-2 inhibitors were not included in the analyses, due to uncertain exposure (unknown amount sold over the counter).

Statistical methods

Continuous variables are presented as mean ± SD. Categorical variables are presented as number and percentage. Comparisons between continuous variables were performed with ANOVA and between categorical with Kruskal-Wallis test.

We performed unadjusted and adjusted logistic regression analysis to calculate Odds ratios (OR) and 95% confidence intervals (CI) for first-ever ACS event. Multivariable logistic regression analysis was performed with adjustments for age, sex, education level, comorbidity index, and medication. The unexposed category was used as the reference group in analysis 1 and the long-term users were used as the reference group in analysis 2.

Statistical analyses were performed by using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Participants

After exclusions for age (N=423), ULT treatment before gout diagnosis (N=7,945), prior history of CHD (N=4,422), treatment with colchicine, febuxostat or probenecid (N=840), and diagnosed hematological malignancy or end stage renal disease (N=444), a total of 18,862 patients with incident gout were included in this study (67% men) (Figure 1). Of these, 41.2% (N=7,780) had at least one dispensed prescription of allopurinol and 58.8% (N=11,082) had no dispensed prescription of allopurinol during the total follow-up period (Figure 1).

Main results

Analysis 1: users vs non-users

Among the patients with incident gout included in this analysis (N=18,862), 15.3% (N=2,892) were exposed to 100 mg allopurinol, 9.1% (N=1,717) were exposed to >100 mg allopurinol, and 75.6% (N=14,253) were not exposed to allopurinol within 125 days before the end of follow-up (Table 1). The mean allopurinol dose in the group exposed to >100 mg was 260 mg in men and 246 mg in women.

Patients exposed to allopurinol were older and had more comorbidities and medication, as compared to those not exposed. No significant differences were observed between patients exposed to 100 mg and >100 mg allopurinol regarding age, comorbidity index, or medication (Table 1, Supplementary Table 2).

In the adjusted model, patients exposed to allopurinol had significantly lower odds of ACS event, compared to those not exposed (OR, 0.77; 95%CI, 0.63-0.94 for 100mg, and OR, 0.61; 95%CI, 0.47-0.81 for >100mg). Compared to low dose of allopurinol (100 mg), a higher dose (>100 mg) was associated with lower odds of ACS event, but the difference was not statistically

significant (p-value for trend, 0.16). In women, exposure to > 100 mg was associated with significantly lower odds of ACS event, whereas exposure to 100 mg did not reach statistical significance (Figure 3).

Analysis 2: initiators vs long-term users

Overall, 489 initiators and 2,916 long-term users were included in this analysis. Initiators were less likely to be treated with anticoagulants and CV drugs, but more likely to be treated with cortisone, compared to the long-term users (Table 2). Male initiators were more likely to have renal disease and COPD and less likely to have hypertension compared to male long-term users. Female initiators were more likely to have renal disease, heart failure and COPD compared to female long-term users (Supplementary Table 3).

In the adjusted multivariate logistic regression analyses, initiators had significantly higher odds of ACS events compared to long-term users, after adjustments for age, education level, comorbidity index, and medication (Figure 3).

Sensitivity analysis

After excluding allopurinol initiators (N= 489), 4,120 patients exposed to allopurinol and 14,253 patients not exposed remained. Patients exposed to allopurinol had significantly lower odds of ACS event compared to those not exposed and similar to ORs observed in Analysis 1 (OR, 0.75; 95%CI, 0.61-0.93 for those exposed to 100 mg allopurinol, and OR, 0.64; 95%CI 0.48-0.85 for those exposed to >100 mg), which is probably explained by the low number of allopurinol initiators.

Discussion

In this population-based cohort study, we studied the effect of allopurinol use on the risk of first-ever ACS event in patients with incident gout and no prior history of CHD. We found that allopurinol users had a significantly lower risk of first-ever ACS, whereas the subgroup of recent allopurinol initiators had an increased risk, possibly reflecting recent flares and a higher contemporary level of systemic inflammation. In the dose-dependent analysis we found that compared to low dose (100 mg), a higher dose of allopurinol (>100 mg) was associated with lower odds of ACS event, but the difference was not statistically significant.

The first finding provide evidence for a potential benefit of allopurinol in primary CV prevention in patients with gout. Allopurinol reduces urate levels, may decrease systemic inflammation and the generation of oxidative species, and may reverse endothelial dysfunction [38]. This may explain the association between allopurinol use and the lower risk of ACS found in our study.

ULT initiation is usually started due to active gout with frequent flares and may be associated with an increased risk of gout flares during the initial period after initiation [37]. A previously published study showed that gout flares were associated with a transient increase in CV events following the flares, possibly due to neutrophilic inflammation which may cause atherosclerotic plaque instability and rupture [36]. This may explain the association between increased risk of ACS events and allopurinol initiation. Allopurinol initiators were more frequently prescribed cortisone compared to long-term users, possibly due to gout flares or as flare prophylaxis. To the best of our knowledge, this study is the first to report an increased risk of ACS event during allopurinol initiation compared to long-term allopurinol use.

Previous observational studies exploring the effect of allopurinol use on CV outcomes in patients with gout have shown conflicting results. Singh *et al* found that allopurinol use was associated with a lower risk of MI in older patients with gout (≥ 65 years) and that risk reduction was associated with the duration of treatment [39]. Allopurinol use for more than 6 months to 2 years and over 2 years was associated with lower risk of MI compared to non-use, whereas allopurinol use for less than 6 months was not. In another study of Singh *et al*, current allopurinol use, defined as a new filled prescription, was associated with lower risk of MI and stroke in patients with gout and diabetes compared to previous allopurinol use [21].

In contrast, the risk of CVD did not differ significantly between the allopurinol and non-allopurinol group in a cohort of gout patients, but 69% of patients in the non-allopurinol group received an uricosuric agent [40]. Lin *et al* showed that allopurinol was not associated with a lower risk of coronary artery disease (CAD) in patients with newly diagnosed gout. However, the dose-stratified analysis showed that the risk of CAD was significantly lower in higher allopurinol doses (>270 defined daily doses [DDDs]) compared to lower doses (0-90 DDDs) [41]. The doses of allopurinol in our study were relatively low, but these are the doses generally used in clinical practice for gout patients in Sweden, where gout remains suboptimally managed [42, 43].

The previously published ALL-HEART study showed that allopurinol treatment does not improve CV outcomes in patients with ischemic heart disease [34]. However, the study excluded patients with a history of gout, the mean urate concentration at baseline in the allopurinol group was low (0.34 mmol/L [5.7 mg/dL]), and the discontinuation rate for allopurinol was high. These differences in the selection of treated patients might explain the divergent results between our study and ALL-HEART study, potentially reflecting different cardiovascular outcomes in patients with normouricemia and those with hyperuricemia/gout. Moreover, the allopurinol doses used in the ALL-HEART trial were higher (300mg daily for patients with renal impairment and 600mg daily for those without) compared to the doses used in our study. The high doses in ALL HEART trial likely contributed to the early and premature cessation of allopurinol in the majority of participants allocated to allopurinol therapy, which makes the results of this trial inconclusive. In contrast, the current study provides epidemiological support for conducting a new RCT comparing allopurinol with placebo in gout patients, using lower doses tailored to urate response, which are likely better tolerated.

This study had several limitations. First, as with all observational studies, there is a risk of residual confounding. To minimize this bias, we controlled for multiple potential confounders. Second, as in other pharmacoepidemiologic studies, it was not certain that allopurinol was taken by the patients. Such misclassification of exposure is however likely to be non-differential between exposed groups and in comparison with those unexposed. Poor adherence would probably result in an underestimation of the reduced risk. Third, it was not possible to verify the indication for each allopurinol prescription, but all cases in this study had a diagnosis of gout, and cases with disorders that could indicate allopurinol use for another reason (i.e., hematological malignancy or end-stage renal disease) were excluded. Fourth, data on gout severity (i.e., tophi, erosions, urate levels) are infrequently reported in the registers and could not be adjusted for in the analyses. However, this may have had only a moderate impact on this study as we included only patients with incident gout. Fifth, in comparisons between allopurinol initiators and long-term users, the study power in the sex-stratified analyses may not have been sufficient to reach statistical significance. Finally, we were not able to adjust for smoking, body mass index, diet, exercise, over the counter NSAID use, and family history of CVD, because these data are not reported in the registers.

This study had several strengths. By excluding patients with dispensed prescription of colchicine, we were able to study the isolated effect of allopurinol on the risk of ACS. Furthermore, this study used data from large population-based registers, and the study

population is representative of the general population in Sweden [44, 45]. The data used were derived from both primary and secondary healthcare, covering all possible phenotypes of gout, from mild to severe disease. Gout cases and ACS events identified using validated definitions to minimize potential misclassification bias. Previous validation studies showed high validity for the diagnoses of gout and myocardial infarction in the Swedish registers [46, 47].

Conclusions

Among patients with incident gout and no prior history of CHD, allopurinol users had a significantly lower risk of a first-ever ACS event compared to non-users. This finding provides evidence for a potential benefit of allopurinol in primary CV prevention for patients with gout. However, the subgroup of recent allopurinol initiators had a higher risk of a first-ever ACS event compared to long-term users. This finding may reflect a higher frequency of gout flares and systemic inflammation both before and initially after allopurinol initiation. Whether this risk is affected by the use of flare prophylaxis needs to be investigated in further studies.

Table 1. Demographic and clinical characteristics of patients with incident gout included in Analysis 1.

	Not exposed		Exposed to 100mg		Exposed to >100mg	
	Men N=9,405	Women N=4,848	Men N=1,941	Women N=951	Men N=1,287	Women N=430
Age, mean (SD), years	62.3 (14.5)	68.5 (14.7)	67.7 (13.8)	76.5 (11.6)	63.6 (13.5)	74.5 (11.3)
Follow-up, years, median (Q1, Q3)	4.1 (1.9, 6.7)	4.1 (1.9, 6.7)	4.4 (1.9, 7.0)	3.7 (1.6, 6.2)	5.0 (2.5, 7.6)	4.1 (1.9, 6.3)
Education level, years						
<9	2,901 (30.9)	1,899 (39.2)	742 (38.2)	509 (53.5)	446 (34.7)	207 (48.1)
9-12	4,275 (45.5)	1,945 (40.1)	803 (41.4)	313 (32.9)	537 (41.7)	159 (37.0)
>12	2,090 (22.2)	932 (19.2)	361 (18.6)	109 (11.5)	271 (21.1)	56 (13.0)
Comorbidity index†, N(%)						
0	2,254 (24.0)	845 (17.4)	217 (11.2)*	20 (2.1)*	1,732 (13.4)*	5 (1.2)*
1-2	3,517 (37.4)	1,877 (38.7)	600 (30.9)*	228 (24.0)*	394 (30.6)*	104 (24.2)*
3-4	2,666 (28.4)	1,527 (31.5)	709 (36.5)*	433 (45.5)*	446 (34.7)*	194 (45.1)*
≥5	968 (10.3)	599 (12.4)	415 (21.4)*	270 (28.4)*	275 (21.4)*	127 (29.5)*
Medication‡, N(%)						
Anticoagulants/ Platelet aggregation inhibitors	2,956 (31.4)	1,630 (33.6)	917 (47.2)*	549 (57.7)*	544 (42.3)*	240 (55.8)*
CV drugs§	5,032 (53.5)	3,066 (63.2)	1,515 (78.1)*	891 (93.7)*	971 (75.4)*	404 (94.0)*
Cortisone	854 (9.1)	600 (12.4)	312 (16.1)*	217 (22.8)*	203 (15.8)*	88 (20.5)*

†Based on number of ever diagnosed comorbidities during the follow-up. Comorbidities included: hypertension, diabetes, hyperlipidemia, obesity, renal disease, heart failure, cardiomyopathy, psoriasis, chronic obstructive pulmonary disease, alcoholism, cerebrovascular disease, atherosclerotic disease, and cancer.

‡Defined as dispensed prescription within six months before the end of follow-up.

§ Drugs included: vasodilator drugs, anti-hypertensive drugs, diuretics, beta blockers, calcium antagonists, and renin-angiotensin-aldosterone inhibitors.

*p-value <0.05 compared to those not exposed.

CV, cardiovascular.

Table 2. Demographic and clinical characteristics of patients with incident gout included in Analysis 2.

	Initiators		Long-term users	
	Men N= 359	Women N= 130	Men N= 2,034	Women N= 882
Age, mean (SD), years	65.1 (14.8)	74.5 (13.3)	66.1 (13.2)	75.1 (11.0)
Follow-up, years, median (Q1, Q3)	1.3 (0.3, 5.1)	0.4 (0.2, 2.5)	5.6 (3.3, 7.8)	4.8 (2.9, 6.9)
Education level, years, N(%)				
<9	117 (32.6)	66 (50.8)	768 (37.8)	459 (52.0)
9-12	164 (45.7)	48 (36.9)	806 (39.6)	291 (33.0)
>12	71 (19.8)	12 (9.2)	417 (20.5)	119 (13.5)
Comorbidity index†, N(%)				
0	93 (25.9)	6 (4.6)	449 (22.1)	52 (5.9)
1-2	140 (39.0)	55 (42.3)	908 (44.6)	401 (45.5)
3-4	93 (25.9)	54 (41.5)	534 (26.3)	330 (37.4)
≥5	33 (9.2)	15 (11.5)	143 (7.0)	99 (11.2)
Medication‡, N(%)				
Anticoagulants/ Platelet aggregation inhibitors	136 (37.9)*	66 (50.8)	959 (47.1)	503 (57.0)
CV drugs§	258 (71.9)*	115 (88.5)*	1,612 (79.3)	830 (94.1)
Cortisone	150 (41.8)*	65 (50.0)*	187 (9.2)	126 (14.3)

†Based on number of ever diagnosed comorbidities during the follow-up. Comorbidities included: hypertension, diabetes, hyperlipidemia, obesity, renal disease, heart failure, cardiomyopathy, psoriasis, chronic obstructive pulmonary disease, alcoholism, cerebrovascular disease, atherosclerotic disease, and cancer.

‡Defined as dispensed prescription within six months before the end of follow-up.

§ Drugs included: vasodilator drugs, anti-hypertensive drugs, diuretics, beta blockers, calcium antagonists, and renin-angiotensin-aldosterone inhibitors.

*p-value <0.05 compared to long-term users.

CV, cardiovascular.

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Data Sharing

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributor

All authors have contributed substantially to the process of completing this study and had full access to the data, specified as follows: PD contributed to the conception and design of the study, managing and interpretation of data, drafting and revising the manuscript. TZS contributed with all statistical analyses, drafting and revising the manuscript. UL and KB contributed to study design, interpretation of data, drafting and revising the manuscript. LJ and MD contributed to the conception and design of the study, as well as interpretation of data, and drafting and revising the manuscript. All authors have approved the manuscript. PD is the guarantor.

Figure legends

Figure 1

Figure 1. Design of study cohort.

*Defined as no recorded diagnosis of gout in the previous seven years.

ULT, urate lowering treatment; CHD, coronary heart disease.

Figure 2

Figure 2. Study exposure of interest.

I. **Analysis 1: Users vs non-users at the end of follow-up.**
   A. Exposure to 100mg.
   B. Exposure to >100mg.
   C. No exposure (reference group).

II. **Analysis 2: Initiators vs long-term users.**
   A. Initiators, defined as having dispensed a prescription of allopurinol within 125 days before the end of follow up AND no dispensed prescription during a look-back period of 365 days.
   B. Long-term users, defined as having dispensed a prescription of allopurinol within 125 days before the end of follow up AND having continuous allopurinol treatment during a look-back period of 365 days.

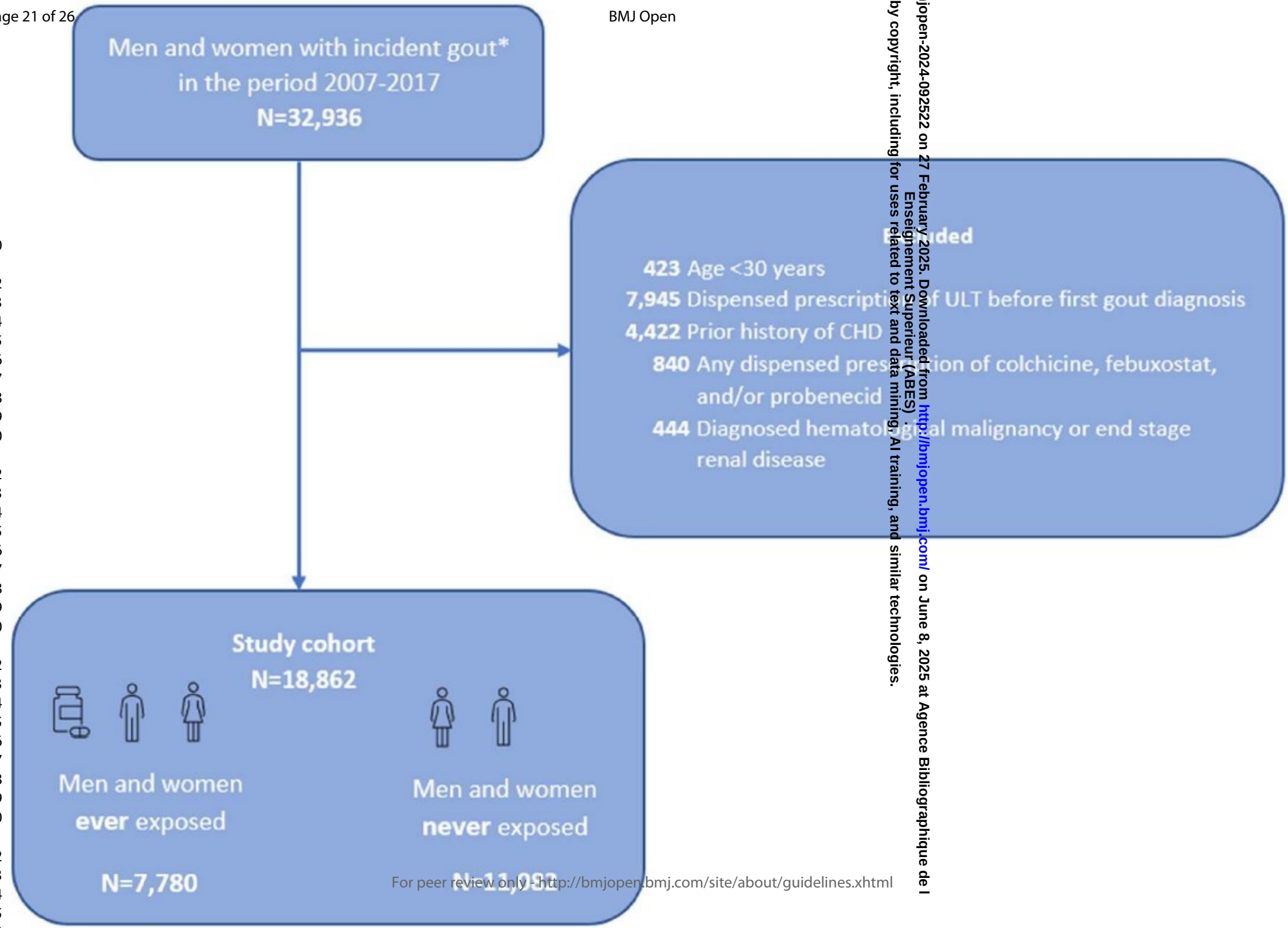
Figure 3

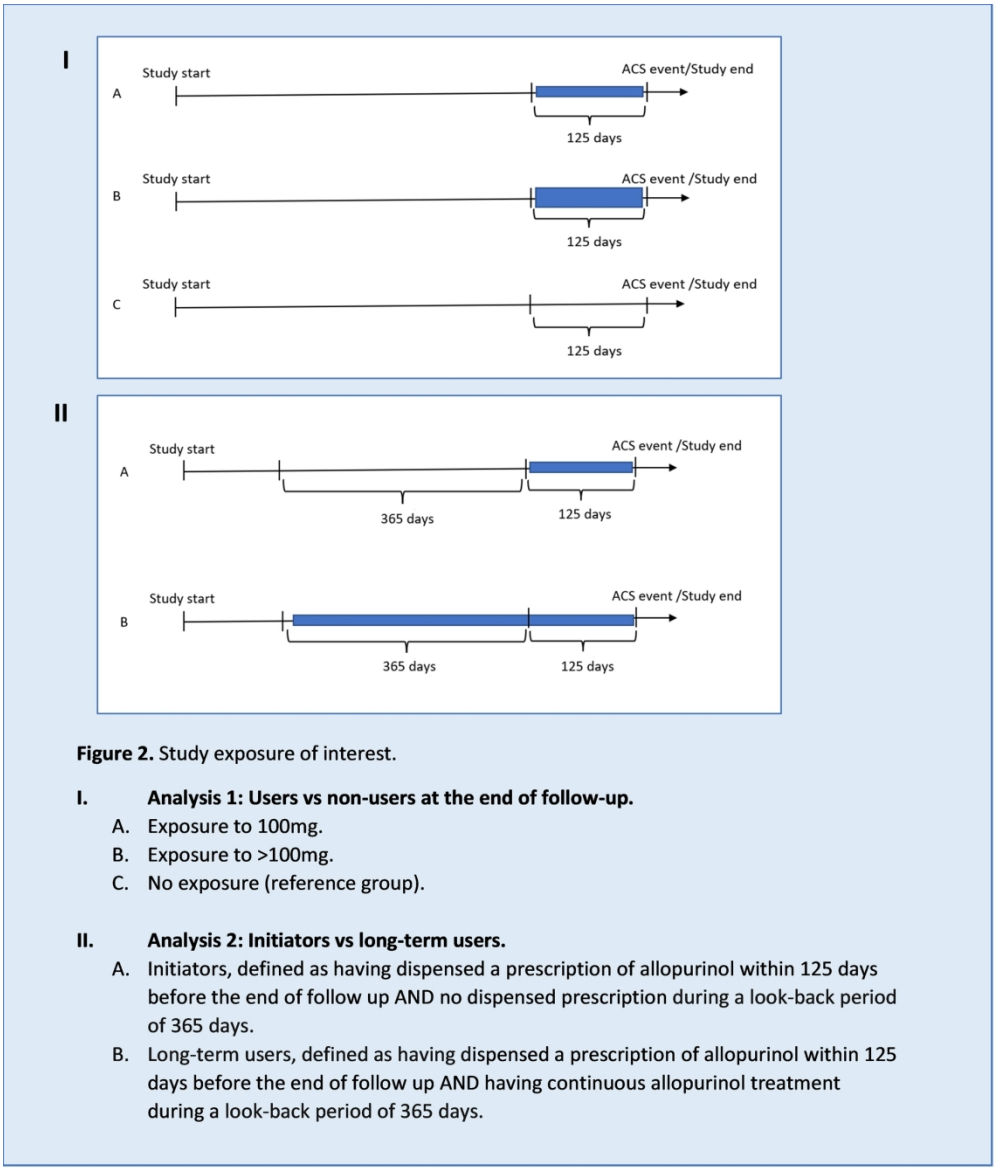
Figure 3. Association between allopurinol exposure and acute coronary syndrome (ACS) events, total and by sex.

Analysis 1: users vs non-users

Analysis 2: allopurinol initiators vs long-term users.

*Adjusted for age, education level, comorbidity index, and medication.





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C. No exposure (reference group).

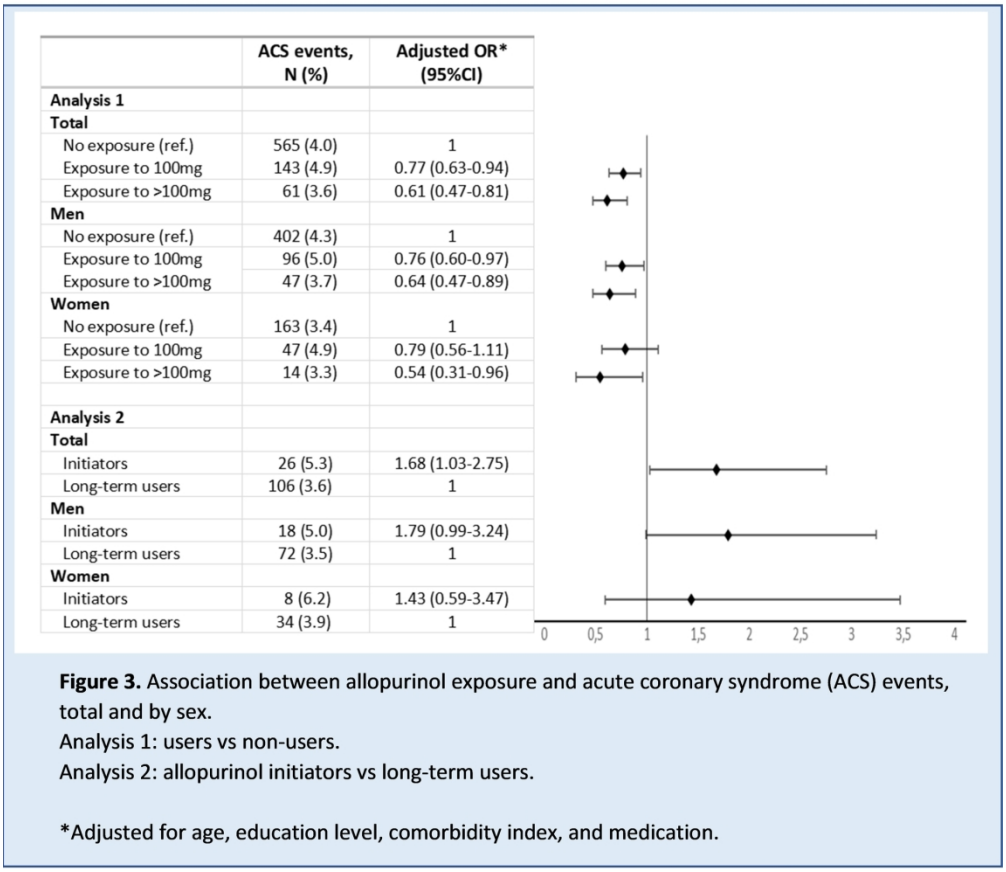
II. Analysis 2: Initiators vs long-term users.

A. Initiators, defined as having dispensed a prescription of allopurinol within 125 days before the end of follow up AND no dispensed prescription during a look-back period of 365 days.
B. Long-term users, defined as having dispensed a prescription of allopurinol within 125 days before the end of follow up AND having continuous allopurinol treatment during a look-back period of 365 days.

Figure 2. Study exposure of interest.
I. Analysis 1: Users vs non-users at the end of follow-up.
A. Exposure to 100mg.
B. Exposure to >100mg.
C. No exposure (reference group).

II. Analysis 2: Initiators vs long-term users.
A. Initiators, defined as having dispensed a prescription of allopurinol within 125 days before the end of follow up AND no dispensed prescription during a look-back period of 365 days.
B. Long-term users, defined as having dispensed a prescription of allopurinol within 125 days before the end of follow up AND having continuous allopurinol treatment during a look-back period of 365 days.

166x193mm (300 x 300 DPI)



	ACS events, N (%)	Adjusted OR* (95%CI)
Analysis 1		
Total		
No exposure (ref.)	565 (4.0)	1
Exposure to 100mg	143 (4.9)	0.77 (0.63-0.94)
Exposure to >100mg	61 (3.6)	0.61 (0.47-0.81)
Men		
No exposure (ref.)	402 (4.3)	1
Exposure to 100mg	96 (5.0)	0.76 (0.60-0.97)
Exposure to >100mg	47 (3.7)	0.64 (0.47-0.89)
Women		
No exposure (ref.)	163 (3.4)	1
Exposure to 100mg	47 (4.9)	0.79 (0.56-1.11)
Exposure to >100mg	14 (3.3)	0.54 (0.31-0.96)
Analysis 2		
Total		
Initiators	26 (5.3)	1.68 (1.03-2.75)
Long-term users	106 (3.6)	1
Men		
Initiators	18 (5.0)	1.79 (0.99-3.24)
Long-term users	72 (3.5)	1
Women		
Initiators	8 (6.2)	1.43 (0.59-3.47)
Long-term users	34 (3.9)	1

Figure 3. Association between allopurinol exposure and acute coronary syndrome (ACS) events, total and by sex.
Analysis 1: users vs non-users.
Analysis 2: allopurinol initiators vs long-term users.

*Adjusted for age, education level, comorbidity index, and medication.

Figure 3. Association between allopurinol exposure and acute coronary syndrome (ACS) events, total and by sex.
Analysis 1: users vs non-users
Analysis 2: allopurinol initiators vs long-term users.

*Adjusted for age, education level, comorbidity index, and medication.

176x178mm (300 x 300 DPI)

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Supplementary Table 1. ICD and ATC codes used for the definition of gout, ACS, comorbidities, and medication.

	ICD codes	ATC codes
Gout	M10, M14.0, M14.1	
Allopurinol		M04AA01
ACS	I20.0, I21	
CHD	I20-25	
Hypertension	I10-15	
Diabetes	E10-14, O24	A10
Hyperlipidemia	E78	C10
Obesity	E66	A08
Renal disease	N00-08, N10-23	
Heart failure	I50	
Cardiomyopathy	I42	
Psoriasis	L40	
COPD	J44	
Alcoholism	Z72.1, F10	
Cerebrovascular disease	I60-69	
Atherosclerotic disease	I70-79	
Cancer	C00-43, C45-97	
Vasodilator drugs*		C01D
Antihypertensive drugs*		C02
Diuretics*		C03
Beta blockers*		C07
Calcium antagonists*		C08
RAAS inhibitors*		C09
Anticoagulants		B01AC04, B01AC06

*Included in the analyses as 'cardiovascular drugs'.

ACS, acute coronary syndrome; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; RAAS, renin-angiotensin-aldosterone system

Supplementary Table 2. Comorbidities in patients with incident gout included in Analysis 1.

	Not exposed		Exposed to 100mg		Exposed to >100mg	
Comorbidities, N (%)	Men N=9,405	Women N=4,848	Men N=1,941	Women N=951	Men N=1,287	Women N=430
Hypertension	4,147 (44.1)	2,693 (55.5)	1,214 (62.5)	801 (84.2)	753 (58.5)	368 (85.6)
Diabetes	1,172 (12.5)	784 (16.2)	347 (17.9)	252 (26.5)	215 (16.7)	132 (30.7)
Hyperlipidemia	2,321 (24.7)	1,368 (28.2)	671 (34.6)	383 (40.3)	401 (31.2)	183 (42.6)
Obesity	911 (9.7)	603 (12.4)	207 (10.7)	180 (18.9)	194 (15.1)	105 (24.4)
Renal disease	679 (7.2)	392 (8.1)	278 (14.3)	168 (17.7)	150 (11.7)	65 (15.1)
Heart failure	590 (6.3)	508 (10.5)	353 (18.2)	264 (27.8)	210 (16.3)	127 (29.5)
Cardiomyopathy	94 (1.0)	28 (0.6)	42 (2.2)	16 (1.7)	43 (3.3)	9 (2.1)
Psoriasis	324 (3.4)	213 (4.4)	61 (3.1)	39 (4.1)	53 (4.1)	16 (3.7)
COPD	408 (4.3)	367 (7.6)	131 (6.7)	104 (10.9)	67 (5.2)	42 (9.8)
Alcoholism	500 (5.3)	102 (2.1)	82 (4.2)	9 (0.9)	64 (5.0)	7 (1.6)
Cerebrovascular disease	592 (6.3)	390 (8.0)	199 (10.3)	122 (12.8)	101 (7.8)	50 (11.6)
Atherosclerotic disease	236 (2.5)	154 (3.2)	77 (4.0)	65 (6.8)	48 (3.7)	16 (3.7)
Cancer	533 (5.7)	282 (5.8)	121 (6.2)	63 (6.6)	84 (6.5)	22 (5.1)

Supplementary Table 3. Comorbidities in patients with incident gout included in Analysis 2.

	Initiators		Long-term users	
Comorbidities, N (%)	Men N= 359	Women N= 130	Men N= 2,034	Women N=882
Hypertension	205 (57.1)*	104 (80.0)	1,282 (63.0)	748 (84.8)
Diabetes	62 (17.3)	33 (25.4)	368 (18.1)	262 (29.7)
Hyperlipidemia	122 (34.0)	50 (38.5)	696 (34.2)	378 (42.9)
Obesity	43 (12.0)	32 (24.6)	264 (13.0)	183 (20.7)
Renal disease	61 (17.0)*	32 (24.6)*	263 (12.9)	126 (14.3)
Heart failure	70 (19.5)	44 (33.8)*	339 (16.7)	223 (25.3)
Cardiomyopathy	7 (1.9)	1 (0.8)	56 (2.8)	17 (1.9)
Psoriasis	20 (5.6)	7 (5.4)	72 (3.5)	38 (4.3)
COPD	31 (8.6)*	20 (15.4)*	111 (5.5)	86 (9.8)
Alcoholism	15 (4.2)	3 (2.3)	88 (4.3)	11 (1.2)
Cerebrovascular disease	36 (10.0)	19 (14.6)	181 (8.9)	104 (11.8)
Atherosclerotic disease	15 (4.2)	10 (7.7)	79 (3.9)	45 (5.1)
Cancer	23 (6.4)	9 (6.9)	122 (6.0)	43 (4.9)

*p-value <0.05 compared to long-term users