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Allopurinol initiation and all-cause mortality in the general population

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Abstract

Background—Allopurinol is the most commonly used urate-lowering therapy, with rare but potentially fatal adverse effects. However, its impact on overall mortality remains largely unknown. In this study, we evaluated the impact of allopurinol initiation on the risk of mortality among individuals with hyperuricaemia and among those with gout in the general population.

Methods—We conducted an incident user cohort study with propensity score matching using a UK general population database. The study population included individuals aged ≥40 years who had a record of hyperuricaemia (serum urate level >357 μmol/L for women and >416 μmol/L for men) between January 2000 and May 2010. To closely account for potential confounders of allopurinol use and risk of death, we constructed propensity score matched cohorts of allopurinol initiators and comparators (non-initiators) within 6-month cohort accrual blocks.

Results—Of 5927 allopurinol initiators and 5927 matched comparators, 654 and 718, respectively, died during the follow-up (mean=2.9 years). The baseline characteristics were well balanced in the two groups, including the prevalence of gout in each group (84%). Allopurinol

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initiation was associated with a lower risk of all-cause mortality (matched HR 0.89 (95% CI 0.80 to 0.99)). When we limited the analysis to those with gout, the corresponding HR was 0.81 (95% CI 0.70 to 0.92).

Conclusions—In this general population study, allopurinol initiation was associated with a modestly reduced risk of death in patients with hyperuricaemia and patients with gout. The overall benefit of allopurinol on survival may outweigh the impact of rare serious adverse effects.

INTRODUCTION

Hyperuricaemia and gout have been shown to be associated with an elevated risk of premature death.[1,2] Allopurinol, the most commonly used uratelowering medication (up to 95% of treated cases), might also have cardiovascular and renal benefits;[3–6] however, its use is not free of adverse effects. A rare but potentially fatal adverse reaction (ie, allopurinol hypersensitivity syndrome) that affects approximately 1 in 260–1540 allopurinol users, usually during the 1st year of use,[7–9] has led to reluctance among some physicians to prescribe allopurinol, even when clinically indicated. If the impact of these severe side effects is substantial, it may shorten the overall survival of patients who were started on allopurinol.

To date, data on the survival impact of allopurinol in patients with hyperuricaemia or gout are scarce. One study based on a US Veterans Affairs (VA) population found that allopurinol initiation was associated with a 23% lower risk of death among individuals with hyperuricaemia.[10] It is unknown whether these findings based on 99% male veteran allopurinol users[10] are replicable among patients with gout or in more generalisable populations. To address these issues, we evaluated the impact of allopurinol initiation on the risk of death among individuals with hyperuricaemia and among patients with gout in a general population context.

METHODS

Study population

We used The Health Improvement Network (THIN) database, which contains computerised medical records entered by general practitioners (GPs) in the UK. The current THIN dataset contains data from 479 practices with a total of 9.1 million patients. The computerised information includes demographics, details from GP visits, diagnoses from specialist referrals and hospital admissions, results of laboratory tests, and additional health information recorded systematically, including height, weight, body mass index (BMI), smoking and alcohol use. THIN uses the Read classification, a hierarchical clinical terminology system routinely used in the UK to code symptoms and medical diagnoses. Prescriptions issued by the GP are directly generated from the computer, and are coded in THIN according to Multilex classification, a standard drug terminology library used throughout the UK that includes information on drug formulation and strength.

Our study population included individuals aged ≥40 years who had a record of hyperuricaemia (serum uric acid (SUA) level >357 μmol/L (6 mg/dL) for women and >416 μmol/L (7 mg/dL) for men) between January 2000 and May 2010. Study cohort members

were required to have ≥2 years of enrolment with the general practice before entering the study cohort to allow for exposure and covariate assessment. Individuals were excluded if they had an estimated glomerular filtration rate of <30 mL/min (estimated according to the Modification of Diet in Renal Disease Equation), a history of dialysis, renal or organ transplantation, malignancy or previous allopurinol use.[10]

The propensity score matched cohorts stratified by time blocks

Confounding by indication can be a major concern in pharmacoepidemiological studies such as ours. Specifically, the baseline characteristics of allopurinol initiators and non-initiators may systematically differ, causing a lack of comparability between the two groups. Therefore, we conducted an incident allopurinol user cohort study with propensity score matching. Furthermore, in order to closely account for potential secular trends in allopurinol use in relation to various confounders at different times,[11] matched cohorts were constructed within 6-month blocks of calendar time (21 blocks from January 2000 to May 2010). Within each cohort accrual block, allopurinol initiators were defined as patients who started to use allopurinol during that 6-month period. Propensity scores (predicted probability of allopurinol initiation) were estimated using logistic regression, separately for each cohort accrual block with stepwise model selection at level of significance α=0.05. For each allopurinol initiator, we identified a propensity score matched subject who did not initiate allopurinol during the accrual block. Matched non-initiators were ineligible for selection in subsequent accrual blocks (greedy matching algorithm).[11] The first allopurinol prescription date was assigned as the index date for allopurinol initiators, and a random date within the 6-month block was assigned as the index date for non-initiators.

The variables included in the propensity score estimation consisted of demographics, BMI, comorbidities, medication use, laboratory measurements and healthcare utilisation, as assessed over 2 years prior to the index date. Specifically, demographics included age at index date and sex. Comorbidities included hypertension, cardiovascular disease, diabetes, gout and Charlson comorbidity index. The Charlson comorbidity index is a composite index of diagnoses that includes myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, peptic ulcer disease, liver disease, diabetes with complications, renal disease, cancer and AIDS/HIV.[12] Medications included statins, fibrates, ACE inhibitors, angiotensin II receptor blockers, β blockers, calcium channel blockers, aspirin, non-steroidal anti-inflammatory drugs, loop diuretics, hydrochlorothiazide, losartan and insulin. Laboratory values included SUA, cholesterol, albumin and glomerular filtration rate, calculated from serum creatine using the simplified Modification of Diet in Renal Disease study equation.[13–15] The number of primary care visits was used as a measure of healthcare utilisation.

Statistical analysis

The outcome of interest was all-cause mortality as defined by the death date recorded in THIN. Allopurinol initiators and matched non-initiators began accruing risk time from the index date until death, discontinuity of enrolment or the end of study period, whichever came first. In the final matched cohort, each individual was identified as either an allopurinol initiator or non-initiator, and retained that exposure status throughout follow-up.

This approach maintains the comparability of these two exposure groups in terms of the baseline characteristics and provides conservative estimates, similar to an intent-to-treat approach used in clinical trials (figure 1).

Cox proportional hazard models were used to estimate the effect of allopurinol initiation on all-cause mortality, stratified by 6-month cohort accrual blocks. Survival plots were generated as estimates of cumulative mortality to identify time-trends in the occurrence of death. In order to address potential residual imbalance between the two comparison groups, multivariate analysis was also performed by further adjusting for all confounders included in propensity score estimation. We repeated the same analyses limited to individuals *with gout* in our hyperuricaemic cohort. We explored a potential interaction of allopurinol initiation and sex by testing the significance of the interaction term. To address the potential for allopurinol initiators to discontinue the drug over time, we performed sensitivity analyses with follow-up time truncated at 1 year, 2 years and 3 years for all subjects. For all HRs, we calculated 95% CIs. All p values were two-sided. All statistical analyses were performed using SAS V.9.2 (SAS Institute, Cary, North Carolina, USA).

RESULTS

There were an average of 289 allopurinol initiators and 5812 allopurinol non-initiators among the subjects who were eligible for propensity score estimation and cohort inclusion in each 6-month accrual block. When a non-initiator was randomly selected for each initiator (without propensity score matching) within each 6-month cohort accrual block, allopurinol initiators had a higher prevalence of comorbidities and use of cardiovascular and other medications at baseline (n=6587 in each group; table 1). As expected, the SUA levels were higher among allopurinol initiators and prevalence of gout was almost three times that of non-initiators (85.4% vs 30.0%, table 1). During the follow-up of these unmatched cohorts, 780 individuals died in the allopurinol initiator group and 586 in the non-initiator group (HR 1.39, 95% CI 1.25 to 1.55, see online web figure 1).

In contrast, after propensity score matching (n=5927 in each group), the baseline characteristics were well balanced in the two comparison groups (table 1). In both groups, 70% were male, the mean age was 67 years. Notably, 84% of each group had gout. There were 654 deaths in the allopurinol initiator group and 718 deaths in the non-initiator group during the follow-up (mean=2.9 years), resulting in incidence rates of 1.5 and 2.1 per 1000 person-years, respectively, and a HR of 0.89 (95% CI 0.80 to 0.99; table 2) associated with allopurinol initiation. Further adjustment for other potential confounders did not change the estimate materially (HR 0.86 (95% CI 0.77 to 0.96)). The effect of allopurinol initiation did not differ across sex (p for interaction=0.5). The HRs in the analyses with follow-up truncated at 1 year, 2 years and 3 years were 0.77 (95% CI 0.63 to 0.94), 0.79 (95% CI 0.68 to 0.93) and 0.82 (95% CI 0.72 to 0.94), respectively (table 2).

When we repeated the matched analysis of patients with hyperuricaemia *with gout* (n=4795 in each group), the HR of allopurinol initiation for mortality was 0.81 (95% CI 0.70 to 0.92). The corresponding HRs in the analyses with follow-up truncated at 1 year, 2 years and 3 years were 0.75, 0.76 and 0.77, respectively (table 2).

DISCUSSION

In this large-scale cohort study of a general population, we found that allopurinol initiation was associated with an 11% lower risk of all-cause mortality compared with non-initiators in patients with hyperuricaemia, and a 19% lower risk of mortality in patients with gout. These risk reductions were apparent from the 1st year and throughout the subsequent years of follow-up. These associations were independent of age, sex, BMI, relevant comorbidities, healthcare utilisation, use of cardiovascular medications and SUA levels.

These results are consistent with the aforementioned VA cohort study finding that allopurinol use was associated with a 23% lower risk of all-cause death in individuals with hyperuricaemia.[10] In the VA study, gout was present in 83% of allopurinol initiators and 20% of controls, and allopurinol users also had higher levels of comorbidities, similar to our study findings. However, that VA study did not provide any gout-specific data. Similarly, a nested case-control study of elderly patients (≥66 years) with gout and congestive heart failure showed that allopurinol use was associated with a 26% lower risk of all-cause mortality.[16] Nevertheless, these previous findings are consistent with our general population data in patients with hyperuricaemia as well as in patients with gout, suggesting that allopurinol could contribute to reducing the 9–28% increased risk of premature death observed in patients with gout.[12]

It remains unclear if the survival benefit observed in allopurinol initiators is due to its urate-lowering effect, reduction in oxidative stress from xanthine oxidoreductase (XOR) inhibition or other mechanisms.[17–21] Allopurinol or oxypurinol was shown to improve endothelial function in patients with hypertension, type II diabetes and dyslipidaemia, in smokers, in patients with hyperuricaemia with elevated cardiovascular risk, and in patients with established coronary artery disease, compared with controls.[221–23] However, the levels of urate reduction from allopurinol and improved endothelial function have not been consistently correlated, and uricosuric agents such as probenecid and benzbromarone did not show similar benefits to endothelial function.[2024] Furthermore, effects of XOR inhibition on accumulation of upstream precursors (eg, inosine and adenosine) may contribute to beneficial effects of XOR inhibition in models of vascular disease. Nevertheless, given allopurinol's low-cost and extensive history of use, it has been favoured for use in clinical trials of potential cardiovascular risk reduction.[25]

Several strengths of our study deserve comment. This is a large-scale study in a general population, and it addressed the limited generalisability of the previous study based on a veteran population and the lack of data specifically on patients with gout. In a pharmacoepidemiological study such as ours, confounding by indication may bias results. Indeed, in the unmatched analysis, allopurinol initiator and non-initiator cohorts lacked comparability in many regards; allopurinol initiators had a greater comorbidity burden (gout, hypertension, diabetes, previous stroke or myocardial infarction, and overall Charlson comorbidity index) and had higher use of medications (non-steroidal anti-inflammatory drugs, aspirin, lipid-lowering drugs and antihypertensives). Thus, allopurinol initiators would be expected to have a greater risk of mortality than non-initiators, as was the finding in the comparison of the unmatched cohorts. However, after propensity score matching to

balance potential confounders between compared cohorts, our study found the opposite, suggesting a protective effect of allopurinol. Our incident user cohort study design with propensity score matching addressed imbalances in numerous baseline characteristics so that the observed protective effect of allopurinol on all-cause mortality is unlikely to be the result of confounding by baseline characteristics. Moreover, matching within 6-month blocks flexibly accounts for changes in the relative importance of confounding variables at different times. The benefits of matching must be weighed against the problem of loss of generalisability that is likely a result from incomplete matching; however, in this study, more than 90% of the allopurinol initiators were matched, making generalisability less of a concern.

Potential limitations of our study also deserve comment. Our study focused on the impact of allopurinol on all-cause mortality in the general population and could not address its potential impact on cause-specific death, because the latter data tend to be incomplete within THIN data. Nevertheless, accurate knowledge on the overall mortality impact is critically important in its own right. Although we speculate that the potential survival benefit with allopurinol use is due to reduction of excess cardiovascular or renal outcomes,[3–6] this hypothesis calls for future studies examining specific causes of death. Finally, our study was observational; thus, we cannot rule out the possibility of residual or unknown confounding.

In conclusion, allopurinol initiation was associated with a modestly reduced risk of death in patients with hyperuricaemia and patients with gout. The overall survival benefit of allopurinol may outweigh the impact of rare, potentially serious adverse effects at a population level.

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Ethical approval This study was approved by THIN Scientific Review Committee (Reference number 12-005), and judged exempt from review by the Boston University Medical Campus Institutional Review Board (Protocol H-31311).

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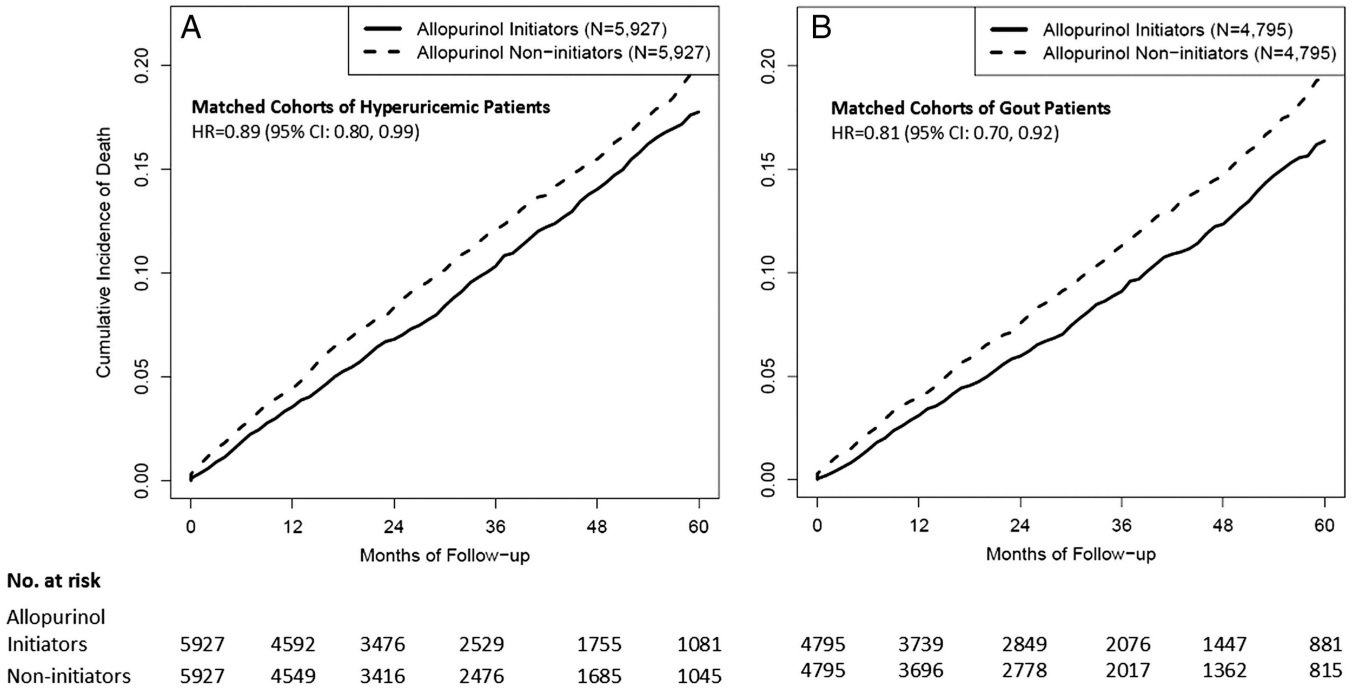

No. at risk

Allopurinol Initiators	5927	4592	3476	2529	1755	1081	4795	3739	2849	2076	1447	881
Non-initiators	5927	4549	3416	2476	1685	1045	4795	3696	2778	2017	1362	815

Figure 1.

Time to death for the propensity score matched cohorts among (A) patients with hyperuricaemia and (B) patients with gout.

Table 1

Baseline characteristics in the unmatched cohorts and propensity score matched cohorts among patients with hyperuricaemia

	Unmatched* cohorts		Propensity score matched cohorts	
Baseline characteristics	**Allopurinol initiators (N=6587)**	**Non-initiators (N=6587)**	**Allopurinol initiators (N=5927)**	**Non-initiators (N=5927)**
Demographics				
Age, years	67.5	66.8	67.4	67.6
Male, %	70	59	69	72
BMI, kg/m^2	30.2	29.6	30.1	30.0
Measures of comorbidity				
Charlson index, mean	1.0	0.8	0.9	0.9
Hypertension, %	67.7	67.6	67.0	69.5
Stroke, %	10.9	9.4	10.5	11.9
Myocardial infarction, %	1.9	1.6	1.8	1.9
Diabetes, %	14.8	14.4	14.1	14.5
Gout, %	85.4	30.0	83.7	84.4
Primary care visits, N	12.4	11.0	12.3	11.8
Medications				
Statin, %	57.8	50.9	57.0	54.6
Fibrate, %	2.7	2.5	2.6	2.3
ACE inhibitors, %	52.0	45.6	50.9	50.1
ARBs, %	15.8	12.6	15.2	14.6
β-blockers, %	44.8	38.1	43.9	44.0
Calcium channel blockers, %	35.5	35.7	35.8	36.5
Aspirin, %	42.8	38.2	41.8	42.2
NSAIDs, %	73.9	49.9	73.0	75.4
Loop diuretics, %	36.3	20.2	34.0	31.1
Hydrochlorothiazide, %	36.1	40.3	36.7	37.3
Losartan, %	4.0	4.3	4.0	4.5
Insulin, %	4.4	3.3	4.0	3.8
Laboratory measurements (baseline)				
Serum uric acid, μmol/L	531	442	522	519
Albumin, mmol/L	41.9	42.2	41.9	42.1
GFR, mL/min per 1.73 m^2	59.26	64.68	60.01	61.00
Cholesterol, mmol/L	4.93	5.06	4.95	4.95

*A non-initiator was randomly selected for each initiator (without propensity score matching) within each 6-month cohort accrual block.

ARB, angiotensin receptor blocker; BMI, body mass index; GFR, glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drug.

Table 2

HR for mortality associated with initiation of allopurinol in the propensity score matched cohorts

	Allopurinol initiators	Non-initiators	HR (95% CI)
Deaths (N)			
Hyperuricaemic cohorts	(N=5927)	(N=5927)	
Total follow-up	654	718	0.89 (0.80 to 0.99)
1 year follow-up	183	233	0.77 (0.63 to0.94)
2-year follow-up	325	395	0.79 (0.68 to 0.93)
3year follow-up	439	521	0.82 (0.72 to 0.94)
Gout cohorts	(N=4795)	(N=4795)	
Total follow-up	483	556	0.81 (0.70 to 0.92)
1 year follow-up	127	169	0.75 (0.59 to 0.94)
2-year follow-up	229	288	0.76 (0.63 to 0.91)
3 year follow-up	312	388	0.77 (0.66 to 0.97)