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REVIEW ARTICLE

Influence of xanthine oxidase inhibitors on all-cause mortality in adults: a systematic review and meta-analysis

Running title: Influence of urate-lowering therapy on all-cause mortality in adults

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ABSTRACT

Xanthine oxidase inhibitors, including allopurinol and febuxostat, are the first-line treatment of hyperuricemia. This meta-analysis investigated the association between urate-lowering therapy and all-cause mortality in different chronic diseases to match its users and non-users in a real-world setting. Overall, 11 studies were included, which reported adjusted hazard ratios for all-cause mortality over at least 12 months. Meta-analysis of all included studies showed no effect of the therapy on all-cause mortality. However, subgroup analyses showed its beneficial effect in patients with chronic kidney disease (14% risk reduction) and hyperuricemia (14% risk reduction), but not in patients with heart failure (28% risk increase). Urate-lowering therapy reduces all-cause mortality among patients with hyperuricemia and chronic kidney disease, but it seems to increase mortality in patients with heart failure and should be avoided in this subgroup.

Keywords: all-cause mortality, allopurinol, febuxostat, hyperuricemia, xanthine oxidase inhibitors
INTRODUCTION

Hyperuricemia is defined as increased serum level of uric acid. When the serum level of uric acid exceeds the solubility threshold for monosodium urate, symptoms of gout may occur. The prevalence of hyperuricemia is estimated at 20% among the US population, whereas the prevalence of gout is estimated at 3.9% of US adults, including 5.2% of men and 2.7% of women [1]. The risk factors for hyperuricemia include genetic vulnerability, male sex, older age, lifestyle factors, chronic kidney disease, and use of numerous pharmaceuticals [2], including diuretics, low-dose aspirin, beta-blockers, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers (except for losartan), and many others [3].

Xanthine oxidase inhibitors (XOI), including allopurinol and febuxostat, remain the first-line treatment of hyperuricemia [2]. Xanthine oxidase (XO) participates in conversion from hypoxanthine and guanine to uric acid, a part of purine catabolism pathway. Inhibition of XO leads, therefore, to a decrease in serum uric acid levels, with a concomitant increase in levels of hypoxanthine, xanthine, and guanine. These substances, however, exhibit significant toxicity [4, 5]. As a result, drugs lowering serum uric acid may lead to increased risk of cancer [6]. Additionally, a U-shaped association between serum uric acid, mortality [7], and cardiovascular risk [8] was reported. On the other hand, uric acid is known as an antioxidant, and it has been proposed to have neuroprotective properties [9]. It should also be noted that the relationship between serum uric acid level and symptoms of gout is not obvious; many patients with hyperuricemia remain asymptomatic, while in some patients with a relatively low serum uric acid level, a flare of gout may appear [2].

Therefore, we feel that it is reasonable to consider the most important endpoint, namely mortality, in decision making on the treatment of hyperuricemia. A reduction of all-cause mortality is a reliable measure of treatment efficacy in various populations. That is why all-cause mortality seems to be an adequate outcome to compare the benefits of urate-lowering
therapy between patients with different diseases. Due to the shortage of randomized controlled trials on the subject, non-randomized studies were analyzed in the present study. Thus, the aim of our work was to analyze the association between urate-lowering therapy and all-cause mortality in different chronic diseases to match its users and non-users in a real-world setting.

MATERIAL AND METHODS

Protocol and registration
The systematic review protocol was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA) guidance [10]. The study protocol was registered at PROSPERO (CRD42022346624).

Data sources and searches
This was a systematic review and meta-analysis. The PubMed, Scopus, and EMBASE electronic databases was searched for articles published in English from January 2000 to January 2023. Last search was performed on January 20, 2023. Relevant keywords were applied alone or in combination to identify data. The search strategy with the number of hits is presented in the study protocol. For abstracts potentially meeting the inclusion criteria, full-text publications were retrieved. Each study was assessed for eligibility by 2 independent reviewers, according to the criteria presented in the study protocol. Reasons for exclusion were briefly documented.

Study selection
Studies that reported adjusted hazard ratios (HR) for all-cause mortality over at least 12 months in febuxostat or allopurinol users vs. non-users in real-world matched cohorts were eligible. Only studies carried out among adults were included.
Data extraction and quality assessment
Two independent investigators (MMN and MN) extracted the following variables: adjusted
HR, sample size, percentage of men, mean age, average follow-up (mean or median), and
number of deaths. Disagreements were resolved by consensus. The total duration of follow-up
was obtained from publications or calculated by multiplying the average follow-up by cohort
size (patient-years). The number of deaths per 1000 patient-years was obtained from
publications or calculated by dividing the number of deaths by the total follow-up duration.
Risk of bias assessment of the included studies was performed by 2 independent authors using
the Newcastle-Ottawa scale (NOS). The NOS consists of 3 domains: (1) selection, (2)
comparability, and (3) outcome [11]. Discrepancies were resolved by discussion. The
certainty of evidence was assessed based on the Grading of Recommendations, Assessment,
Development, and Evaluations (GRADE) framework.

Data synthesis and analysis
We conducted a meta-analysis of adjusted HRs for changes in all-cause mortality
cardiovascular death in febuxostat or allopurinol users. Standard errors were calculated from
95% confidence intervals or from P-values [12]. The log-transformed values of point
estimates and of standard errors were used in an inverse variance random-effects meta-
analysis, with the restricted maximum-likelihood estimator for $\tau^2$ and the Q-profile method
for the confidence interval of $\tau^2$ and $\tau$. Heterogeneity was expressed with the $I^2$ statistic
and evaluated with Cochran’s Q test. Prediction intervals were calculated to aid the
interpretation of the estimates, with consideration of heterogeneity [13]. Influential studies
with the greatest impact on the estimate and heterogeneity were explored by a visual
inspection of the Baujat plot [14]. Subgroup analyses were performed in the cohorts of
patients with kidney disease, hyperuricemia, and heart failure. Also, we performed another
subgroup analysis depending on the use of propensity score matching.
A restricted maximum-likelihood random-effects meta-regression analysis was used to explore heterogeneity, with the following covariates assessed: percentage of men, mean age, publication year, average follow-up, and number of deaths per 1000 person-years. A funnel plot and the Egger’s test were used to assess publication bias [15]. A P value of less than 0.05 was considered statistically significant. R software (version 4.1.2) and the meta and dimeter packages were used for all analyses [16, 17]. The study did not receive any funding.

RESULTS

Study characteristics
A total of 300 citations were identified, and 36 potentially eligible articles were retrieved in full text. Overall, 11 studies were included in the review (Figure 1) [18–28]. Risk of bias assessment using NOS showed that the studies have low risk of bias. The characteristics of the included studies are summarized in Table 1. In the analysis, we included 2 cohorts from the study by Wei et al.

Allopurinol and febuxostat use and all-cause mortality.
We found no significant correlation between allopurinol and febuxostat use and all-cause mortality (HR = 0.94; 95% CI, 0.82–1.07), but there was significant heterogeneity (I² = 88%, tau² = 0.0408, p < 0.01; prediction interval, 0.58–1.50; Central Illustration). Egger’s test showed no trend for a publication bias (p = 0.285).

Subgroup analysis
Subgroup analyses showed a beneficial effect of XOI use on all-cause mortality in patients with chronic kidney disease (HR = 0.86; 95% CI, 0.78–0.93) and hyperuricemia (HR = 0.86; 95% CI, 0.75–0.99) but not with heart failure (HR = 1.28; 95% CI, 0.99–1.64) (Figure 2). The beneficial effect of XOI use on all-cause mortality was also observed in the group of studies using propensity score matching (HR = 0.87; 95% CI, 0.78–0.97) (Figure 3).
Allopurinol and febuxostat use and cardiovascular mortality.

There was no beneficial effect of allopurinol and febuxostat therapy on cardiovascular death (HR = 1.08; 95% CI, 0.86–1.37) (Figure 4).

DISCUSSION

Our systematic review evaluated evidence from real-world studies assessing the impact of treatment of hyperuricemia on all-cause mortality [29]. Meta-analysis of all included studies showed no correlation between the treatment and all-cause mortality. However, subgroup analyses showed its beneficial effect on all-cause mortality in patients with chronic kidney disease, and hyperuricemia, with risk reduction in both clinical conditions by 14%, but not in those with heart failure, with risk increase of 28%. Substantial heterogeneity was noted both in the main analysis, and in subgroup analyses. Additionally, only in 7 included studies was propensity score matching used. Therefore, the overall evidence about the association of urate-lowering therapy with all-cause mortality in real-world clinical settings is of suboptimal quality. However, the funnel plot suggested a low possibility of publication bias towards studies reporting favorable effects of XOI.

In patients with heart failure, cellular damage leads to increased amounts of hypoxanthine and xanthine, which are converted to uric acid. Therefore, increased serum uric acid levels in patients with heart failure are frequently observed. Moreover, elevated serum uric acid levels in this population are considered a risk factor for poor outcome. XOI were proven to improve cardiac function in early studies. However, a series of clinical trials on urate-lowering therapy in heart failure failed to show clinical benefits [30]. XO, mediating conversion from hypoxanthine and xanthine to uric acid, forms reactive oxygen species, resulting in oxidative stress. However, other metabolic pathways are also involved in the generation of reactive
oxygen species in heart failure [31]. Most probably, this is the reason why XOI are not effective in limitation of oxidative stress in heart failure, which results in lack of clinical benefits, as shown in our meta-analysis. In other words, overproduction of uric acid is a compensatory mechanism, eliminating toxic products of purine catabolism, and serum uric acid level is a marker of severity of cell death and oxidative stress in heart failure. The treatment with uric acid-lowering drugs may increase mortality and should be avoided in this subgroup of patients.

It should be mentioned that the impact of allopurinol on major cardiovascular outcomes in patients with ischemic heart disease was assessed in the ALL-HEART study, which included more than 5700 participants aged 60 years or older, with ischemic heart disease, but without gout, and without heart failure in most cases. No benefits of allopurinol therapy were observed; however, harmful effects were also absent [32]. Possibly, increased mortality on allopurinol is limited to patients with developed heart failure.

We feel that our results should lead to modification of existing guidelines on urate-lowering therapy in patients with high cardiovascular risk. For example, according to the Polish-Italian expert consensus [33], XOI are first-line urate-lowering medicines, and they are recommended for achievement of targeted serum uric acid $< 6 \text{ mg/dL}$, or $< 5 \text{ mg/dL}$ in those with high cardiovascular risk. Based on the above arguments, we think that indications for XOI should be narrowed, and this group of medicines should be used much more cautiously in patients with cardiovascular diseases, especially heart failure.

Chronic kidney disease is often accompanied by the retention of serum uric acid [34]. In patients with chronic kidney disease, increased serum levels of uric acid accelerate the progression of renal failure. On the other hand, XOI use does not slow the disease progression [9, 34]. However, there is evidence for the reduction of cardiovascular risk in chronic kidney disease patients with the reduction of serum uric acid levels, most probably via inhibition of
atherogenesis. While chronic kidney disease is associated with extremely high cardiovascular risk [34], this may be the explanation for the positive correlation between urate-lowering therapy and mortality in this group of patients.

Of note, in one study [19] that included patients with autosomal dominant polycystic kidney disease (ADPKD), the effect of XOI on all-cause mortality was unfavorable. ADPKD is one of the common reasons for chronic kidney disease. However, it differs in many aspects from other conditions leading to chronic kidney disease. Therefore, even though the cited study [19] included a relatively low number of patients, and the number of person-years was the lowest among studies included in our meta-analysis, these results cannot be marginalized. Mechanisms of cell death participate in the pathogenesis of ADPKD [35], and, possibly, serum uric acid levels reflect the intensity of these processes, but they should not be considered a target for therapy. Thus, before further studies on mortality of ADPKD patients on urate-lowering therapy are published, this group of pharmaceuticals should be used cautiously in this subgroup, especially because, contrary to other causes of chronic kidney disease, hyperuricemia was not reported to be a risk factor for the progression of chronic kidney disease in ADPKD [36].

The results of subgroup analysis in which studies on patients with hyperuricemia, including gout, were analyzed show a beneficial effect of urate-lowering therapy in this group. Inflammation during flare causes not only pain and debilitation [2] but may also lead to further consequences. It is believed that hyperuricemia is associated with increased cardiovascular risk in people without chronic kidney disease [32]. It may explain the positive impact of XOI in this population, as shown by our analysis.

Some limitations of our study should also be mentioned. First, as noted above, the quality of available data is far from optimal. Second, our main question was whether urate-lowering therapy impacts all-cause mortality. As we mentioned, a U-shaped relationship between serum
uric acid levels and clinical outcomes has been reported [7, 8]. Therefore, it cannot be excluded that not the therapy itself, but rather the serum level of uric acid achieved with it, is what impacts the mortality. Third, the diversity of effects achieved in different subpopulations limits the clinical utility of our results; in clinical settings different clinical conditions frequently coexist. Therefore, our results do not elucidate whether to treat or not, for instance, the patients with heart failure and co-existing chronic kidney disease. Thus, further investigation is needed to facilitate clinical decision-making in the future.

CONCLUSIONS
According to available data, the effect of urate-lowering therapy on all-cause mortality depends on the indication for initiation of therapy. It reduces all-cause mortality among patients with hyperuricemia and chronic kidney disease, except for ADPKD. On the other hand, in patients with heart failure it may increase mortality and should be avoided. Due to the suboptimal quality of literature data, further research is needed in this field.

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Conflict of Interest Statement: The authors declare no conflict of interest.

Contribution statement: Conceptualization, MMN and LP; methodology, MMN; validation, MMN, MN, and LP; formal analysis, SG and LP; investigation, MMN and MN; data curation, MN; writing—original draft preparation, MMN and MN; writing—review and editing, SG and LP; visualization, MN; supervision, LP; project administration, SG and LP. All authors have read and agreed to the published version of the manuscript.

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32. Mackenzie IS, Hawkey CJ, Ford I, et al. ALL-HEART study group. allopurinol versus usual care in UK patients with ischaemic heart disease (ALL-HEART): a multicentre, prospective,


Central Illustration. Meta-analysis of all-cause mortality
Records identified from PubMed (n = 48)
Records identified from Scopus (n = 126)
Records identified from EMBASE (n = 126)

Records removed before screening:
Duplicate records removed (n = 95)
Records marked as ineligible by automation tools (n = 0)
Records removed for other reasons (n = 0)

Records excluded (n = 169):
Meta-analysis, clinical study protocols, outside the scope of the study, conference abstracts

Records excluded (n = 25):
Incorrect methodology or lack of comparator

Abstract screened for eligibility (n = 205)
Full-text articles screened for eligibility (n = 36)

Studies included in the review (n = 11)

**Figure 1.** PRISMA flow diagram
**Figure 2.** Subgroup analysis of all-cause mortality – by disease type
**Figure 3.** Subgroup analysis of all-cause mortality – by propensity score matching

**Figure 4.** Meta-analysis of cardiovascular death
### Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Population</th>
<th>Continent</th>
<th>Drug</th>
<th>Sample (total)</th>
<th>Sample (drug)</th>
<th>Mean age</th>
<th>Male %</th>
<th>Follow-up Person-years</th>
<th>PSM</th>
<th>Adjustment covariates</th>
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<tbody>
<tr>
<td>Watanabe, 2020</td>
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<td>A</td>
<td>2797</td>
<td>697</td>
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<td>54</td>
<td>4.80</td>
<td>3.35</td>
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<tr>
<td>Ju, 2019</td>
<td>Gout</td>
<td>Asia</td>
<td>A or F</td>
<td>7214</td>
<td>3607</td>
<td>72</td>
<td>71</td>
<td>1.97</td>
<td>7.11</td>
<td>+</td>
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<tr>
<td>Hung, 2020</td>
<td>ADPKD</td>
<td>Asia</td>
<td>A</td>
<td>651</td>
<td>71</td>
<td>47</td>
<td>48</td>
<td>3.90</td>
<td>0.28</td>
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<tr>
<td>Kao, 2015</td>
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<td>Europe</td>
<td>A</td>
<td>7038</td>
<td>3519</td>
<td>64</td>
<td>72</td>
<td>3.00</td>
<td>10.56</td>
<td>+</td>
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<tr>
<td>Larsen, 2015</td>
<td>Hyperuricemia</td>
<td>Europe</td>
<td>A</td>
<td>10338</td>
<td>5197</td>
<td>63</td>
<td>73</td>
<td>5.08</td>
<td>26.40</td>
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<tr>
<td>Weisman, 2021</td>
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<td>5937</td>
<td>1304</td>
<td>75</td>
<td>64</td>
<td>1.11</td>
<td>1.45</td>
<td>+</td>
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<td>Luk, 2009</td>
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<td>A</td>
<td>9924</td>
<td>2483</td>
<td>64</td>
<td>99</td>
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<td>5.96</td>
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<td>Wei J, 2022</td>
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<td>Europe</td>
<td>A</td>
<td>10454</td>
<td>5227</td>
<td>74</td>
<td>61</td>
<td>5.00</td>
<td>26.14</td>
<td>+</td>
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<tr>
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<td>11854</td>
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<td>69</td>
<td>2.90</td>
<td>17.19</td>
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<tr>
<td>Wei L, 2009 (prevalent users)</td>
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<td>Europe</td>
<td>A</td>
<td>4518</td>
<td>258</td>
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<tr>
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<td>Europe</td>
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</table>

**Abbreviations:** PSM, propensity score matching; A, allopurinol; F, febuxostat; CKD, chronic kidney disease; ADPKD, autosomal dominant polycystic kidney disease, ESRD, end-stage renal disease