PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

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

Authors

Drivelegka, Panagiota; Jacobsson, Lennart; Sandström, Tatiana Zverkova; Lindström, Ulf; Bengtsson, Karin; Dehlin, M

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Rongen, Gerard**
Affiliation	**Radboud university medical center**
Date	**24-Sep-2024**
COI	**None**

Only two comments:

1. Please elaborate in your discussion on the used allopurinol dose in the ALL HEART trial (600 mg/day in patietns without renal imapirment; 300 mg/day in patients with renal impairment, without monitoring of plasma urate response) which contrasts to the relatively low alopurinol dose in this cohort of allopurinol users (100-300 mg/day). The high dose in ALL HEART likely contributed to the early and premature cessation of allopurinol in the large majority of participants allocated to allopurinol therapy which makes the results of this trial inconclusive. The current study provides epidemiological support to do a new RCT with allopurinol vs placebo using a lower dose (preferably guided by urate response) which is likely much better tolerated.

2. Please provide a justification in introduction or methods section why you decided to focus on myocardial infarction (and not to include stroke/peripheral ischemic vascular events as outcomes).

Reviewer	**2**
Name	**van Herwaarden, Noortje**

Affiliation	**Sint Maartenskliniek, Rheumatology**
Date	**27-Oct-2024**
COI	**None**

The authors present a Swedish registry data study to investigate the effect of allopurinol on cardiovascular (CV) events in patients with gout. Looking at different time periods of allopurinol use is a relevant topic.

- I have some concern about the generalizability of this gout population and even is this all gout.

- The percentage of males is lower than expected in a typical gout population.

- 75% does not start allopurinol, that is also low. Do patients often start other urate lowering therapy?

- Confounding by indication might be an issue in the allopurinol versus no allopurinol users.

- Patients with prescriptions of colchicine were excluded to minimize confounding. However including these patients/data would offer the opportunity to study the effect of this drug on the CV risk which is highly relevant. Consider adding this to the manuscript?

- Were patients using platelet aggregation inhibitors excluded as well, as this indicates a previous CV event?

- Healthy survivor bias might be an issue as only the last 125 days of the study period are investigated.

- Please elaborate on the rationale behind choosing low and higher dose allopurinol. Why was a cut off of 100 mg allopurinol chosen? And also why investigating different doses? Surrogate for gout severity? Although not statistically significant, there seems to be a dose effect relation. Consider adding this in the discussion?

- Did starting dose of allopurinol have an effect on the CV event risk?

- Page 19, line 46/47: “We found that allopurinol users at the time of the ACS event had a significantly lower risk of first-ever ACS, …” Please rephrase, I think “at the time of the ACS event” should be removed.

- The fact that allopurinol initiators more often used cortisone could indeed indicate flares. This could be added to the discussion

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1
Prof. Gerard Rongen, Radboud university medical center

Comments to the Author:
Only two comments:
1. Please elaborate in your discussion on the used allopurinol dose in the ALL HEART trial (600 mg/day in patietns without renal imapirment; 300 mg/day in patients with renal impairment, without monitoring of plasma urate response) which contrasts to the relatively low alopurinol dose in this cohort of allopurinol users (100-300 mg/day). The high dose in ALL HEART likely contributed to the early and premature cessation of allopurinol in the large majority of participants allocated to allopurinol therapy which makes the results of this trial inconclusive. The current study provides epidemiological support to do a new RCT with allopurinol vs placebo using a lower dose (preferably guided by urate response) which is likely much better tolerated.

Answer: Thank you for this relevant comment.

Action taken: We addressed this relevant point by adding the following sentences in the Discussion, page 11, lines 10-16: '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.'

2. Please provide a justification in introduction or methods section why you decided to focus on myocardial infarction (and not to include stroke/peripheral ischemic vascular events as outcomes).

Answer: Thank you for this comment. By choosing to focus on myocardial infarction and not to other cardiovascular outcomes, we aimed to conduct a study which provides robust results regarding the relationship between allopurinol use and coronary events. While stroke and peripheral ischemic vascular events are important cardiovascular outcomes, they often involve additional risk factors (for instance atrial fibrillation) or have different pathophysiological mechanisms.

Action taken: We have addressed this relevant point by adding the following sentence in the Methods, page 6, lines 19-21: '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.'

Reviewer: 2
Dr. Noortje van Herwaarden, Sint Maartenskliniek
Comments to the Author:
The authors present a Swedish registry data study to investigate the effect of allopurinol on cardiovascular (CV) events in patients with gout. Looking at different time periods of allopurinol use is a relevant topic.

- I have some concern about the generalizability of this gout population and even is this all gout.

Answer: Thank you for this valuable comment. This study is based on data from large population-based registers. The ICD-coded definition of gout used in our analyses has been validated in a previous study, which showed high level of validity for this definition (1).

Action taken: None.

- The percentage of males is lower than expected in a typical gout population.

Answer: Thank you for this comment. This study utilized data from population-based registers which cover both primary and specialized healthcare. Furthermore, we excluded all patients with a prior history of coronary heart disease, which is more prevalent in men than in women. These differences in study design and population characteristics may, to some extent, account for the lower percentage of males in our study compared to other studies.

Action taken: None.

- 75% does not start allopurinol, that is also low. Do patients often start other urate lowering therapy?

Answer: Thank you for this relevant comment. Unfortunately, gout in Sweden is suboptimally treated, with a low percentage of patients initiating urate lowering therapy (ULT) and low doses among those who do. This was demonstrated in a previous study, which showed that only 32% of gout patients initiated ULT within one year of diagnosis (2). Among those who started ULT, the majority (75%) did not continue with it beyond two years. This relevant point is addressed in the Discussion, pages 10-11, lines 31,1,2: '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.'

Action taken: None.

- Confounding by indication might be an issue in the allopurinol versus no allopurinol users.

Answer: Thank you for this remark. This study includes only patients with a diagnosis of gout. However, confounding by indication remains a potential concern and to minimize this we excluded all patients with hematological malignancy and/or end stage renal disease (Methods, page 6, lines 11-13).

Action taken: We have addressed this relevant point by modifying the sentence '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).' in Methods, page 6, lines 11-14.

The new sentences now read: 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).

- Patients with prescriptions of colchicine were excluded to minimize confounding. However including these patients/data would offer the opportunity to study the effect of this drug on the CV risk which is highly relevant. Consider adding this to the manuscript?

Answer: Thank you for this valuable comment. It would be very interesting to study the effect of colchicine; however, its use among gout patients in Sweden is very limited. In our study, only 3.2% of gout patients were prescribed colchicine during the follow-up period. Due to this low usage, we were unable to access its potential impact on cardiovascular risk within the scope of this study.

Action taken: None.

- Were patients using platelet aggregation inhibitors excluded as well, as this indicates a previous CV event?

Answer: Thank you for this comment. We excluded patients with previous history of coronary heart disease. To address the use of platelet aggregation inhibitors, we included these drugs, along with other anticoagulants, as adjustments in our analyses.

Action taken: To clarity this, we have included 'platelet aggregation inhibitors' alongside anticoagulants under the 'Medication' category in Table 1 and Table 2, which present the medications we adjusted for in our analyses.

- Healthy survivor bias might be an issue as only the last 125 days of the study period are investigated.

Answer: Thank you for highlighting this potential limitation. While we acknowledge the possibility of healthy survivor bias using this study design, this period was chosen to capture the most recent period of exposure, as the aim of this study was to investigate the temporal association between allopurinol use and MI.

Action taken: None.

- Please elaborate on the rationale behind choosing low and higher dose allopurinol. Why was a cut off of 100 mg allopurinol chosen? And also why investigating different doses? Surrogate for gout severity? Although not statistically significant, there seems to be a dose effect relation. Consider adding this in the discussion?

Answer: Thank you for this comment. We chose a cutoff of 100mg allopurinol, as this is the most commonly prescribed dose for gout patients in Sweden. We also investigated different doses to access whether there is a dose-dependent effect on the risk of MI.

Action taken: We have addressed this relevant point in the Discussion, by adding the following sentence in pages 9-10, lines 31,1-3: '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.'

- Did starting dose of allopurinol have an effect on the CV event risk?

Answer: Thank you for this valuable comment. The most commonly prescribed starting dose of allopurinol in Sweden is 100mg. While this is an important aspect to consider, investigating the impact of the starting dose of allopurinol was beyond the scope of this study.

Action taken: None.

- Page 19, line 46/47: "We found that allopurinol users at the time of the ACS event had a significantly lower risk of first-ever ACS, …" Please rephrase, I think "at the time of the ACS event" should be removed.

Answer: Thank you for this comment.

Action taken: We removed 'at the time of the ACS event' in Page 9, line 29.

- The fact that allopurinol initiators more often used cortisone could indeed indicate flares. This could be added to the discussion

Answer: Thank you for this remark. The fact that allopurinol initiators more frequently used cortisone could indicate the occurrence of flares. However, it is more likely that cortisone was prescribed as flare prophylaxis, as cortisone is the most commonly used drug for that purpose in Sweden.

Action taken: We have addressed this point by adding the following sentence in Discussion, page 10, lines 14-16: 'Allopurinol initiators were more frequently prescribed cortisone compared to long-term users, possibly due to gout flares or as flare prophylaxis.'

1. Dehlin M, Stasinopoulou K, Jacobsson L. Validity of gout diagnosis in Swedish primary and secondary care - a validation study. BMC Musculoskelet Disord. 2015;16:149.
2. Dehlin M, Ekström EH, Petzold M, Strömberg U, Telg G, Jacobsson LT. Factors associated with initiation and persistence of urate-lowering therapy. Arthritis Res Ther. 2017;19(1):6.

VERSION 2 - REVIEW

Reviewer	**2**
Name	**van Herwaarden, Noortje**
Affiliation	**Sint Maartenskliniek, Rheumatology**
Date	**30-Jan-2025**
COI	

My comments have been adequately addressed