J Rheum Dis 2024;31(2):108-115
https://doi.org/10.4078/jrd.2023.0059
pISSN: 2093-940X, eISSN: 2233-4718

Original Article

Urate-lowering therapy is associated with a reduced risk of arrhythmias: a systematic review and meta-analysis

Palapun Waitayangkoon, M.D.[1]*, Thiratest Leesutipornchai, M.D.[2]*, Witina Techasatian, M.D.[2], Noppawit Aiumtrakul, M.D.[2], Manasawee Tanariyakul, M.D.[2], Chinnawat Arayangkool, M.D.[2], Tatchaya Kanthajan, M.D.[3], Todd Nagamine, M.D.[2], Jakrin Kewcharoen, M.D.[4]

[1]Department of Medicine, MetroWest Medical Center, Tufts University School of Medicine, Framingham, MA, [2]Department of Internal Medicine, University of Hawaii, Honolulu, HI, USA, [3]Department of Medicine, Srinakharinwirot University, Bangkok, Thailand, [4]Department of Cardiology, Loma Linda University Medical Center, Loma Linda, CA, USA

Objective: While urate-lowering therapy (ULT) is linked to increased cardioprotective benefits on primary prevention of cardiovascular events such myocardial infarction or heart failure, little is known regarding their effects on arrhythmia risk. The purpose of this study was to investigate the relationship between incident arrhythmias and ULT.

Methods: We searched MEDLINE and Embase from inception to May 2023. Included studies were randomized controlled trials and cohort studies that compared the risk of cardiac arrhythmias among ULT users with non-ULT users.

Results: A total of 12,420 patients from five studies were analyzed, comprising 7,359 subjects in the ULT group and 5,061 subjects in the non-ULT group. Our results showed that ULT users had significant reductions in the risk of arrhythmias (pooled relative risk [RR] 0.82, 95% confidence interval [CI]: 0.74~0.92, p<0.001, I^2=0.0%) compared to non-ULT users. Subgroup analysis did not show that ULT users had a significant reduced risk of atrial fibrillation (pooled RR 0.76, 95% CI: 0.54~1.05, p=0.096 with I^2=15.4%) compared to non-ULT users.

Conclusion: ULT is associated with lower risk of overall arrhythmias. Further studies are warranted to confirm our findings.

Keywords: Arrhythmias, cardiac, Allopurinol, Febuxostat

INTRODUCTION

Uric acid (UA) is a breakdown product from xanthine and hypoxanthine through xanthine oxidase (XO) in purine metabolism and has long been recognized as an antioxidant [1]. However, studies have shown that it can also generate oxygen free radicals in different types of cells, including cardiac myocytes and endothelium, leading to oxidative stress [2]. Increased UA promotes pro-oxidative and inflammatory state [3] by intensifying XO activity and interfering with renin-angiotensin system, which induces vascular endothelial injury [4,5], resulting in a variety of cardiovascular diseases, such as atherosclerosis and hypertension. Hyperuricemia is an independent unfavorable risk factor for cardiovascular diseases and mortality [6,7].

According to recent studies, hyperuricemia is linked to a higher prevalence of atrial and ventricular arrhythmias [8,9]. Urate-lowering therapy (ULT) may also have cardioprotective benefits through lowering UA levels and the direct effects of the medication [10-12]. However, little is known about their effects on arrythmia risk. We aim to investigate the link between

Received September 18, 2023; **Revised** November 5, 2023; **Accepted** November 6, 2023, **Published online** December 28, 2023

Corresponding author: Palapun Waitayangkoon, https://orcid.org/0000-0003-4447-4972
Department of Medicine, MetroWest Medical Center, Tufts University School of Medicine, 115 Lincoln Street, Framingham, MA 01702 , USA. **E-mail:** palapun@gmail.com
*These authors contributed equally to this work.

ULT and incident arrhythmias through a systematic review and meta-analysis.

MATERIALS AND METHODS

Design

This systematic review has been carried out following the recommendations of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement and guidelines for systematic reviews.

Search strategy

Potentially eligible studies were identified by two investigators (TL, PW) through independent searches of PubMed and Embase databases, from inception to May 2023. The search terms used were derived from those related to "Arrhythmias" and "Urate-lowering therapy", as described in the Supplementary Material 1. No restrictions were applied on study design or language in the search strategy. If necessary, relevant articles in languages other than English were translated using Google Translate or other appropriate methods. Furthermore, additional relevant studies were searched manually by examining the references of the retrieved articles.

Study selection criteria

The study being sought must be cohort study, which compares patients who use ULT and the other group of patients who do not use ULT (comparator). The main objective of the study is to compare the prevalence of cardiac arrhythmias in each group and determine the size of the effect with a 95% confidence interval (CI). Two investigators (TL and PW) independently reviewed the articles to determine if they met the criteria for inclusion in the study. If there were any disagreements, a third investigator, JK, helped to resolve them through discussion. The quality of each study was assessed by three investigators (PW, MT, and TK), using the Newcastle-Ottawa quality assessment scale (NOS) [13] for cohorts and the Revised Cochrane Risk-of-Bias tool (RoB2) for randomized controlled trials (RCTs) [14]. If two studies used the same database, only the study with the greatest number of participants would be taken into consideration for inclusion.

Data extraction

We utilized a standardized form to collect data, which included the last name of the first author, country where the study was conducted, study design, publication year, population of participants, recruitment of participants, diagnosis of cardiac arrhythmias (Arrhythmias of interest include supraventricular tachycardia, ventricular tachycardia and atrial fibrillation/flutter), ULT (Xanthine oxidase inhibitors (XOIs): allopurinol and febuxostat, uricosuric agents: probenecid and benzbromarone, and uricase agents: pegloticase) use, mean age of participants, percentage of female participants, and variable adjusted in multivariate analysis. This extraction process was independently carried out by three investigators (PW, MT, and CA). Any inconsistencies in the data were resolved by referring back to the original articles.

Quality of included studies

For the cohort studies, the researchers used the NOS to assess the quality of the included studies. This scale uses a star grading system, with a range of 0 to 9, to assess the studies in three areas:

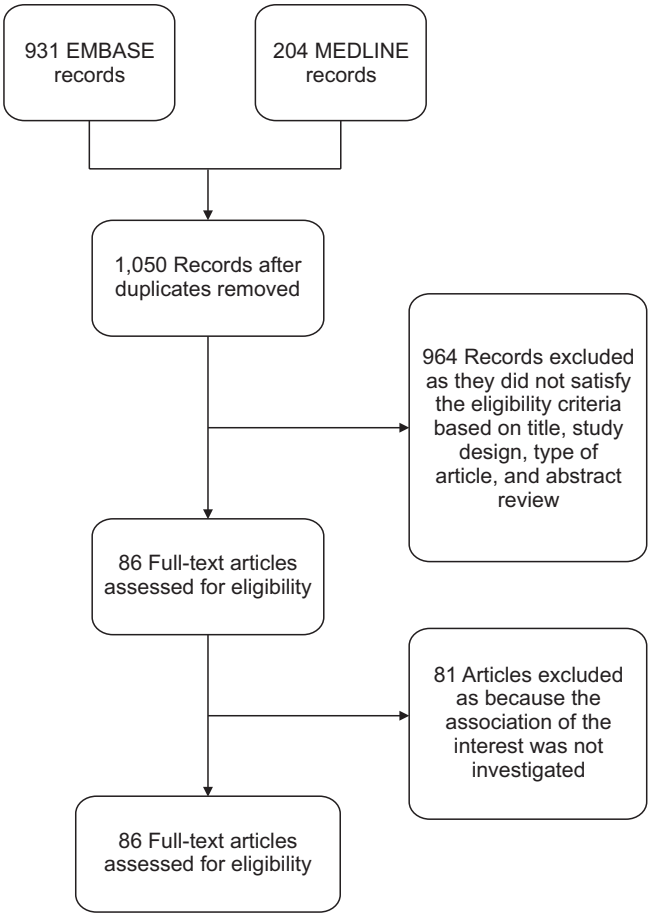

Figure 1. Study identification and literature review process.

Table 1. Main characteristics of the cohort studies included in the meta-analysis

	Rashid and William-Olsson [17]	Tabayashi et al.[12]	Singh and Yu [11]	Tai et al. [18]	Kojima et al. [16]
Country	Sweden	Japan	USA	Taiwan	Japan
Study design	Prospective randomized study	Prospective double-blind randomized study	Retrospective cohort study	Retrospective cohort study	Prospective randomized study
Year of publication	1991	1991	2017	2021	2022
Patient / Population	Patients who underwent elective CABG	Patients who underwent CABG or valve replacements or repairs	Patients without atrial fibrillation at baseline (at least 365 days) from the 5% random Medicare Claims data from 2006 to 2012	Patients aged 20 years or older with a new diagnosis of in-hospital myocardial infarction by ICD-9-CM code: 410 and ICD-10-CM code: I21 and I22 between January 1, 2005, and December 31, 2016	Patients with asymptomatic hyperuricemia from post hoc analysis of febuxostat for cerebral and cardiorenovascular events prevention study trial
Exposure	Patients who received allopurinol twice a day for 2 days preoperatively, 600 mg given as single dose on the morning of operation day and 300 mg given twice a day for 2 days postoperatively.	Patients who received 1,200 mg and 2,400 mg allopurinol preoperatively	Patients who received allopurinol as a new therapy, indicated by a filled allopurinol prescription, after a baseline period of at least 365 days	Patients who used XOIs (allopurinol or febuxostat) or uricosuric agents (benzbromarone, probenecid, or sulfinpyrazone), identified according to the Anatomical Therapeutic Chemical classification system and the corresponding drug codes in the NHI database.	Patients who received febuxostat
Total number of patients with ULT use	45	60	5,754	963	537
Comparators	Patients who did not receive allopurinol	Patients who did not receive allopurinol	Patients who did not receive allopurinol	Patients who did not receive ULT	Patients who did not receive febuxostat
Total number of comparators	45	30	3,490	963	533
Outcome	Atrial fibrillation, atrial flutter, sinus tachycardia, ventricular tachycardia, and blocks appearing more than 24 hours postoperatively	Atrial, supraventricular and ventricular arrhythmias	Incidient atrial fibrillation from 2006 to 2012	Supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, and atrial flutter	Atrial fibrillation (including paroxysmal atrial fibrillation)

Table 1. Continued

	Rashid and William-Olsson [17]	Tabayashi et al.[12]	Singh and Yu [11]	Tai et al. [18]	Kojima et al. [16]
Average age of participants at index date (yr), mean (SD)					
Patients with ULT	61.9 (11)	54.5 (12.4)	78.4 (7.1)	65.6 (13.3)	75.4 (6.7)
Patients without ULT	62.5 (9)	51.8 (14.5)	78.0 (7.3)	65.5 (13.8)	76 (6.5)
Percentage (%) of female					
Patients with ULT	32.3	53.8	56.3	22.9	30.9
Patients without ULT	32.3	57.8	57.5	22.9	31
Variables adjusted in multivariate analysis	None	None	Age, sex, race, Charlson–Romano comorbidity score and cardiac medications	Age, sex, other possible confounders and the use of major CV medications	Age, sex, and comorbidities
Newcastle-Ottawa score			Selection: 4 Comparability: 1 Outcome: 2	Selection: 4 Comparability: 1 Outcome: 2	

CABG: coronary artery bypass grafting, ICD-9-CM: The International Classification of Disease, 9th Revision, Clinical Modification, ICD-10-CM: The International Classification of Disease, 10th Revision, Clinical Modification, XOIs: xanthine oxidase inhibitors, NHI: National Health Insurance, ULT: urate lowering therapy, SD: standard deviation, CV: cardiovascular.

participant recruitment and selection, group comparability, and the determination of the outcome of interest in cohort studies. A higher grade corresponds tohigher quality. For the RCTs, we utilized the RoB2 for quality assessment, which consists of 5 domains, including biases arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was evaluated and stratified into one of the three types of bias judgments: low, high, and some concerns. Three investigators (MT, CA, TK) independently evaluated the quality of each study, and any differing opinions were resolved through discussion with a fourth investigator (PW).

Statistical analysis

We conducted a meta-analysis of the studies included in our research using a random-effects model and the generic inverse-variance method of DerSimonian and Laird [15]. Our analysis focused on examining the incidence of arrhythmia and the use of ULT as reported in these studies. To assess the heterogeneity of the effect size estimates, we used forest plots to check for any non-overlapping confidence intervals and calculated the Q statistic and the I^2 statistic. For the Q statistic, substantial heterogeneity was defined as $p<0.10$. The I^2 statistic ranges from 0 to 100%, with values below 25% indicating low heterogeneity, values between 25% and 50% indicating moderate heterogeneity, and values above 50% indicating substantial heterogeneity. We performed a sensitivity analysis to examine the impact of individual studies on our overall results by removing one study at a time. We did not utilize funnel plots and Egger's test to investigate publication bias since the number of included studies was not sufficient to reject the assumption of no funnel plot asymmetry. All statistical tests were conducted using STATA 17 software (College Station, TX, USA).

RESULTS

From the Embase and MEDLINE databases, we found a total of 1,135 articles. After eliminating duplicate articles, we were left with 1,050 articles to review. Of these, 964 articles did not meet the eligibility criteria based on title, study design, type of article, and abstract review. As a result, we identified 86 articles that were considered relevant and were thoroughly reviewed. Ultimately, 81 more articles were excluded as they did not meet the inclusion criteria or did not have comparable outcomes of inter-

est. No additional articles were found through manual search. Thus, a total of 5 articles [11,12,16-18] met all the eligibility criteria and were included in the data analysis. Figure 1 provides an overview of the search methodology and selection process used in this study.

The 5 included articles are comprised of three RCTs and two retrospective cohorts from 1991 to 2022. These articles involved 12,420 subjects, with 7,359 subjects in the ULT group and 5,061 subjects in the non-ULT group. Among the 5 articles, 3 focused on allopurinol, 1 on febuxostat, and 1 used combined ULTs without specifying a specific drug. Four articles specifically examined the relationship with atrial fibrillation (AF). Additional characteristics of the included studies can be found in Table 1. Both retrospective cohort studies [11,18] were of high quality, as indicated by the high Newcastle-Ottawa score (Table 1). The risk of bias assessment for RCTs [12,16-17] shown in Figures 2 and 3 demonstrated some concerns arising from the randomization process and the deviations from the intervention but there were no apparent factors that affect the results and outcome evaluations.

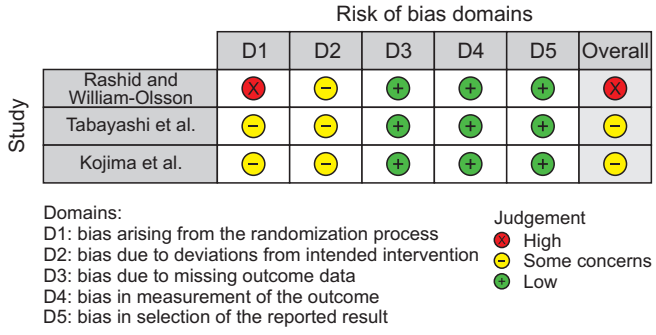

Figure 2. Risk of bias results for the included studies.

Primary outcome

1) ULT and the risk of arrhythmias

Our study showed that ULT users had significant reductions in the risk of arrhythmias (pooled relative risk [RR] 0.82, 95% CI: 0.74~0.92, p<0.001, I^2=0.0%) as shown in Figure 4. Supplementary Table 1 demonstrated a table of the primary analysis results.

Subgroup analysis

1) ULT and the risk of AF

Subgroup analysis did not show that ULT users had a significant reduced risk of AF (pooled RR 0.76, 95% CI: 0.54~1.05, p=0.096 with I^2=15.4%) compared to non-ULT users as shown in Figure 5.

Subgroup analysis for the retrospective cohorts showed the significant reduction in the risk of arrhythmias (pooled RR 0.83, 95% CI: 0.74~0.93, p=0.001, I^2=0.0%) (Supplementary Figure 1) but the subgroup analysis for three RCTs showed no significant reduced risk of arrythmia (pooled RR 0.53, 95% CI: 0.27~1.03, p=0.062, I^2=0.0%) (Supplementary Figure 2). There were insufficient data to perform additional analysis for supraventricular tachycardia and ventricular arrythmia (VA).

Publication bias

As there were only five studies in the primary analysis, the number was insufficient to reject the assumption of no funnel plot asymmetry. Therefore, neither Egger's test nor a funnel plot was performed.

Sensitivity analysis

A sensitivity analysis was performed to assess the influence

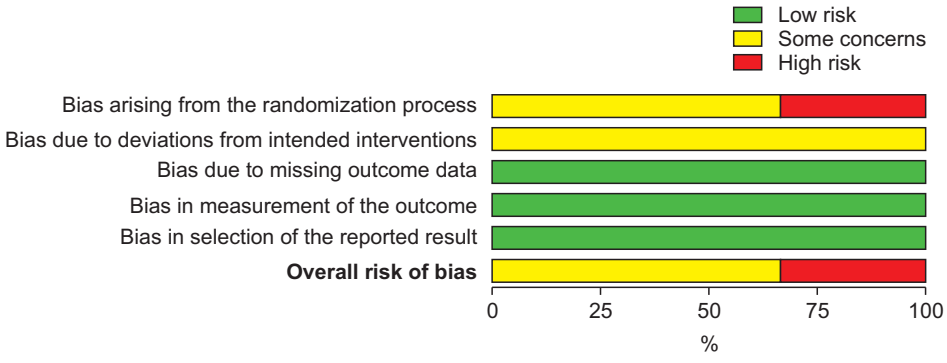

Figure 3. Risk of bias summary chart for the included studies.

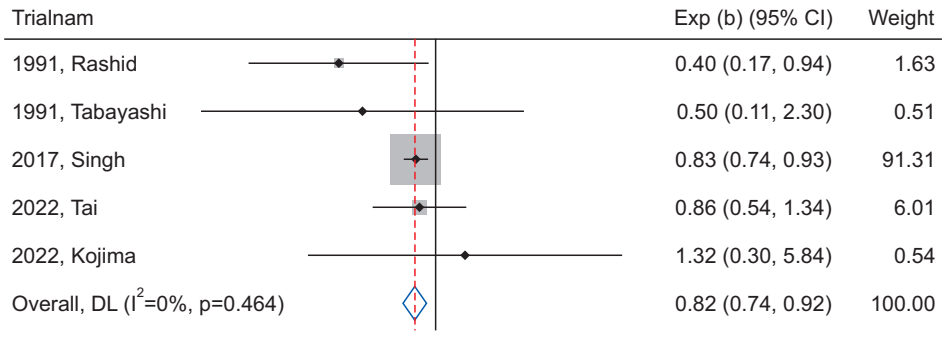

Figure 4. Forest plot of the meta-analysis for urate-lowering therapy and risk of arrhythmias. DL: DerSimonian-Laird method used for the random effects model, CI: confidence interval.

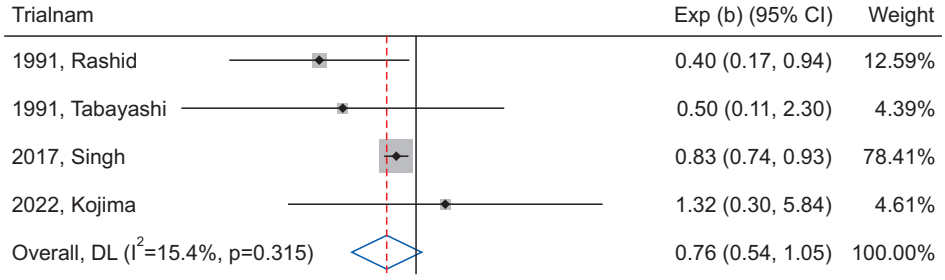

Figure 5. Forest plot of the meta-analysis for urate-lowering therapy and atrial fibrillation. DL: DerSimonian-Laird method used for the random effects model, CI: confidence interval.

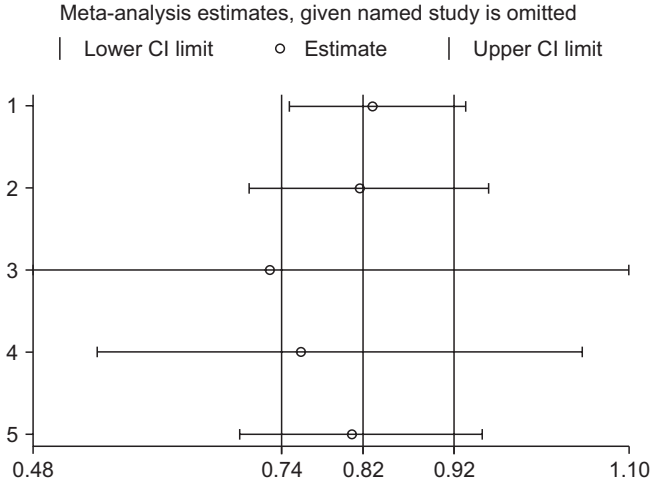

Figure 6. Sensitivity analysis of the meta-analysis for urate-lowering therapy and risk of arrhythmias. CI: confidence interval.

of the individual studies on the overall results by omitting one study at a time as shown in Figure 6.

DISCUSSION

To our knowledge, this is the first comprehensive review and analysis that explores the connection between ULT and arrhythmias. The use of ULT has been linked to a decreased risk of arrhythmias. However, the specific reasons behind this association are not yet fully understood. We propose several potential explanations.

One of the main reasons for the reduced risk of arrhythmias with ULT is likely the direct effect it has on lowering levels of serum UA as hyperuricemia is associated with an increased risk of both AF and VA. Various mechanisms contribute to the higher AF risk in patients with elevated UA levels, particularly when the levels exceed 7.0 mg/dL in men and 5.7 mg/dL in women [19]. It is believed that UA contributes to the structural and electrophysiological remodeling of the atrium, which disrupts signaling pathways and molecules involved in AF onset and perpetuation [8]. Additionally, UA can enter atrial myocytes and produce reactive oxygen species, which are a key stimulus for AF development [20]. Limited data exist on the relationship between hyperuricemia and VA. However, in patients with ST-elevation myocardial infarction, high UA levels have been found to reduce the susceptibility of the ventricular myocardium and impair coronary artery reperfusion, leading to VAs [21]. Yamada et al. [9] demonstrated that patients with left ventricular (LV) hypertrophy have increased risk of VA when UA is elevated and hypothesized that LV myocardium damage may be provoked by increased UA.

Additionally, inhibiting XO enzyme activity has been shown to weaken sympathetic innervation and reduce arrhythmias in an independent manner from its direct effect of reducing UA levels. Lee et al. [10] conducted a study using rats and found that inhibiting XO decreased the production of ROS, which

are known to cause inflammation and disrupt cardiac electrical and structural remodeling, promoting AF [22]. XO is one of the major sources of ROS in the heart [23]. By suppressing XO, the CaMKII oxidation and RyR2 hyperphosphorylation were restored, resulting in a decrease in intracellular ROS and a reduced vulnerability to AF [24]. These effects on oxidative stress and sympathetic innervation were XOI dependent and not yet demonstrated on the use of uricosuric or uricase agents [10]. The majority of ULT included in our study are XOI, allopurinol and febuxostat.

Apart from reduced serum urate, antioxidant action, and decreased sympathetic activity, allopurinol may prevent VAs by anti-ischemic effect [25], lowering blood pressure [26] and reducing LV mass [27]. In a study using a canine model, allopurinol suppressed AF by attenuating the interstitial fibrosis of the atrium, which is a pathological substrate for AF induction [28]. This effect might be the unique feature of allopurinol to mitigate arrythmia. Although it is believed that the anti-ischemic effect results from XO inhibition [25], none of the studies have investigated this effect on febuxostat, which appears to be a more potent XOI [29]. Future studies should explore whether this is a class effect or exclusive to allopurinol.

The main strengths of this study are that we included a large number of participants, and the results remain robust even after we performed the sensitivity analysis as there is only little change in the overall outcome estimate. The statistical heterogeneity of the meta-analysis was insignificant to low (I^2 0.0%~15.4%), most likely because of variations in participant characteristics and study design. However, there are a few limitations in our study. The majority of the included studies focused on allopurinol and AF, with only one study specifically examining the effects of febuxostat. Furthermore, none of the studies specifically investigated VA. The studies related to allopurinol and VA were all related to myocardial infarction, which may not be applicable to other types of VA.

CONCLUSION

According to our findings, ULT may be able to prevent arrhythmias in addition to decreasing UA levels. More research is required to fully understand our findings and investigate the intricacies behind the mechanisms.

SUPPLEMENTARY DATA

Supplementary data can be found with this article online at https://doi.org/10.4078/jrd.2023.0059

FUNDING

None.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

P.W. and T.L. contributed equally to this work including the design and implementation. W.T., M.T., C.A., and T.N. performed the data collection and extraction. T.L. analyzed the data. M.T., C.A. and T.K. assessed the quality of the studies. P.W. took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

ORCID

Palapun Waitayangkoon, https://orcid.org/0000-0003-4447-4972
Thiratest Leesutipornchai, https://orcid.org/0000-0001-8436-1142
Witina Techasatian, https://orcid.org/0009-0006-3404-8004
Noppawit Aiumtrakul, https://orcid.org/0000-0003-0479-7785
Manasawee Tanariyakul, https://orcid.org/0009-0007-1191-8780
Chinnawat Arayangkool, https://orcid.org/0009-0002-5877-8651
Tatchaya Kanthajan, https://orcid.org/0009-0000-7145-3857
Todd Nagamine, https://orcid.org/0000-0002-2472-8173
Jakrin Kewcharoen, https://orcid.org/0000-0003-0959-5576

REFERENCES

1. Kushiyama A, Nakatsu Y, Matsunaga Y, Yamamotoya T, Mori K, Ueda K, et al. Role of uric acid metabolism-related inflammation in

the pathogenesis of metabolic syndrome components such as atherosclerosis and nonalcoholic steatohepatitis. Mediators Inflamm 2016;2016:8603164.
2. Polito L, Bortolotti M, Battelli MG, Bolognesi A. Xanthine oxidoreductase: a leading actor in cardiovascular disease drama. Redox Biol 2021;48:102195.
3. Gherghina ME, Peride I, Tiglis M, Neagu TP, Niculae A, Checherita IA. Uric acid and oxidative stress-relationship with cardiovascular, metabolic, and renal impairment. Int J Mol Sci 2022;23:3188.
4. Yu MA, Sánchez-Lozada LG, Johnson RJ, Kang DH. Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. J Hypertens 2010;28:1234-42.
5. Sautin YY, Nakagawa T, Zharikov S, Johnson RJ. Adverse effects of the classic antioxidant uric acid in adipocytes: NADPH oxidase-mediated oxidative/nitrosative stress. Am J Physiol Cell Physiol 2007;293:C584-96. Erratum in: Am J Physiol Cell Physiol 2010;299:C726.
6. Johnson RJ, Bakris GL, Borghi C, Chonchol MB, Feldman D, Lanaspa MA, et al. Hyperuricemia, acute and chronic kidney disease, hypertension, and cardiovascular disease: report of a scientific workshop organized by the National Kidney Foundation. Am J Kidney Dis 2018;71:851-65.
7. Verdecchia P, Schillaci G, Reboldi G, Santeusanio F, Porcellati C, Brunetti P. Relation between serum uric acid and risk of cardiovascular disease in essential hypertension. The PIUMA study. Hypertension 2000;36:1072-8.
8. Deng Y, Liu F, Yang X, Xia Y. The key role of uric acid in oxidative stress, inflammation, fibrosis, apoptosis, and immunity in the pathogenesis of atrial fibrillation. Front Cardiovasc Med 2021;8:641136.
9. Yamada S, Suzuki H, Kamioka M, Kamiyama Y, Saitoh S, Takeishi Y. Uric acid increases the incidence of ventricular arrhythmia in patients with left ventricular hypertrophy. Fukushima J Med Sci 2012;58:101-6.
10. Lee TM, Lin SZ, Chang NC. Effects of urate-lowering agents on arrhythmia vulnerability in post-infarcted rat hearts. J Pharmacol Sci 2016;131:28-36.
11. Singh JA, Yu S. Allopurinol and the risk of atrial fibrillation in the elderly: a study using Medicare data. Ann Rheum Dis 2017;76:72-8.
12. Tabayashi K, Suzuki Y, Nagamine S, Ito Y, Sekino Y, Mohri H. A clinical trial of allopurinol (Zyloric) for myocardial protection. J Thorac Cardiovasc Surg 1991;101:713-8.
13. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa, Ottawa Hospital Research Institute, 2000.
14. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
15. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
16. Kojima S, Uchiyama K, Yokota N, Tokutake E, Wakasa Y, Hiramitsu S, et al. Optimal uric acid levels by febuxostat treatment and cerebral, cardiorenovascular risks: post hoc analysis of a randomized controlled trial. Rheumatology (Oxford) 2022;61:2346-59.
17. Rashid MA, William-Olsson G. Influence of allopurinol on cardiac complications in open heart operations. Ann Thorac Surg 1991;52:127-30.
18. Tai CJ, Wu CC, Lee KT, Tseng TG, Wang HC, Chang FR, et al. The impact of urate-lowering therapy in post-myocardial infarction patients: insights from a population-based, propensity score-matched analysis. Clin Pharmacol Ther 2022;111:655-63.
19. Gao Z, Shi H, Xu W, Guan Z, Su X, Guo N, et al. Hyperuricemia increases the risk of atrial fibrillation: a systematic review and meta-analysis. Int J Endocrinol 2022;2022:8172639.
20. Anzai N, Ichida K, Jutabha P, Kimura T, Babu E, Jin CJ, et al. Plasma urate level is directly regulated by a voltage-driven urate efflux transporter URATv1 (SLC2A9) in humans. J Biol Chem 2008;283:26834-8. Erratum in: J Biol Chem 2008;283:32152.
21. Mandurino-Mirizzi A, Crimi G, Raineri C, Pica S, Ruffinazzi M, Gianni U, et al. Elevated serum uric acid affects myocardial reperfusion and infarct size in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. J Cardiovasc Med (Hagerstown) 2018;19:240-6.
22. Liang X, Zhang Q, Wang X, Yuan M, Zhang Y, Xu Z, et al. Reactive oxygen species mediated oxidative stress links diabetes and atrial fibrillation. Mol Med Rep 2018;17:4933-40.
23. D'Oria R, Schipani R, Leonardini A, Natalicchio A, Perrini S, Cignarelli A, et al. The role of oxidative stress in cardiac disease: from physiological response to injury factor. Oxid Med Cell Longev 2020;2020:5732956.
24. Xu D, Murakoshi N, Tajiri K, Duo F, Okabe Y, Murakata Y, et al. Xanthine oxidase inhibitor febuxostat reduces atrial fibrillation susceptibility by inhibition of oxidized CaMKII in Dahl salt-sensitive rats. Clin Sci (Lond) 2021;135:2409-22.
25. Noman A, Ang DS, Ogston S, Lang CC, Struthers AD. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial. Lancet 2010;375:2161-7.
26. Beattie CJ, Fulton RL, Higgins P, Padmanabhan S, McCallum L, Walters MR, et al. Allopurinol initiation and change in blood pressure in older adults with hypertension. Hypertension 2014;64:1102-7.
27. Rekhraj S, Gandy SJ, Szwejkowski BR, Nadir MA, Noman A, Houston JG, et al. High-dose allopurinol reduces left ventricular mass in patients with ischemic heart disease. J Am Coll Cardiol 2013;61:926-32.
28. Sakabe M, Fujiki A, Sakamoto T, Nakatani Y, Mizumaki K, Inoue H. Xanthine oxidase inhibition prevents atrial fibrillation in a canine model of atrial pacing-induced left ventricular dysfunction. J Cardiovasc Electrophysiol 2012;23:1130-5.
29. Chou HW, Chiu HT, Tsai CW, Ting IW, Yeh HC, Huang HC, et al. Comparative effectiveness of allopurinol, febuxostat and benzbromarone on renal function in chronic kidney disease patients with hyperuricemia: a 13-year inception cohort study. Nephrol Dial Transplant 2018;33:1620-7.