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THE IMPACT OF HYPERURICEMIA ON CARDIOVASCULAR RISK. REVIEW OF THE EXISTING LITERATURE

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ABSTRACT

Objectives: The aim of the current work was to assess, following analysis of existing and widely available literature, whether increased levels of uric acid in blood serum have an impact on increased cardiovascular risk, and is urate-lowering treatment beneficial.
Materials and Methods: A review was conducted using the PubMed database, limited to full-text, freely available publications from the past 10 years. The analysis focused primarily on randomized controlled trials, meta-analyses, and systematic reviews related to hyperuricemia and cardiovascular risk.
Results: The evidence indicates a consistent association between hyperuricemia and increased cardiovascular risk, including higher all-cause and cardiovascular mortality. Although threshold values for hyperuricemia varied across studies, cardiovascular risk was shown to rise even with levels above 5 mg/dl. SGLT2 inhibitors demonstrated both urate-lowering and cardioprotective effects. In contrast, traditional xanthine oxidase inhibitors (e.g., allopurinol, febuxostat) did not show a significant benefit in reducing cardiovascular events.
Conclusions: Hyperuricemia is an independent risk factor for the increase in mortality and other adverse cardiovascular outcomes. SGLT2 inhibitors have shown to be promising in improving cardiovascular prognosis, while xanthine oxidase inhibitors presented no advantages. Further research in this subject is suggested.

KEYWORDS

Hyperuricemia, Uric Acid, Cardiovascular Risk, Urate-Lowering Therapy

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Introduction

Hyperuricemia, increased concentration of uric acid in blood serum, is a prevalent abnormality often present in patient populations treated for various diseases. Mainly associated with gout, the significance of increased serum uric acid levels in the pathophysiology of various abnormal states seems to be misunderstood. Often in clinical practice, we can see patients treated for various cardiovascular diseases having been put on urate-lowering therapy as soon as uric acid levels slightly increase above a certain point. This behavior, although it may seem logical, is generally controversial, as some existing studies have already questioned such practices. Moreover, a strict cut-off point suggesting when hyperuricemia should be treated is not clearly identified. This raises questions, whether treating an increased uric acid level is a correct approach, with a positive impact on patients' prognosis, or, to the contrary, is it just adding to the risk of polypragmasy. However, due to previous findings, hyperuricemia has already been recognized as an independent factor for increased cardiovascular risk by ESH and included in the European guidelines for hypertension (Maloberti et al., 2025; Mancia et al., 2023).

Purpose of the publication

The aim of the current work was to assess, following analysis of existing and widely available literature, whether increased levels of uric acid in blood serum have an impact on increased cardiovascular risk, and is urate-lowering treatment beneficial in cardiological patients at any given point. That way, we hope to deepen the understanding of the significance of hyperuricemia, as well as give some clinical advice on whether we should treat that abnormal state at any point, having cardiac risk in mind.

Methodology

Search for proper publications was done using PubMed, applying filters: 10-year publication date, available full free text, for article type we mainly focused on: clinical trial, meta-analysis, systematic review, randomized controlled trial. For searching, we were focusing on terms: hyperuricemia, cardiac risk. The searching results were then analyzed, and papers not associated with the subject of the current work were rejected, resulting in the inclusion of the referenced articles.

In this paper, we included mainly randomized controlled trials and different systematic reviews and meta-analyses, as well as some other various studies, to have a full spectrum of recent studies investigating the subject of interest of the current article. Some of the reviews and meta-analyses used in this work have incorporated the same several studies in their analyses. Nonetheless, we aimed at possibly the broadest available references being mentioned in our work; additionally, various publications often adopted different outcomes, therefore we have not rejected such papers.

Hyperuricemia - pathophysiology and links to cardiovascular disorders

Uric acid (UA) originates from purine catabolism. At the end stage of the spoken process, hypoxanthine is converted into xanthine and uric acid. This takes place due to the activity of xanthine dehydrogenase and xanthine oxidase. Both enzymes catalyze the conversion of hypoxanthine to uric acid, but xanthine oxidase has additionally been associated with the production of reactive oxygen species (ROS) in the process, an important factor for toxic possibilities.

Normally, UA is cleared mainly by the kidneys and to a lesser extent by the intestines. Hyperuricemia can result from either overproduction or underexcretion, which is generally a more common mechanism. Among factors that can lead to increased UA production are increased activity of the pentose phosphate pathway (PPP) - a key pathway for purine synthesis, genetics, obesity (high BMI), and tumor lysis syndrome. The most prevalent cause for underexcretion of UA and hyperuricemia in total is renal underexcretion. This state can occur due to impaired kidney function, diuretic use, or genetic causes (Maloberti et al., 2025; Packer, 2024).

Uric acid is a poorly soluble metabolic end product, and when its serum concentration exceeds 6.8 mg/dl, it can crystallize as monosodium urate, leading to joint and kidney deposition - a key mechanism in gout and urate nephropathy (Maloberti et al., 2025). Additionally, uric acid may also contribute to cardiovascular and metabolic diseases through non-crystal mechanisms. Xanthine oxidase-mediated production of reactive oxygen species is one of them (SN et al., 2023). Except for oxidative stress, there are other mechanisms through which UA has an impact on diseases. These include pathways involving RAAS activation and insulin resistance. In states like diabetes, heart failure, and chronic kidney disease, glucose-6-phosphate dehydrogenase (G6PD) - the key limiting step of purine synthesis - and, respectively, the PPP are upregulated, leading to increased purine synthesis and, as a result, to increased UA production (Packer, 2024). Simultaneously, nutrient surplus conditions activate mTOR and HIF-1α and suppress SIRT1 and AMPK, particles essential in UA synthesis, further promoting it, resulting in further cellular hypertrophy, inflammation, and oxidative damage (Packer, 2024). Elevated uric acid levels, but specifically the urinary UA/creatinine ratio, have also been linked to arterial stiffness (Wang et al., 2020).

Summary of possible mechanisms, connecting uric acid to cardiovascular disorders:

- Urate crystal deposition, occurring when the uric serum concentration gets above a certain point, a mechanism more specific to gout and kidney stones.
- Oxidative stress, induced by reactive oxygen species and leading to endothelial damage and dysfunction.
- Inflammation.
- Activation of the renin-angiotensin-aldosterone system (RAA), combined with impairment in renal sodium management, is the mechanism for hypertension development.
- Promoting arterial stiffness (Wang et al., 2020).

Evidence linking hyperuricemia and cardiovascular diseases

To assess the evidence linking increased uric acid levels to cardiovascular diseases, we have analyzed studies on the subject, the key points are presented below.

The aim of the first reviewed meta-analysis was to evaluate whether hyperuricemia is an independent risk factor for coronary heart disease (CHD) incidence and mortality in CHD-free adult populations. The authors also tried to identify a clinically relevant uric acid threshold for increased risk and examine potential gender differences. The analysis found a statistically significant association between hyperuricemia and

increased risk of coronary heart disease. The effect was more pronounced in the female population than in males. Similarly, hyperuricemia was associated with a slight increase in the risk of coronary heart disease mortality, driven primarily by female participants again. A uric acid threshold of >7.0 mg/dl was most often associated with increased CHD risk, particularly in women (Braga et al., 2016).

Another meta-analysis also aimed to evaluate whether hyperuricemia is associated with an increased risk of coronary heart disease and all-cause mortality. The results showed that hyperuricemia was significantly associated with increased risk of coronary heart disease mortality and all-cause mortality. Each 1 mg/dl increase in serum uric acid level was associated with a 20% increase in risk of coronary heart disease mortality and a 9% increase in all-cause mortality. Gender-specific analyses revealed that the risk was again notably higher in women than in men (Zuo et al., 2016).

The third meta-analysis aimed to assess the prospective association between hyperuricemia and the risk of coronary heart disease, adopting similar endpoints as previous analyses. The results showed that hyperuricemia was associated with an increased risk of coronary heart disease morbidity. Similarly, there was an association with coronary heart disease mortality. Notably, for every 1 mg/dl increase in serum uric acid, CHD mortality risk increased by 15%, with a more pronounced effect in females compared to males, corresponding with the results of previously mentioned analyses. While analysis did not support a clear linear relationship for coronary heart disease morbidity for males, the findings for females suggest a potentially important sex-specific risk (M. Li et al., 2016).

Meta-analysis, which aimed to identify the impact of various risk factors on mortality in adult patients with ST-elevation myocardial infarction (STEMI) who underwent percutaneous coronary intervention (PCI), showed that hyperuricemia was a significant risk factor for mortality. The presence of hyperuricemia was associated with an increased risk of death. The mortality rate in STEMI patients with hyperuricemia after PCI was 12%. This suggests a meaningful association between elevated uric acid levels and post-PCI mortality risk in patients with STEMI (Yan et al., 2023). However, it has to be stated that these results come from the analysis of only 2 previous studies, with an overall studied population of a little over 1000 patients, which makes the evidence considerably lower quality. Therefore, it seems that further research should be conducted on this subject.

Regarding the prominence of increased uric acid concentration in patients with acute heart failure, one meta-analysis aimed to evaluate the prognostic value of serum uric acid levels in patients with acute heart failure. The review assessed the association between UA levels and adverse outcomes such as all-cause mortality and the combined endpoint of death or readmission. The analysis found that elevated uric acid levels were significantly associated with increased risk of all-cause mortality and death or readmission combined. Additionally, each 1 mg/dl increase in UA was linked to an 11% and 12% rise in risk for these outcomes, respectively (G. Huang et al., 2019).

There were also other studies, highlighting different objectives. One of the meta-analyses tried to evaluate the prevalence of various cardiovascular diseases in patients with gout and then compare the risk with non-gout participants. The study focused on such cardiovascular outcomes as myocardial infarction, cerebrovascular accidents, heart failure, venous thromboembolism, and hypertension. The prevalence of hypertension was highest among the mentioned conditions, occurring in 63, 9% of gout patients, followed by heart failure (8, 7%), then cerebrovascular accident (4, 3%), myocardial infarction (2, 8%), and venous thromboembolism (2, 1%). Comparisons with non-gout participants revealed that gout patients had consistently increased risk for most cardiovascular outcomes, especially myocardial infarction, venous thromboembolism, and cardiovascular mortality. Overall, the findings highlight that cardiovascular risk in gout patients is increased, as there is higher morbidity on various disorders in patients with established gout (Cox et al., 2021).

The meta-analysis aiming to evaluate the association between serum uric acid levels and coronary artery calcification unsurprisingly showed similar results. The researchers conducted a search of observational studies with participants who were free from known coronary artery disease, chronic kidney disease, or gout and were not receiving uric acid-lowering therapy. The study found that patients with hyperuricemia had a significantly higher likelihood of having coronary artery calcification and a 31% increased risk of coronary artery calcification progression up to over 6 years of follow-up observation (Liang et al., 2019).

Increased UA levels have also a proven impact on an elevated risk of stroke. According to the meta-analysis that aimed to assess the relationship between serum uric acid levels and the risk of stroke, the results showed that each 1 mg/dl increase in serum UA was associated with a significantly higher risk of stroke: 10% in men and 11% in women. The evidence was particularly apparent for ischemic stroke in both sexes (Zhong et al., 2017).

As an interesting addition, hyperuricemia seems to have an impact on the prevalence of supraventricular arrhythmias such as atrial fibrillation. The study, which aimed to determine the association of hyperuricemia with non-valvular atrial fibrillation, revealed that hyperuricemia was independently associated with a significantly increased risk of atrial fibrillation. Also, serum uric acid showed moderate predictive value for non-valvular atrial fibrillation, particularly among women (Lin et al., 2019).

Hyperuricemia also seems to have an impact on the presence of left atrial thrombus or left atrial spontaneous echo contrast. The formation of the left atrial thrombus is accountable for the risk of stroke, further supporting the relationship between increased uric acid and stroke risk, which was already mentioned above. A meta-analysis, which focused on the presence of left atrial thrombus or left atrial spontaneous echo contrast, showed a statistically significant association between increased serum uric acid levels and the presence of the mentioned left atrial pathologies. The presence of these pathologies was assessed using transesophageal echocardiography. However, there is a crucial disclaimer to that discovery, as the study showed no proven evidence for this association in patients with atrial fibrillation alone. This may imply that comorbidities are crucial for increasing cardiovascular risk in this group of patients (Zhang et al., 2016).

Another systematic review aimed to evaluate the association between hyperuricemia and congestive heart failure, finding consistent evidence linking hyperuricemia with worse outcomes in both acute and chronic heart failure. Elevated uric acid was often associated with increased xanthine oxidase activity and oxidative stress, strengthening its potential in pathophysiology. Despite this discovery, the study stated that trials using xanthine oxidase inhibitors like allopurinol and febuxostat showed mixed results with limited clinical benefit, suggesting that while hyperuricemia is a strong prognostic marker for adverse heart failure outcomes, its role as a therapeutic target remains uncertain (SN et al., 2023).

Defining an appropriate cutoff point in serum uric acid levels seems crucial to the discussion about associated overall cardiac risk. A number of studies tried to give a respectable answer to that question. One such studies, designed as a case-control study, aimed to evaluate the impact of levels above 5 mg/dl on the prevalence of cardiac complications in patients with very high cardiovascular risk, particularly with chronic coronary disease and hypertension. Patients were all with coexisting hypertension and set for invasive cardiology diagnostics. The study divided them into two groups based on uric acid levels: 5 mg/dl and below in the first group, and above 5 mg/dl in the remaining group. The findings revealed that those who had uric acid levels above 5 mg/dl also had significantly higher rates of heart failure (47, 41% vs. 33, 5%) and atrial fibrillation (10, 96% vs. 3, 45%) compared to those with serum UA concentration below the established point. Hyperuricemia was associated with lower left ventricular ejection fraction, enlarged cardiac chambers, higher BMI, and abnormalities in lipid profile (Muszyński et al., 2023).

The findings of a different study suggest that increased serum uric acid can act as a biomarker for mortality risk stratification in cardiometabolic patients as well. The study aimed to evaluate whether serum uric acid levels can independently predict all-cause and cardiovascular mortality in patients with early or moderate cardiometabolic disease and no established cardiovascular disease. Interaction with triglyceride levels was also assessed. The discussed work was a sub-analysis of the URRAH study, where patients with already existing cardiovascular disease or severe metabolic disorders were excluded. Serum uric acid cut-offs were set at $\geq$ 4.7 mg/dl for all-cause mortality assessment and $\geq$ 5.6 mg/dl for cardiovascular mortality assessment. Values above this set point were considered hyperuricemia. Hypertriglyceridemia was defined as TG $\geq$ 150 mg/dl. The results showed that both elevated uric acid and triglyceride levels independently predicted all-cause mortality, while only hyperuricemia predicted cardiovascular mortality (Mengozzi et al., 2023).

The last referred study in this section, the retrospective cohort study, aimed to assess the prognostic value of serum uric acid levels in patients hospitalized for acute heart failure. According to the results, elevated serum uric acid has been identified as a predictor of both all-cause and cardiovascular mortality in acute heart failure patients. These results showed no diversity, no matter if the left ventricular ejection fraction was preserved or reduced (W. M. Huang et al., 2016).

Are there any benefits of urate-lowering therapy in the management of cardiovascular risk in patients with hyperuricemia?

Several studies focused primarily on the effect of various medications on not only the concentration of uric acid in serum, but also their influence on cardiovascular risk. This way, we can assess whether the use of those medications is beneficial in certain patients with increased uric acid levels. This aspect cannot be underestimated, as hyperuricemia has a proven impact on the increase of cardiac risk, a statement that can be easily derived based on the already mentioned studies. If risk truly increases, there needs to be treatment of

proven sufficiency to successfully help patients who otherwise would develop serious diseases. On the subject of medicine use in hyperuricemia and its impact on patient clinical outcomes, large randomized trials have been conducted. Studies concerned different medications, from SGLT2 inhibitors to classic urate-lowering medicines acting on enzymatic pathways involved in uric acid metabolism.

The EMPEROR trials evaluated the effects of the SGLT2 inhibitor empagliflozin on serum uric acid levels and clinical outcomes in patients with heart failure. The trial was divided to assess the use of empagliflozin in patients with heart failure with preserved ejection fraction (HFpEF, LVEF > 40%) and separately for patients with heart failure with reduced ejection fraction (HFrEF). The EMPEROR-Reduced trial examined patients with HFrEF (mostly LVEF ≤ 30%). Patients were stratified into sex-specific tertiles of serum uric acid and followed for outcomes including cardiovascular death, heart failure hospitalization, all-cause mortality, and renal deterioration. Higher baseline uric acid levels were associated with worse heart failure severity and an increased risk of cardiovascular events and mortality. Patients in the highest serum uric acid tertile had a 60-80% higher risk of cardiovascular and all-cause mortality events compared to the lowest tertile. Empagliflozin managed to significantly reduce hyperuricemia within 4 weeks of treatment and sustained this reduction over time. It also decreased the incidence of clinically relevant events by 32%. The benefits regarding mentioned earlier clinical outcomes when using empagliflozin were consistent across different uric acid levels, although its impact on mortality appeared to be more pronounced in patients with more severe hyperuricemia (Doehner et al., 2022). The analysis of the EMPEROR-Preserved trial included patients with HFpEF and simultaneously elevated NT-proBNP levels, who were randomized to receive 10 mg of empagliflozin daily or placebo. Hyperuricemia was present in 49% of participants and was associated with more advanced heart failure, as well as higher comorbidity. Interestingly, the risk of mortality has not risen significantly. Empagliflozin led to a rapid reduction of uric acid, especially in patients with higher baseline levels, and reduced clinically relevant events by 38%. The benefits have been shown to be independent of baseline serum uric acid (Doehner et al., 2024).

Another study that conducted an analysis of randomized clinical trials, the DAPA-HF and DELIVER trials, aimed to examine the relationship between gout and clinical outcomes in patients with heart failure, simultaneously examining the efficacy of the SGLT2 inhibitor dapagliflozin. The trials were divided by left ventricular ejection fraction, which was estimated at ≤ 40% in DAPA-HF (HFrEF) and > 40% in the DELIVER trial. The participants received either 10 mg dapagliflozin or a placebo added to guideline-recommended therapy. The assessed primary outcome was the composite of worsening heart failure or the occurrence of cardiovascular death. The results showed that approximately 10% of participants had a history of gout; these patients had more comorbidities and worse heart failure profiles. However, the benefits of dapagliflozin use were consistent regardless of gout status, as dapagliflozin reduced the risk of deterioration of heart failure or cardiovascular death. Notably, the medicine also significantly reduced the need for initiation of uric acid-lowering therapy by 57% and colchicine by 46%, suggesting an additional clinical benefit related to its uric acid-lowering effects (Butt et al., 2023).

Comparison of the safety of febuxostat and allopurinol in patients with gout and established cardiovascular disease was conducted in the CARES randomized controlled trial. Patients received either febuxostat or allopurinol, with doses adjusted based on urate levels and renal function. The research primary endpoint was a combination of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or urgent need for revascularization due to unstable angina. The results showed that febuxostat and allopurinol outcomes were similar regarding the cardiovascular risk - occurrence of the primary end point in both groups appeared at a rate over 10%. However, febuxostat was associated with significantly higher mortality compared to allopurinol. While the rates of nonfatal cardiovascular events were similar between the groups, sudden cardiac death was notably more frequent in the febuxostat group. These findings raise concerns about febuxostat's safety in high-risk cardiovascular populations, despite its superior efficacy in lowering uric acid levels (White et al., 2018).

Another clinical controlled trial, named the FREED study, focused mainly on febuxostat, trying to evaluate whether it could reduce the risk of cerebral, cardiovascular, and renal events in elderly patients (aged 65 and above) with asymptomatic hyperuricemia. The participants were at high risk of cardiovascular diseases. Hyperuricemia was defined as serum uric acid > 7.0 to ≤ 9.0 mg/dl. The participants were randomized to receive either febuxostat or conventional therapy - mostly lifestyle modification, some receiving allopurinol in low doses if needed. The measured outcome - primary composite endpoint - included fatal and non-fatal cardiovascular events, renal impairment, atrial fibrillation, and death from all other causes. The study found that febuxostat significantly lowered serum uric acid levels compared to the control group, with over 85% of febuxostat patients achieving levels of <

6.0 mg/dl in blood serum. The incidence of the primary composite endpoint was significantly lower in the febuxostat group, although mainly caused by a reduction in renal impairment events. However, no significant differences were observed in such endpoints as all-cause death or major cardiovascular events, questioning febuxostat's benefits on cardiovascular outcomes (Kojima et al., 2019).

To similar conclusions came another study. The Chinese retrospective cohort study, which aimed to evaluate whether febuxostat could improve clinical outcomes in heart failure patients with concurrent asymptomatic hyperuricemia, found no such evidence. Despite significantly lowering serum uric acid levels, febuxostat did not reduce the risk of cardiovascular outcomes compared to controls, nor did it significantly improve cardiac function (Long et al., 2025).

A randomized study, BEYOND-UA, tried to compare the effects of two xanthine oxidoreductase inhibitors, topiroxostat and febuxostat, on arterial stiffness, uric acid levels, and blood pressure in patients with hyperuricemia and hypertension. While both drugs significantly reduced serum uric acid levels and morning home systolic blood pressure, neither showed a significant effect on arterial stiffness. Topiroxostat uniquely reduced urinary albumin-creatinine ratio, particularly in patients with microalbuminuria, suggesting potential renoprotective advantages. The overall results suggest that although topiroxostat and febuxostat effectively reduce uricemia and blood pressure, their impact on arterial stiffness and cardiovascular outcomes remains uncertain (Kario et al., 2021).

A prospective randomized controlled study (the PRIZE trial) has recruited Japanese patients with asymptomatic hyperuricemia, which was determined as serum uric acid > 7.0 mg/dl and additionally carotid intima-media thickness ≥ 1.1 mm, randomizing them to either febuxostat treatment plus lifestyle modification or lifestyle modification alone. Analysis of the study, which included 326 randomized patients, aimed to identify factors associated with carotid intima-media thickness progression in patients with asymptomatic hyperuricemia. The results showed no significant overall change in mean or maximum intima-media thickness over the study period. Most importantly, febuxostat treatment and baseline uric acid levels were not significantly associated with changes in intima-media thickness (Saito et al., 2023). Another subanalysis of the PRIZE study aimed to evaluate the effects of febuxostat on cardiac function, specifically left ventricular diastolic function. This time, a subgroup of 65 patients from the trial underwent echocardiographic evaluation at certain points in time. Key echocardiographic variables and biomarkers such as NT-proBNP and troponin I were measured to assess structural and functional cardiac changes. Over the 24-month period of observation, febuxostat significantly lowered serum uric acid levels compared to the control group. While there were no significant changes in left ventricle mass index, LV ejection fraction, or cardiac biomarkers, febuxostat appeared to decrease the worsening of diastolic function. These findings imply that febuxostat may help preserve diastolic function in hyperuricemic patients (Kusunose et al., 2022). These results may sound promising, although the study consisted of a relatively small group of patients. Additionally, correlating these findings with the results of previously mentioned studies suggests the need for more large-scale studies to evaluate the findings of the discussed analysis.

Focusing on a different approach, a randomized controlled trial called the ALL-HEART study tried to assess whether allopurinol could improve major cardiovascular outcomes in patients aged 60 and older with known ischemic heart disease, but with no previous history of gout. The participants were assigned either to receive allopurinol daily in addition to their usual care or to continue with usual care alone. The measured outcome was a composite of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. Interestingly, the study found no significant difference in the occurrence of primary cardiovascular events between the allopurinol and usual care groups, nor in all-cause mortality or other measured outcomes. The study suggested that allopurinol should not be recommended for secondary prevention of cardiovascular events in patients with ischemic heart disease without gout (Mackenzie et al., 2024). Although this study focused on the presence of gout and not the exact serum uric acid level, it undoubtedly questions the routine use of allopurinol, as its benefits in reducing uric acid-related cardiovascular risk remain uncertain.

On the subject of medication use in hyperuricemia and its influence on cardiovascular disorders, some systematic reviews and meta-analyses have been published as well. Overall results of conducted meta-analyses on the subject seem to further confirm findings presented from the trials above. A meta-analysis that assessed the prognostic value of serum uric acid levels and the effects of uric acid-lowering therapy in patients with heart failure with preserved ejection fraction (HFpEF) revealed that elevated uric acid levels were significantly associated with increased risks of all-cause mortality and cardiovascular mortality. A 1 mg/dl increase in serum uric acid was linked to a 20% increased risk of all-cause mortality. Regarding treatment, uric acid-lowering therapy did not significantly reduce all-cause or cardiovascular mortality in HFpEF patients. Subgroup

analyses suggested that traditional therapies may even increase mortality risk. However, the analysis also showed an association between uric acid-lowering therapy and decreased risk of heart failure hospitalization, implying possible advantages of treatment (L. Li et al., 2024).

To very similar conclusions came different analysis, assessing the impact of allopurinol and febuxostat on all-cause and cardiovascular mortality. The overall analysis showed no significant association between allopurinol or febuxostat use and all-cause, as well as cardiovascular mortality. Interestingly, subgroup analyses indicated a 14% reduction in mortality for patients with chronic kidney disease and hyperuricemia, but in those with heart failure, although not significant, a trend towards increased mortality was observed. These findings may suggest a potential benefit of urate-lowering therapy in some populations, mainly patients with chronic kidney disease, but also a possible risk, especially in patients with heart failure, indicating the need for caution in use and further research to fully assess possible hazards (Nowak et al., 2024).

Another analysis evaluated the effects of urate-lowering therapies, mainly xanthine oxidase inhibitors and uricosuric agents, on heart failure outcomes. Results showed no statistically significant benefit of pharmacological therapies over placebo in improving LVEF, BNP, and NT-pro-BNP levels or six-minute walk test distance. Mortality outcomes also did not differ significantly between groups. Subgroup analysis revealed a modest, statistically significant BNP and NT-pro-BNP reduction in the uricosuric group but not with xanthine oxidase inhibitors (Xu et al., 2021).

A meta-analysis that aimed to compare the cardiovascular safety of febuxostat to allopurinol in Asian patients with hyperuricemia found concurrent conclusions to the previously mentioned studies. Patients were either symptomatic or asymptomatic, whereas included studies assessed cardiovascular outcomes such as acute coronary syndrome, stroke, acute decompensated heart failure, atrial fibrillation, cardiovascular, and all-cause mortality. Findings from cohort studies indicated that febuxostat was associated with a significantly increased risk of several cardiovascular outcomes compared to allopurinol, particularly in Chinese groups. On the other hand, randomized controlled trials did not reveal statistically significant differences in these outcomes, possibly due to smaller sample sizes and limited diversity of population - mostly elderly Japanese patients. The findings suggest that febuxostat may carry higher cardiovascular risks than allopurinol, further confirming findings from the previously discussed studies (Deng et al., 2024).

Discussion

Hyperuricemia happens to be a frequent disorder in many cardiovascular patients. Several studies have already tried to assess the influence of serum uric acid levels on cardiovascular risk increase, with generally consistent results. A number of systematic reviews and meta-analyses have been published, some with the exact objectives, some with uniquely different ones. Regardless of the detailed objective of the study, among the analyses included in this paper, the results have shown a consistent rise in cardiovascular risk due to increased serum uric acid levels. Hyperuricemia has been shown to increase the risk of adverse outcomes in patients with coronary heart disease, influencing the rise in both all-cause and cardiovascular mortality (Braga et al., 2016; M. Li et al., 2016; Zuo et al., 2016). Furthermore, even a slight increase in serum UA levels, by 1 mg/dl, has been proven to impact the probability of occurrence of the mentioned outcomes. Although different across studies, generally a 1 mg/dl increase is related to a 15-20% rise in cardiovascular mortality risk (M. Li et al., 2016; Zuo et al., 2016). Interestingly, a higher risk due to hyperuricemia was observed in females (Braga et al., 2016; M. Li et al., 2016). Studies have also shown a higher probability of mortality in patients with hyperuricemia and comorbidities such as STEMI (however, there are some limitations to this finding, such as relatively low sample size, translating to limited strength of the evidence). Increased serum uric acid levels are also responsible for worse prognosis in acute heart failure as well as chronic heart failure (G. Huang et al., 2019; W. M. Huang et al., 2016; SN et al., 2023). The risk of stroke has also been proven to increase by 10% and 11% for every 1 mg/dl of uric acid concentration, in males and females, respectively (Zhong et al., 2017). Among other proven cardiovascular outcomes in hyperuricemia patients are increased risks of atrial fibrillation, the occurrence of left atrial thrombus, and arterial stiffness, although there are some limitations reducing the value of this evidence, including a relatively monogenic population of the studies (Asian patients) (Lin et al., 2019; Wang et al., 2020; Zhang et al., 2016). Hyperuricemia has also been connected with a higher risk of coronary artery calcification (Liang et al., 2019). Regarding patients with established gout, in this group, the cardiovascular risk has also been proven to be more prominent than in patients with no gout, especially regarding such outcomes as myocardial infarction, venous thromboembolism, and cardiovascular mortality (Cox et al., 2021).

Although hyperuricemia was consistently related to adverse cardiovascular outcomes, the threshold value was not generally the same among the reviewed studies. There is evidence that even uric acid levels above 5 mg/dl have a significant influence on higher risk profiles of various outcomes, such as heart failure and atrial fibrillation (Muszyński et al., 2023). An elevated uric acid level predicted all-cause mortality and cardiovascular mortality when the cut-off was set at ≥ 4.7 mg/dl for all-cause mortality and ≥ 5.6 mg/dl for cardiovascular mortality assessment (Mengozzi et al., 2023). Other studies found that a uric acid value of above 7 mg/dl was most associated with increased cardiac risk, particularly in coronary heart disease (Braga et al., 2016). In general, the definition of hyperuricemia varied across different studies. In some studies, including studies assessed in meta analyses, hyperuricemia was defined as uric acid concentration > 7 mg/dl in men and > 6 mg/dl in women or averaged > 6, 5 mg/dl (G. Huang et al., 2019), in other publications threshold varied form 5.3 mg/dl to 7.7 mg/dl (Braga et al., 2016) or 5.6 mg/dl to 7.0 mg/dl in men and 5.4 mg/dl to 7.0 mg/dl in women (Zuo et al., 2016). Some studies adopted risk stratification in percentage for each increase of 1 mg/dl in serum urate (G. Huang et al., 2019; L. Li et al., 2024; M. Li et al., 2016; Zhong et al., 2017; Zuo et al., 2016). Depending on the study, the findings varied, but consistently and significantly showed an increase in risk for each 1 mg/dl of serum uric acid concentration. Due to the mentioned inconsistencies, it is difficult to explicitly point out the exact threshold used to define hyperuricemia. Although further research might be needed to indisputably set proper cutoff point, as there are publications suggesting that even serum urate concentrations above 5 mg/dl can cause increase in cardiovascular risk, with the risk of some adverse outcomes such as stroke rising significantly over 6 mg/dl, it seems that patients should be observed more strictly when reaching those urate levels in blood serum.

Several studies aimed to assess the influence of uric acid-lowering pharmacotherapy on hyperuricemia and the cardiovascular system. Studies that included SGLT2 inhibitors showed consistent results in decreasing risk of clinically important adverse cardiovascular outcomes, which applied to patients with heart failure, both with reduced and preserved ejection fraction (Doehner et al., 2022, 2024). These results relate to empagliflozin, but studies about dapagliflozin also showed similar results, decreasing the risk of either deterioration or death in heart failure patients with gout, regardless of ejection fraction (Butt et al., 2023). Overall, SGLT2 inhibitors seem to successfully lower serum uric acid levels and improve patients' prognosis in heart failure with concurrent hyperuricemia.

Sadly, this cannot be said about xanthine oxidase inhibitors, as febuxostat or allopurinol. Studies were generally consistent, showing no evident advantages in decreasing cardiovascular risk. Although there is a significant uric acid-lowering ability of these drugs, which is especially related to febuxostat (Butt et al., 2023), the incidence of cardiovascular events, as well as the mortality rate, has not decreased significantly (Kojima et al., 2019; Long et al., 2025). Febuxostat and allopurinol showed generally similar results, as neither has proven to be effective in lowering the rate of cardiovascular mortality (Mackenzie et al., 2024; White et al., 2018). Moreover, some studies have shown a higher mortality for febuxostat than allopurinol (Deng et al., 2024; White et al., 2018). Routine use of allopurinol in order to improve patients' prognosis in ischemic heart disease and prevent cardiovascular death has also been questioned, as there was no evidence of allopurinol achieving such goals (Mackenzie et al., 2024). Available meta-analyses further suggest that there is no significant influence of uric acid-lowering therapy on mortality, especially in heart failure patients (L. Li et al., 2024). Moreover, the evidence even implies the possible increase in mortality risk in heart failure by the use of traditional urate-lowering treatment, as allopurinol or febuxostat (L. Li et al., 2024; Nowak et al., 2024). Research comparing uricosuric agents and xanthine oxidase inhibitors found again no significant benefits in patients receiving drugs; only uricosuric agents showed some benefit - a decrease in natriuretic peptides levels (Xu et al., 2021). There also seems to be no influence of treatment, mainly with febuxostat, on arterial stiffness (Kario et al., 2021). Only a few possible advantages have been found. A potential for lowering morning blood pressure may exist for febuxostat and topiroxostat, and there is a possibility that febuxostat may help to preserve diastolic function in hyperuricemic patients; however, due to limitations of the reporting study, this discovery requires further research (Kario et al., 2021; Kusunose et al., 2022). Additionally, for uric acid-lowering treatment in general, there seems to be evidence suggesting that therapy can decrease the risk of heart failure hospitalization (L. Li et al., 2024).

Limitations

One of the main limitations of this article is the heterogeneity of the included studies, especially regarding the definitions of hyperuricemia, which varied in serum uric acid thresholds. This led to the limiting comparability of the studies and the ability to define a precise cut-off for cardiovascular risk. While the article focuses on high-quality sources such as meta-analyses and randomized controlled trials, some referenced data are based on small sample sizes or subgroup analyses, reducing the strength of the findings. In some studies, there was a predominance of Asian cohorts, which may limit applicability to different populations. Lastly, the article's reliance on freely available full-text studies from PubMed within a 10-year window may have excluded relevant data from other sources or older foundational studies.

Conclusions

In reviewed studies, the evidence has shown that hyperuricemia has been consistently associated with increased cardiovascular risk and adverse cardiovascular outcomes, such as higher all-cause and cardiovascular mortality, increased risk of stroke, atrial fibrillation, and heart failure. Although the exact threshold for defining hyperuricemia varied across studies, evidence suggests that uric acid levels above 5 mg/dl may already elevate cardiovascular risk. The role of uric acid-lowering therapy remains unclear. SGLT2 inhibitors, such as empagliflozin or dapagliflozin, demonstrated cardiovascular benefits and improved prognosis in heart failure patients with hyperuricemia. However, traditional xanthine oxidase inhibitors such as allopurinol and febuxostat, despite high effectiveness in lowering uric acid, did not significantly reduce the risk of cardiovascular events or mortality. Some studies even suggest that traditional uric acid-lowering treatments may increase potential risk. Further research is needed to determine precise uric acid thresholds and optimize treatment strategies.

Disclosure

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In preparing this work, the authors used ChatGPT for the purpose of improving language, grammar, and text formatting. After using this tool, the authors reviewed and edited the text as needed and accept full responsibility for the substantive content of the publication.

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