Role of hyperuricemia in cardiovascular disease and its treatment options: A review article

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Abstract
Cardiovascular disease (CVD) is one of the leading causes of mortality and morbidity worldwide. Several studies highlighted the association of CVD with hyperuricemia. We searched PubMed, EMBASE, Scopus, and DOAJ with the following keywords, including hyperuricemia and cardiovascular disease, to address these topics: (a) Mechanism of hyperuricemia, (b) Relationship of hyperuricemia with cardiovascular disease, (c) Treatment of hyperuricemia.

Keywords: Cardiovascular disease, Uric acid, Hyperuricemia, Oxidative stress, Endothelial dysfunction, Urate-lowering therapy


Introduction
Cardiovascular disease (CVD) is one of the most common causes of mortality and morbidity globally. In 2019, the American Heart Association (AHA) announced that 48% of people over the age of 20 in the United States have CVD, which includes coronary heart disease (CHD), heart failure (HF), hypertension, and stroke (1).

Risk factors for CVD, such as blood pressure, cholesterol, glucose levels, physical activity, body mass index, and diet, have received their due attention (2). Hyperuricemia is one of the potential risk factors for CVD via multiple mechanisms, including endothelial dysfunction induction, oxidative stress, and proinflammatory effects. Uric acid (UA) is one of the end products of the purine cycle. Although there is no universally accepted definition of hyperuricemia, it is typically defined as a serum urate level greater than 6.8 mg/dL. A recent systematic review and meta-analysis demonstrated that hyperuricemia is associated with an increased risk of major cardiovascular events compared to the control group (3).

This review will briefly discuss the UA production pathway and the relation between hyperuricemia and cardiovascular disease, followed by suggested treatment options.

Methods
We searched for articles using the following keywords in the title and abstracts of the articles in PubMed, EMBASE, Scopus, and DOAJ: uric acid, hyperuricemia, cardiovascular disease, heart failure, atrial fibrillation, atherosclerosis, oxidative stress and treatment.

Uric acid production
The liver is the main organ responsible for UA production; however, intestines, kidneys, muscles, vascular endothelium, apoptotic cells, and other organs are all involved in UA metabolism. The purine cycle produces uric acid as a byproduct. Exogenous purine is derived from proteins and fructose catabolism. In contrast, endogenous purine is derived from nucleic acid breakdown during the cell cycle, and the production of UA can be increased by alcohol intake and excessive exercise (4).

Purine synthesis begins with the formation of inosine monophosphate (IMP), which is then converted into hypoxanthine. Hypoxanthine is transformed into xanthine and then into uric acid with the help of the enzyme Xanthine oxidoreductase. There are two types of xanthine oxidoreductase enzymes: xanthine dehydrogenase (XD) and xanthine oxidase (XO). XD is the most common type in the body, whereas XO is a modified version of XD that is strongly expressed in certain physiological and pathological circumstances, resulting in superoxide anion (O2) and hydrogen peroxide (H2O2) production (4).

Atherosclerosis
Atherosclerosis is caused by lipid-based and inflammatory mechanisms, and hyperuricemia accelerates atherosclerosis via multiple mechanisms. Elevated UA level is associated...
Hypertension

Hyperuricemia-related hypertension is caused by a two-stage mechanism. Uric acid causes vasoconstriction in the first phase, which is reversible, by activating the renin-angiotensin system and lowering circulating nitric oxide levels. Secondary arteriolosclerosis develops due to UA being incorporated into vascular smooth muscle cells and the subsequent proliferation of these cells. This is the irreversible phase, during which pressure natriuresis is hindered, resulting in sodium-sensitive hypertension (6).

Several studies showed the relationship between hypertension and hyperuricemia. For instance, a large-scale retrospective cohort analysis in Japan showed hyperuricemia was identified as an independent risk factor for future hypertension development. This connection remained significant after adjusting for age, gender, hypertension, obesity, diabetes, dyslipidemia, current smoking, daily alcohol use, regular exercise, and chronic kidney disease. In addition, the stratified analysis demonstrated that the effects of hyperuricemia on the onset of hypertension were more pronounced in people with CKD than those without CKD (7). A systematic review and meta-analysis was conducted by Grayson et al which stated high blood pressure went up by 13% for every 1mg/dL increase in serum uric acid level (8). The risk was higher for younger people and genders. Based on these numbers, it seems likely that the relationship between serum uric acid levels and high blood pressure is linear. Also, in a randomized trial, uric acid-lowering modalities (e.g., Allopurinol, fruits, vegetables, and exercise) have been shown to lower blood pressure (7).

Cardiovascular disease

Maloberti et al stated that UA could affect the coronary arteries and left ventricle function in the early stages of the disease (9). Hyperuricemia has been proven to be a reliable, independent predictor of cardiovascular death in patients with stable CAD. SUA levels of more than 7.5 mg/dL were connected to a 1.6-fold higher risk of death. Each 1 mg/dL rise in SUA levels was linked to a 31% greater chance of death in the first year in patients with stable CAD who underwent percutaneous coronary intervention (10). According to a study by Liang et al, patients with no signs of coronary artery calcification (CAC) have an increased chance of developing or worsening CAC. If they have hyperuricemia, Analyses demonstrated a nearly 1.5-fold rise in the likelihood of CAC presence (11). Several studies have evaluated the relationship between hyperuricemia and CAD in different ages and gender. Sun et al demonstrated that hyperuricemia and CAD had significant connections only in females (especially in women over 80 years old), but not in males (12). Patients with increased blood uric acid levels (>6.7 mg/dL) had a greater mortality rate than their counterparts in an observational study in Japan. In the same way, patients with chronic coronary syndrome who had a serum uric acid level of more than 6.5 mg/dL had a higher risk of target lesion revascularization after stent implantation (13).

Studies of different ages and genders are recommended to achieve an accurate cut-point assessment of the level of UA in both men and women of different ages in acute or chronic CAD. Following research, it may be possible to use SUA levels as a readily observable biomarker for ACS or stable CAD patients to monitor for unfavorable outcomes. According to meta-analysis research by Kim et al, each additional 1 mg/dL of SUA levels increases cardiovascular mortality by up to 12% in individuals with coronary artery disease (CAD), especially in women (14).

Atrial fibrillation

Worldwide frequency and incidence of atrial fibrillation (AF) have gradually increased, substantially impacting related morbidity and death. These findings have consequences for public health policy and healthcare expenses. Based on the number of people with AF, systematic, global surveillance of AF is needed to make effective prevention and treatment plans (15).

Wang et al, in a meta-analysis study, found serum uric acid (SUA) was strongly linked to AF, and SUA levels went up as AF lasted longer. SUA was significantly higher in people with persistent AF (16). Additionally, the prospective Cohort study showed hyperuricemia is a sign of decreased ejection fraction (EF) in those with AF.
who have normal renal function. The connection between UA and EF is unaffected by renal function or the use of common HF medicines like diuretics. To predict an EF of less than 40%, 6.69 mg/dL of UA concentration was the cut-off point for higher UA concentrations (17).

Heart failure
In both clinical and public health terms, HF is an enormous concern. At five and ten years after HF diagnosis, the estimated survival rates are 50% and 10%, respectively. Despite improvements in reducing HF-related mortality, hospitalizations for HF are still common, and readmission rates are rising. To prevent hospitalizations, a complete characterization of readmission predictors in HF patients is required. In patients with chronic HF, hyperuricemia is an independent predictor of all-cause mortality. All-cause mortality, HF hospitalization, and the composite endpoint of HF hospitalization appear to be better predicted by the combination of UA and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (18).

It appears that treatment with low doses of Allopurinol does not enhance the prognosis of HF patients in acute HF, and even patients with SUA ≥500 μmol/L treated with a low dose of allopurinol had a poorer prognosis than the untreated group in acute HF (19).

Treatment
Management of hyperuricemia is determined by various factors, including the presence of symptoms, the severity of hyperuricemia, and evidence of other comorbidities. The risk-to-benefit profile should be considered in the treatment of asymptomatic hyperuricemic patients. Occasionally, hyperuricemia is a side effect of medications such as thiazides or loop diuretics, which can be resolved quickly by discontinuing them. Regarding medication management for hyperuricemia, two classes of drugs are commonly used, including uricosurics (e.g., allopurinol and febuxostat) and uricosurics (e.g., probenecid, benz bromaron, and lesinurad). Uricostatic medications decrease the production of UA by inhibiting the xanthine oxidase enzyme. Whereas uricosuric drugs enhance renal excretion of UA by targeting renal tubules and blocking UA reabsorption (20). Uricosuric medications are more available and have been reported to be more effective than uricosurics.

Many studies have been conducted to evaluate the CVD effect of different lowering serum urate drugs. For instance, according to a network meta-analysis, allopurinol treatment for hyperuricemia in patients with HF can mitigate the adverse effects of prolonged hyperuricemia while not being associated with a lower risk of mortality compared to leaving hyperuricemia untreated (21). In a multicenter randomized controlled trial, Suzuki et al. concluded that individuals with chronic HF and hyperuricemia might benefit more from febuxostat than Allopurinol (22). In contrast, White et al. stats that all-cause mortality and cardiovascular mortality were higher with febuxostat than with allopurinol (23).

Recently, a comparison was made between topiroxostat as a novel xanthine oxidoreductase inhibitor and Allopurinol. Interestingly, topiroxostat did not exhibit significant advantages over allopurinol in patients with CHF and HU. However, topiroxostat may be preferable to allopurinol in HF with reduced ejection fraction (HFrEF) patients due to its possible benefits in lowering left ventricular end-diastolic pressure, preventing aggravation of oxidative stress in the proximal renal tubule, and renoprotection (24).

Uricostatic agents have shown metabolic benefits as well. Allopurinol may reduce systemic inflammation and improve insulin resistance in patients with asymptomatic hyperuricemia. In patients with non-alcoholic fatty liver disease (NAFLD), treatment with allopurinol for three months significantly improves serum levels of transaminases, cholesterol, and triglycerides (25).

U.A.-lowering medications, especially uricosurics, can be beneficial in preventing cardiovascular disease. A retrospective study reported hypertensive adults who received allopurinol had less incidence of cardiovascular events (26). Several studies showed treatment with Allopurinol in patients with congestive heart failure (CHF) leads to improvement in endothelial dysfunction, peripheral vasodilator capacity, and blood flow. In patients with CAD, treatment with a high dose of allopurinol can reduce vascular oxidative stress and decrease mortality (27).

Uricosuric medications were shown to decrease serum uric acid levels and improve insulin resistance, but they do not improve hemodynamic parameters (e.g., heart rate, blood pressure, and left ventricular EF) (28).

The superiority of uric acid medications in comparison with uricosuric agents can be justified by their role in declining intracellular uric acid levels and decreasing vascular oxidative stress. While uricosuric agents only affect urate transport without any effect on the pro-oxidative system (29).

It is recommended to start the treatment at a low dose and titrate up as tolerated to get to the target serum uric acid levels. Clinical providers should be aware of the potential side effects of UA-lowering medications and always consider these medications’ risk/benefit profiles, especially when treating asymptomatic patients. The adverse reactions of allopurinol range from mild dermatitis to severe and life-threatening reactions like Stevens-Johnson syndrome (30). Based on the CARES trial and in the post-marketing experience, febuxostat has been reported to be rarely associated with sudden cardiac death (23).

Conclusion
Overtreatment can drive to abnormally low SUA, termed hypouricemia (defined as serum uric acid level less than

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or equal to 2.0 mg/dL). Hypouricemia augments lipid peroxidation by loss of antioxidant capacity of plasma; therefore, “the lower, the better” does not apply to serum uric acid levels.

**Authors’ contribution**

Conceptualization: AP, FK.
Methodology: AP, FK.
Validation: SB, BB.
Formal Analysis: BB, SVR, KTR.
Investigation: PY.
Resources: PY.
Data Curation: PY, FK.
Writing—original draft preparation: PY, AP.
Writing—review and editing: AP, FK, SB
Visualization: FK.
Supervision: AP, SB.
Project administration: PY.
Funding acquisition: SVR, KTR.

**Conflicts of interest**

The authors declare that they have no competing interests.

**Ethical issues**

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**References**


25. Salama SSSOABSH, Mokhles MA. Assessment of the therapeutic effect of allopurinol on patients with non-alcoholic fatty liver disease associated with hyperuricemia by cytokeratin 18. J Gastrointest Dig Syst. 2016;06. doi: 10.4172/2161-069X.C1.044.


