Hyperuricemia and Cardiovascular Disease

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Uric acid (UA), the metabolic mediator of gout and urate renal stones, is associated with increased cardiovascular risk burden. Hyperuricemia is a common metabolic disorder, and interaction among UA and cardiovascular diseases has been clearly described. Several illnesses, including hypertension, myocardial infarction, metabolic syndrome, and heart failure, are related to increases in UA levels. In this article, we discuss the pathophysiology of hyperuricemia and describe the biologic plausibility of this metabolite's participation in the pathogenesis of cardiovascular illness. We conclude by discussing the implications of lowering plasma UA concentrations to reduce the risk of cardiovascular events, including myocardial infarction, stroke, heart failure, and cardiovascular death.

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KEY WORDS

Hyperuricemia • Uric acid • Inflammation • Cardiovascular disease • Risk

The association between elevated uric acid (UA) levels and cardiovascular disease has been known for almost 50 years.[1] Hyperuricemia is a common metabolic disorder. It is reported to affect approximately 5% of the general population and more than 25% of hospitalized patients.[2,3] Plasma UA concentration is established by a balance among food intake, endogenous purine degradation, and the elimination of UA by the bowel and kidney. Cellular turnover provides a large number of

nucleic acids, which are involved in the metabolism of UA. The human body partially recycles nitrogen bases and the excess is removed as urate. UA levels can also increase with the intake of high-protein and fructose-rich foods.

Fructose must first be phosphorylated in the liver to be metabolized. Phosphorylation is achieved through the hydrolysis of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and inorganic phosphate (P_i). This process thus consumes ATP and depletes the concentration of P_i in the liver, driving the hydrolysis reaction forward. The accumulated ADP then serves as a substrate for a catabolic pathway that results in the formation of UA.[4,5] ADP is further hydrolyzed into adenosine monophosphate (AMP) and P_i. AMP can then undergo a deamination to form inosine monophosphate, which is then dephosphorylated into inosine, or AMP can be dephosphorylated to form adenosine, which then undergoes deamination to form inosine.[6] Adenosine and inosine are intermediates in the formation of UA.

Adenosine reacts with purine nucleoside phosphorylase to form adenine, which then undergoes deamination to form hypoxanthine, whereas inosine directly reacts with purine nucleoside phosphorylase to form hypoxanthine.[6] Xanthine oxidase (XO) converts hypoxanthine to xanthine and further converts xanthine to UA.[6] Reactive oxygen species (ROS) are created during this conversion. The main players of this molecular rearrangement are urate transporter 1—predominantly expressed in the apical domain of renal tubular epithelium—and glucose transporter 9 (GLUT9) carriers—expressed in the basolateral domain. Minor evidence exists for the other two conveyors, organic anion transporter 1 and organic anion transporter 3.[3,7,8] Figure 1 illustrates the biochemical pathways associated with the degradation of purines to UA.

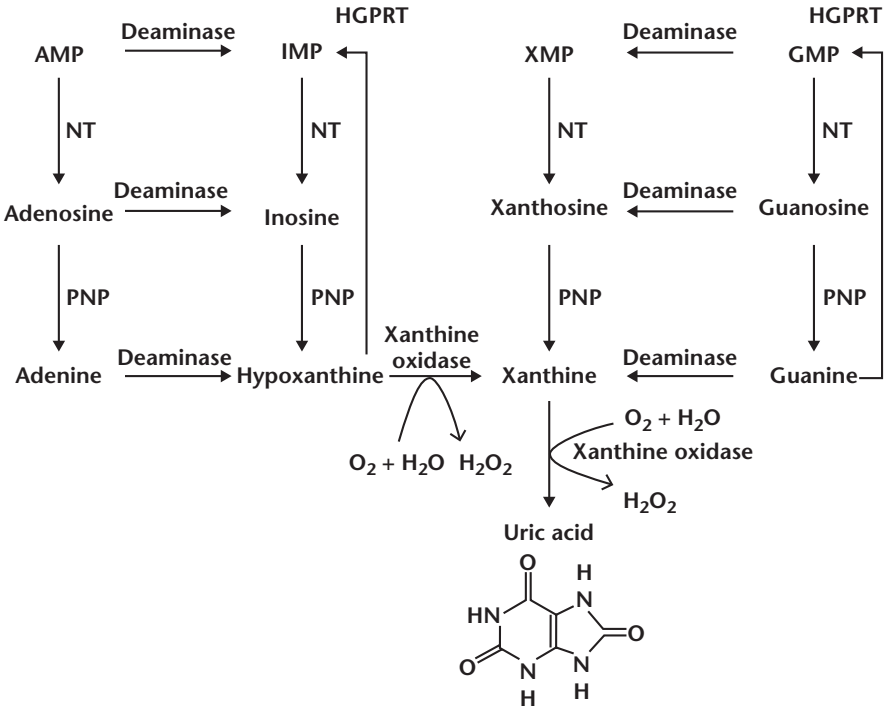

Figure 1. Purine metabolism results in the production of uric acid. The enzyme deaminase converts adenine to hypoxanthine. The enzyme xanthine oxidase then converts hypoxanthine to xanthine and xanthine to uric acid. AMP, adenosine monophosphate; GMP, guanosine monophosphate, HGPRT, hypoxanthine-guanine phosphoribosyltransferase; IMP, inosine monophosphate; NT, nucleotidase; PNP, purine nucleoside phosphorylase; XMP, xanthosine monophosphate. Reprinted with permission from Jin M et al.[6]

A total of 25% of UA clearance occurs in the intestine and 75% of UA is eliminated via the kidney. The renal process can be divided into four stages: glomerular filtration, early tubular absorption, tubular secretion, and postsecretory tubular reabsorption. Under normal physiologic circumstances, only 5% to 10% of the filtered UA is excreted by the kidneys.[7] Many factors modulate the reabsorption of UA in the proximal tubule of the kidney. Low intravascular volume and Na^+ concentration of ultrafiltrate increase tubular reabsorption, angiotensin II reduces the secretory processes, and norepinephrine increases serum UA level by changing the distribution of renal blood flow.[9] Therefore, hyperuricemia may result from an increased production of UA or by an altered renal and bowel excretion, or by the combination of both mechanisms. Reduced excretion of UA in the urine is the more prevalent etiology of hyperuricemia, responsible for 90% of cases.[10]

Role of Monosodium Urate Crystals and Inflammation in Gout and Cardiovascular Diseases

A clinical consequence of hyperuricemia is the development of gouty arthritis, an excruciatingly painful condition characterized by severe inflammation of the joints and surrounding tissues. Patients with UA concentrations >8.0 mg/dL can deposit as monosodium urate (MSU) crystals in articular joints and bursal tissues.[11] Many studies have demonstrated that the nascent inflammatory response arises as the macrophages that reside within the joint space phagocytose MSU crystals.[11] Once these crystals have been engulfed by the macrophages, they engage with pathogen recognition

and toll-like receptors that trigger a pathway leading to the development and activation of the nod-like receptor pyrin domain 3 (NLRP3) inflammasome protein complex.[11] This complex then activates caspase-1 and causes the release of interleukin (IL)-1β, a proinflammatory cytokine.[11] IL-1β, other proinflammatory cytokines, tumor necrosis factor-α, IL-6, and IL-8 stimulate the inflow of neutrophils, which is known to be the primary step in the pathogenesis of gout.[12] Recruited neutrophils are responsible for the eventual deterioration of the affected joints and cartilage through their extracellular release of detrimental reactive mediators such as proteolytic enzymes, chemokines, cytokines, ROS, and prostaglandin E_2.[13,14]

As previously discussed, the activation of inflammasomes results in caspase-1 release by immune cells and activation of IL-1β, a proinflammatory cytokine. Van der Heijden and colleagues[15] studied the effect of selectively inhibiting the NLRP3 inflammasome protein complex using MCC950 to limit the atherosclerotic lesion development in apolipoprotein E knockout mice. The targeted inhibition of the NLRP3 inflammasome using the MCC950 treatment resulted in a significant decrease in the development of atherosclerotic lesions in these murine models, as indicated by measurements of the plaque volume, average plaque size, and maximal stenosis.[16]

Previous investigations have demonstrated that cholesterol crystals, like MSU crystals, also activate the NLRP3 inflammasome protein complex, which results in the release of IL-1β.[16] An inflammation pathway is thus triggered. IL-1β induces IL-6,[17] causing the liver to engage in an acute-phase response.[18] As many clinical investigations have elucidated, the C-reactive protein that is formed during an acute-phase response is a biomarker for a risk of developing acute cardiovascular events.[19] The induced inflammation causes a remodeling of the arterial wall and destabilizes atherosclerotic plaque.[20] Figure 2 illustrates the role of the NLRP3 inflammasome in gout, atherosclerosis, and heart failure (HF).

Role of Hyperuricemia in Metabolic Syndrome

Metabolic syndrome is characterized by the presence of abdominal obesity associated with at least two of the following conditions: hypertriglyceridemia, low high-density lipoprotein cholesterol level, hypertension, increased levels of fasting glucose, or insulin resistance. Patients with metabolic syndrome are at a high risk for developing cardiovascular diseases.[21,22] Increased UA levels are often associated with metabolic syndrome, but it is unknown whether this condition is merely a consequence of metabolic dysfunction or a causal factor in the development of cardiovascular diseases.[23]

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Hyperuricemia and hyperinsulinemia are often concomitant. An increase in UA levels precedes insulin resistance in diabetic subjects. Otherwise, insulin reduces renal UA secretion by distal tubular reabsorption. Renal clearance of urate is inversely related to insulin resistance.[24,25] A possible explanation for this is that hyperuricemia prevents pulmonary arterial endothelial cells from relaxing by reducing the propagation of nitric oxide (NO) in these cells. The consequent vasoconstriction leads to reduced glucose uptake in peripheral tissue, particularly in skeletal muscles.[26] A second hypothesis considers the effects of UA on adipocytes, in which prothrombotic and proinflammatory factors are overexpressed and negatively modulate the expression of peroxisome proliferator-activated γ receptors. Thus, the physiologic activity of peroxisome proliferator-activated γ receptors regarding the capture of polyunsaturated fat from circulation and subsequent uptake by adipocytes is altered. Insulin sensibility mediates this process.[27]

Hyperuricemia is also associated with obesity. UA can affect adipocytes by inducing the up-regulation of proinflammatory factors such as the adipokine monocyte chemoattractant protein-1 and the down-regulation of the production of an insulin sensitizer and anti-inflammatory factor adiponectin, mimicking the effects seen in obesity.[28] Lowering UA levels using allopurinol in mice with metabolic syndrome and hyperuricemia improved the proinflammatory endocrine imbalance in the adipose tissue, decreased macrophage infiltration of the adipose tissue, and decreased insulin resistance.[29]

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Hyperuricemia may also play a role in the pathogenesis of hypertension. A recent meta-analysis reported an association between hyperuricemia and hypertension, independent of other risk factors for hypertension. A 13% increase in the

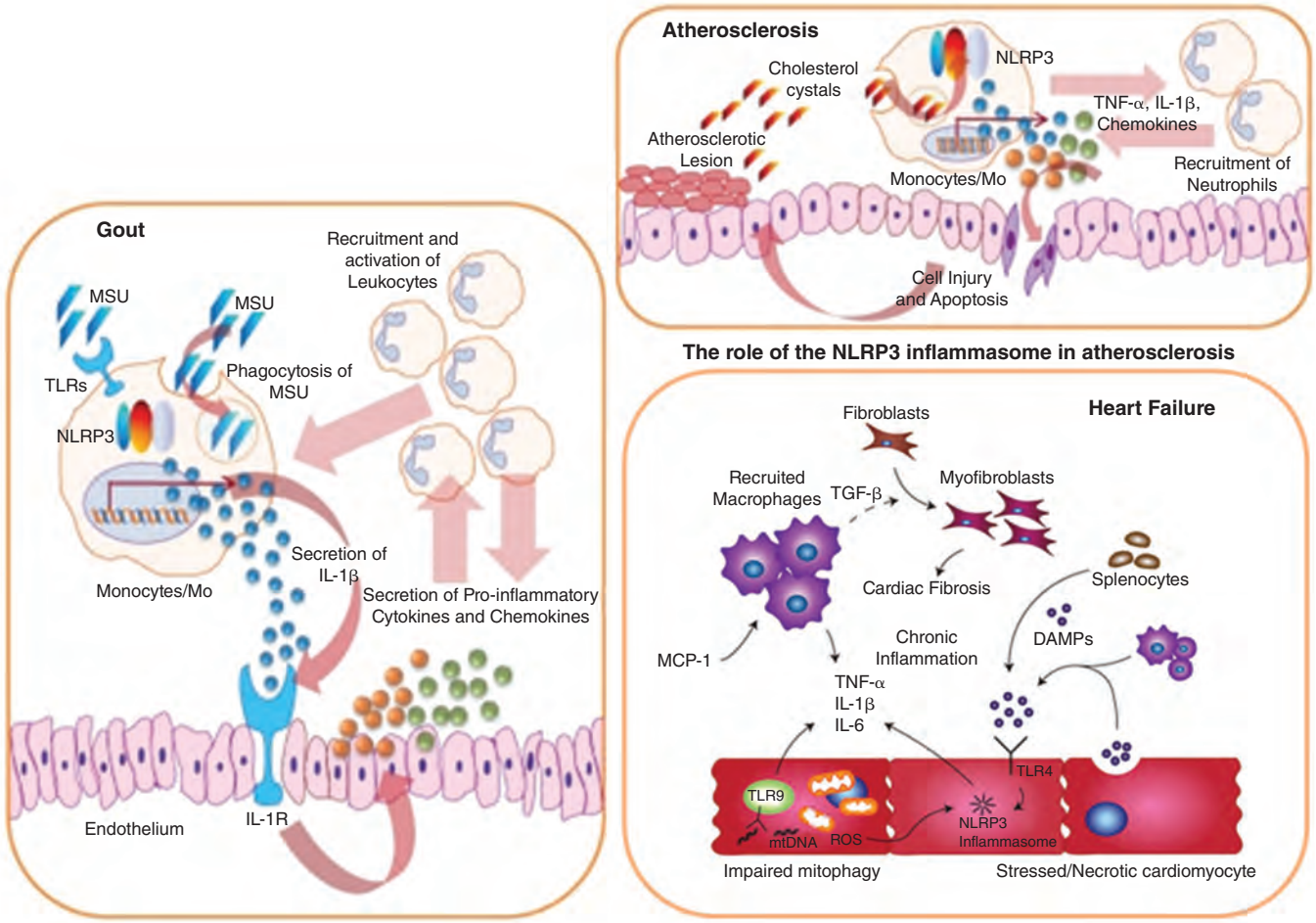

Figure 2. The NLRP3 inflammasome is associated with several diseases, such as gout, atherosclerosis, and heart failure. Gout progresses as monosodium urate crystals become phagocytosed by macrophages, engage with receptors (such as TLRs), and activate the NLRP3 inflammasome. This eventually results in the release of the proinflammatory cytokine IL-1β, which acts with other factors to stimulate the influx of leukocytes (neutrophils) into the affected area. These neutrophils further facilitate the secretion of proinflammatory cytokines and chemokines. Atherosclerosis progresses as the cholesterol crystals present within atherosclerotic lesions trigger the NLRP3 inflammasome present within macrophages, inducing inflammation and cell infiltration. This cascade of inflammation results in the aggregation of extracellular lipids, which leads to cell injury and/or death, and an increase in the advancement of atherosclerosis. Inflammatory cytokine expression in chronic heart failure may result from multiple mechanisms. Cardiomyocyte activation may occur in response to DAMPs present in the extracellular space that are released by stressed or necrotic cardiomyocytes, immune cells (such as macrophages), or splenocytes. Response to DAMPs includes TLR signaling to activate the NLRP3 inflammasome via TLR4 in chronic heart failure; this gives rise to proinflammatory cytokine release. The NLRP3 inflammasome may also be activated by ROS, as is the case with diabetes. States of inflammation perpetuate macrophage enlistment via MCP-1, which can further increase the amount of cytokines released. Cardiac macrophages are also known to enlist and differentiate myofibroblasts, pushing cardiac fibrosis forward during chronic heart failure (perhaps TGF-β dependent, but this is not definitively known). DAMPs, damage-associated molecular patterns; IL-1R, interleukin-1 receptor; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; MSU, monosodium urate, NLRP3, nod-like receptor pyrin domain 3; ROS, reactive oxygen species; TGF-β, transforming growth factor-β; TLR, toll-like receptor; TNF-α, tumornecrosis factor-α. Data from Dhanasekar C et al,[11] Sabina EP et al,[13] Kodithuwakku ND et al,[14] Yang CS et al,[95] and Dick and Epelman.[96]

risk of an incidence of hypertension was reported per 1 mg/dL increase in serum UA level. There was a linear relationship between UA levels and hypertension with no cutpoint or threshold. This correlation was more prominent in young individuals and women.[29] Potential mechanisms linking hyperuricemia and the development of hypertension include NO and renin-angiotensin pathways.[30,31] The lack of NO available in pulmonary arterial endothelial cells due to a cellular state of hyperuricemia induces the vasoconstriction, a causal factor associated with hypertension. UA is also reported as an independent risk factor for a decrease in renal functioning and end-stage renal disease.[32,33]

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A possible explanation of the extent of the effect of hyperuricemia in hypertension and impaired renal functioning was explained in a study on rats: hyperuricemia causes glomerular hypertension and thickening of vascular walls, which leads to obliteration of lumen of the preglomerular vessel, which in turn results in arterial hypertension.[34] This is significant due to the role that glomerular hemodynamic modifications play in the genesis and advancement of renal disease.[35]

Ruggiero and associates[35] reported a greater prevalence of inflammatory markers, including high levels of C-reactive protein and IL-6 in individuals possessing high UA levels in the elderly group they studied, suggesting that UA might contribute to the proinflammatory state that characterizes many chronic diseases typical of old age.[35] Finally, UA has a mitogenic effect on vascular smooth muscle cells, which suggests that production of UA following an arterial injury such as ischemia/reperfusion can contribute to atherogenesis and intimal proliferation.[36]

Role of Hyperuricemia in Coronary Disease

Although the association between cardiovascular risk and UA has been explained and data suggest that the incidence of cardiovascular events is linearly related to UA level,[37] some studies, including the Framingham Heart Study[38] and the Atherosclerosis Risk in Communities (ARIC) study,[39] did not confirm this association. Conversely, the Multiple Risk Factors Intervention Trial (MRFIT)[40] and Rotterdam study[41] have reported an increased risk of coronary artery disease (CAD) in patients with hyperuricemia after adjustment for traditional risk factors. In consensus with the latter data, a large prospective study from Taiwan found that hyperuricemia is independently associated with CAD development, even in patients with a low metabolic risk profile.[42] The increased risk appears to be more pronounced in women, as indicated by a 12% increase in their mortality per year.[43]

Several single-center studies investigated the various associations that occur between UA and CAD. In a retrospective study comparing different laboratory biomarkers, Baumann and associates did not find a correlation between major adverse cardiac events and UA level.[44] In another report, it was found that, although UA levels were related to antioxidant capacity and coronary vessel disease severity, hyperuricemia per se, in a multivariate model, did not add new prognostic insight beyond traditionally measured risk factors.[45] Conversely, Lazzeri and colleagues[46] reported a prognostic role for UA regarding in-hospital mortality in patients admitted with acute ST-elevation myocardial infarction (MI) who were treated with percutaneous coronary intervention (PCI). In a cohort study of more than 5000 patients with acute coronary syndrome who underwent PCI, hyperuricemia was shown to be an independent predictor of 1-year mortality, but high levels of UA did not predict the occurrence of nonfatal MI or stroke or the necessity for revascularization 1 year after PCI.[47]

Zuo and coworkerss[48] conducted an updated meta-analysis that demonstrates that hyperuricemia is related to a modest but statistically significant increased risk of all-cause mortality and coronary heart disease (CHD). The analysis revealed that for every 1 mg/dL-increase in serum UA, an individual's overall risk of all-cause mortality increased by 9% and his or her risk of developing CHD increased by 20%.[49] Their sex-based subgroup analysis indicated that hyperuricemia increased women's risk of CHD mortality (compared with men), as well as all-cause mortality.[49] White and associates[49] performed Mendelian randomization analyses to study the effect of plasma UA concentration on CHD. The conventional Mendelian randomization analysis that they conducted suggested a causal role of UA in the development of CHD, but the researchers acknowledged that this could be due to the distortive effects of hidden pleiotropy.[50] To address this possibility, the researchers executed a multivariate and Egger Mendelian randomization analysis (which adjusts for pleiotropy).[50] These analyses revealed that UA has a minimal, if any, causal role in CHD (the confidence intervals for both analyses included the null).[50] Such evidence suggests that future research should further consider the pleotropic and confounding effects possibly present in order to establish a definitive conclusion regarding the role of UA in the development of CHD.

Extracellular UA has a protective role through its reduction of oxidative stress, whereas UA is destructive in the intracellular space. When integrated into blood circulation, UA is an antioxidant. UA also acts as a vehicle for NO, so it aids in decreasing vascular tone while increasing blood flow and protecting vascular endothelial cells from external oxidative stress. When UA enters the endothelium or a myocyte, or is produced as a terminal metabolite of purine degradation, it turns into a potent pro-oxidant. Degradation of xanthine to UA by XO generates ROS, such as $O2^-$ and hydrogen peroxide. $O2^-$ interacts with sarcolemma and mitochondria membranes, which may lead to cardiac dysfunction. It also reduces NO bioavailability, causing endothelial dysfunction through vasoconstriction.[27,50,51] Overall, UA-related endothelial dysfunction appears to be more impactful than UA extracellular antioxidant abilities.[52]

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Role of Hyperuricemia in Heart Failure

Many studies have revealed a connection between increased UA levels and increased HF symptoms, according to the New York Heart Association (NYHA) functional classification system, including reduced exercise tolerance, systemic congestion, and decreased cardiac function.[53-55] Moreover, current evidence suggests that UA could be both an indicator of poor prognosis and a potential determinant in the pathogenesis of HF.[55,56] Hyperuricemia is correlated with a higher risk of development of HF, as well as an unfavorable outcome in patients who already have HF. A recent meta-analysis showed that, for every 1 mg/dL-increase in serum UA, the odds of developing HF increase by 19% and the risk of all-cause mortality increases by 4%.[57]

Amin and associates[58] found a significant correlation between UA levels and the severity of the clinical signs of HF, NYHA class, levels of mean pulmonary arterial pressure, and pulmonary capillary wedge pressure. Another study reported that UA levels are associated with a more impaired right ventricular systolic function and reduced left atrial function in patients with newly diagnosed HF.[59] Hyperuricemia is also associated with diastolic dysfunction in chronic HF.[60]

Although the positive statistical relationship between increased UA levels and chronic HF is known, the clinical and prognostic role of increased levels of UA in acute settings remains controversial and needs to be clarified. Our group recently found a strong association between increased UA levels and risk of death and rehospitalization during the 6-month follow-up period in patients hospitalized for acute HF.[61] Post-hoc analysis of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial revealed a significant correlation between high serum UA levels and NYHA functional class.[62]

Because most HF patients with hyperuricemia have some degree of renal dysfunction, it remains undetermined whether UA plays an active role in this disease's development and progression, or if it is just a marker of other metabolic processes and chronic kidney disease. In these patients, hyperuricemia may result from an increased production of UA, an altered excretion of UA, or by the combination of both mechanisms.[55-57] In other words, the pathogenesis of hyperuricemia may depend on the amplified activity of XO, resulting from reduced tissue perfusion and an altered metabolic state, or it may depend on an increase in the renal tubular reabsorption processes. A combination of these two biochemical factors could possibly be the cause. The second hypothesis was supported by Pascual-Figal and colleagues.[63] Their study revealed that patients with more elevated UA levels had more severe renal dysfunction. Nevertheless, our findings and another two reports concerning patients with both acute and chronic HF did not confirm a significant association between the prognostic role of UA and renal dysfunction.[57,62,63] Thus, increased XO action can be considered the trigger for potentially harmful processes such as increased cytokine levels, endothelial dysfunction, apoptosis, and energetic alterations in myocardial cells.

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Cardiovascular Benefits of Treating Hyperuricemia

Xanthine Oxidase Inhibitors

Various investigators have studied cardiovascular endpoints using the treatment of hyperuricemia, yet it remains controversial whether the cardioprotective effects of UA therapy are due to an effective antioxidant capability or due to the improvement of the metabolic profile. The most utilized drugs are XO inhibitors such as allopurinol, oxypurinol, and febuxostat. The role of allopurinol in improving the metabolic profile was reported in a recent meta-analysis in which the drug was noted to decrease creatinine and blood pressure in hyperuricemic patients.[64] It has been shown that allopurinol treatment is associated with a decreased cardiovascular risk among hyperuricemic patients.[65] In a canine model, allopurinol did not limit the infarct size in induced MI.[66] However, the intravenous administration of allopurinol before a coronary bypass demonstrated an improved cardiac function. This effect was likely facilitated by protection against free radical–mediated injury.[67] In a more recent randomized study, allopurinol improved ischemic threshold as well as electrocardiographic signs in subjects with chronic stable angina. During a standard exercise test, administration of high-dose allopurinol resulted in the prolongation of the time to ST depression or angina together with an improvement of the total exercise time and ischemic threshold.[68]

Trials are ongoing comparing the effects of allopurinol and febuxostat with a placebo to better understand the role that these drugs can play in cardiovascular endpoints.[69,70] Active therapy has provided mixed results regarding HF. Although recent reports have raised the possibility of preventing HF using UA-lowering therapy, the literature contains

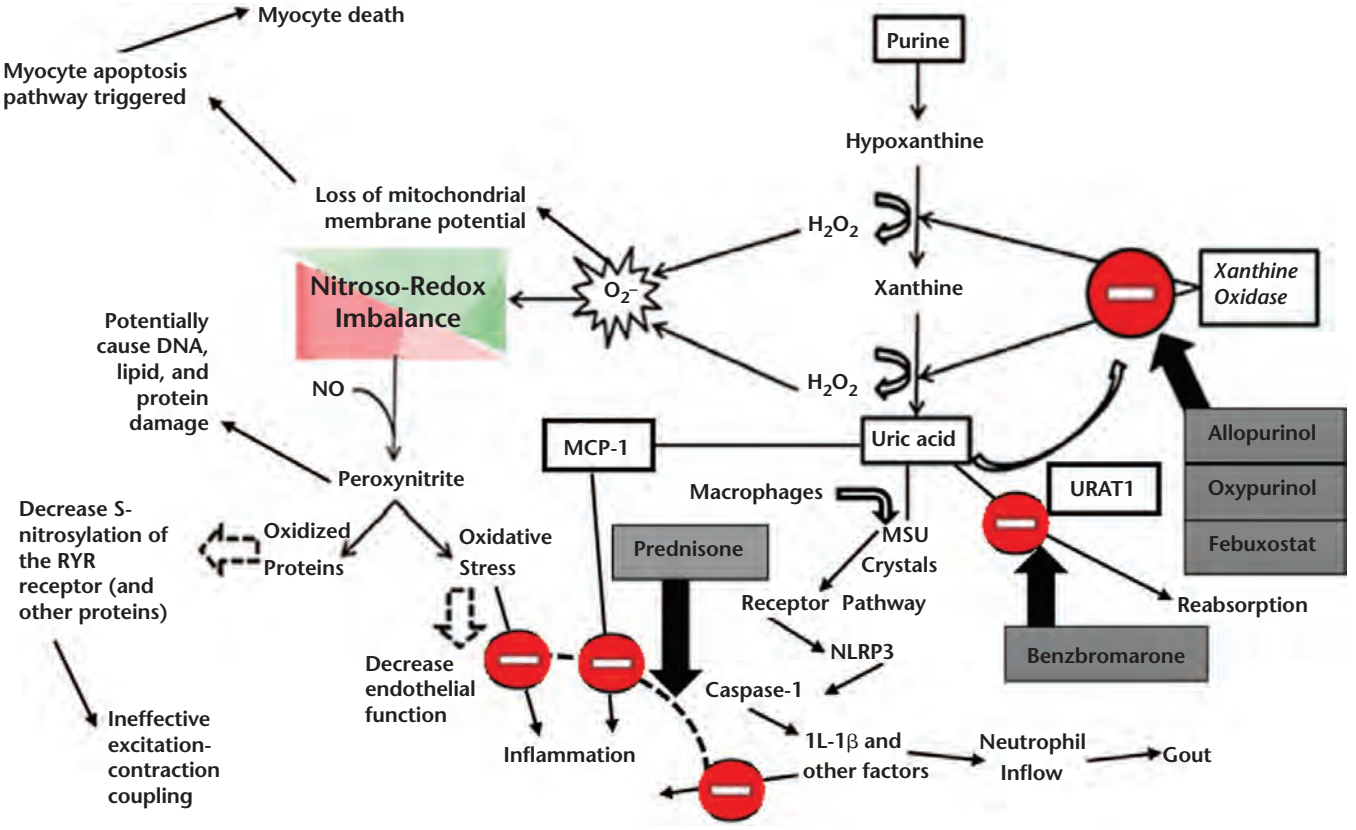

Figure 3. ROS are byproducts of purine metabolism and can contribute to nitroso-redox imbalance. Allopurinol, oxypurinol, and febuxostat inhibit XO and decrease formation of ROS. Benzbromarone inhibits URAT1, decreasing UA reabsorption and promoting UA excretion. Prednisone is used to treat the joint inflammation associated with gouty arthritis. H_2O_2, hydrogen peroxide; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MSU, monosodium urate; NLRP3, nod-like receptor pyrin domain 3; NO, nitric oxide; O_2^-, superoxide ion; ROS, reactive oxygen species; RYR, ryanodine receptor; UA, uric acid; URAT1, urate transporter-1; XO, xanthine oxidase. Reprinted with permission from Karantalis V et al.[97]

conflicting results regarding whether the reduction in UA will result in a significant clinical benefit.[71] In a randomized placebo-controlled trial, Gavin and Struthers[72] found that allopurinol did not improve exercise tolerance in HF, despite decreasing B-type natriuretic peptide (BNP) levels.[72] As a surrogate measure, BNP reflects left ventricular (LV) wall tension and increased intravascular volume.[73] The La Plata study[74] found that the use of oxypurinol did not change LV systolic function in an entire cohort of HF patients; however, it increased the LV ejection fraction (LVEF) by approximately 7% in patients exhibiting a baseline LVEF ≤40%. Another uricosuric agent, benzbromarone, had no significant effect on BNP levels, LV function, or NYHA class, suggesting no clinical benefit in LV dysfunction.[75] Other studies showed endothelium-dependent vasodilation improvement after allopurinol or oxypurinol therapy in patients with CAD and chronic HF. One possible explanation is that XO inhibition leads to an improved energetic efficiency, cardiac remodeling, LVEF, and peripheral perfusion.[76-78]

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Lastly, the emerging selective XO inhibiting agent febuxostat has been tested in patients with mild to moderate renal impairment and early-stage chronic HF patients. The cardiovascular safety profile and effects of this drug compared with allopurinol are currently being studied in two prospective, randomized intervention trials enrolling subjects with high cardiovascular risk.[71,79] Figure 3 illustrates the role of these drugs in the treatment of hyperuricemia, as well as the adverse effects of free radical species (produced by purine metabolism) in the cardiovascular system.

Sodium-glucose Cotransporter 2 Inhibitors

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a group of medications used in the treatment of type 2 diabetes. Dapagliflozin, empagliflozin, and canagliflozin are the SGLT2 inhibitors approved by the US Food and Drug Administration for use in the United States. From this SGLT2

group, ipragliflozin, luseogliflozin, and tofogliflozin were approved for use in Japan.[80] Chino and coworkers[81] used luseogliflozin to study the mechanism of the UA-lowering effect of SGLT2 inhibitors. They noticed a negative correlation between changes in the serum UA level and the urinary excretion rate of UA after administration of luseogliflozin. An increase in the urinary excretion rate of UA was positively correlated with an increase in the urinary excretion of D-glucose. They suggested that the UA-lowering effect of SGLT2 inhibitors can be attributed to the glycosuria that they cause. Glycosuria is the result of the effect that SGLT2 inhibitors have on the GLUT9 isoform 2, which is known to exchange glucose for UA, or any other transporter in the renal proximal tubules, and may inhibit UA reabsorption mediated by GLUT9 isoform 2 at the collecting ducts of the renal tubules.[82]

Post hoc analysis of pooled data from four placebo-controlled, phase 3 studies evaluated the effect of canagliflozin on serum UA levels in patients with type 2 diabetes and in a subgroup of patients with hyperuricemia. Canagliflozin was reported to decrease serum UA levels in diabetic patients (~13% reduction in UA level), including a subset of patients with hyperuricemia. More patients in the hyperuricemic group (20%-30%) achieved serum UA $<$6 mg/dL with canagliflozin.[82] Neal and coworkers[83] assessed the cardiovascular outcomes associated with treating patients with canagliflozin by analyzing the combined data from the Canagliflozin Cardiovascular Assessment Study (CANVAS) and the CANVAS Renal-Endpoints (CANVAS-R) trial. A consequentially lower number of patients treated with canagliflozin (in comparison with placebo) had a primary outcome event (defined as the composite of nonfatal MI, nonfatal stroke, or death from cardiovascular causes).[84] Patients that were treated with canagliflozin were also at a lower risk for HF hospitalization.[84]

Zinman and colleagues[84] noted a small reduction in the serum UA level of patients with type 2 diabetes who received empagliflozin during the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial. Administration of empagliflozin in addition to standard treatment resulted in a lower rate of death from cardiovascular causes, modest weight loss, and a decrease in systolic and diastolic blood pressure.[85] Additionally, empagliflozin treatment led to a considerably lowered risk of HF hospitalization.[85] Taken together, these reports show a reduction of total cardiovascular mortality related to better glucose metabolism by the use of SGLT2. Despite the current results, the specific role of these drugs in UA homeostasis and the consequent clinical impact remain unknown. These aspects need to be better evaluated by detailed study protocols and Trials. Figure 4 summarizes the results of clinical trials that tested the cardiovascular effects related to the treatment of hyperuricemia.

Hyperuricemia as a Novel Marker for Atrial Fibrillation Risk

Recent reports showed circulating UA that is the hallmark of gout is associated with the development of atrial fibrillation (AF). Hyperuricemia was also reported to be an independent risk factor for ischemic stroke in patients with permanent AF. However, all the studies reporting a positive relationship investigated hospitalized patients with high cardiovascular risk burden.[85-87] Many subjects had associated diseases such as hypertension, diabetes, HF, and metabolic syndrome.

In their 2011 study, Tamariz and Hare[88] retrospectively reviewed 15,382 hospitalized subjects who were followed over a 17-year period; they found that elevated serum UA levels at enrollment were associated with a greater risk for incident AF. In adjusted Cox proportional hazards models, the hazard ratio of AF associated with a standard deviation increment in serum UA was 1.16 (95% CI, 1.06-1.26). This difference was more pronounced in black subjects and women.[88] Elevated UA levels are also associated with endothelial dysfunction, metabolic syndrome, and diabetes.[89]

The association of UA, diabetes, and increased arrhythmic risk has been reported in two recent studies: in a 4-year study of hospitalized patients, among 29% patients having hyperuricemia, 11% showed persistent or permanent AF, and a significantly greater prevalence of AF overall (20.6% vs 7.1% in patients without hyperuricemia; $P <.001$).[90]

A longer study followed a cohort of 400 outpatients with type 2 diabetes with no AF at baseline and revealed that the cumulative incidence of AF was 10.5%. Elevated serum UA was associated with an increased risk of AF, with an unadjusted odds ratio of 2.43.[91] Finally, in the meta-analysis including six cross-sectional studies, the relative risk of AF for hyperuricemic patients was 1.67 compared with those with normal UA levels.[92] These data point to associations

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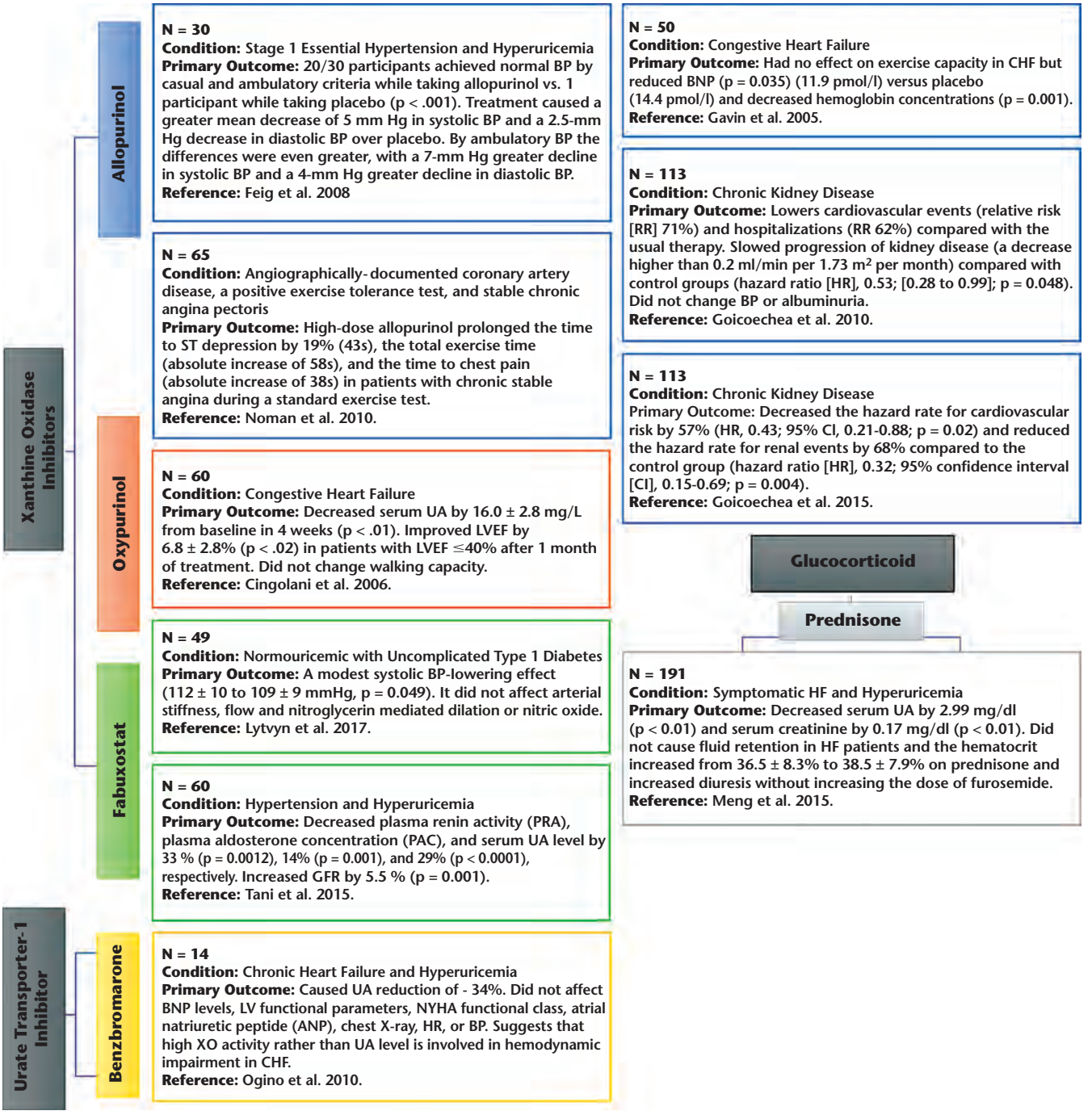

Figure 4. Summary of clinical trials assessing the cardiovascular outcomes associated with the treatment of hyperuricemia. ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; BP, blood pressure; CHF, congestive heart failure; GFR, glomerular filtration rate; HF, heart failure; HR, hazard ratio; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAC, plasma aldosterone concentration; PRA, plasma renin activity; RR, relative risk; UA, uric acid; XO, xanthine oxidase. Data from Noman A et al,[68] Cingolani HE et al,[74] Ogino K et al,[75] Gavin and Struthers,[72] Feig DI et al,[98] Lytvyn Y et al,[99] Tani S et al,[100] Goicoechea M et al,[101] Goicoechea M et al,[102] and Meng H et al.[103]

between UA levels and left atrial remodeling and the risk for AF.

Several mechanisms could explain this association: patients with increased UA levels revealed an enlarged atrial size associated with increased inflammatory markers and insulin resistance. Thus, it is possible that UA per se could be a potential promoter of left atrial enlargement by direct damage to atrial myocites.[93] Alternatively, XO activation could play a role via oxidative damage and by inducing inflammation in cardiac and endothelial cells. These features could contribute to electrical stimulus fragmentation, alteration of atrial potential duration, and decreased threshold for reentry circuit, thus inducing AF.[94] These findings raise the question of whether management of UA could reduce the risk of AF.

Conclusions

Hyperuricemia can arise due to an increase in the activity of the enzyme XO, which degrades xanthine—an intermediate molecule in the degradation of purines—to UA, or it can arise due to a decrease in the amount of excreted UA. Hyperuricemia can lead to the development of gout through the deposition of MSU crystals in the joints and inflammation, which causes extreme pain for those who are affected. Inflammation also plays a significant role in cardiovascular diseases such as atherosclerosis and HF. The NLRP3 inflammasome is involved in the inflammation cascade characteristic of gout, atherosclerosis, and HF. There is also copious evidence demonstrating a direct correlation between increased serum UA levels (hyperuricemia) and cardiovascular ailments such as coronary disease and HF. Additionally, there is a significant amount of evidence that demonstrates the cardiovascular benefits of treating hyperuricemia. Two forms of UA-lowering therapy are XO inhibitors and SGLT2 inhibitors. The latter have been associated with improved cardiovascular outcomes, particularly regarding HF. Considering this new knowledge, should the gout treatment guidelines be adjusted to be more aggressive in preventing cardiac events? And, what is the role of XO inhibitors, including allopurinol? XO appears to play a role in ischemic and vascular events, and XO inhibition has been the cornerstone of gout treatment for decades. Future clinical trials will either confirm or refute the role of lowering UA in preventing and treating cardiovascular illness, particularly in patients with cardiometabolic syndrome. ■

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MAIN POINTS

- Hyperuricemia is a common metabolic disorder. It is reported to affect approximately 5% of the general population and more than 25% of hospitalized patients. Reduced excretion of uric acid (UA) in the urine is the more prevalent etiology of hyperuricemia, responsible for 90% of cases.
- Patients with metabolic syndrome are at a high risk for developing cardiovascular diseases. Increased UA levels are often associated with metabolic syndrome, but it is unknown whether this condition is merely a consequence of metabolic dysfunction or a causal factor in the development of cardiovascular diseases. Hyperuricemia may also play a role in the pathogenesis of hypertension.
- A recent meta-analysis demonstrated that hyperuricemia is related to a modest but statistically significant increased risk of all-cause mortality and coronary heart disease (CHD). The analysis revealed that for every 1 mg/dL increase in serum UA, an individual's overall risk of all-cause mortality increased by 9% and his or her risk of developing CHD increased by 20%. Current evidence also suggests that UA could be both an indicator of poor prognosis and a potential determinant in the pathogenesis of heart failure.
- Various investigators have studied cardiovascular endpoints using the treatment of hyperuricemia, yet it remains controversial whether the cardioprotective effects of UA therapy are due to an effective antioxidant capability or due to the improvement of the metabolic profile.

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