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Allopurinol as a Kidney-Protective, Cardioprotective, and Antihypertensive Agent: Hype or Reality?

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Abstract
Numerous experimental and clinical studies suggest that uric acid might have pathobiologic implications in the development and progression of hypertension, kidney disease, and coronary heart disease, among others, resulting in renewed interest in uric acid as a potential pathogenic mediator in these clinical conditions. Despite encouraging animal studies showing beneficial roles of allopurinol, clinical studies and randomized controlled trials remain scarce, and, despite available clinical evidence supporting a therapeutic role for allopurinol, multiple issues remain before routine use of allopurinol can be recommended for use in patients with hyperuricemia and hypertension, kidney disease, or coronary heart disease. These include a need for more robust clinical trial data that evaluate efficacy on hard clinical outcomes, optimal dose, duration of treatment, and the potential for serious allergic reactions. In this article we review the current available evidence describing the effects of allopurinol in hypertension, kidney disease, and coronary heart disease, highlighting unresolved issues surrounding allopurinol use for uric acid lowering in individuals without gout.

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Introduction

In the last decade interest in uric acid has resurfaced after a long period of inertia, largely reflecting results from experimental studies that show detrimental effects of uric acid on blood pressure and kidney function. Until recent years, uric acid was considered in the context of an end-product of purine degradation and implicated only in gout arthropathy and, to a lesser extent, in kidney function impairment in individuals with longstanding gout. Initially considered an antioxidant molecule, uric acid is now further recognized as the end-product of an enzyme system which is a major source of vascular oxygen radicals, namely the xanthine oxidoreductase system.

The authors declare there are no conflicts of interest.

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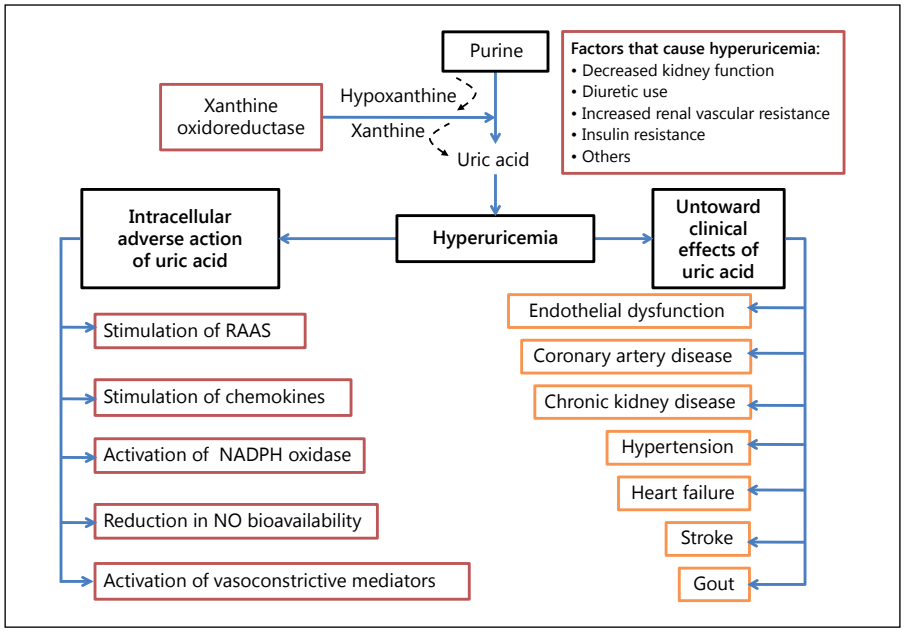


Fig. 1. Possible mechanisms of adverse effects of hyperuricemia.

Elaborately conducted experimental studies have shown unequivocal results in which elevated serum uric acid levels have led to increased oxidative stress and inflammation, higher blood pressure, kidney function deterioration, and propagation of atherosclerosis (fig. 1). Improvement in these risk factors following administration of allopurinol, a xanthine oxidase inhibitor that lowers serum uric acid levels, supports the hypothesis that hyperuricemia is associated with deleterious effects. However, there is an ongoing debate as to whether uric acid itself, free oxygen radicals produced while generating uric acid, or both are the main culprits responsible for these effects. In this review, the epidemiology of hyperuricemia, the association of hyperuricemia with cardiovascular and kidney disease risk factors, and manifestations of hyperuricemia as well as experimental and clinical studies in which allopurinol is used to reverse these pathological processes is reviewed. We also discuss safety and dosing issues of allopurinol and practical issues related to allopurinol use. Finally, we highlight some unanswered questions, such as the role, if any, of routine use of allopurinol in individuals with hypertension, including both those with and without prominent hyperuricemia.

Allopurinol in Hypertension

The association between uric acid and hypertension was first described in the late 1870s; however, it is only recently that the putative causal pathophysiologic relation between increased serum uric acid levels and elevated blood pressure has been revealed, with a 2001 landmark experimental study in rats demonstrating a causal relationship between uric acid elevation and development of hypertension [1]. Despite subsequent extensive experimental data demonstrating and clinical data suggesting a relationship between uric acid and hypertension, the precise mechanisms and even the presence of true causality are still matters of hot debate [2, 3]. A few factors have been put forward to argue against uric acid as a causal factor for hypertension. First, and somewhat ambiguously, uric acid acts both as a pro-oxidant and antioxidant molecule [4]. Second, while uric acid is being produced, cells concurrently produce significant amounts of free oxygen radicals as well. This increased oxidative stress may in turn cause endothelial dysfunction. Thus, this close coupling with the oxidative system makes it difficult to attribute observed detrimental effects associated with hyperuricemia solely to uric acid. To reconcile this, Johnson et al. [2] proposed that uric acid behaves differently in intra- and extracellular environments, serving as a pro-oxidant in the former and an antioxidant in the latter.

In an experimental rat model, allopurinol both prevented development of blood pressure elevation and significantly reduced already increased blood pressure [1]; however, few clinical studies have investigated the effects of allopurinol treatment on blood pressure in people. Kanbay et al. [5] treated 48 hyperuricemic patients with

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allopurinol 300 mg/day for 3 months and reported a significant reduction in systolic and diastolic blood pressures. In contrast, Kostka-Jeziorny et al. [4] did not find a meaningful antihypertensive effect of allopurinol treatment (150 mg/day for 8 weeks) in individuals who previously were randomized to either perindopril or hydrochlorothiazide. There are few randomized controlled studies to date assessing the efficacy of allopurinol treatment in hypertensive individuals. Feig et al. [6] treated newly diagnosed hypertensive adolescents with allopurinol 200 mg twice daily for 8 weeks, using a crossover design. Compared with placebo treatment, allopurinol treatment was associated with significant ambulatory and casual systolic and diastolic blood pressure reductions. In another recent RCT, Soletsky and Feig [7] treated prehypertensive obese adolescents with allopurinol, probenecid, or placebo. Allopurinol reduced systolic and diastolic blood pressures significantly compared with placebo-treated patients. One of the important results of this study was that probenecid therapy was associated with similar decreases in blood pressure as allopurinol therapy, a result that is in line with previous experimental studies and strongly suggests that lowering serum uric acid level independent of the xanthine oxidoreductase system may have favorable blood pressure effects [8]. Given the lack of trials, a recent systematic review by the Cochrane group lacked sufficient data to perform a meta-analysis on pharmacotherapy for hyperuricemia in hypertensive patients [9]. However, these data are subjective, and a definitive clinical trial assessing hard outcomes remains to be performed.

Allopurinol for Prevention of Kidney Disease Progression

To date, several studies have evaluated whether allopurinol could prevent or at least slow the progression of kidney disease. Fairbanks et al. [10], in a retrospective observational study, reported that early treatment of patients with familial juvenile hyperuricemic nephropathy with allopurinol reduced the morbidity and mortality from kidney failure as compared with their untreated siblings and previous generations of recruited families. Later Siu et al. [8] conducted a prospective randomized controlled trial of 54 hyperuricemic individuals with chronic kidney disease, randomizing participants to allopurinol, dosed at 100–300 mg/day, or usual therapy for 12 months. There was a trend toward a lower serum creatinine level in the treatment group compared with controls at study completion, although this difference did not reach statistical significance ($p = 0.08$). In the allopurinol group, 16% reached the combined endpoints of significant deterioration in kidney function or dialysis dependence compared with 46% in the control group ($p = 0.02$). In a shorter, nonrandomized study, we recruited 48 hyperuricemic patients without hypertension or diabetes mellitus and with estimated glomerular filtration rate (eGFR) >60 ml/min/1.73 m^2 [5]. Participants received allopurinol 300 mg/day for 3 months. Compared with 21 nonparticipating control patients, eGFR, but not proteinuria, significantly improved in allopurinol-treated patients. Another prospective randomized trial of 113 individuals with eGFR <60 ml/min/1.73 m^2 found that eGFR decreased 3.3 ± 1.2 ml/min/1.73 m^2 in the control group, but increased 1.3 ± 1.3 ml/min/1.73 m^2 in the allopurinol group after 24 months [11]. This effect of allopurinol on kidney function was independent of age, gender, diabetes, C-reactive protein, albuminuria, and renin-angiotensin system blocker use. Currently, a randomized controlled trial testing the efficacy of allopurinol to prevent nephropathy development in type 1 diabetes mellitus patients is underway [12]. Despite a limited number of recruited patients and scarcity of randomized trials, the available data suggest favorable effects of allopurinol use with respect to kidney function.

Allopurinol in Heart Disease

Multiple studies have demonstrated that allopurinol administration improves endothelial dysfunction, which may be the earliest indicator of vascular disease [13–15]. Thus, when viewed in conjunction with findings of studies which demonstrate that hyperuricemia is independently associated with the presence of coronary artery disease, it is plausible that allopurinol may benefit patients with coronary artery disease.

Limited clinical data to date support this supposition. In a double-blind placebo-controlled clinical trial, high-dose allopurinol treatment (600 mg/day) was an effective antianginal drug in patients with established stable coronary artery disease, significantly increasing exercise tolerance when compared to placebo [16]. In a second placebo-controlled randomized trial by these investigators examining optimally treated coronary artery disease patients, high-dose allopurinol profoundly reduced vascular tissue oxidative stress and improved endothelial function assessed by forearm venous occlusion plethysmography, flow-mediated dilation, and pulse wave analy-

sis [17], suggesting potential mechanisms for the beneficial effects on exercise tolerance.

Similar benefits have been seen in heart failure patients. Wei et al. [18] showed lower mortality with high-dose allopurinol compared with low-dose allopurinol in patients with heart failure, while Gotsman et al. [19], examining cardiac-related hospitalizations and death in 6,204 patients with heart failure, described an association of increased uric acid levels at baseline and an increase in uric acid during follow-up with increased morbidity and mortality. In this study, treatment with allopurinol was associated with improved survival.

The authors speculated that the observed benefit in hard outcomes reflected a novel action of allopurinol in patients with heart failure [20, 21]. Supporting this hypothesis, in a study of 16 adults with nonischemic cardiomyopathy, allopurinol 300 mg intravenously acutely improved the relative and absolute concentrations of myocardial high-energy phosphates and ATP flux through creatine kinase, providing increased substrate for cardiac contraction.

Allopurinol in Kidney Transplant Recipients

Hyperuricemia is common in kidney transplant recipients (KTRs), with prevalence as high as 40% [22]. The vast majority of KTRs, despite working allografts, have reduced kidney function, and immunosuppressive medications used to maintain KTRs, specifically calcineurin inhibitors, are associated with hyperuricemia, making KTRs a population at particularly high risk [23]. In a recent meta-analysis, Huang et al. [24] showed that hyperuricemia was a risk factor of chronic allograft nephropathy [adjusted HR = 1.65 (95% CI: 1.02–2.65)] and graft loss [adjusted HR = 2.01 (95% CI: 1.39–2.94)]. In an experimental rat study, Mazali et al. [25] showed that increased serum uric acid exacerbated cyclosporine nephropathy, and these changes could be reversed or, if administered early, prevented with allopurinol or uricosuric drug administration. To the best of our knowledge, there is no clinical trial assessing safety and efficacy of allopurinol in KTRs to date. Critically, concerns do exist regarding the use of allopurinol in KTRs. These include appropriate dose reduction for reduced GFR and a potentially very serious drug interaction with azathioprine. Once the backbone of kidney transplant immunosuppression protocols, azathioprine is seldom used for this purpose nowadays. Moreover, recent studies have shown that the low-dose combination of azathioprine and allopurinol in patients with inflammatory bowel disease, who have an unfavorable tioguanine metabolite profile, is safe [26].

Dose Adjustment and Safety of Allopurinol in Patients with CKD

Allopurinol is most commonly used to reduce serum uric acid levels in patients with recurrent gout, with most dosing recommendations targeting serum uric acid levels <6 mg/dl (fig. 2). Allopurinol is metabolized after absorption to oxypurinol by xanthine oxidase. Allopurinol and oxypurinol, which are structural analogs of the purine bases hypoxanthine and xanthine, respectively, competitively inhibit xanthine oxidase, thereby preventing the conversion of both hypoxanthine to xanthine and xanthine to uric acid [27]. Oxypurinol is primarily excreted by kidneys, and the half-life of allopurinol may be extended up to 1 week in patients with advanced kidney disease [28].

Approximately 2% of patients receiving allopurinol develop a mild cutaneous rash [29]. Rarely, a life-threatening severe allergic reaction called allopurinol hypersensitivity syndrome (AHS) can occur. Despite its rare occurrence, one study reported that the most common cause of toxic epidermal necrolysis and Stevens Johnson syndrome was allopurinol use [30]. Although described as an idiosyncratic delayed type cellular hypersensitivity reaction, there may be an association with kidney function. In 1984, Hande et al. [31] described an association between AHS and kidney function, recommending dose adjustment in individuals with reduced GFR. Other risk factors linked to AHS include high starting doses of allopurinol, recent initiation of allopurinol treatment, use for asymptomatic hyperuricemia, presence of HLA-B*5801 with chronic kidney disease, concurrent exposure to thiazide diuretics, and female gender [12]. Two recent population-based studies found that HLA-B*58:01 positivity was strongly associated with adverse drug reactions related to allopurinol use [32, 33]. On the other hand, more recent studies found no increased risk of AHS and other adverse reactions associated with allopurinol use at higher than recommended doses in patients with reduced kidney function [12, 22]. Moreover, reductions of allopurinol dose based on creatinine clearance may result in inadequate reduction of serum uric acid levels in patients with gout [23]. On the other hand a retrospective case-control study found that starting allopurinol at a dose of 1.5 mg per 1 ml/min of eGFR may be associated with a reduced risk of AHS [34]. Accordingly, these authors rec-

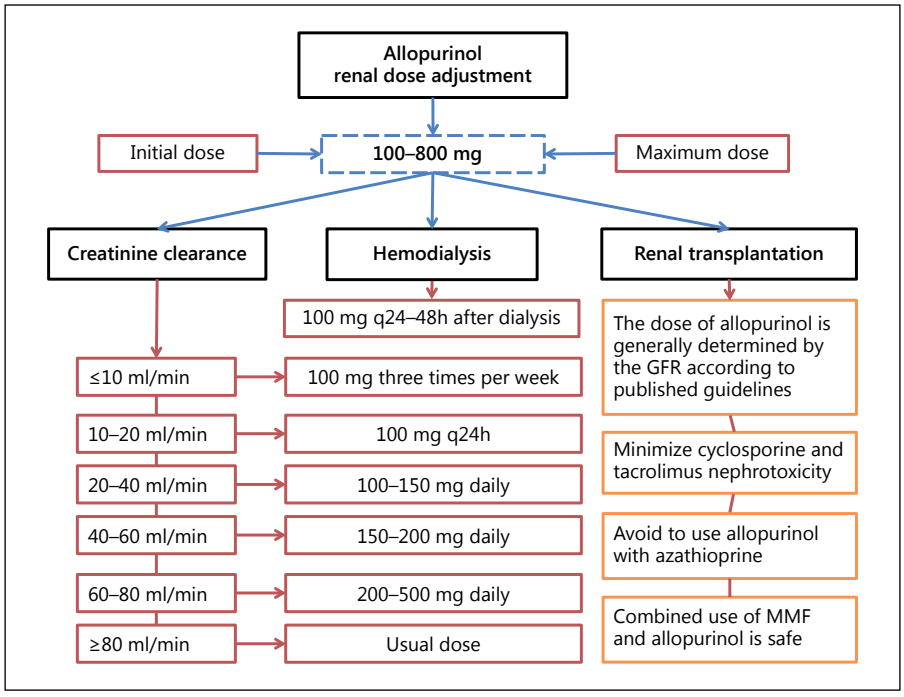


Fig. 2. Dose adjustment of allopurinol in patients with kidney disease.

ommended initiating allopurinol at lower doses, gradually increasing the dose as the patient tolerates. In sum, optimal allopurinol dosing remains uncertain, both in asymptomatic hyperuricemia and in clinically apparent gout, where benefits of uric acid-lowering therapy are better demonstrated.

A recent review study reported by Thurston et al. [35] discussed efficacy and safety of allopurinol in patients with CKD. The authors reported that, some trials have demonstrated an increased risk of allopurinol-induced adverse reactions in patients with CKD, whereas others have not confirmed renal insufficiency as a risk factor. More CKD patients achieved a target uric acid level in studies where the allopurinol dose was titrated to effect as compared with those studies in which patients were given renally adjusted or untitrated allopurinol doses [35].

Febuxostat is a newer xanthine oxidase inhibitor with at least equal efficacy in lowering serum urate compared with allopurinol. Only one case of an AHS-like syndrome has been reported in the literature to date with febuxostat [26]. There are no adequate studies on the effects of febuxostat on hypertension, kidney disease progression, or cardiovascular disease. It remains to be determined whether febuxostat could be a safer agent for widespread use than allopurinol, assuming that uric acid lowering is demonstrated in adequately powered clinical trials to improve hard clinical outcomes.

Nonpharmacologic Approaches to Uric Acid Reduction

Along with allopurinol treatment, the use of low-protein and low-purine diet enhances the effectiveness of drug therapy for hyperuricemia (table 1). Limitation of protein-rich and purine-rich foods such as turkey, mackerel, sardines, shellfish, beef, lamb, goat, pork, deer, elk, and cricket nymphs, could prevent the high protein load and formation of purine products which directly affects the serum uric acid levels [36, 37].

Several studies have reported beneficial effects of a Mediterranean diet in prevention and treatment of hyperuricemia and gout [32, 38]. This diet is characterized by abundant plant foods (fruit, vegetables, breads, cereals, potatoes, beans, nuts, and seeds), fresh fruit, olive oil, and dairy products (cheese and yogurt), and low amounts of fish, eggs, red meat, and wine [39].

Increase in water intake can reduce the risk of kidney stones, but there is no evidence of a primary reduction of blood uric acid levels [40]. Excluding all alcoholic drinks from one's dietary menu can also prevent purine attacks in hyperuricemic patients and gout [33, 41, 42].

As sodium bicarbonate induces alkaline diuresis and increases tubular uric acid elimination, it may also reduce uric acid serum level [43]. Sodium bicarbonate also helps to make uric acid more soluble and

Table 1. Other approaches to reduce serum uric acid level

Approaches	Explanation
Diet	Reduce or cut intake of protein-rich and purine-rich foods, especially turkey, mackerel, sardines, and shellfish, beef, lamb, goat, pork, deer, elk, etc. Cricket nymphs cannot be recommended for people with hyperuricemia or gout A Mediterranean diet can be recommended for prevention and treatment of hyperuricemia and gout
Water intake	Increase in water intake can reduce the risk of kidney stones, but there is no evidence for a primary reduction of blood uric acid levels; also excluding all alcoholic drinks from the dietary menu can prevent purine attacks in hyperuricemic patients and gout
Sodium bicarbonate	Sodium bicarbonate induces alkaline diuresis and increases tubular acid uric elimination, thus reducing uric acid serum level; sodium bicarbonate also helps to make uric acid more soluble, dissolves crystals, and prevents formation of kidney stones
Avoid using diuretics	Avoid potential drugs such as thiazidic diuretics or furosemide

dissolves crystals and prevents formation of kidney stones [44].

Sustained use of drugs such as thiazide diuretics or furosemide can also happen when treating hyperuricemia. Avoiding these diuretics is recommended in patients with elevated serum uric acid levels [45].

Questions To Be Answered before Mass Use

Many questions regarding uric acid lowering remain unanswered, as the use of allopurinol to treat conditions other than prevention of gouty arthritis is still in its infancy based on the available data. Before proceeding further, unequivocal answers to several questions are required. First, the efficacy of allopurinol use for prevention of development of cardiovascular disease, hypertension, and progression of kidney disease needs to be demonstrated in well-designed and adequately powered clinical trials. Second, the appropriate clinical targets of allopurinol use needs to be defined. When treating hypertension, for example, should allopurinol use be guided by normalization of serum uric acid levels or should treatment be tailored to blood pressure levels regardless of serum uric acid levels? What is the safest and most efficacious allopurinol dose? Specifically, should dosing be different in distinct pathophysiologic conditions, namely coronary artery disease, kidney disease, and hypertension? Considering potentially severe allergic reactions to allopurinol in the context of other medications and strategies available for treatment of hypertension and cardiovascular disease, what line of therapy does allopurinol represent? Only when these questions are answered will we know how to utilize this potentially promising medication to treat patients with these increasingly common conditions.

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