

Asymptomatic hyperuricemia: to treat or not a threat? A clinical and evidence-based approach to the management of hyperuricemia in the context of cardiovascular diseases

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Asymptomatic hyperuricemia is defined by serum uric acid levels above 6.2 mg/dl in women and 7 mg/dl in men. In the presence of monosodium urate crystal formation and articular inflammation, hyperuricemia may become symptomatic (namely nephrolithiasis and gout). Uric acid results from purine catabolism and is at the centre of a complex metabolic interplay that involves oxidative stress, inflammation, renin–angiotensin–aldosterone system (RAAS) activation and insulin resistance. Uric acid levels present a continuous relation with conditions like hypertension and chronic kidney disease (CKD) and are reported to have an impact on risk of cardiovascular events. However, whether elevated uric acid is a causal agent and thus a possible therapeutic target is still uncertain and matter of further investigation. Treating symptomatic hyperuricemia involves lowering uric acid drugs and controlling inflammation. Urate-lowering agents are well tolerated but show minimal impact on cardiovascular events in patients with gout. Use of direct-acting urate-lowering agents in asymptomatic hyperuricemia associated with cardiovascular diseases does not warrant a clear benefit, whereas addressing cardiovascular issues with guideline-recommended therapies lowers uric acid and reduces the occurrence of cardiovascular events. Regular assessment of uric acid and clinical symptoms is advised before starting and renewing a urate-lowering treatment.

Keywords: chronic kidney disease, functional rehabilitation, heart failure, hypertension, hyperuricemia, ischemic heart disease, stroke

Abbreviations: ACS, acute coronary syndromes; ALL-HEART, allopurinol versus usual care in UK patients with ischaemic heart disease; AMI, acute myocardial infarction; AMP, adenosine monophosphate; ARBs, angiotensin receptor blockers; ARIC, Atherosclerosis Risk in Communities; BCRP, breast cancer resistance protein; BP, blood pressure; CAD, coronary artery disease; CARES, cardiovascular safety of febuxostat or allopurinol in patients with gout; CASTEL, CArdiovascular STudy in the Elderly; CCBs, calcium channel blockers; CHD, coronary

heart disease; CKD, chronic kidney disease; CKD-FIX, Effects of Allopurinol on the Progression of Chronic Kidney Disease; CONFIRMS, The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EULAR, European Alliance for Association of Rheumatology; EXACT-HF, The Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients; FAST, long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout; FDA, Food and Drug Administration; FEATHER, Febuxostat Therapy for Patients With Stage 3 CKD and Asymptomatic; FREED, Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDY; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; GLUT9, glucose transporter 9; GMP, guanine monophosphate; HF, heart failure; HFREF, heart failure with reduced ejection fraction; IHD, ischemic heart disease; LEAF-HF, Randomized Trial of Effect of Urate-Lowering Agent Febuxostat in Chronic Heart Failure Patients with Hyperuricemia; MI, myocardial infarction; MRP4, multidrug resistance protein 4; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; OAT4, organic anion transporter 4; PERL, Preventing Early Renal Loss in Diabetes; PNP, purine nucleoside phosphorylase; RAS, renin–angiotensin system; Re-Prosper-HF, Repurposing Probenecid for the Treatment of Heart Failure; ROS, reactive oxygen species; SGLT2, sodium-glucose cotransporter 2; SUA, serum uric acid; ULT, urate-lowering therapy; URAT1, urate anion transporter 1; URRAH, Uric Acid Right for heArt Health; XO, xantine oxidase inhibitor

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INTRODUCTION

Uric acid is the final product of purine catabolism. Purines play a key role in cells as nitrogenous bases necessary for the formation of nucleic acids, as well as numerous other coenzymes. They are also involved in signal transduction, neurotransmission, and muscle metabolism. Generally, there must be a balance between purine synthesis and elimination. Although purines are necessary for cell proliferation and survival, an excess of their waste product, uric acid, can be harmful.

Despite the increasing interest of the topic, the therapeutic management of hyperuricemia still represents a debated issue with unsolved questions such as its relevance role in the estimation of cardiovascular risk and the efficacy of pharmacological treatment in improving cardiovascular outcomes.

The aims of this narrative review are: presenting the most updated evidence on the continuous prognostic relations between serum uric acid (SUA) levels and cardiovascular disease [1]. In addition, we systematically discuss the safety and potential cardiovascular benefits of conventional and also nonconventional urate-lowering agents in symptomatic and asymptomatic hyperuricemia across a broad range of cardiovascular conditions [2].

URIC ACID METABOLISM

The degradation of purines, adenine, and guanine to uric acid involves many enzymes. First, adenosine monophosphate (AMP) is converted to inosine monophosphate by removing an amine group through deaminase. Inosine monophosphate is then dephosphorylated by nucleotidase

to form inosine. Guanine monophosphate (GMP) is transformed into guanosine only through dephosphorylation with nucleotidase. Subsequently, purine nucleoside phosphorylase (PNP) converts inosine and guanosine into hypoxanthine and guanine, respectively. Guanine deaminase converts guanine into xanthine. Finally, the enzymes xanthine oxidoreductase oxidizes hypoxanthine and xanthine to form uric acid, the final product of purine metabolism. It is synthesized in the liver, muscle, and intestine, and primarily eliminated by the kidneys (about 65–75%) and intestines (25–35%) [1].

Almost all uric acid is filtered by the glomeruli, so the amount of uric acid excretion is regulated by uric acid reabsorption and secretion. Uric acid reabsorption occurs at the proximal tubular level through transporters such as urate anion transporter 1 (URAT1) and organic anion transporter 4 (OAT4), which exchange intracellular anions for uric acid. Glucose transporter 9 (GLUT9) reabsorbs both uric acid and glucose into tubular cells. Uric acid secretion occurs in the S2 segment of the proximal tubule through transporters such as OAT1, OAT3, multidrug resistance protein 4 (MRP4/ABCC4), and breast cancer resistance protein (BCRP/ABCG2) [2]. Postsecretory reabsorption occurs at a more distal site of the proximal tubule, with approximately 10% of filtered uric acid appearing in the urine (see Fig. 1).

SUA levels vary widely in the general population, and many factors can influence them. Increased uric acid production, impaired renal uric acid excretion, or a combination of both can lead to hyperuricemia. Genetic differences (polymorphisms) in the enzymes that produce uric acid can modify its serum concentration, as well as an individual's

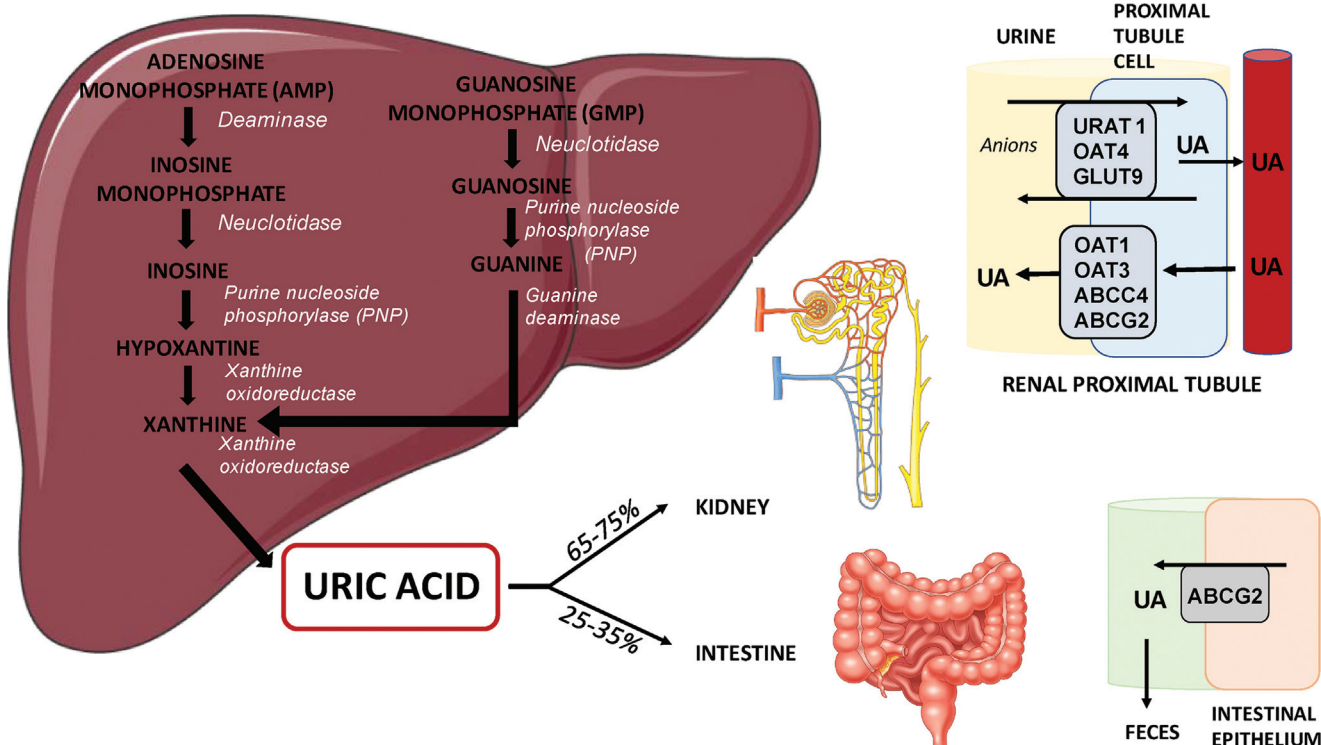


FIGURE 1 Uric acid metabolism and excretion. ABC, ATP binding cassette; GLUT, glucose transporter; OAT, organic anion transporter; URAT, urate anion transporter.

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diet (purine intake from food), the amount of uric acid excretion by the renal system and intestine, or the presence of diseases that increase cell turnover (neoplasms) [3] (Fig. 1).

CLINICAL IMPLICATIONS OF HYPERURICEMIA

Hyperuricemia is defined by the presence of circulating levels of SUA levels higher than 6.2 mg/dl in women and 7 mg/dl in men. When SUA concentration exceeds 6.2 mg/dl, it surpasses its solubility limit and predisposes to the precipitation of uric acid as monosodium urate crystals.

Uric acid plays a dual role within the human body, and several studies have attempted to demonstrate the different mechanisms by which it has simultaneous antioxidant, pro-inflammatory, and pro-oxidative effects. Extracellular uric acid primarily protects cells from oxidative stress and prevents lipid peroxidation by scavenging reactive oxygen species (ROS) [4]. On the other hand, intracellular uric acid exerts a pro-inflammatory and pro-oxidative effect. It reduces endothelial nitric oxide (NO) production and inhibits NO-mediated vasodilation. It activates the renin-angiotensin system (RAS) and stimulates endothelin-1 production through the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases. Additionally,

uric acid may trigger the inflammatory pathway through the inflammasome-IL1 signalling [5] (Fig. 2).

Elevated levels of SUA have been found to contribute to development and progression of asymptomatic organ damage and increase the risk of various diseases, beyond its established role in gout. These diseases include hypertension, obesity, metabolic syndrome, type 2 diabetes, ischemic heart disease, heart failure, chronic kidney diseases, cerebrovascular disease, and pulmonary hypertension [6] (see Fig. 2).

In this regard, the Uric acid Right for heArt Health (URRAH) project [7] defined the SUA levels above which the independent risk of cardiovascular disease significantly increases [8], which are lower than the cutoff usually used to define "hyperuricemia".

SUA levels have been shown to correlate with cardiovascular deaths and the optimal cut point identified for predicting cardiovascular mortality is 5.6 mg/dl [9]. An age-stratified analysis of URRAH study participants was conducted and for patients in the age group 65–74 years, a cutoff of 4.8 mg/dl was the best threshold for both all-cause mortality and cardiovascular mortality; no association was found between patients older than 75 years and mortality [10].

Another study of Working Group on Uric Acid and Cardiovascular Risk of the Italian Society of Hypertension

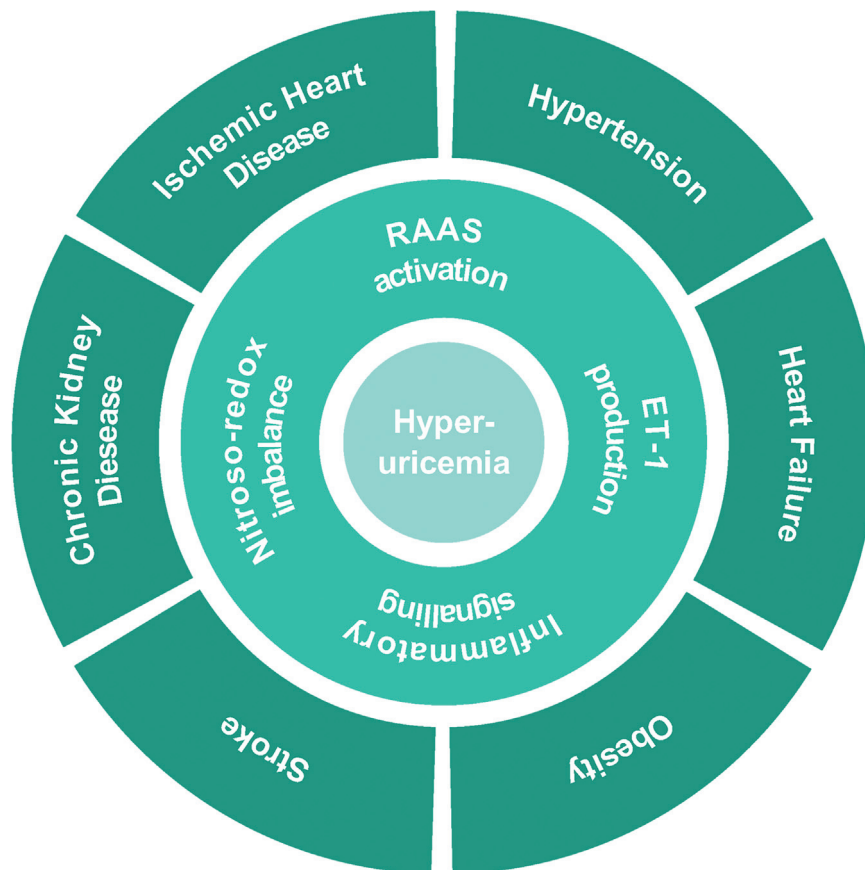


FIGURE 2 Hyperuricemia-related pathophysiology. Elevated serum uric acid levels induce the activation of multiple pathways known to be deleterious in the wide spectrum of cardiovascular disease, from the vasoactive response to the oxidative stress, passing through inflammation and neurohormonal activation. ET, endothelin; RAAS, renin-angiotensin-aldosterone system.

demonstrated a significant relationship between SUA and fatal myocardial infarction (MI) only in women with a prognostic cut-off value for fatal MI prediction of 5.70 mg/dl [11].

Furthermore, the URRAH project found that SUA is an independent risk factor for all heart failure and fatal heart failure and the prognostic cut-off values of SUA are 5.34 and 4.89 mg/dl, respectively [12]. An association between SUA and stroke was found as well and a prognostic cut-off value of 4.79 mg/dl was identified as the best threshold [13].

Finally, given the bidirectional relationship between SUA levels and chronic kidney disease (CKD) demonstrated by consistent evidence [14], the URRAH project proposed to use a SUA cut-off higher than 7.0 mg/dl defining asymptomatic hyperuricemia in patients with CKD and a cut-off of SUA adjusted for creatinine of 5.35 to identify patients at higher risk of developing cardiovascular events [15].

A large cohort study explored the risk of incident CVD among individuals without hyperuricemia (SUA 3–6 mg/dl) or other traditional CVD risk factors [16]. A multivariable-adjusted spline regression model showed a J-shaped association between SUA and the risk of CVD, stroke, and myocardial infarction in this specific population.

Hyperuricemia is more common in men than in women. The average value of plasma level of uric acid in men is about 1 mg/dl higher than in women, at least before menopause. This is partially due to the uricosuric effect of oestrogens [17].

Tanaka *et al.* [18] described a longitudinal association between SUA and endothelial function in 650 treated hypertensive patients, this association was even greater among women where the impact of SUA on vascular function seems to be more susceptible to aging and subsequent changes in hormonal and metabolic state, compared with males.

Simon *et al.* [19] showed how postmenopausal treatment with oestrogen and progestin lowered SUA levels but did not reduce coronary artery disease risk. As a matter-of-fact, women seem to have a higher risk to develop cardiovascular comorbidities at lower uric acid levels [20].

These findings lead to questioning whether a lower cut-off for the definition of abnormal SUA levels should be considered for uric acid in women [21].

Hypertension

The association between hyperuricemia and hypertension remains controversial. Traditional cardiovascular risk factors often associated with hyperuricemia may have introduced biases in different clinical studies reporting positive and significant relations between SUA and blood pressure levels. However, two separate meta-analyses have identified hyperuricemia as an independent risk factor for the development of hypertension. The risk increases linearly with higher levels of SUA [22,23].

Studies utilizing rodent models and cell cultures suggest that hyperuricemia may contribute to hypertension by activating the RAS, reducing nitric oxide production, and promoting inflammation [24,25]. A recent longitudinal study in Chinese adults suggests microalbuminuria may follow elevated uric acid and partially mediate its effect on future risk of hypertension [26].

Obesity and metabolic syndrome

Metabolic syndrome is a clinical condition characterized by central or visceral obesity associated with hypertension, dyslipidaemia and impaired fasting glucose. The presence of elevated SUA levels is common in patients affected by metabolic syndrome.

Yuan *et al.* suggest through a meta-analysis of 11 prospective studies that higher SUA levels correlate with an increased risk of developing metabolic syndrome. The results are consistent in showing a linear relationship between these two conditions: a 1 mg/dl increment on SUA levels led to a 30% increase in the risk for metabolic syndrome [27].

Overeating and the over-intake of purine-rich food (meat, shellfish, anchovies) is probably at the basis of this association, but the existence of a hyper-insulinemic state in metabolic syndrome could also play a role. Insulin stimulates sodium and urate reabsorption in the renal proximal tubule [28]. Facchini *et al.* [29], also support this pathophysiological hypothesis in a cross-sectional study of healthy individuals, showing a relationship between insulin resistance and increased SUA levels despite differences in sex, age, BMI and ratio of waist-to-hip girth.

The association of gout with elevated triglyceride and LDL-cholesterol suggests that dyslipidaemia, as a metabolic syndrome component, might also be related to hyperuricemia [30].

Ischemic heart disease

There is no clear evidence supporting uric acid as an independent risk factor for coronary artery disease (CAD). Different studies and meta-analyses have yielded conflicting conclusions.

The Framingham Heart Study examined the relationship between SUA and risk of ischemic heart disease, as well as all-cause and cardiovascular mortality. The study found no causal link in men, suggesting that any apparent association is likely due to the relationship between SUA and traditional cardiovascular risk factors [31]. In women, however, after adjustment for age, SUA level was predictive of CAD. This association is lost after adjustment for cardiovascular risk factors such as hypertension, which in turn may probably be favoured by SUA, making its inclusion among the adjusting factors questionable.

Similar conclusions were reached in the ARIC Study by Moriarity in 2000, where multivariable adjustments for cardiovascular risk factors showed little evidence of this association in both men and women [32].

More recent evidence supports the hypothesis that uric acid serves as a marker or independent risk factor for ischemic heart disease. The Rotterdam Study in 2006 demonstrated a strong association between elevated SUA levels, increased risk of ischemic heart disease, and stroke, even after adjusting for other cardiovascular risk factors [33]. SUA is also considered a predictor of adverse events related to acute myocardial infarction. In a retrospective multicentre observational study, SUA levels were associated with Killip's class classification in patients hospitalized for acute coronary syndrome (ACS). Hyperuricemia was linked to short-term adverse events, an increased risk of postinfarction left ventricular failure and overall mortality [34].

Several smaller studies and meta-analyses also support SUA as a risk factor for ischemic heart disease, demonstrating its prognostic role in both stable CAD and ACS. Timóteo *et al.* found that for every 1 mg/dl increase in SUA levels, the adjusted risk of 1-year mortality increased by 26% in patients with ACS [35,36].

Heart failure

Inflammation and endothelial dysfunction due to oxidative stress have been demonstrated to contribute to the development of heart failure [37].

Hyperuricemia and heart failure have been related in different studies and meta-analysis. Increased SUA levels seem to play an important role in the development of heart failure and correlate with a worse prognosis [30].

In 1997, Leyva demonstrated an inverse relationship between SUA levels and functional capacity in patients with heart failure, regardless of the cause. This suggests that hyperuricemia is associated with heart failure itself [38]. The mechanisms involved in heart failure-related hyperuricemia likely include impaired renal function and increased xanthine oxidase activity. Xanthine oxidase-derived ROS can contribute to pathophysiological processes involved in heart failure, such as myocardial fibrosis, left ventricular remodelling, and impaired contractility.

Chronic kidney disease

Hyperuricemia has been identified as a potential risk factor for the development of CKD, although it is not always clear whether increased SUA levels result from glomerular filtration impairment or contribute to renal damage.

In a cohort study involving 7893 participants, each 1 mg/dl increase in SUA was associated with a faster reduction in estimated glomerular filtration rate (eGFR) of 0.19 ml/min/1.73 m² per year. Several meta-analyses have identified hyperuricemia as an independent risk factor for developing newly diagnosed CKD. This association appears stronger in hypertensive patients and after long-term follow-up [39,40].

Hyperuricemia can influence renal function through various mechanisms. Its association with hypertension may trigger subclinical kidney damage. Hyperuricemia is linked to the activation of the RAS, which leads to reduced renal plasma flow. Additionally, hyperuricemia is associated with oxidative stress and a pro-inflammatory state, which promote proliferation of glomerular endothelial cells. Elevated SUA levels may also contribute to tubular damage through urate crystal deposition. Hyperuricemia resulting from reduced excretion in subclinical kidney disease can initiate a vicious cycle of worsening renal function [41]. However, hyperuricemia due to declining glomerular filtration of SUA (renal hyperuricaemia) seems to be less harmful than hyperuricemia resulting from overproduction of uric acid (metabolic hyperuricaemia) [42].

Stroke

The association between hyperuricemia and stroke has been studied in different settings and patients.

Elevated SUA levels have been associated to a major incidence of stroke events in middle-aged patients with diabetes despite of other cardiovascular risk factors such as

hypertension, use of diuretics, nephropathy and overweight [43]. We have similar data from a population-based study performed in Northeast Italy, the Cardiovascular Study in the ELderly (CASTEL), in which hyperuricemia was found to be a strong and independent predictor of stroke mortality in the 3282 over-65 years old patients taking part in the study [44].

The mechanisms involved are not clear. Hyperuricemia can be associated to hypertension, one of the most common risk factors for stroke, moreover, uric acid's role in favouring endothelial dysfunction, oxidative stress, systemic inflammation and vascular smooth muscle proliferation could be involved [45].

Nardi *et al.* [46] collected carotid atherosclerotic plaques during carotid endarterectomy showing how uric acid is expressed in atherosclerotic carotid plaques, and how its expression was positively correlated with SUA levels, and with patients' symptoms, suggesting its involvement in plaque inflammation and vulnerability.

Pulmonary hypertension

Pulmonary hypertension is a rare condition associated with unfavourable prognosis [47]. Usually pulmonary hypertension has been related to elevated SUA levels in a cause-effect manner, probably due to local and systemic hypoxia [48]. SUA could have a secondary contributory role in the pathogenesis or progression of pulmonary hypertension for its proinflammatory and vasoconstrictive effects [49]. Hyperuricemia indeed seems associated with the subsequent development, worse severity and poor prognosis of pulmonary hypertension [50], irrespective of diuretic use and glomerular filtration.

Primary pulmonary hypertension (pulmonary arterial hypertension, PAH Group 1 [51]) presents a positive correlation between the central venous pressure and SUA level [52]. Baseline SUA and variations during follow-up has a prognostic significance both in idiopathic PAH (IPAH) [53] and in connective tissue disease (CTD)-related PAH [54].

URATE-LOWERING THERAPY

According to the 2016 updated recommendations of the European Alliance for Association of Rheumatology (EULAR) [55], the implementation of urate-lowering therapies (ULT) should be considered and discussed with every patient diagnosed with gout from the first presentation. ULT is indicated for patients with recurrent flares (≥ 2 /year), tophi, urate arthropathy, and/or renal stones. A fast-track initiation of ULT is recommended after the initial diagnosis for patients presenting at a young age (< 40 years), or with a very high SUA level (> 8 mg/dl), and/or comorbidities (renal impairment, hypertension, ischemic heart disease, heart failure). The goal of this ULT strategy is to achieve an SUA target level below 6 mg/dl to prevent monosodium urate crystallization, facilitate tophi dissolution, and ultimately prevent gout flare-ups.

In EULAR document on cardiovascular risk management in rheumatic disease [56], a SUA level below 6 mg/dl, it is recommended to potentially lower the risk of cardiovascular events and mortality, with no preference for a particular ULT from the cardiovascular point of view.

Direct urate-lowering therapy

The first-line treatment for most people with gout requiring ULT is allopurinol [57], a purine-based xanthine oxidase inhibitor (XOI) that inhibits urate production. Allopurinol is generally well tolerated, but in 1–2% of patients, it may cause a rash that requires discontinuation of therapy. In rare cases, allopurinol can lead to a potentially life-threatening hypersensitivity syndrome characterized by severe cutaneous reactions (Stevens–Johnson syndrome), acute kidney injury, hepatitis, and eosinophilia. Febuxostat, a potent nonpurine XOI, is used as a second-line ULT. It is metabolized in the liver, allowing its use in patients with mild-to-moderate kidney failure without dose adjustment.

Uricosuric agents, such as probenecid, sulfapyrazone, and benzbromarone, are recommended, whenever available, either alone or in combination with allopurinol for patients who do not achieve proper control with allopurinol alone. This class of medications promotes urate excretion in the renal tubules by blocking the function of URAT1. Uricosuric agents should be avoided in patients with current or previous urolithiasis, and all patients taking uricosurics should maintain a high-fluid intake.

'Ancillary' urate-lowering therapy

In clinical cardiology practice, the diagnosis of hyperuricemia, mostly asymptomatic, is usually incidental. At the time of detecting SUA levels above the upper established limit, the majority of patients are either not receiving cardiovascular drugs or are undergoing treatment with medications that have a negative metabolic impact on SUA.

Diuretics, for example, are among the most important causes of secondary hyperuricemia [58]. Loop and thiazide diuretics inhibit basolateral organic anion transporters (OAT1 and OAT3) involved in the active uptake of plasma uric acid in renal proximal tubules. Hydrochlorothiazide also significantly increases uric acid uptake via organic anion transporter OAT4. Additionally, diuretics induce salt and water loss, leading to volume contraction, which stimulates uric acid reabsorption. Conversely, many medications currently used to treat various cardiovascular diseases have a positive secondary effect on SUA metabolism and SUA levels.

Dang *et al.* [59] conducted a multicentre study across 20 clinical institutions to investigate the effects of losartan or irbesartan on SUA levels. Participants with baseline mild-to-moderate hypertension and a SUA level at least 7.0 mg/dl were randomized to receive either losartan 50 mg daily or irbesartan 150 mg daily. Losartan decreased SUA levels from 7.09 mg/dl at baseline to 6.17 mg/dl at week 4 ($P < 0.0001$). A systematic review [60] exploring the relationship between angiotensin receptor blockers (ARBs) and SUA metabolism found that losartan was the only ARB significantly lowering SUA levels and promoting its urinary elimination.

Dihydropyridine calcium channel blockers (CCBs) demonstrated an uricosuric effect in a murine model of urate under-excretion [61]. In a study of Rubio-Guerra *et al.* [60,62], hypertensive patients were randomized to receive either losartan in combination with hydrochlorothiazide or amlodipine. Both combinations reduced blood pressure to the same extent, but the losartan–amlodipine combination

promoted a reduction in SUA levels, whilst the losartan–hydrochlorothiazide showed a nonsignificant increase. This evidence suggests a synergistic effect of amlodipine with losartan in reducing metabolic risk in hypertensive patients.

Hypertriglyceridemia is common among patients with gout, and fenofibrate is typically used to reduce triglyceride levels. Fenofibrate has a rapid and reversible urate-lowering effect in patients with hyperuricemia and gout who are on established allopurinol prophylaxis [63]. A more recent retrospective study [64] suggests that adding fenofibrate is a reasonable option for treating gout in patients with high triglyceride levels. Similarly, atorvastatin, a cornerstone of lipid-lowering therapy, demonstrated a reduction in SUA levels by enhancing its urinary fractional excretion in a randomized trial involving 180 normouricemic patients treated for primary hyperlipidaemia [65].

SUA concentration is an independent predictor of worse outcomes (cardiovascular death, heart failure hospitalization and all-cause mortality) after multivariable adjustment in patients with heart failure with reduced ejection fraction (HFrEF) [66]. In a post hoc analysis of the PARADIGM-HF trial, sacubitril/valsartan, compared with enalapril, reduced SUA by 0.24 (0.17–0.32) mg/dl over 12 months ($P < 0.0001$) and improved outcomes regardless of SUA concentration. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, a class of drugs used to treat diabetes, have also been repurposed for managing heart failure. In both the DAPA-HF and EMPEROR-Reduced trials, hyperuricemia was highly prevalent among patients, with no differences between sexes. Post hoc analyses of these trials showed that both dapagliflozin and empagliflozin rapidly and sustainably reduced SUA levels and clinical events related to hyperuricemia [67,68].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), primarily used to treat type 2 diabetes, have shown increasing evidence supporting their use in managing obesity. They improve glucose tolerance, increase insulin secretion and induce weight loss. A systematic review and meta-analysis of 17 randomized controlled and observational studies revealed that GLP-1 RAs result in a significant reduction in SUA concentration. However, this reduction is less pronounced compared with insulin, metformin and SGLT-2 inhibitors [69].

TREATMENT OF SYMPTOMATIC HYPERURICEMIA: GOUT

The risk of cardiovascular events, including death, is substantially higher in people with hyperuricemia and gout. ULT and colchicine are commonly used in the treatment and prophylaxis of gout, demonstrating benefits in reducing flare-ups, SUA levels and disease progression. However, the relationship between the implementation of these treatments and cardiovascular prognosis is less clear.

In this section, we analyse the available data concerning the cardiovascular protective effects of ULT in patients with an established indication for this treatment (gout, symptomatic hyperuricemia). The positive effect of colchicine on inflammation is subject of study and extensive debate. The use of colchicine is growing widely, beyond the context of hyperuricemia and the subject of this review.

Xanthine oxidase inhibitors

Allopurinol, with its antioxidant and anti-inflammatory properties, was initially considered a potential candidate to reduce cardiovascular risk. However, some cohort studies [70,71] did not show any significant benefits and even detected a modest increase in cardiovascular risk associated with allopurinol use. A meta-analysis of randomized controlled trials comparing allopurinol and febuxostat [72] found no significant difference in cardiovascular events, but longer studies hinted at potentially less favourable outcomes with febuxostat.

During its development, febuxostat has been tested with placebo and allopurinol in large clinical trials involving more than 5000 patients [73–75]. These studies advanced the hypothesis of a modest increase in major cardiovascular events that was imputable to febuxostat. Despite the CONFIRMS trial [76] showed an equal distribution of cardiovascular events between febuxostat and allopurinol-treated patients, uncertainty persisted concerning febuxostat and cardiovascular safety.

To address concerns about febuxostat's cardiovascular safety, large clinical trials were conducted, such as the CARES trial [46] in the US and the FAST trial [47] in Europe. Although CARES showed similar rates of composite cardiovascular events between febuxostat and allopurinol groups, febuxostat-treated patients had higher all-cause mortality, particularly at lower drug doses. The FAST trial, on the other hand, found febuxostat to be noninferior to allopurinol in terms of the composite primary outcomes and did not show an increased risk of death or serious adverse events with long-term use. Subsequent analysis and a meta-analysis [77] of these trials indicated that febuxostat may have a similar cardiovascular profile to allopurinol in patients without a history of cardiovascular disease. However, in patients with preexisting cardiovascular conditions, allopurinol appeared to be associated with lower cardiovascular mortality compared with febuxostat.

Uricosurics

Probenecid is an uricosuric agent that effectively lowers SUA levels similar to allopurinol [78]. It has positive pharmacodynamic effects, acting as a partial agonist of the TRPV2 channel, which improves cardiomyocyte contractility and promotes vasodilation [79]. An observational study on elderly patients showed that probenecid use was associated with a modest reduction in cardiovascular events, including hospitalization for myocardial infarction or stroke [80]. However, considering comorbidities such as chronic kidney disease and nephrolithiasis, using probenecid in older gout patients can be challenging.

Benzbromarone is another uricosuric agent with high efficacy and safety, particularly for patients with chronic kidney disease. It was withdrawn from some European countries because of hepatotoxicity reports. Recent cohort studies comparing allopurinol and benzbromarone found conflicting results regarding their effects on cardiovascular risk [81,82].

Overall, evidence on ULTs and cardiovascular outcomes in gout patients comes from retrospective studies and meta-analyses, which may have biases. The data suggest a limited impact of ULTs in normalizing cardiovascular risk in this

population. However, large randomized controlled trials support the well tolerated use of ULTs in patients at risk or with established cardiovascular disease, with allopurinol and benzbromarone being preferred choices.

TREATMENT OF ASYMPTOMATIC HYPERURICEMIA IN DIFFERENT CARDIOVASCULAR CONDITIONS

Asymptomatic hyperuricemia refers to persistently elevated SUA levels without clinical manifestations of urate crystal deposition. According to EULAR [55] evidence-based recommendations, asymptomatic hyperuricemia does not warrant ULT. However, recent evidence has shown a significant independent association between asymptomatic hyperuricemia and increased cardiovascular mortality and major adverse cardiovascular events. Asymptomatic hyperuricemia is considered a nonconventional risk factor, with elevated SUA levels implicated in promoting cardiovascular, cerebrovascular, and renal damage. As a result, several clinical trials have been conducted to investigate whether reducing SUA levels can effectively manage this metabolic risk factor.

This section systematically examines the available evidence on the treatment of asymptomatic hyperuricemia and its impact on clinical outcomes.

Hypertension

Epidemiological studies have shown a link between uric acid and incident hypertension. Studies in children with normal renal function revealed a strong correlation between uric acid concentration and blood pressure [83]. Two randomized controlled trials investigated if reducing uric acid levels could lower blood pressure in adolescents with hypertension [84,85]. The trials showed that allopurinol and probenecid led to a significant reduction in SBP and DBP (see Table 3).

However, in young-adult [86] and adult [87] patients with established essential hypertension, the benefits of uric acid reduction on blood pressure were inconsistent. Meta-analysis [88] of various studies demonstrated a small but significant blood pressure reduction with allopurinol treatment, though less effective than in young individuals (see Table 1).

In line with the presented studies, a two-step hypothesis has been postulated by Feig [89], explaining the inconstant interaction between SUA-lowering and hypertension. In the initial (young) phase of the disease, elevated SUA concentrations (possibly emerging from a context of metabolic syndrome) might exert a negative effect on endothelial function, decreasing endothelial nitric oxide synthase and activating renin–angiotensin–aldosterone system (RAAS). At this stage, the elimination of a possible hypertensive trigger can produce a stable reduction in blood pressure (BP). In the second (adult) phase, the structural effect of uric acid on kidney function is mediated by proliferation of vascular smooth muscles cells, periglomerular vascular injury, glomerular hypertension, and ultimately interstitial fibrosis. Once renal damage has occurred because of a combination of hyperuricemia and high BP, the reduction of SUA levels is no more effective as a vicious circle of salt-sensitive hypertension is now established [90].

TABLE 1. Clinical trials on ULT effect on hypertension and stroke

First author, year [ref]	Trial	Patients (N)	Inclusion criteria	Exclusion criteria	UA-lowering regimen	Baseline UA (mg/dl)	Duration of follow-up	Outcomes	Results
Hypertension Feig et al., 2008 [84]	Randomized double-blind placebo-controlled trial NCT00288184	30	Age 11–17 years Stage I HT SUA >6mg/dl	Stage II HT Prior or current antihypertensive treatment	Allopurinol 400 mg/day versus placebo	7/6.2	4 Weeks	Change in casual BP and ambulatory monitoring parameters	Reduction of SBP and DBP with allopurinol
Soletsky et al., 2012 [85]	Randomized double-blind placebo-controlled trial NC100288158	60	Age 11–17 years SUA >5mg/dl Obesity Prehypertension	Stage I–II HT Elevated SeCr	Allopurinol 400 mg/day versus probenecid 1 g/day versus placebo	6.8/6.7/6.6	8 Weeks	Change in casual BP and ambulatory monitoring parameters	Significant reduction of SBP and DBP with ULT
McMullan et al., 2017 [87]	Randomized, double-blind placebo-controlled trial NC101320722	149	Age > 18 years SUA >5 mg/dl Overweight or obesity No history of HT	eGFR <60 ml/min CAD Diabetes	Allopurinol 600 mg/day versus Probenecid 1 g/day versus placebo	6.1/6.1/6.1	8 Weeks	Change in kidney and systemic RAS activity BP ambulatory monitoring parameters	Neutral effect
Gaffo et al., 2021 [86]	Randomized, double-blind placebo-controlled trial NCT02038179	99	Age 18–40 years SBP 120–160 mmHg or DBP 80–100 mmHg SUA >5 mg/dl	Current antihypertensive treatment Gout Current smoking Diabetes	Allopurinol 300 mg/day versus placebo	5.8/5.9	4 Weeks	Change in SBP Endothelial function High-sensitivity C-reactive protein levels	Neutral effect on BP Improvement in endothelial function with allopurinol
Stroke Muir et al., 2008 [126]	Randomized double-blind placebo-controlled trial	50	Recent (72 h) ischemic stroke	eGFR <60 ml/min	Allopurinol 300 mg/day versus Allopurinol 100 mg/day versus placebo	6.3/6.13/6.13	6 Weeks	Change in expression of inflammatory markers	Attenuation of the rise in intercellular adhesion molecule-1 levels with allopurinol
Kahn et al., 2008 [127]	Randomized double-blind placebo-controlled trial ISRCTN 98638368	30	Ischemic or haemorrhagic stroke survivors SUA >7 mg/dl	n.a.	Allopurinol 300 mg/day versus placebo	8.45/8.28	8 Weeks	Change in vascular augmentation index (Aix)	Reduction of arterial stiffness (Aix) with allopurinol
Higgins et al., 2018 [128]	Randomized, double-blind placebo-controlled trial ISRCTN11970568	80	Age > 18 years Ischemic stroke or TIA in the past year	Gout eGFR <50 ml/min	Allopurinol 300 mg/day versus placebo	5.76/5.4	1 Year	Change in central blood pressure (CBP), arterial stiffness and CIMT progression	Allopurinol lowers CBP and reduces CIMT progression at 1 year
Tanaka et al., 2020 [124]	Multicentre, randomized trial UMIN00012911	483	Age >20 years SUA >7 mg/dl CIMT >1.1 mm	Gout	Febuxostat 10-60 mg/day versus lifestyle changes	7.76/7.73	24 Months	Percentage change in mean CIMT	Neutral effect

ACS, acute coronary syndrome; ADHF, acute decompensated heart failure; AKI, acute kidney injury; BNP, brain-derived natriuretic peptide; BP, blood pressure; CAD, coronary artery disease; CIMT, carotid intima-media thickness; CRT, cardiac resynchronization therapy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ETT, exercise tolerance test; GDMT, guideline-directed medical therapy; HT, hypertension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; QoL, quality of life; ROS, reactive oxygen species; SUA, serum uric acid; TIA, transient ischemic attack; UA/Cr, urine albumin-creatinine ratio.

A propensity-matched cohort study in older hypertensive patients [91] showed that allopurinol treatment, particularly at higher doses, was associated with a lower risk of stroke and cardiac events after a prolonged follow-up. The cardiovascular benefit of XOIs may be independent of UA levels: XOI should not be titrated to the SUA target, yet to balance the XO dysregulation [92]. (Table 1).

Ischemic heart disease

Two case–control studies [93,94] suggested that allopurinol, in addition to its urate-lowering property, might have a protective effect on CAD. Allopurinol use was associated with a significant reduction in the risk of nonfatal acute myocardial infarction (AMI), especially in men, with prolonged therapy (>180 days) and higher dosage (>300 mg/day).

Allopurinol has been shown to improve peripheral endothelium-dependent vasodilation [95], vascular oxidative stress, and arterial stiffness [96] in patients with chronic coronary syndrome and ischemic heart disease (IHD). High doses of allopurinol were found to reduce left ventricular mass and improve left ventricular hypertrophy in patients with IHD. Intracoronary oxypurinol infusions have been effective in correcting abnormal vasospasm in patients with nonelevated SUA levels [97], indicating a direct reduction of coronary ROS levels by inhibiting xanthine oxidase activity (see Table 2).

Together, this evidence can explain the results of a double-blind randomized controlled trial conducted on 65 patients with stable angina, angiographically documented coronary artery disease, and a positive exercise tolerance test [98]. The administration of a high dose of allopurinol (600 mg) compared with placebo significantly increased total exercise time, time to ST depression, and time to symptoms. No correlation was found between baseline SUA levels and the positive impact of allopurinol.

More recently, a multicentre, prospective, randomized, open-label, blinded-endpoint trial, known as ALL-HEART [99], explored the efficacy of allopurinol in preventing AMI, stroke and cardiovascular death (primary end-point) among patients aged 60 years or older with ischemic heart disease but no history of gout. Patients with renal impairment or moderate–severe heart failure were excluded. The patients were randomized to receive either allopurinol 600 mg or placebo in a 1 : 1 manner. After a mean follow-up of nearly 5 years, there was no difference in the primary outcome. Additionally, there was no difference between the two groups of patients in terms of changes in symptoms (assessed by the Seattle Angina Questionnaire), rates of serious adverse events, or incidence of cancers. These results were consistent regardless of the baseline level of SUA and were also confirmed in the higher quartile of SUA concentration (see Table 2).

Based on this cutting-edge, high-quality evidence, the use of allopurinol for secondary prevention in patients with established coronary artery disease is not supported (Table 2).

Heart failure

A recent meta-analysis [100] showed that high levels of SUA independently predict increased all-cause mortality, cardiovascular mortality, and cardiac events in heart failure

patients. Several studies have explored the potential benefits of ULTs in heart failure patients.

Allopurinol (XOI) has been investigated in heart failure patients with mixed results [101]. Some studies suggested beneficial effects on systemic vasodilation [102], endothelial function [103], myocardial efficiency [104] and performance [105], but others did not show improvements in exercise capacity [59] (see Table 1). The OPT-CHF Study [106], evaluating oxypurinol (the active metabolite of allopurinol), found no significant clinical improvements except in patients with elevated SUA levels. By comparing this trial with previous studies on XOI and based on FDA data on bioequivalence, some authors emphasized a problem with the selection of participants (600 mg oxypurinol has a relative bioavailability equivalent to 81 mg allopurinol), which could have affected the results of this RCT [107]. The Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) Study [108] was designed to overcome these limitations by including only heart failure patients with SUA levels greater than 9.5 mg/dl and using a fixed dose of 600 mg allopurinol as the target dose for the intervention arm. Unfortunately, the EXACT-HF study failed to demonstrate any clinical or functional impact of the XOI in high-risk HFrEF after 24 weeks.

A randomized multicentre trial included 263 patients with chronic heart failure and hyperuricemia (SUA >7 mg/dl) to compare febuxostat and allopurinol in terms of cardiovascular event-free rate [109]. The study did not find a statistically significant superiority of febuxostat over allopurinol, although the febuxostat group showed a trend towards higher rates of patients free from hospitalization because of worsening heart failure. The potential benefits of febuxostat's more potent and selective xanthine oxidase inhibition in heart failure are being investigated further in the ongoing LEAF-HF trial (Randomized Trial of Effect of Urate-Lowering Agent Febuxostat in Chronic Heart Failure Patients with Hyperuricemia) [110] (see Table 3).

Probenecid, a uricosuric agent, has shown positive effects on cardiac function in animal models and human trials [111]. The Re-Prosper-HF study [112] is currently investigating probenecid's potential as a calciotropic-inotropic agent in heart failure patients.

A recent meta-analysis of ULTs in heart failure patients [113] found no significant impact on systolic function, BNP/NT-pro-BNP levels, functional capacity, all-cause mortality, or cardiovascular death.

Overall, the evidence on the use of ULTs in heart failure patients remains inconclusive, with some studies suggesting potential benefits, but more robust research is needed to establish their efficacy in this population (Table 3).

Chronic kidney disease

High SUA levels are associated with an increased risk of developing renal disease [114]. As said before, hyperuricemia induces high BP, renal afferent arteriopathy, increased glomerular hydrostatic pressure and renal scarring. Therefore, SUA level may be a modifiable agent in progression of CKD. Interventional studies have been conducted to explore the nephroprotective effects of ULT and its potential as a renal risk factor.

TABLE 2. Clinical trials on urate-lowering therapies and ischemic heart disease

First author, year [ref]	Trial	Patients (N)	Inclusion criteria	Exclusion criteria	UA-lowering regimen	Baseline UA (mg/dl) treatment/control group	Duration of follow-up	Outcomes	Results
Noman et al., 2010 [98]	Randomized, double-blind placebo-controlled trial ISRCTN 82040078	65	Proven CAD Stable angina	Recent ACS or revasc. LVEF <45% Active gout eGFR <45 ml/min	Allopurinol 600 mg/day versus placebo	n.a.	6 Weeks	Time to ST-depression, total exercise time, and time to chest pain at ETT Endothelial function Vascular oxidative stress	Increased time to ST-depression, total exercise time, and time to chest pain with allopurinol Improvement of endothelium-dependent vasodilation and correction on vascular OS with allopurinol Regression of LV hypertrophy and reduction of LVESV with allopurinol
Rajendra et al., 2011 [95]	Randomized, double-blind placebo-controlled trial ISRCTN15253766	80	Proven CAD Preserved LVEF	UA HF eGFR <30 Uncontrolled hypertension	Allopurinol 600 mg/day versus placebo	n.a.	8 Weeks		
Rekhrj et al., 2013 [96]	Randomized, double-blind placebo-controlled trial ISRCTN73579730	66	Proven CAD LV Hypertrophy	Active gout HF eGFR <60 ml/min Uncontrolled hypertension	Allopurinol 600 mg/day versus placebo	10.6/10	9 Months	Change in LV mass and volumes	Regression of LV hypertrophy and reduction of LVESV with allopurinol
Mackenzie et al., 2022 [99]	ALL-HEART	5721	Age >60 years IHD	Active gout HF (NYHA >II) eGFR <60 ml/min	Allopurinol 300–600 mg/day versus placebo	6.3/6.5	4.8 years (mean)	Composite cardiovascular endpoint (nonfatal MI, nonfatal stroke, or CV death)	Neutral effect

ACS, acute coronary syndrome; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HF, heart failure; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; UA, uric acid.

TABLE 3. Clinical trials on urate-lowering therapy and heart failure

First author, year [ref]	Trial	Patients (N)	Inclusion criteria	Exclusion criteria	UA-lowering regimen	Baseline UA (mg/dl) treatment/control group	Duration of follow-up	Outcomes	Results
Heart failure Hare et al., 2008 [106]	OPT-CHF	405	Age 18–85 years LVEF <40% NYHA III–IV Clinical instability	/	Oxyprurinol 600 mg/day versus placebo	7.9/7.8	24 Weeks	Composite clinical end point (HF morbidity, mortality, QoL)	Neutral effect
Givertz et al., 2015 [108]	EXACT-HF	253	High-risk HF LVEF <40% SUA >9.5 mg/dl	eGFR <20 ml/min	Allopurinol 300/600 mg/day versus placebo	11.0/11.1	24 Weeks	Composite clinical end point (HF morbidity, mortality, QoL)	Neutral effect
Suzuki et al., 2021 [109]	Multicentre randomized trial ISRCTN00009817	263	NYHA II–III stable HF on GDMT SUA >7 mg/dl	Recent ACS ADHF Severe hypotension SeCr >2 mg/dl	Allopurinol 100–200 mg versus Febuxostat 10–60 mg/day	8.7/8.6	3 Years	Change in oxidative stress CV events HF hospitalizations	Reduction of ROS Trend towards a reduction of hospitalizations in HFPEF with Febuxostat n.a.
Yokota et al., 2018 [110]	LEAF-HF ongoing	200	NYHA II–III LVEF <40% SUA >7 mg/dl Elevated BNP	Recent ACS eGFR <30 ml/min Serious liver disease	Febuxostat 10–60 mg/day versus placebo	7–10	24 Weeks	Difference in BNP levels	n.a.
Rubinstein et al., 2022 [112]	Re-Prospere-HF ongoing	120	NYHA II–III stable HF on GDMT	Recent ACS or revasc. CRT-P/D eGFR <30 ml/min	Probenecid 1 g/day versus placebo	n.a.	6 Months	Change in EF Functional status Self-reported health status	n.a.

ACS, acute coronary syndrome; eGFR, estimated glomerular filtration rate; GDMT, guideline directed medical therapy; HF, heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; MI, myocardial infarction; UA, uric acid.

TABLE 4. Clinical trials on urate-lowering therapy and chronic kidney disease

Reference	Trial	Patients (N)	Inclusion criteria	Exclusion criteria	Urate-lowering regimen	Baseline UA (mg/dl)	Duration of follow-up	Outcomes	Results
Chronic kidney disease Goicoechea et al., 2010 [115]	Randomized, double-blind trial ISSN1555-9041/508-0001	113	eGFR <60 ml/min Stable renal condition Stable clinical condition	Gout Severe hepatic disease HIV	Allopurinol 100 mg/day versus standard of care	7.97.3	2 Years	Renal disease progression Cardiovascular events Hospitalization of any causes	Allopurinol independently slows down renal disease progression and reduces CV risk Neutral effect
Kimura et al., 2018 [118]	FEATHER	443	eGFR <60 ml/min SUA >7 mg/dl	Gout Uncontrolled hypertension Uncontrolled diabetes Recent AKI	Febuxostat 10–40 mg/day versus placebo	7.87.8	2 Years	Slope (ml/min per year) of eGFR Change in eGFR	Neutral effect
Kojima et al., 2019 [119]	FREED	1070	Age >65 years SUA >7 mg/dl HT or DM or CVD or Cerebrovascular disease	Gout eGFR <30 ml/min Uncontrolled hypertension Recent ACS Recent AKI	Febuxostat 10–40 mg versus standard of care	7.54/7.50	3 Years	Cerebral, cardiovascular and renal events and all deaths	Febuxostat decreased the exacerbation of albuminuria or proteinuria Neutral effect on CV and cerebrovascular outcomes
Doria et al., 2020 [116]	PERL	530	Type I diabetes eGFR 40–100 ml/min Albuminuria Stable decline in renal function SUA >4.5 mg/dl	Gout Uncontrolled hypertension HIV Significant hepatic disease	Allopurinol 300–400 mg/day versus placebo	6.1/6.1	3 Years	Change in baseline-adjusted GFR Decrease in the iohexol-based GFR per year Urinary albumin excretion rate Change in eGFR	Neutral effect
Badve et al., 2020 [117]	CKD-FIX	369	eGFR 15–60 ml/min UA CR >265 Stable decline in renal function	Gout Recent AKI	Allopurinol 100–300 mg versus placebo	8.2/8.2	2 Years	Change in eGFR	Neutral effect

eGFR, estimated glomerular filtration rate; UA, uric acid.

One study [115] found a significant inverse correlation between SUA levels and the eGFR, suggesting that lowering SUA with allopurinol may slow down the progression of renal disease. However, two landmark trials, the PERL Trial [116] and the CKD-FIX Trial [117], did not show a significant difference in kidney-function decline between allopurinol and placebo groups (see Table 4).

Febuxostat, another urate-lowering medication, has also been tested in trials. The FEATHER study [118] did not find a significant effect on kidney function decline in patients with stage 3 CKD and asymptomatic hyperuricemia. Subgroup analysis demonstrated a significant benefit from febuxostat in patients without proteinuria and for whom serum creatinine concentration was lower than the median. In the FREED study [119], patients with an early-stage kidney damage treated with febuxostat showed a slower decline in kidney function, driven by lesser development of proteinuria. Likewise, the URIC-CKD study found no difference in the effect of febuxostat and benzbromarone on the decline of renal function in stage G3 CKD complicated by hyperuricemia and hypertension, except for the group in the CKDG3a in which reduction of eGFR was less than in benzbromarone group [120].

Overall, the evidence does not strongly support a causal role of urate levels in the progression of CKD in its established phase (see Table 4). However, febuxostat may have a beneficial effect in the early stages of renal disease by preventing glomerular damage and proteinuria [121]. Further randomized controlled trials are needed to confirm these findings and establish the true nephroprotective potential of febuxostat (Table 4).

Stroke

SUA plays a marginal but synergic role in the residual risk of stroke, making the primary prevention of cerebrovascular disease challenging. Studies have shown that allopurinol use is associated with a lower risk of ischemic stroke [122], especially with prolonged treatment [123]. However, the correlation between allopurinol's effect on stroke risk and reduction in SUA levels is not clear.

A randomized controlled trial on asymptomatic hyperuricemia patients with increased carotid artery thickness [124] did not find significant differences in carotid artery thickness between those receiving febuxostat and those modifying their lifestyle (see Table 3).

Allopurinol has shown to have beneficial effects on stroke survivors [125], reducing inflammatory markers [126], arterial stiffness and central blood pressure [127,128]. It also improves functional status independently of SUA reduction [129] (see Table 1). A meta-analysis of randomized controlled trials showed a favourable effect of ULT on SBP and cardiovascular events (including nonfatal stroke) in patients with previous cardiovascular disease [130].

Allopurinol use in the context of secondary prevention of stroke among patients with asymptomatic hyperuricemia is indeed common in clinical practice, though at the best of our knowledge, RCTs and clear recommendations are lacking even in this scenario.

In conclusion, current studies consistently demonstrate that elevated levels of SUA are associated with an increased risk of hypertension and cardiovascular events, such as MI, stroke, hospitalization for heart failure (HF), and renal impairment. Based on these epidemiological data, there has been a growing debate on the potential role of uric acid as a cardiovascular risk factor and particularly whether it acts as a causal agent, a bystander or a surrogate biomarker.

The selectively unfavourable role of SUA has recently been confirmed in a cohort study that enrolled patients without other cardiovascular risk factors aside from hyperuricemia [16]. This study demonstrated that elevated SUA levels per se are associated with a higher risk of major cardiovascular events and hospitalizations. However, the magnitude of SUA prognostic impact appears to be modulated by the lipid profile [131], the presence of standard modifiable cardiovascular risk factors [132] and background renal function [42].

After a comprehensive analysis, across multiple clinical conditions, there are currently no randomized trials demonstrating the effectiveness of direct ULT in reducing or preventing cardiovascular events. Therefore, a large prospective study with a sufficiently long follow-up appears to be needed to define the cause–effect relationships between the reduction of SUA levels and cardiovascular protection or primordial prevention.

Concerning nonconventional urate-lowering agents, we highlight how implementing all recommended treatments for concurrent cardiovascular diseases leads to a synergistic and consistent decrease in SUA levels, accompanied by a significant reduction in major cardiovascular events. In this contemporary landscape, SGLT2 inhibitors merit a specific mention: whereas promoting renal urate excretion, these agents induce a state of starvation mimicry. Upregulating nutrient deprivation signalling (SIRT1 and AMPK) and counteracting nutrient surplus signalling (mTOR and HIF-1a), they target the metabolic dysregulation of purine catabolism and urate synthesis [133]. It is, therefore, good clinical practice to periodically reassess SUA level, the presence of clinical manifestations of hyperuricemia and ultimately the appropriate indication for ULT after the initiation or up-titration of cardiovascular medications.

At the current stage, the definition of hyperuricemia as a conventional risk factor is still uncertain. In spite of that, it should be mentioned that only half of the incident cardiovascular diseases can be attributable to five conventional major modifiable risk factors [134]: Together with other emerging risk factors, Hyperuricemia can play a role within the broad area of cardiovascular residual risk.

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Conflicts of interest

There are no conflicts of interest.

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