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Review Article

Crystal clear – part I: The role of uric acid in cardiorenal disease

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ABSTRACT

This review opens a two-part series by exploring the evolutionary origins, vascular implications, renal pathophysiology, and prognosis related to serum uric acid (SUA). We begin by examining the ancestral loss of uricase in hominoids, which conferred elevated SUA—initially advantageous for sodium retention and antioxidant defense, yet maladaptive in today's purine- and fructose-abundant diet. UA thus re-emerges as a biologically active molecule, exhibiting both protective antioxidant effects and harmful pro-inflammatory actions.

We then delineate SUA's vascular effects: it drives oxidative stress, endothelial dysfunction, and metabolic signaling disruption, magnified in chronic kidney disease (CKD) by impaired clearance and systemic inflammation. Elevated SUA is independently linked to renal function decline, as shown in prospective cohorts across diverse populations.

We also evaluate urate-lowering therapies (ULT), discussing mixed evidence of benefit on kidney outcomes and emphasizing the need for more precise risk targeting. Finally, we outline strong associations between hyperuricemia and increased all-cause and cardiovascular mortality, particularly in high-risk groups (CKD, heart failure, diabetes, gout).

Taken together, this first installment highlights the importance of stratified treatment strategies in hyperuricemia, suggesting that future trials should focus on interventions tailored to specific clinical phenotypes, avoiding unnecessary UA reduction in low-risk populations.

1. Uric acid: an evolutionary legacy with dual implications

Uric acid (UA), the terminal product of purine catabolism in humans, arises from both endogenous nucleic acid turnover and exogenous sources—particularly diets rich in animal protein and fructose. While hepatic xanthine oxidoreductase (XOR) is the main enzyme involved in UA generation, other tissues, including the intestines, kidneys, muscles, and vascular endothelium, contribute to circulating levels [1–3]. UA is predominantly confined within peroxisomes and circulates in a dissociated soluble salt form under physiological pH and temperature [4]. When serum levels exceed 6.8 mg/dL—the solubility threshold—monosodium urate (MSU) crystals can form, especially in peripheral tissues exposed to lower temperatures or acidic microenvironments. These crystals can trigger inflammation and clinical manifestations such as gout [5,6]. Stress, ethanol, hypoxia, and lactic acidosis further favor crystallization, and recent evidence suggests MSU may induce specific antibody responses that accelerate aggregation [7].

Unlike most mammals, humans and other hominoids lack uricase, the enzyme that converts UA into the more soluble allantoin. This evolutionary loss, dated to ~15 million years ago, has led to chronically higher serum UA (SUA) levels in humans [8,9]. It is believed that this mutation conferred survival benefits in ancient environments by supporting blood pressure regulation and energy storage—traits now maladaptive in the context of modern high-purine and fructose-rich diets [9,10]. Today, elevated SUA is a recognized risk factor for hypertension, obesity, insulin resistance, and cardiovascular disease (CVD). Notably, populations adhering to traditional lifestyles—like the Yanomamo—maintain much lower SUA levels, similar to uricase-expressing species [11].

Despite this pathogenic potential, UA also serves protective roles. It acts as a powerful antioxidant, modulates inflammatory signaling, and supports endothelial progenitor cell function [12]. Genetic forms of hypouricemia, such as those involving SLC22A12/URAT1 mutations, are linked to vascular dysfunction, highlighting the importance of UA homeostasis [13]. However, persistent hyperuricemia promotes systemic inflammation, activates the renin-angiotensin system, and

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damages the endothelium [12].

Recent single-cell transcriptomic data reveal that distinct tubular cell subsets are involved in renal urate handling, with minimal overlap between reabsorptive and secretory pathways [14]. The pathological impact of UA extends beyond crystallization: MSU crystals activate pattern recognition receptors (e.g., toll-like receptors) and the NLRP3 inflammasome [15]. In macrophages, MSU also reduces NAD^+ via CD38, amplifying inflammation – a process that can be reversed byCD38 inhibitors [15]. In endothelial cells, high UA impairs autophagy and accelerates apoptosis, effects attenuated by hydroxychloroquine through restoration of mitochondrial quality control [16].

Moreover, the method of MSU crystal preparation influences their inflammatory activity. Crystals generated via alkali titration are more immunogenic than those formed under neutral or acidic conditions, providing improved models for studying urate-driven inflammation [17]. Taken together, these findings underscore UA's multifaced biological activity. Its effects -spanning from endothelial dysfunction to innate immune activation— can be conceptually mapped across the main physiological systems involved, providing a unifying framework for understanding its dual role in human health and disease.

2. The vascular face of uric acid: friend, foe, or both?

UA, which has been long regarded as a passive end-product of purine metabolism, is now recognized as an active participant in vascular pathology. Beyond its classical association with gout, UA exerts a wide array of effects on the cardiovascular system, involving not only inflammation but also oxidative stress, endothelial dysfunction, and structural remodeling of blood vessels—all of which contribute to the progression of CVD [18].

UA has the capacity to infiltrate vascular smooth muscle cells (VSMCs), where it promotes hypertrophic changes and stimulates the expression of pro-inflammatory molecules [19,20]. These cellular modifications are linked to enhanced arterial stiffness and elevated systemic blood pressure. In vitro studies support these observations, showing that UA encourages VSMCs proliferation and activates signaling pathways that potentiate the effects of the renin–angiotensin system, thus reinforcing its vasoconstrictive and pro-inflammatory actions [21].

Among UA's most critical targets is the vascular endothelium. Chronic hyperuricemia interferes with endothelial function through multiple biochemical mechanisms. One of the most detrimental effects involves impairment of insulin-mediated signaling within endothelial cells. Specifically, UA disrupts the activation of insulin receptor substrate (IRS) proteins and suppresses downstream PI3K/Akt pathways, thereby reducing endothelial nitric oxide synthase (eNOS) activity and lowering nitric oxide (NO) availability [22]. This decline in NO impairs vasodilation and promotes systemic insulin resistance, establishing a pathophysiological link between hyperuricemia, endothelial dysfunction, and metabolic disease [22].

Concurrently, XOR, the enzyme responsible for UA generation, serves as a significant source of ROS during purine metabolism. Elevated XOR activity leads to increased oxidative stress, which exacerbates endothelial injury and inflammation, ultimately contributing to the pathogenesis of hypertension and atherosclerosis. Inhibiting XOR has been shown to reduce ROS production and improve vascular function, positioning it as a promising therapeutic target [23].

The vascular toxicity of UA becomes even more pronounced in patients with chronic kidney disease (CKD), where impaired clearance allows UA and other uremic solutes to accumulate. These compounds collectively activate deleterious signaling pathways—including ROS, mitogen-activated protein kinases (MAPK), nuclear factor kappa B (NF-κB), and receptor for advanced glycation end-products (RAGE)—which promote leukocyte adhesion, endothelial apoptosis, and a prothrombotic phenotype [24]. This context-dependent synergy underscores UA's role as a co-contributor to vascular damage in multisystem disease states.

Emerging concepts such as "vascular gout" have expanded the traditional understanding of UA's role in disease. This paradigm suggests that UA, even in its soluble form, can be internalized by endothelial and smooth muscle cells, altering intracellular metabolic pathways and epigenetic profiles [18]. These alterations promote a state of chronic low-grade inflammation and "trained immunity" within innate immune cells, contributing to persistent vascular injury even in the absence of crystalline deposits. Supporting this model, urate-lowering therapies—especially when combined with agents like colchicine—have demonstrated beneficial effects on endothelial function and reduced rates of major adverse cardiovascular events (MACE) in individuals with coronary artery disease [18].

Nevertheless, recent findings advise caution in aggressively lowering UA levels. Clinical trials involving heart failure (HF) patients treated with XOIs have revealed a non-linear relationship between UA levels and endothelial function. The best outcomes, assessed via the reactive hyperemia index (RHI), were observed in individuals with moderate UA concentrations, while both low and high extremes were associated with diminished vascular responsiveness [25]. These results imply a U-shaped curve in the association between serum UA and endothelial health, suggesting that overly aggressive urate reduction could be counterproductive.

Further evidence of UA's impact on the vasculature comes from research in elderly patients with cerebrovascular and metabolic disorders [26]. In these populations—particularly those experiencing acute ischemic stroke, vascular dementia, or type 2 diabetes mellitus (T2DM)—changes in markers of endothelial repair (e.g., CD31, CD34, CD144) and immune dysregulation (notably elevated Th17-like cells) indicate ongoing microvascular injury and impaired regenerative capacity [27]. These findings reflect a chronic state of vascular inflammation and endothelial exhaustion. Interestingly, skeletal muscle appears to play a substantial role in systemic purine turnover and UA production, while endothelial cells also contribute significantly. Therefore, therapeutic strategies aimed at restoring endothelial progenitor cell activity may offer novel means of mitigating UA-related vascular and neurological damage in these vulnerable individuals [27].

Today, UA should no longer be viewed solely as a metabolic waste product or a trigger of gout. Instead, it should be considered a multifaceted mediator of vascular dysfunction, with roles in promoting smooth muscle proliferation, altering endothelial insulin signaling, enhancing oxidative stress, and perpetuating low-grade inflammation. The recognition of its diverse effects is reshaping therapeutic approaches to hyperuricemia—not only to prevent gout, but also to address its systemic vascular consequences. A nuanced and individualized strategy to modulate UA levels, tailored to the underlying clinical context, appears essential for improving cardiovascular outcomes in affected populations.

3. The cardiovascular burden of uric acid

Accumulating evidence implicates SUA as an active contributor to CVD through multiple pathogenic mechanisms. Elevated SUA levels have been associated with endothelial dysfunction, oxidative stress, systemic inflammation, and impaired renal function—all of which are known to play a critical role in the development of adverse CV outcomes [28]. Clinically, hyperuricemia exerts deleterious effects across several target organs, with particularly strong associations observed in coronary and cerebrovascular pathology.

Although the relationship between SUA and cardiovascular risk has been extensively investigated [29,30], findings remain partially heterogeneous. These discrepancies are often attributed to variations in study design and insufficient adjustment for confounders, particularly blood pressure—a variable showing a linear correlation with SUA concentrations [31–33]. Nonetheless, large-scale cohort studies have provided robust data supporting a link between increasing SUA levels and

heightened cardiovascular risk. Notably, the Rotterdam Study demonstrated a progressive and linear association between SUA levels and the incidence of coronary artery disease, myocardial infarction (MI), and stroke [34]. Importantly, the risk appeared to manifest at SUA thresholds lower than those typically used to define hyperuricemia in the context of gout, suggesting the need for reevaluation of current clinical reference ranges.

This hypothesis is further supported by findings from the URRAH study, which reported that both cardiovascular-specific and all-cause mortality increased significantly in individuals with SUA values even below 6.0 mg/dL [35]. Such observations challenge the notion that only overt hyperuricemia carries clinical significance and underscore the need to assess SUA as a continuous variable in cardiovascular risk stratification—particularly in patients with coexisting risk factors. Similar results have been provided by Tian et al., shoving a progressive increase in the risk of major cardiovascular diseases in patients with mildly elevated SUA levels and without any concomitant risk factors thereby excluding the responsibility of confounding conditions as a contributor to cardiovascular complications [36].

Mendelian randomization studies have added a genetic dimension to this association, providing causal evidence for the role of elevated SUA in coronary artery disease and sudden cardiac death [37]. In parallel, a comprehensive meta-analysis focused on hypertensive patients demonstrated that higher SUA levels independently predicted cardiovascular and all-cause mortality, as well as an increased risk of coronary artery disease and MACE, although no consistent association with stroke was observed [38].

Despite these promising associations, the cardiovascular efficacy of SUA-lowering therapies remains a subject of ongoing debate [39]. A large meta-analysis involving over 3.8 million patients found that xanthine oxidase inhibitors (XOIs) did not significantly reduce cardiovascular events compared to placebo. However, subgroup analyses indicated that febuxostat may confer greater benefit in reducing HF risk relative to allopurinol [40]. Moreover, phenome-wide Mendelian randomization analyses suggest that genetically lowered SUA levels are associated with reduced risks of coronary atherosclerosis, HF, cerebrovascular occlusion, and peripheral artery disease [41].

In patients with acute HF, longitudinal SUA measurements offer additional prognostic insight. Persistent elevation of SUA during hospitalization, rather than isolated baseline values, has been independently associated with increased cardiovascular and all-cause mortality [42]. These findings highlight the clinical importance of monitoring dynamic changes in SUA, particularly in high-risk populations.

Renal function further modulates the prognostic impact of SUA on CVD. In advanced CKD, both low and high SUA levels have been associated with increased CV mortality risk, whereas in patients with only mild renal impairment, lower SUA values correlate with improved outcomes [43]. This interaction underscores the need for individualized therapeutic targets based on renal and cardiovascular profiles [44]. Supporting this, a recent prospective cohort study including over 7000 patients with diabetes found that higher SUA levels were independently associated with increased risks of all-cause and cardiovascular mortality, with those in the highest SUA quintile showing a 28 % and 41 % greater risk respectively compared to the lowest quintile [45].

Taken together, these data support the conceptualization of SUA not merely as an inert metabolic byproduct, but as a modifiable factor contributing to the CVD burden. While interventional trials have yet to definitively establish cardiovascular benefit from SUA-lowering therapies in the general population, emerging evidence suggests potential utility in select patient subsets. Future studies should aim to identify optimal SUA targets and clarify sex- and kidney-function-specific risk thresholds to better guide clinical decision-making.

4. Rethinking uric acid in chronic kidney disease: from biomarker to target

Elevated SUA has emerged as an independent predictor of renal function decline across diverse populations. In healthy normotensive individuals, higher SUA levels predicted significant reductions in eGFR over a 5-year period [46]. Longitudinal data from the Jerusalem cohort further confirmed SUA as a GFR-independent risk factor for both acute and chronic renal insufficiency [47]. Similarly, in a large Southeast Asian cohort, hyperuricemia was associated with a nearly twofold increase in the risk of developing reduced kidney function over 12 years [48].

More recently, a large community-based Japanese study demonstrated that even slight increases of UA within the normal range were independently associated with accelerated eGFR decline and higher incidence of renal insufficiency, with a more pronounced effect among females and individuals with T2DM or proteinuria [49]. The role of hypertension as a potential mediator was highlighted by findings showing stronger associations between elevated SUA and kidney function decline in hypertensive compared to normotensive subjects [50].

Additionally, pooled data from two large U.S. cohorts revealed that elevated baseline SUA modestly increased the risk of incident kidney disease over an 8.5-year follow-up (OR per 1 mg/dL increase: 1.07–1.11), independent of multiple cardiovascular and demographic factors [51]. Among patients with diabetes, both type 1 and type 2, hyperuricemia has been linked to early progressive loss of renal function and higher risk of incident CKD (OR per 1 mg/dL increase: 1.4 (95 % CI: 1.1–1.8) in type 1 diabetes, and adjusted OR: 2.10 (95 % CI: 1.16–3.76) in T2DM), suggesting UA as a relevant risk factor in this high-risk population as well [52,53].

A notable cohort study involving over 5000 patients demonstrated that individuals in the highest quintile of SUA had a renal failure prevalence of up to 42 %, defined by an eGFR below 60 mL/min/1.73 m^2. However, the association with progressive kidney function decline was modest, with an adjusted odds ratio (OR) up to 1.49 (95 % CI, 1.00–2.22) in the fifth quintile, and SUA was not significantly associated with incident CKD [54].

Further research has corroborated the role of hyperuricemia as a predictor of end-stage kidney disease (ESKD) [55,56], graft loss post-kidney transplantation [57,58], and early renal damage in hypertensive patients undergoing primary prevention [59,60]. These findings suggest that elevated SUA levels may not only result from impaired renal function but also contribute to its deterioration. UA has also been implicated in renal impairment through several mechanisms including tubular precipitation, oxidative stress, endothelial dysfunction, and inflammatory cytokine production. These pathways may contribute to renal and cardiovascular pathology even in asymptomatic individuals [61].

The interplay between hyperuricemia and CVD is also increasingly recognized as clinically relevant. Renal dysfunction, a well-established risk factor for CVD, may amplify CV risk in patients with hyperuricemia, as the associated decline in eGFR contributes to increased cardiovascular events. Conversely, impaired renal function reduces urate excretion, further exacerbating hyperuricemia and its related CV burden. In patients with HF, higher rates of mortality and hospitalization have been reported among individuals with preserved renal function, suggesting a potential link between elevated XOR activity, oxidative stress, and CV outcomes [62,63]. Notably, a study on ambulatory patients with HF and reduced ejection fraction (HFrEF) found that elevated SUA levels were associated with poorer one-year cardiovascular outcomes - particularly in patients without CKD – indicating that SUA may have independent prognostic value in this subgroup [64].

Importantly, recent evidence suggests that SUA is not merely associated with disease progression but may serve as an independent predictor of mortality. A meta-analysis involving over 260,000 patients undergoing hemodialysis reported a paradoxical inverse relationship

Table 1
Urate-lowering therapies and their impact on cardiovascular and renal outcomes.

Pharmacological class	Agent	Cardiovascular and Renal effects	Pivotal clinical evidence	Key clinical considerations
Xanthine oxidase inhibitors	Allopurinol	Neutral effect on renal / cardiovascular outcomes	Randomized controlled clinical trials	Widely used, good safety profile
	Febuxostat	Potential ↓ in cardiovascular events; eGFR preservation	Network meta-analysis	Greater urate-lowering potency
URAT1 inhibitors	Lesinurad, Dotinurad	Limited data on CV outcomes	Preliminary studies	Often used in combination with a xanthine oxidase inhibitor
Anti-inflammatory therapy	Colchicine (low-dose)	Improved endothelial function; ↓ MACE in patients with CAD	Cohort studies	Adjunctive anti-inflammatory potential

CAD= Coronary artery disease; eGFR= Estimated glomerular filtration rate; MACE= Major adverse cardiovascular event; URAT1= Urate transporter 1.

between SUA levels and both CV and all-cause mortality [65]. Specifically, each 1 mg/dL increase in SUA was associated with a 9 % reduction in CV mortality and a 6 % reduction in all-cause mortality [65]. These findings point to a phenomenon of reverse epidemiology in advanced CKD and underscore the complexity of interpreting SUA levels in this population.

Further supporting this complexity, recent evidence from a large retrospective cohort of peritoneal dialysis (PD) patients revealed a U-shaped relationship between time-averaged SUA (TA-SUA) and mortality [66]. Both low (<5.1 mg/dL) and high (>6.8 mg/dL) TA-SUA levels were associated with increased all-cause and cardiovascular mortality over a 48-month follow-up [66]. Importantly, lower TA-SUA levels were independently predictive of mortality after adjusting for age, diabetes, malnutrition, and other confounders. Each 1 mg/dL decrease in TA-SUA was associated with a 23 % increase in all-cause mortality (HR = 0.81, 95 % CI: 0.71–0.94) [66]. These findings further illustrate the potential reverse epidemiology of SUA in advanced CKD and emphasize the need for individualized interpretation of SUA values in dialysis populations.

Emerging data also suggest that adjusting SUA for serum creatinine (SUA/sCreat ratio) may improve risk stratification, potentially distinguishing individuals with heightened cardio-metabolic risk. This approach reflects a shift in focus from urate underexcretion to urate overproduction, particularly in patients predisposed to CV complications [67,68]. The global rise in both CKD and hyperuricemia—frequently coexisting with metabolic syndrome—highlights the urgency of defining clinically actionable SUA thresholds. Current challenges include inconsistent outcomes from ULT trials and varying SUA cut-offs predictive of CV risk depending on CKD stage, as highlighted by the URRAH project [69].

Experimental models showed that elevated SUA can accelerate CKD progression in the absence of crystal deposition, implicating soluble UA as the mediator [70]. Though once considered an antioxidant, UA has been found to induce oxidative stress, impair endothelial function, activate the renin-angiotensin system, and promote proinflammatory pathways including NF-κB and the inflammasome [71,72]. Interestingly, despite Mendelian randomization studies suggesting no causal link between UA and CKD, substantial epidemiologic and interventional data support a pathogenic role, particularly via intracellular urate toxicity. The main benefit of ULT may lie in CV protection rather than renal preservation [73].

Pilot studies and meta-analyses have suggested potential benefits of urate-lowering therapy (ULT), particularly with XOIs, in slowing CKD progression [74,75]. A recent meta-analysis of randomized controlled trials further demonstrated that ULT in patients with asymptomatic hyperuricemia preserved eGFR and reduced serum creatinine levels over both short- and long-term periods, although it did not reduce the risk of acute kidney injury (AKI) [76]. However, large randomized trials such as PERL (patients with type 1 diabetes and CKD stages 2–3) and CKD-FIX (CKD stages 3–4) failed to demonstrate significant renal benefit from allopurinol therapy [77,78]. This was probably due to the type of the population.

These findings led many experts to conclude that routine ULT in CKD is not warranted unless indicated for gout prevention [79]. Some even suggest that asymptomatic hyperuricemia may be beneficial in CKD patients [80], while others suggests caution. Nonetheless, it is becoming increasingly clear that a blanket approach may be inappropriate [81]. Importantly, both PERL and CKD-FIX trials excluded patients with gout—who may represent up to one-third of the CKD population—and did not restrict inclusion to hyperuricemic individuals, potentially underestimating the therapeutic benefit. Supporting this, a recent large cohort study using a target trial emulation approach found that achieving a target SUA level (<6 mg/dL) with ULT in patients with gout and CKD stage 3 was associated with a significantly lower risk of progression to severe or end-stage kidney disease (HR 0.89; 95 % CI, 0.80–0.98) [82].

A comparative overview of urate-lowering agents and their respective impacts on CV and renal outcomes underscores the importance of tailoring treatment based on patient-specific risk profiles (Table 1).

A network meta-analysis comparing febuxostat and allopurinol in patients with CKD stages 3–5 and asymptomatic hyperuricemia showed that febuxostat may provide greater improvements in kidney function (mean difference in eGFR: +4.99 mL/min/1.73 m^2 vs allopurinol; 95 % CI, −0.65 to 10.78) and more effective SUA reduction, without increased cardiovascular risk [83]. Specific therapies such as febuxostat have also shown promising results in reducing kidney events, slowing eGFR decline, and lowering albuminuria in patients with gout or hyperuricemia, underscoring its renoprotective potential [84].

Specific patient subgroups are likely to benefit from targeted therapy. These include patients with gout, who often remain undertreated despite evidence of urate crystal deposition in coronary arteries, aorta, and kidneys, as well as those with urate crystalluria, which can activate inflammasomes in renal tubular cells and promote local injury. Despite the high prevalence of gout in CKD patients, fewer than a quarter receive effective treatment. This is due in part to therapeutic complexities—drug contraindications, required dose adjustments, and inter-specialist coordination. Nephrologists are urged to take a more active role in managing gout as a major complication of CKD [85].

Additionally, cancer survivors with CKD and hyperuricemia face increased risks of both all-cause and cardiovascular mortality [86]. In China, where dialysis prevalence is rapidly increasing, hyperuricemia affects a substantial portion of patients and promotes ESKD through purine crystallization, inflammation, and RAS activation [87]. A cross-sectional study confirmed that nearly half of CKD patients on hemodialysis present with hyperuricemia, with common comorbidities including hypertension and anemia [88].

Genetic factors may also modulate treatment response. A recent genome-wide association study (GWAS) identified 377 loci associated with gout and UA metabolism. This study revealed that inflammation, including NLRP3 inflammasome activity, plays a critical role in gout pathogenesis and may represent a key therapeutic target [89]. Ultimately, generalized treatment of hyperuricemia—particularly with XOIs—may not be the optimal strategy due to the significant heterogeneity among hyperuricemic patients and the complex interplay of oxidative stress, inflammation, and renal accumulation. Personalized treatment strategies that incorporate clinical phenotype, biochemical

markers (e.g., SUA/sCreat ratio), and genetic predispositions may more effectively identify those who will benefit from urate-lowering therapy.

5. Uric acid and mortality

Current guidelines and expert consensus increasingly recognize elevated SUA as an independent CV risk factor, particularly in patients with comorbidities such as hypertension, chronic kidney disease, and heart failure. Emerging evidence supports a continuum of risk for all-cause and cardiovascular mortality across a wide range of SUA values and patient populations.

Higher SUA levels have been associated with increased all-cause mortality, with reported relative risks (RR) ranging from 1.20 (95 % CI, 1.13–1.28) [90] to 1.24 (95 % CI, 1.09–1.42) [91]. For each 1-mg/dL increase in SUA, the risk of all-cause mortality increased by 9 % [92], though the sex specific nature of this association remains inconsistent across studies [91,93].

Hyperuricemia has also been linked to higher cardiovascular (CV) mortality, with a reported RR of 1.37 (95 % CI, 1.19–1.57) for the highest SUA category [91] and a hazard ratio (HR) of 1.45 (95 % CI, 1.33–1.58) [57]. The association appears to be stronger in women than in men. A random-effects dose-response model demonstrated a positive nonlinear relationship between SUA levels and CV mortality. Data from the URRAH study clearly showed increased risk of both all-cause and cardiovascular mortality at SUA levels as low as 4.5–5.5 mg/dL [57,94].

Moreover, a large meta-analysis including over 2.5 million individuals from 34 general population-based cohort studies showed that elevated SUA levels were significantly associated with increased risk of all-cause mortality (RR: 1.32; 95 % CI: 1.26–1.39), with a particularly strong association observed in women (RR: 1.91) compared to men (RR: 1.16) [95]. These findings reinforce the role of SUA as an independent predictor of fatal outcomes, especially in middle-aged adults, individuals of Caucasian ethnicity, and those living in OECD countries.

Hyperuricemia has been linked to higher all-cause and cardiovascular mortality in individuals with hypertension, with those exhibiting both conditions at an even greater risk (HR 1.87, 95 % CI: 1.43–2.82) [96].

In a separate large cohort of 13,363 hypertensive patients from the NHANES database (2001–2018), both high and low SUA levels were associated with elevated all-cause and cardiovascular mortality [97]. Specifically, all-cause mortality (ACM) HRs across SUA quartiles were: 1.00 (reference), 1.557 (1.387–1.747), 1.312 (1.154–1.492), and 1.393 (1.228–1.580), all $p < 0.01$. CV mortality HRs were 1.00, 1.308 (1.043–1.641), 1.182 (0.938–1.490), and 1.151 (0.904–1.464). These results suggest a U-shaped relationship between SUA levels and mortality in hypertensive individuals, with both extremes associated with increased risk.

Additionally, in osteoarthritis (OA) patients, hyperuricemia independently increased the risk of both all-cause and CVD mortality (HR: 1.22, 95 % CI: 1.06–1.41 for all-cause; HR: 1.32, 95 % CI: 1.02–1.72 for CVD) [98]. Furthermore, a combination of hyperuricemia and CKD significantly elevated long-term mortality risks in HF patients (HR for hyperuricemia+/CKD+ group: 1.59, 95 % CI: 1.43–1.76) [99]. Hyperuricemia has also been identified as a potential risk factor for stroke, with pooled relative risks of 1.42 (95 % CI: 1.31–1.53) for stroke incidence and 1.53 (95 % CI: 1.18–1.99) for stroke mortality, particularly in females [100]. The presence of hyperuricemia is also correlated with an increased risk of CHD mortality, with a relative risk of 1.14 (95 % CI: 1.06–1.23) for CHD mortality and 1.20 (95 % CI: 1.13–1.28) for all-cause mortality in general populations [90]. Moreover, hyperuricemia in combination with hyperinsulinemia has been found to significantly augment the mortality risk, particularly in normal-weight individuals and those over the age of 40 (HR: 2.32, 95 % CI: 1.66–3.25) [101]. Additionally, among CKD patients, hyperuricemia, especially in conjunction with anemia, has been associated with higher all-cause mortality, with a potential synergistic effect (RERI: 0.630, AP: 0.291) [102].

Emerging evidence has also highlighted a strong interaction between SUA levels and systemic inflammation in CAD patients. In a cohort of 16,598 individuals with available hsCRP and SUA data, higher SUA quintiles were significantly associated with increased risk of major adverse cardiovascular and cerebrovascular events (MACCE), but only in those with hsCRP $\geq$ 2 mg/L [103]. Each unit increase in SUA levels conferred an 11.3 % increased risk of MACCE (adjusted $p < 0.001$). No such association was observed in those with hsCRP $<$ 2 mg/L, suggesting the prognostic relevance of SUA is amplified in the context of chronic low-grade inflammation [103]. These findings support a potential benefit of combining ULT with anti-inflammatory strategies in this subgroup.

Altogether, these data underscore the clinical importance of monitoring SUA levels not only as a metabolic marker but as a modifiable risk factor, especially in high-risk groups.

Meta-analyses have shown an association between hyperuricemia and coronary artery disease (CAD) mortality, with RRs ranging from 1.14 to 1.27 [104–107]. Each 1-mg/dL increase in SUA was associated with a 12 % to 20 % increase in CAD mortality, a finding also confirmed by the URRAH study [108].

Elevated SUA is also associated with increased stroke mortality, with RRs ranging from 1.36 (95 % CI, 1.03–1.69) to 1.33 (95 % CI, 1.24–1.43). The latter association was significant in women but not in men [109]. In patients with established hypertension, hyperuricemia was associated with higher all-cause mortality (HR 1.12; 95 % CI, 1.02–1.23), although this association lost significance after adjustment for confounders [110].

Several recent studies have reported an increased risk of acute MI and stroke with progressive exposure to elevated SUA levels (see paragraphs 6.1 and 6.3) [111,112], emphasizing the importance of repeated SUA measurements to enhance prognostic accuracy.

In patients with HF, higher SUA levels were associated with increased all-cause mortality (RR 1.43; 95 % CI, 1.31–1.56). Each 1-mg/dL increase in SUA was linked to an 11 % increase in all-cause mortality [113]. A meta-analysis involving approximately 1500 HF patients with a median left ventricular ejection fraction of 32 % identified SUA as a strong predictor of all-cause mortality, with a pooled RR of 2.13 (95 % CI, 1.78–2.55) for SUA levels >6.5 mg/dL compared with ≤6.5 mg/dL. The URRAH study confirmed these findings, using even lower cut-off levels for predicting all-cause and CV mortality [114].

Among patients with acute coronary syndrome, hyperuricemia was independently associated with increased all-cause (RR 1.86; 95 % CI, 1.49–2.32) and CV mortality (RR 1.74; 95 % CI, 1.36–2.22) [115]. In patients with suspected or confirmed CAD, the highest SUA category was associated with a pooled adjusted RR of 2.09 (95 % CI, 1.45–3.02) for CV mortality and 1.80 (95 % CI, 1.39–2.34) for all-cause mortality, compared with the lowest SUA category. Each 1-mg/dL increase in SUA corresponded to a 12 % increase in CV mortality and a 20 % increase in all-cause mortality [116].

In patients with CKD, higher SUA levels were associated with increased CV mortality, with an HR of 1.47 (95 % CI, 1.11–1.96) compared to the lowest SUA levels. Each 1-mg/dL increase in SUA raised CV mortality risk by 12 % [117].

In gout patients, a pooled analysis of over 200,000 individuals free from CVD found gout to be associated with elevated CV mortality (HR 1.29; 95 % CI, 1.14–1.44) and CAD mortality (HR 1.42; 95 % CI, 1.22–1.63) [118].

Hyperuricemia has also been associated with increased mortality in patients with T2DM. A meta-analysis involving 11,750 diabetic patients initially identified a modest association between SUA and all-cause mortality (HR 1.06; 95 % CI, 1.03–1.09) [119]. A recent study of >7000 diabetic patients from NHANES (1999–2018) reported increased CV mortality (RR 1.41; 95 % CI, 1.03–1.94) [120], consistent with findings from a meta-analysis of 13 studies that showed a pooled HR of 1.08 (95 % CI, 1.05–1.11) for all-cause and 1.05 (95 % CI, 1.03–1.06) for

Table 2
Suggested therapeutic strategies based on clinical phenotype.

Clinical Scenario	Recommended Therapeutic Strategy	Supporting Rationale
Gout with CKD (stage ≥3)	Xanthine oxidase inhibitor (± URAT1 inhibitor) to achieve SUA <6 mg/dL	Associated with reduced risk of ESKD
CKD without clinical gout	Initiate therapy only if SUA >7–8 mg/dL	Limited benefit; urate-lowering at low SUA may be harmful
Atherosclerotic CVD with elevated inflammation (hsCRP ≥2 mg/L)	Xanthine oxidase inhibitor plus anti-inflammatory therapy (e.g., low-dose colchicine)	Reduction in MACCE in patients with concomitant inflammation and hyperuricemia
Asymptomatic individuals at low risk	No pharmacological urate-lowering therapy	No demonstrated clinical benefit; risk of overtreatment

CKD= Chronic kidney disease; CVD= Cardiovascular disease; hsCRP: high-sensitivity C reactive protein; ESKD= End-stage kidney disease; MACCE= Major adverse cardiovascular and cerebrovascular events; SUA= Serum uric acid; URAT1= Urate transporter 1.

CV mortality per 1-mg/dL increase in SUA. Elevated SUA may also contribute to renal dysfunction in this population, further amplifying its detrimental impact on the cardiometabolic system.

6. Beyond gout: rethinking uric acid in modern medicine

The control of SUA levels has emerged as a critical challenge in the prevention and management of cardiovascular, metabolic, and renal diseases. Once regarded as a biologically inert waste product of purine metabolism, UA is now recognized as a dynamic and pathophysiologically active compound. Hyperuricemia, or elevated SUA levels, is not merely a marker of disease risk but actively contributes to pro-inflammatory and pro-oxidative processes that affect the heart, blood vessels, kidneys, and metabolic pathways [121]. Mounting epidemiological evidence supports the role of SUA as an independent predictor of both CV and renal morbidity and mortality, prompting a shift in clinical perspective toward more proactive monitoring and management strategies [122].

From an evolutionary standpoint, the loss of the uricase enzyme in humans led to a chronic elevation in SUA levels—likely advantageous in prehistoric environments marked by sodium scarcity and caloric stress [123]. However, this adaptation has become maladaptive in the context of modern diets rich in purines, fructose, and salt, which collectively exacerbate hyperuricemia and contribute to a wide range of chronic conditions. The overproduction of UA—largely driven by XOR activity—is a central pathogenic mechanism, fueling oxidative stress, inflammation, and endothelial dysfunction [23]. While impaired renal excretion of UA also contributes to elevated SUA, recent insights suggest that overproduction may be the more critical driver of tissue injury, though the interplay between these mechanisms remains complex and, at times, confounding in the interpretation of treatment outcomes [124].

Mechanistic studies have demonstrated that hyperuricemia induces endothelial dysfunction by reducing NO bioavailability and impairs insulin signaling, linking it to hypertension, metabolic syndrome, and T2DM [3]. Simultaneously, UA activates the renin–angiotensin system and promotes vascular smooth muscle cell proliferation and oxidative damage, compounding its role in vascular remodeling and atherosclerosis [125]. These findings are reinforced by clinical observations showing increased risk of coronary artery disease, HF, stroke, and CKD progression among individuals with elevated SUA, even in the absence of gout [126].

In conclusion, UA should be redefined not as a passive metabolic endpoint, but as a clinically relevant and modifiable factor in the pathogenesis of cardiovascular and renal diseases [61]. While debate persists as to whether hyperuricemia is a cause or consequence of these conditions, the convergence of genetic, mechanistic, and interventional evidence supports a contributory, if not causative, role. A comprehensive, individualized approach—including pharmacologic therapy when indicated, lifestyle modification, and nutritional strategies—offers the most effective means of managing SUA and improving long-term health outcomes.

In light of these complexities, a phenotype-driven therapeutic approach may better reflect the clinical heterogeneity of hyperuricemia and its systemic implications (Table 2).

Continued research, particularly into the complex interactions between diet, inflammation, and UA metabolism, is essential to refine risk stratification and guide future preventive strategies.

Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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