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Uric acid in cardiovascular and renal disease: Marker, mediator, or therapeutic target?

Aymen Doumi [1], Mohammed omer Eltayeb [2], Walaa yousif Suliman Hamid [3], Nesreen Bushara [4], ShamesEldeen Amara Amer [5], Sahar Abdalla Mohamed Abdalla [6], Sara Abdalla Mohamed Abdalla [7], Abdulrahman Sami Hamad Mohamed [8], Sara Mohamed Mirghani Ali [9], Shadi Mahmoud [10], Alaa Awad [11], Amel Mustafa Elbashir Mohammed Ahmed [12], Elmuhanad Abdalla [13], Hind MohammedAhmed ElShareef SeadAhmed [14] and Tagwa kalool fadlalla Ahmed [15,*]

[1] *Registrar of Acute, General and Intensive Care Medicine, Harrogate District Hospital, UK.*
[2] *Atbara Teaching Hospital, medicine department.*
[3] *Department of medicine Assiut university hospital Country of Egypt.*
[4] *University Hospitals of Morecambe Bay NHS Foundation Trust Furness General Hospital Cumbria UK.*
[5] *Associate Professor of General Surgery Faculty of Medicine and Health Sciences University of Kordofan.*
[6] *Emergency Medicine department, Kerry university Hospital, Tralee, Co.Kerry, Ireland.*
[7] *Neuro rehabilitation Salford Royal Foundation Trust Manchester Country: United Kingdom.*
[8] *Department of medicine Shoaa Medical center, Riyadh, Saudi Arabia.*
[9] *Department of medicine, Ahfad University for Women, Omdurman,Sudan.*
[10] *NHS Fife, Victoria Hospital Kirkcaldy, Acute Medicine, Kirkcaldy, United Kingdom.*
[11] *Manchester, UK General Practice, Salford and Trafford.*
[12] *Royal Stoke Hospital UHNM NHS trust.*
[13] *Rehabilitation medicine, National Rehabilitation Hospital, Dublin, Ireland.*
[14] *Imperial College healthcare NHS Trust London UK.*
[15] *Department of medicine, Ahfad university for women, Omdurman, Sudan.*

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Abstract

Background: Hyperuricemia is increasingly prevalent worldwide, paralleling the epidemics of metabolic syndrome and chronic kidney disease. While its causal role in gout is unequivocal, the position of uric acid in cardiovascular and renal disease remains deeply controversial, with competing interpretations as an innocent biomarker, a pathogenic mediator, or a modifiable therapeutic target. This study aimed to critically appraise the experimental, epidemiological, genetic, and clinical trial evidence concerning the role of uric acid in cardiorenal pathophysiology and the utility of urate-lowering therapy.

Methods: Narrative review integrating mechanistic studies, observational cohorts, Mendelian randomization analyses, and major randomized controlled trials of xanthine oxidase inhibitors and uricosurics.

Key Findings: Uric acid exerts pleiotropic, context-dependent effects: extracellular antioxidant activity contrasts with intracellular pro-oxidant signaling, endothelial dysfunction, RAAS activation, NLRP3 inflammasome stimulation, and vascular smooth muscle cell proliferation. Animal models demonstrate that hyperuricemia can directly induce hypertension and renal arteriolopathy. Large observational studies consistently associate elevated serum uric acid with incident hypertension, chronic kidney disease, and cardiovascular events, and Mendelian randomization studies partly support causality. However, landmark placebo-controlled trials—including CKD-FIX, PERL, and FEATHER—have not

* Corresponding author: Tagwa kalool fadlalla Ahmed.

demonstrated slowing of kidney function decline or reduction in cardiovascular events with urate-lowering therapy in asymptomatic hyperuricemia, and febuxostat was associated with excess mortality in the CARES trial. Current guidelines therefore restrict pharmacotherapy to gout and, cautiously, to high-risk subgroups with early hypertension or mild kidney disease.

Conclusion: Uric acid functions as both a biomarker and a context-dependent mediator of cardiorenal injury. The failure to translate compelling mechanistic and observational data into clinical benefit suggests that any pathogenic role is likely confined to early disease stages. Resolving the controversy will require precision-medicine trials that identify responsive phenotypes and intervene early.

Keywords: Uric Acid; Hyperuricemia; Cardiovascular Disease; Renal Disease

1. Introduction

Uric acid (UA), the terminal product of purine metabolism in humans, has long occupied an ambiguous position in clinical medicine. Historically, hyperuricemia was recognized primarily as the essential precursor to gouty arthritis and urate nephrolithiasis. However, over the past three decades, a substantial body of epidemiological, experimental, and clinical evidence has accumulated, suggesting that elevated serum uric acid (SUA) levels are independently associated with a spectrum of cardiovascular and renal diseases, including hypertension, coronary artery disease, heart failure, stroke, and chronic kidney disease (CKD) [1–4].

The global epidemiological burden of hyperuricemia has escalated dramatically. A landmark systematic review and modelling analysis published in *The Lancet Rheumatology* estimated that the worldwide prevalence of hyperuricemia increased from 6.7% to 11.2% in women and from 12.3% to 18.6% in men between 2000 and 2023, with prevalent cases rising from 126 million to 305 million in women and from 226 million to 500 million in men [5]. This rising prevalence parallels the global epidemics of obesity, metabolic syndrome, type 2 diabetes mellitus, and CKD, suggesting shared pathogenic drivers [6].

Hyperuricemia is conventionally defined as a SUA concentration exceeding 6.8 mg/dL (approximately 404 μmol/L), the physiological solubility threshold of monosodium urate at 37°C [7]. However, a crucial distinction exists between symptomatic hyperuricemia—characterized by clinical manifestations such as gouty arthritis, tophi, or urate nephrolithiasis—and asymptomatic hyperuricemia, in which SUA is elevated without overt clinical signs. While the therapeutic mandate in symptomatic hyperuricemia is well established, the management of asymptomatic hyperuricemia remains profoundly controversial [8].

The central debate surrounding UA revolves around three interconnected questions: Is UA merely an innocent biomarker reflecting underlying metabolic dysfunction and declining renal function, or does it act as a pathogenic mediator directly contributing to tissue injury? If the latter, does urate-lowering therapy (ULT) represent a viable therapeutic strategy for improving cardiovascular and renal outcomes? This review critically examines the evidence addressing these questions, integrating insights from biology, pathophysiology, experimental models, observational epidemiology, genetic studies, and randomized controlled trials (RCTs) to provide a balanced, contemporary perspective.

2. Uric Acid Biology and Metabolism

2.1. Purine Metabolism

UA is a weak organic acid (pKa 5.75) that exists primarily as monosodium urate at physiological pH. It is generated through the sequential oxidation of hypoxanthine to xanthine and finally to UA, reactions catalyzed by xanthine oxidoreductase (XOR), which exists in two interconvertible forms: xanthine dehydrogenase (XDH), which preferentially utilizes NAD+ as an electron acceptor, and xanthine oxidase (XO), which transfers electrons directly to molecular oxygen, generating reactive oxygen species (ROS) including superoxide anion and hydrogen peroxide [9]. Purine substrates derive from endogenous sources—primarily cell turnover and de novo synthesis—and exogenous dietary sources, particularly purine-rich foods such as red meat, seafood, and alcohol [10].

2.2. Evolutionary Perspective

A pivotal event in primate evolution was the progressive loss of uricase (urate oxidase) activity due to multiple independent mutations in the uricase gene, rendering humans and certain higher primates incapable of oxidizing UA to

the more soluble end-product allantoin [11]. This evolutionary adaptation has been hypothesized to confer several advantages: UA's potent antioxidant properties may have contributed to increased lifespan and reduced cancer risk, while its capacity to stimulate sodium reabsorption and raise blood pressure may have provided survival benefits in low-salt environments [11,12]. However, in the context of modern Western diets—characterized by high purine, fructose, and sodium intake—this once-adaptive hyperuricemia may have become maladaptive.

2.3. Uric Acid Homeostasis

UA homeostasis is maintained through a balance between production and elimination. Approximately two-thirds of daily UA excretion occurs via the kidneys, with the remaining third eliminated through the gastrointestinal tract, where intestinal bacteria expressing uricase degrade UA [13]. Renal handling of UA involves glomerular filtration, near-complete proximal tubular reabsorption, subsequent secretion, and post-secretory reabsorption—a complex four-component process. The fractional excretion of urate (FEua) normally ranges from 7–12% and is determined by the integrated function of a sophisticated network of urate transporters [14].

2.4. Urate Transporters

The molecular identification of urate transporters has transformed our understanding of UA physiology. URAT1 (SLC22A12), located on the apical membrane of proximal tubular epithelial cells, is the primary transporter responsible for urate reabsorption from the tubular lumen [15]. GLUT9 (SLC2A9), expressed on the basolateral membrane, mediates the efflux of reabsorbed urate into the interstitium, representing the rate-limiting step in renal urate reabsorption [16]. Genome-wide association studies (GWAS) have consistently identified SLC2A9 variants as the strongest genetic determinants of SUA levels [17]. The integrated function of these renal and extra-renal transporters is illustrated in **Figure 1**.

Counterbalancing reabsorptive pathways, secretory transporters include the organic anion transporters OAT1 (SLC22A6) and OAT3 (SLC22A8) on the basolateral membrane, which mediate urate uptake from the peritubular interstitium, and apical efflux transporters including ABCG2 (BCRP), MRP4 (ABCC4), and NPT1 (SLC17A1) [14,15]. Notably, ABCG2 has emerged as a critical regulator of both renal and extra-renal urate excretion; its expression in the intestinal epithelium mediates significant UA elimination, and ABCG2 dysfunction is strongly associated with hyperuricemia and gout [18]. Genetic variants in ABCG2, particularly the Q141K polymorphism, reduce urate transport capacity by approximately 50% and are associated with early-onset hyperuricemia and gout [18].

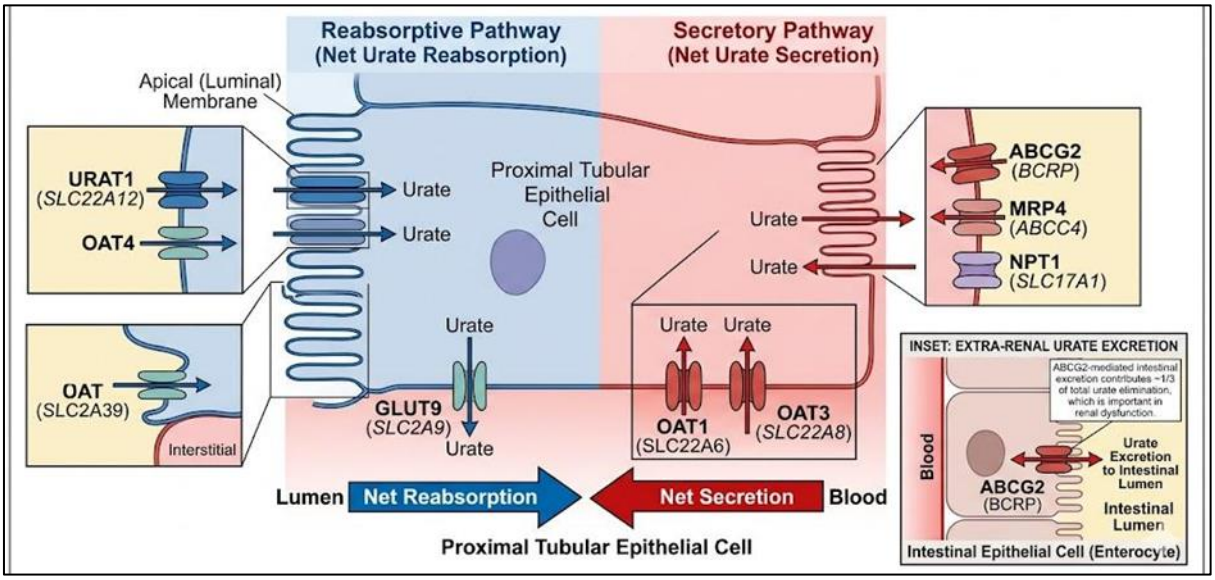

Figure 1 Schematic Representation of Urate Handling in the Renal Proximal Tubule

2.5. Determinants of Serum Uric Acid Levels

SUA levels are influenced by a complex interplay of genetic, dietary, metabolic, and pharmacological factors. Heritability estimates for SUA range from 40–70%, underscoring a strong genetic component [17]. Dietary contributors include fructose, which increases UA production through ATP depletion and purine nucleotide degradation [19]; purine-rich

foods such as red meat, organ meats, and seafood; and alcohol, particularly beer, which contains both purines and ethanol, the latter stimulating adenosine monophosphate deaminase and reducing renal urate excretion [20].

Obesity and insulin resistance are major metabolic determinants of hyperuricemia. Insulin reduces renal urate excretion by stimulating URAT1-mediated reabsorption and inhibiting tubular secretion, thereby linking hyperinsulinemia—a hallmark of the metabolic syndrome—to elevated SUA [21]. Declining kidney function represents another critical determinant; as glomerular filtration rate falls, compensatory increases in fractional urate excretion are often insufficient to maintain net UA excretion, resulting in progressive hyperuricemia [22]. Several commonly prescribed medications exacerbate hyperuricemia, including thiazide and loop diuretics (which increase net proximal tubular urate reabsorption), low-dose aspirin (which has a biphasic effect on urate handling, inhibiting secretion at low doses), and calcineurin inhibitors such as cyclosporine, which reduce renal urate clearance [10].

3. Pathophysiological Mechanisms Linking Uric Acid to Cardiorenal Disease

Multiple converging mechanistic pathways have been identified through which UA may contribute to cardiovascular and renal pathology. An overview of the proposed pathogenic pathways is presented in **Figure 2.**

3.1. Endothelial Dysfunction

UA impairs endothelial function through several mechanisms. Exposure of endothelial cells to UA reduces nitric oxide (NO) bioavailability by inhibiting NO synthase activity, promoting NO degradation through superoxide-mediated peroxynitrite formation, and triggering endothelial nitric oxide synthase (eNOS) uncoupling [23]. Clinically, hyperuricemia is associated with impaired flow-mediated dilation (FMD), a validated measure of endothelial function, and treatment with XO inhibitors has been shown to improve FMD in patients with cardiovascular risk factors [23,24].

3.2. Oxidative Stress

The relationship between UA and oxidative stress is complex and context-dependent. In the extracellular environment, UA functions as a potent antioxidant, scavenging superoxide, hydroxyl radicals, and singlet oxygen, and is estimated to account for up to 60% of the total antioxidant capacity of human plasma [25]. However, upon entry into the intracellular compartment via specific urate transporters, UA exerts pro-oxidant effects, stimulating NADPH oxidase activity, promoting mitochondrial dysfunction, and generating additional ROS [26]. Furthermore, XO activity generates superoxide as a byproduct of purine oxidation, contributing directly to vascular oxidative stress [9]. This dual antioxidant-pro-oxidant nature of UA, often termed the "uric acid paradox," complicates interpretation of its net biological effect.

3.3. Inflammation and Immune Activation

UA has been recognized as a damage-associated molecular pattern (DAMP) capable of activating innate immune pathways. Soluble UA, even in the absence of monosodium urate crystal formation, can activate the NLRP3 inflammasome in renal tubular epithelial cells, triggering caspase-1-mediated cleavage of pro-interleukin (IL)-1β and pro-IL-18 to their bioactive forms, and inducing the release of pro-inflammatory cytokines including IL-6 and tumor necrosis factor-alpha (TNF-α) [27,28]. This chronic low-grade inflammatory state is increasingly recognized as a key mediator of both atherosclerosis and renal fibrosis.

3.4. Renin–Angiotensin–Aldosterone System Activation

Experimental studies have demonstrated that UA stimulates renin expression via activation of the intrarenal renin-angiotensin-aldosterone system (RAAS), leading to angiotensin II-mediated vasoconstriction, sodium retention, and vascular smooth muscle cell hypertrophy [29]. UA also upregulates angiotensin II type 1 receptor expression, amplifying RAAS signaling [29]. This pathway provides a mechanistic link between hyperuricemia and the development of hypertension, particularly in the context of high sodium intake.

3.5. Vascular Smooth Muscle Cell Proliferation

UA stimulates vascular smooth muscle cell (VSMC) proliferation and phenotypic switching from a contractile to a synthetic phenotype through activation of the mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK) pathways, as well as through platelet-derived growth factor receptor phosphorylation [30]. These changes contribute to arteriolopathy, arterial stiffness, and microvascular rarefaction, hallmarks of hypertensive vascular disease.

3.6. Renal Hemodynamic Alterations

In the kidney, hyperuricemia induces afferent arteriolopathy, characterized by smooth muscle cell proliferation and luminal narrowing, which impairs renal autoregulation and predisposes to glomerular hypertension [31]. Sustained glomerular hypertension promotes proteinuria, podocyte injury, and progressive tubulointerstitial fibrosis. UA also directly stimulates epithelial-to-mesenchymal transition in tubular epithelial cells, promoting renal fibrogenesis [31].

3.7. Metabolic Dysregulation

UA and fructose metabolism are intricately linked. Fructose phosphorylation by fructokinase (ketohexokinase) consumes ATP, generating AMP that enters the purine degradation pathway, ultimately producing UA [19]. UA, in turn, further stimulates fructokinase activity, establishing a positive feedback loop that accelerates fructose-driven metabolic dysfunction, including hepatic steatosis, insulin resistance, and visceral adiposity [19,21]. This amplificatory cycle positions UA as both a consequence and a driver of the metabolic syndrome.

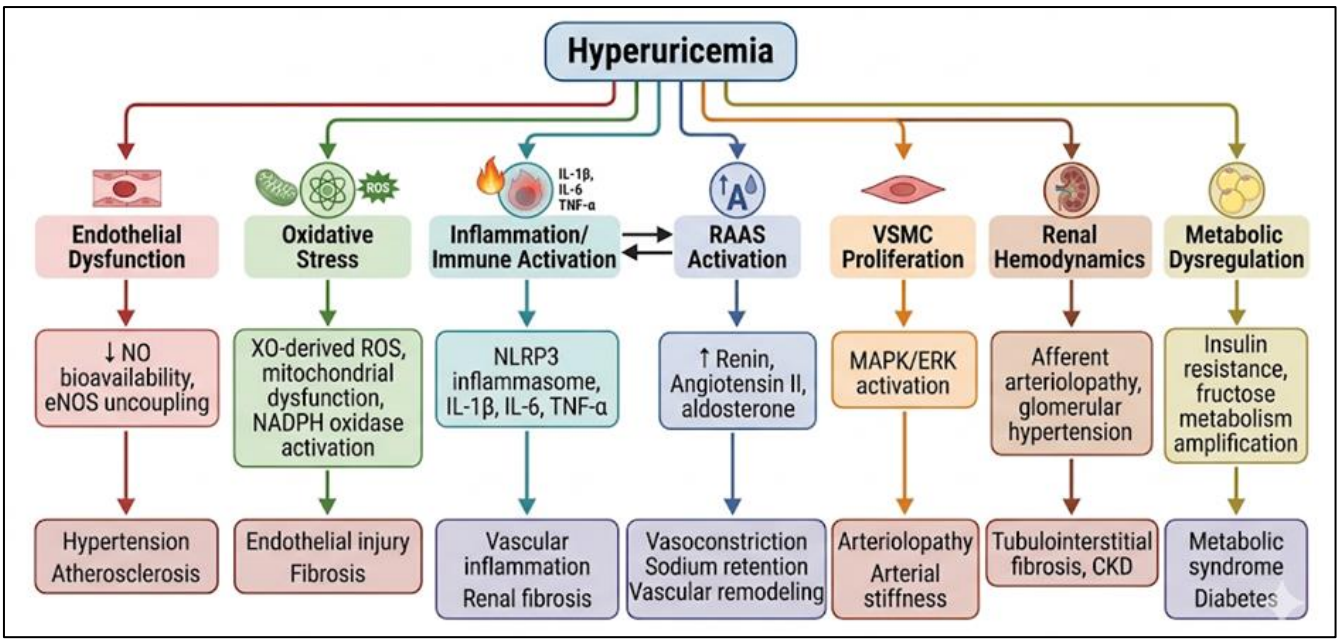

Figure 2 Mechanistic Pathways From Elevated Uric Acid to Cardiovascular and Renal Injury

4. Evidence from Experimental and Translational Studies

4.1. Animal Models

The strongest evidence supporting a causal role for UA in cardiorenal disease derives from experimental animal models. In rodents, pharmacologically induced mild hyperuricemia—achieved through administration of the uricase inhibitor oxonic acid—results in the development of hypertension, afferent arteriolopathy, and glomerular hypertrophy within weeks, lesions that are preventable or reversible with UA-lowering interventions [32]. These hypertensive changes are mediated by RAAS activation, endothelial dysfunction, and oxidative stress.

A recent advance has been the generation of genetically modified mouse models. CRISPR/Cas9-mediated deletion of the urate oxidase (Uox) gene produces spontaneous, severe hyperuricemia (SUA approximately 1,350 μmol/L) accompanied by hypertension, left ventricular remodeling, systolic dysfunction, aortic endothelial dysfunction, hyperglycemia, hypercholesterolemia, hepatic steatosis, and renal insufficiency [33]. These Uox-knockout mice recapitulate the human phenotype of hyperuricemia-associated multi-organ disease and provide a valuable tool for mechanistic and therapeutic studies.

However, it is important to acknowledge that not all animal studies have been concordant. Some investigations have reported that mild hyperuricemia may attenuate salt-sensitive hypertension and kidney damage in specific experimental contexts, highlighting the complexity of UA biology [34].

4.2. Cellular and Molecular Studies

At the cellular level, UA has been shown to inhibit endothelial cell proliferation and migration, induce endothelial cell senescence, and promote monocyte adhesion to endothelial cells—key early events in atherogenesis [23]. In VSMCs, UA stimulates proliferation, migration, and production of pro-inflammatory mediators [30]. In renal tubular cells, UA induces oxidative stress, mitochondrial injury, and activation of pro-fibrotic signaling cascades, including transforming growth factor-beta (TGF-β) and connective tissue growth factor (CTGF) [31].

4.3. Translational Relevance to Humans

While experimental evidence provides compelling proof-of-principle that UA can induce cardiorenal injury, translation to the human context is complicated by several factors. Humans lack uricase and have SUA levels substantially higher than those of wild-type rodents, making the incremental effect of modest UA changes difficult to extrapolate [11]. Furthermore, the interplay between UA and comorbid conditions—hypertension, diabetes, CKD—in humans is far more intricate than in controlled experimental settings, and effects observed in young, otherwise healthy animals may not be replicated in older, multimorbid human populations.

5. Epidemiological Evidence

5.1. Hyperuricemia and Hypertension

A strong, independent, and graded association between SUA and incident hypertension has been documented across numerous large, prospective cohort studies. A meta-analysis including over 55,000 participants demonstrated that each 1 mg/dL increase in SUA was associated with a 13% increased risk of incident hypertension (hazard ratio 1.13; 95% CI 1.06–1.20) [35]. This association is particularly robust in younger individuals and those with early hypertension, suggesting that UA may play a more prominent role in the initiation rather than the maintenance of established hypertension [36]. Resistant hypertension has also been linked to higher SUA levels, with hyperuricemia prevalence rates of up to 60% in this population [37]. Sex-specific analyses generally reveal stronger associations in women, although absolute SUA levels and hyperuricemia prevalence are higher in men [5].

5.2. Hyperuricemia and Chronic Kidney Disease

The relationship between SUA and CKD has been extensively studied. A systematic review and meta-analysis of 18 CKD incidence studies (n=398,663) and six CKD progression studies (n=13,575) found that lower UA levels were protective for both CKD incidence (RR 0.65; 95% CI 0.56–0.75) and progression (RR 0.55; 95% CI 0.44–0.68) [38]. The pooled prevalence of hyperuricemia in patients with established CKD is approximately 43.6% (35.2–52.4%), reflecting the impaired renal clearance of UA [39]. However, the bidirectional nature of this relationship—hyperuricemia may both result from and contribute to renal dysfunction—complicates causal inference from observational data alone.

5.3. Hyperuricemia and Cardiovascular Disease

Elevated SUA has been associated with an increased risk of coronary artery disease, myocardial infarction, stroke, heart failure, and cardiovascular mortality in multiple large-scale cohort studies [4,40]. A 2025 systematic review confirmed that serum uric acid has emerged as a significant biomarker for CVD risk assessment, with the relationship often appearing below conventional hyperuricemia thresholds [4]. Notably, U-shaped associations have been described in some cohorts, particularly in men, where both very low and very high SUA levels are associated with increased cardiovascular risk, possibly reflecting the dual antioxidant and pro-oxidant roles of UA [40].

Heart failure deserves particular attention. UA is a strong prognostic marker in both acute and chronic heart failure, with elevated levels independently predicting mortality, rehospitalization, and adverse outcomes [41]. The association may partly reflect increased XO activity and oxidative stress in the failing myocardium, as well as UA's relationship with congestion and diuretic use.

5.4. Hyperuricemia and Metabolic Disease

Hyperuricemia is intimately associated with components of the metabolic syndrome. Insulin resistance reduces renal urate clearance, while hyperuricemia may in turn impair insulin signaling, creating a vicious cycle [21]. SUA is an independent predictor of incident type 2 diabetes mellitus, and hyperuricemia is present in a substantial proportion of individuals with obesity and non-alcoholic fatty liver disease [6].

5.5. Strengths and Limitations of Observational Studies

Observational studies benefit from large sample sizes, extended follow-up periods, and the ability to adjust for multiple confounders. However, they remain susceptible to residual confounding—given UA's tight correlation with established cardiovascular risk factors—as well as reverse causality, wherein declining renal function raises SUA, generating a spurious association with cardiovascular events. The influence of concomitant medications, particularly diuretics, introduces further complexity, and heterogeneity in applied SUA thresholds across studies limits comparability [4].

6. Is Uric Acid a Marker or a Mediator?

The critical question of whether UA is a causal mediator of cardiorenal disease or merely an innocent bystander—a biomarker of underlying metabolic and renal dysfunction—remains intensely debated.

6.1. Arguments Supporting a Causal Role

Proponents of causality cite biological plausibility—the well-characterized mechanistic pathways including endothelial dysfunction, oxidative stress, RAAS activation, and inflammation [9,23,27,29]. Experimental evidence from animal models demonstrates that hyperuricemia can induce hypertension, renal injury, and metabolic disturbances independently of other risk factors [32,33]. Temporal relationships observed in longitudinal cohort studies further support a causal role, with hyperuricemia preceding the development of hypertension and CKD by years [35,38].

6.2. Counterarguments

Skeptics emphasize the inextricable association between hyperuricemia and established cardiovascular risk factors, particularly obesity, insulin resistance, and CKD, arguing that residual confounding cannot be fully excluded even with rigorous statistical adjustment [8]. They also highlight reverse causality: CKD reduces UA excretion, and hyperuricemia frequently develops secondary to reduced kidney function rather than preceding it [22]. The phenomenon of reverse epidemiology—where higher UA levels appear paradoxically protective in advanced CKD and dialysis populations—further complicates interpretation [42].

6.3. Mendelian Randomization Studies

Mendelian randomization (MR) studies leverage genetic variants associated with SUA as instrumental variables to assess causality while circumventing confounding and reverse causality. Recent MR analyses have provided evidence supporting a causal role for genetically predicted SUA in cardiovascular disease. An MR study utilizing GWAS data demonstrated that a genetic predisposition to elevated SUA significantly increased the risk of coronary artery disease (OR 1.227; 95% CI 1.107–1.360), hypertension (OR 1.318; 95% CI 1.184–1.466), myocardial infarction (OR 1.184; 95% CI 1.108–1.266), and heart failure (OR 1.158; 95% CI 1.066–1.258) [43]. Similarly, a transcriptomic-informed MR analysis supported a causal relationship between SUA and coronary artery disease, stable angina pectoris, and myocardial infarction [44].

However, contradictory MR findings exist, with some studies failing to detect causal associations between SUA and cardiovascular or renal outcomes, or reporting that the effects are substantially attenuated after adjusting for confounders [45]. Interpretation challenges include pleiotropy—where genetic variants influence multiple pathways—and population stratification.

6.4. Applying Bradford Hill Criteria

Application of the Bradford Hill criteria for causality yields a mixed picture. The strength of association between SUA and cardiovascular outcomes is modest (RR typically 1.1–1.4). Consistency across diverse populations and study designs is reasonably strong. The biological gradient—a dose-response relationship—is well documented. Plausibility is supported by extensive mechanistic data. However, experimental evidence from human intervention trials has been largely disappointing. This discordance suggests that UA may play a causal role in specific contexts—early disease stages, particular phenotypes—rather than uniformly across all populations.

6.5. Current Interpretation of the Evidence

An integrated appraisal suggests that UA operates as both marker and mediator, with its pathogenic role likely dependent on clinical context, disease stage, and individual susceptibility. In early hypertension, mild CKD, and metabolic syndrome, UA may contribute causally to disease pathogenesis, whereas in advanced CKD and established cardiovascular disease, its value may be primarily prognostic as a biomarker of oxidative stress and metabolic dysfunction [2,3,8].

7. Urate-Lowering Therapy: Evidence and Controversies

7.1. Xanthine Oxidase Inhibitors

7.1.1. Allopurinol

Allopurinol, a structural isomer of hypoxanthine, inhibits XO, reducing both UA production and XO-derived ROS generation. It is rapidly metabolized to its active metabolite oxypurinol, which has a longer half-life and is primarily renally cleared, necessitating dose adjustment in CKD [46]. Beyond UA lowering, allopurinol's inhibition of XO-mediated oxidative stress may confer additional cardiovascular benefits.

7.1.2. Febuxostat

Febuxostat is a potent, selective, non-purine XO inhibitor with primarily hepatic metabolism, making it an alternative for patients intolerant of allopurinol or with renal impairment. However, cardiovascular safety concerns have clouded its clinical use.

7.2. Uricosuric Agents

Probenecid and lesinurad (the latter now largely discontinued) inhibit URAT1-mediated urate reabsorption, promoting renal urate excretion. Emerging therapies targeting specific urate transporters, including selective URAT1 inhibitors and ABCG2 modulators, represent avenues of active investigation [14,47].

7.3. Major Randomized Controlled Trials

A summary of the key cardiovascular and renal outcome trials is provided in **Table 1**.

7.3.1. CARES (2018)

The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial randomized 6,190 patients with gout and established cardiovascular disease to febuxostat or allopurinol. Febuxostat was noninferior to allopurinol for the primary composite cardiovascular endpoint (10.8% vs. 10.4%), but was associated with significantly higher all-cause mortality (7.8% vs. 6.4%; HR 1.22; p=0.04) and cardiovascular mortality (4.3% vs. 3.2%; HR 1.34; p=0.03) [48]. These findings prompted FDA black-box warnings and ongoing debate regarding febuxostat safety.

7.3.2. FAST (2020)

The Febuxostat versus Allopurinol Streamlined Trial (FAST), conducted in Europe, randomized 6,128 patients with gout and at least one additional cardiovascular risk factor. In contrast to CARES, FAST demonstrated that febuxostat was noninferior to allopurinol for both the primary cardiovascular endpoint and all-cause mortality (HR 0.94; 95% CI 0.79–1.12) [49]. Differences in study design—including the inclusion of lower-risk patients and lower rates of early discontinuation—may explain the discrepant results.

7.3.3. CKD-FIX (2020)

The CKD-FIX trial randomized 369 adults with stage 3–4 CKD and no history of gout to allopurinol (up to 300 mg daily) or placebo. After 104 weeks, there was no significant difference in eGFR decline between groups (mean difference −0.10 mL/min/1.73m^2 per year; p=0.85) [50]. These results challenged the hypothesis that UA reduction slows CKD progression, at least in advanced disease.

7.3.4. PERL (2020)

The Preventing Early Renal Loss in Diabetes (PERL) study randomized 530 patients with type 1 diabetes and early-to-moderate diabetic kidney disease to allopurinol or placebo. Despite effective UA reduction, allopurinol did not slow the decline in iohexol-measured GFR over three years (mean difference 0.6 mL/min/1.73m^2; p=0.39) [51].

7.3.5. FEATHER

The Febuxostat Versus Placebo Randomized Controlled Trial Regarding Reduced Renal Function in Patients with Hyperuricemia Complicated by Chronic Kidney Disease Stage 3 (FEATHER) study evaluated febuxostat versus placebo in 395 patients with stage 3 CKD and asymptomatic hyperuricemia. Febuxostat effectively reduced SUA but did not influence the eGFR slope compared with placebo [52].

Table 1 Major Placebo-Controlled or Comparative RCTs Evaluating Urate-Lowering Therapy on Cardiovascular and Renal Endpoints

Trial (Year)	Population	Intervention	Comparator	Primary Endpoint	Key Result	Interpretation/Comment
CARES (2018)	Gout + CVD (n=6,190)	Febuxostat	Allopurinol	Composite CV (MI, stroke, CV death)	CV mortality higher with febuxostat; all-cause mortality ↑	FDA black-box warning
FAST (2020)	Gout + ≥1 CV risk factor (n=6,128)	Febuxostat	Allopurinol	Hospitalization for non-fatal MI/ACS, non-fatal stroke, CV death	Non-inferior; no mortality difference	Reassuring European data
CKD-FIX (2020)	Stage 3–4 CKD (n=369)	Allopurinol	Placebo	eGFR decline over 104 weeks	No significant difference	No slowing of CKD progression
PERL (2020)	Type 1 diabetes, early DKD (n=530)	Allopurinol	Placebo	Iohexol-GFR decline over 3 years	No significant difference	No renoprotection in diabetic kidney disease
FEATHER (2018)	Stage 3 CKD, asymptomatic HUA (n=395)	Febuxostat	Placebo	eGFR slope	No difference vs placebo	No renal benefit of febuxostat

7.4. Effects of ULT on Clinical Outcomes

Meta-analyses of ULT in CKD patients with asymptomatic hyperuricemia have reported modest preservation of eGFR (weighted mean difference 2.55 mL/min/1.73m^2; $p<0.001$), but no significant reduction in cardiovascular events ($p=0.052$) or all-cause mortality ($p=0.370$) [53]. In heart failure, a meta-analysis found that UA-lowering treatment increased all-cause mortality (RR 1.15; 95% CI 1.05–1.25), suggesting potential harm in this population [41].

7.5. Why Have Clinical Trials Produced Mixed Results?

Several factors may account for the discrepancy between promising observational and experimental data and the largely neutral RCT results. The timing of intervention may be critical: UA may contribute primarily to early disease pathogenesis, and trials enrolling patients with advanced, established disease may be unable to reverse structural damage [2,3]. Inadequate follow-up duration, heterogeneous study populations, and the distinction between UA lowering per se versus XO inhibition (with its additional antioxidant effects) further complicate interpretation. The reliance on surrogate endpoints rather than hard clinical outcomes in many RCTs is another important limitation.

8. Cardiovascular Disease Focus

8.1. Hypertension

The mechanistic links between UA and hypertension are particularly robust, involving RAAS activation, endothelial dysfunction, and arteriolopathy [29,32]. Clinical studies have consistently associated hyperuricemia with incident hypertension, and early intervention trials suggest that UA lowering may reduce blood pressure in younger individuals with early or prehypertension, while benefits are less apparent in older patients with long-standing hypertension [36]. This observation supports the concept that UA may be more important in the initiation of hypertension than in its chronic maintenance.

8.2. Atherosclerosis and Coronary Artery Disease

UA contributes to atherogenesis through endothelial injury, oxidative stress, and promotion of VSMC proliferation [23,30]. Observational studies demonstrate associations between SUA and both subclinical atherosclerosis (measured by coronary artery calcium scoring and carotid intima-media thickness) and clinical coronary events [4]. However, the independent contribution of UA to atherosclerosis beyond conventional risk factors remains modest.

8.3. Heart Failure

In heart failure, elevated SUA reflects several interlinked processes: increased XO activity and oxidative stress, impaired renal perfusion, diuretic-induced hyperuricemia, and tissue hypoxia with ATP depletion and purine degradation [41]. UA is a robust independent predictor of adverse outcomes, but the failure of ULT to improve prognosis suggests that UA may be a marker rather than a mediator in this context.

8.4. Stroke and Cerebrovascular Disease

Hyperuricemia is associated with an increased risk of ischemic stroke, potentially mediated through hypertension, endothelial dysfunction, and pro-thrombotic effects [4]. Paradoxically, some studies have suggested that elevated UA may confer neuroprotection in acute ischemic stroke due to its antioxidant properties, further illustrating UA's complex, context-dependent biology [25].

9. Chronic Kidney Disease Focus

9.1. Hyperuricemia in CKD

Hyperuricemia in CKD results from both reduced UA excretion—as declining nephron mass limits filtration and tubular secretion—and, in some cases, increased production from diuretic-induced volume contraction and enhanced proximal tubular reabsorption [22]. The pooled prevalence of hyperuricemia in CKD populations approaches 44% [39].

9.2. 9.2 Hyperuricemia as Cause vs. Consequence

The bidirectional relationship between UA and renal function complicates causal inference. While experimental models demonstrate that UA can cause renal injury, hyperuricemia frequently develops secondary to reduced kidney function in clinical settings. Longitudinal studies with repeated measures and careful temporal analysis support a role for UA in both the genesis and progression of CKD [38].

9.3. Evidence from CKD Trials

The CKD-FIX and PERL trials represent the most rigorous tests of the hypothesis that UA lowering preserves renal function, and both were negative for their primary endpoints [50,51]. However, these trials enrolled patients with relatively advanced disease and may not have targeted the optimal therapeutic window. Subgroup analyses have suggested possible benefit in patients with mild CKD and preserved kidney function, but these findings require prospective validation.

9.4. Hyperuricemia in Dialysis and Advanced CKD

In patients with end-stage kidney disease on dialysis, the relationship between SUA and mortality often exhibits a U-shaped or even inverse pattern, with higher UA appearing protective—a phenomenon attributed to UA's antioxidant properties and its role as a marker of better nutritional status [42]. This reverse epidemiology underscores the limitations of extrapolating associations observed in the general population to patients with advanced disease.

10. Clinical Implications

10.1. Should Asymptomatic Hyperuricemia Be Treated?

The weight of current evidence does not support routine pharmacotherapy for asymptomatic hyperuricemia, given the lack of definitive cardiovascular or renal outcome benefit from ULT in large RCTs and the potential for adverse effects [8,54]. Lifestyle modifications—including weight loss, dietary purine and fructose restriction, reduced alcohol intake, and regular physical activity—represent the cornerstone of management [20]. The decision to initiate pharmacotherapy should be individualized, considering SUA levels, cardiovascular and renal risk profile, and the presence of comorbidities.

10.2. Current Guideline Recommendations

Guidelines from rheumatology societies universally recommend ULT for patients with gout, with target SUA levels typically below 6.0 mg/dL (or below 5.0 mg/dL in patients with tophi) [7]. Nephrology guidelines acknowledge the association between hyperuricemia and CKD but diverge on recommendations for asymptomatic treatment [55]. Cardiovascular perspectives, including the 2023 Expert Consensus for the Diagnosis and Treatment of Patients with Hyperuricemia and High Cardiovascular Risk, advocate for the integration of SUA into cardiovascular risk assessment and suggest that SUA levels should be maintained below 6.0 mg/dL, and below 5.0 mg/dL in patients with elevated cardiovascular risk [56].

10.3. Risk Stratification

SUA measurement is warranted as part of cardiovascular risk assessment, particularly in individuals with hypertension, metabolic syndrome, or CKD. High-risk subgroups that may derive greater benefit from UA-lowering interventions include young patients with early hypertension, individuals with mild CKD and preserved eGFR, and those with metabolic syndrome without established target organ damage [36].

10.4. Precision Medicine and Personalized Approaches

The heterogeneity in clinical responses to ULT underscores the need for precision medicine approaches. Genetic stratification—based on urate transporter polymorphisms influencing UA production versus excretion phenotypes—may guide selection of XO inhibitors versus uricosuric agents. Biomarker-guided therapy, incorporating measures of oxidative stress, inflammation, and endothelial function, could identify patients most likely to benefit.

11. Future Directions

The persistent uncertainties regarding UA's role in cardiorenal disease demand well-designed RCTs that address the limitations of prior studies. Key requirements include enrollment of patients with early disease stages, sufficient follow-up duration to capture clinically meaningful outcomes, standardized SUA thresholds and therapeutic targets, and stratification by disease phenotype and genetic background [2,3]. Trials comparing XO inhibitors with uricosuric agents may help distinguish between the effects of UA lowering per se and those of XO inhibition.

The identification of responsive phenotypes—through integration of genomics, metabolomics, and proteomics—represents a critical priority for advancing the field toward precision medicine [14,17]. Novel urate transporter-targeted therapies, including selective URAT1 inhibitors and ABCG2 activators, offer the potential for more effective and individualized UA management [47]. Combination cardiorenal therapies that simultaneously address UA and associated metabolic risk factors warrant investigation. Furthermore, the intriguing findings from studies of sodium-glucose cotransporter-2 (SGLT2) inhibitors, which exhibit uricosuric properties in addition to their established cardiovascular and renal benefits, suggest that UA modulation may contribute to the pleiotropic effects of these agents [14].

12. Conclusion

The evidence linking UA to cardiovascular and renal disease is extensive and compelling, yet the critical question—whether UA is a marker, mediator, or both—remains incompletely resolved. Biological plausibility, experimental evidence in animal models, and observational epidemiological data collectively support a pathogenic role for UA in hypertension, CKD, and cardiovascular disease. Mendelian randomization studies have strengthened the case for causality, though with caveats. However, the translation of this evidence into demonstrable clinical benefit through ULT has been largely unsuccessful in large-scale RCTs.

This apparent paradox likely reflects the complexity of UA biology—its dual antioxidant and pro-oxidant roles, its integration into broader metabolic networks, and its context-dependent pathogenic mechanisms. In early disease stages—particularly in younger individuals with hypertension, mild CKD, and metabolic syndrome—UA may function as a disease mediator, and targeted UA-lowering interventions may yield clinical benefits that remain to be demonstrated in appropriately designed trials. In advanced disease, UA may serve primarily as a prognostic biomarker, reflecting oxidative stress and metabolic dysfunction rather than contributing directly to ongoing tissue injury.

The management of hyperuricemia should be guided by careful risk stratification, with lifestyle modification as the universal foundation, pharmacotherapy reserved for symptomatic hyperuricemia, and individualized decision-making for asymptomatic patients with high cardiovascular or renal risk. Future research must embrace precision medicine

approaches to identify the subgroups most likely to benefit from UA-lowering interventions, thereby resolving the long-standing controversy surrounding the role of uric acid in cardiorenal disease.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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