European Journal of Internal Medicine 142 (2025) 106554

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Review Article

Crystal clear – Part II: the role of uric acid in cardiorenal disease

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ARTICLE INFO

Keywords:
Uric acid
Hypertension
Coronary artery disease
Heart failure
Stroke
Peripheral artery disease
Xanthine oxidase inhibitors
SGLT2 inhibitors

ABSTRACT

Building on the foundational mechanistic and epidemiological knowledge from Part I, this second part of the review further unpacks the cardiovascular implications of abnormalities in serum levels of uric acid (UA). With a focus on hypertension, coronary artery disease (CAD), heart failure (HF), stroke, and peripheral artery disease (PAD), we provide a nuanced synthesis of how elevated serum UA influences disease risk and clinical outcomes.

We describe mechanistic pathways including endothelial dysfunction, vascular smooth muscle proliferation, oxidative stress, inflammation, and renin–angiotensin system activation. Large cohort studies demonstrate linear or U-shaped relationships between serum UA (SUA) and cardiovascular events, with risk often appearing below conventional hyperuricemia thresholds.

We also analyze interventional evidence for UA-lowering treatments such as xanthine oxidase inhibitors, urate transporter 1 (URAT-1) inhibitors and sodium-glucose transport protein 2 (SGLT2), highlighting context-dependent benefits in patients with hypertension or heart failure, both with and without preserved ejection fraction. Importantly, we discuss sex differences, kidney function influence, and the U-shaped association seen in men.

Finally, we argue that SUA should be integrated into cardiovascular risk stratification, potentially serving as both a biomarker and a therapeutic target, while recognizing the need for personalized approaches based on comorbidities and biochemical profiles. This completes the two-part series by bridging mechanistic insights with practical clinical implications.

1. Uric Acid and hypertension: pathophysiological mechanisms and epidemiological evidence

The hypothesis that uric acid (UA) plays a role in blood pressure regulation was first advanced by Alexander Haig in the late 19th century, long before the molecular mechanisms linking hyperuricemia and cardiovascular (CV) disease (CVD) were understood [1,2]. Although initially speculative, this early observation has gained increasing credibility through extensive experimental data and large-scale epidemiological studies over the past few decades. The accumulating evidence supports the view that elevated serum UA (SUA) is not merely a bystander in hypertensive disease but may actively contribute to its initiation and progression.

One of the seminal experimental studies in this area involved the use of oxonic acid, a uricase inhibitor, to induce mild hyperuricemia in rodent models [3]. Researchers observed a clear elevation in systemic blood pressure following UA accumulation. Importantly, when these animals were treated with urate-lowering agents—either the xanthine oxidase inhibitor allopurinol or the uricosuric drug benziodarone—the hypertensive response was fully prevented [4]. Furthermore, the extent of blood pressure reduction was directly proportional to the degree of SUA lowering, providing strong evidence for a causal link between UA and blood pressure regulation in this model [3].

Histological analyses revealed that hyperuricemia was associated with pathological changes in the renal microvasculature, particularly within the preglomerular arterioles. These changes included vascular smooth muscle proliferation, arteriolar wall thickening, and reduced luminal diameter, consistent with ischemic injury and early arteriosclerosis. Interestingly, such structural damage was ameliorated by treatment with angiotensin converting enzyme (ACE) inhibitors, even when systemic blood pressure remained unchanged, suggesting a direct "vasculotoxic" effect of UA independent of its hemodynamic impact [5]. At the molecular level, hyperuricemia induced an upregulation of renin expression in the juxtaglomerular apparatus, downregulation of

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https://doi.org/10.1016/j.ejim.2025.106554
Received 9 August 2025; Accepted 15 October 2025
Available online 18 October 2025

endothelial nitric oxide synthase (eNOS) in the macula densa, and increased expression of angiotensinogen, ACE, and angiotensin II receptors [6]. These changes can produce a pro-hypertensive renal environment leading to intrarenal vasoconstriction, reduced natriuresis, and enhanced sodium reabsorption, all of which contributed to salt-sensitive hypertension [3].

Beyond the experimental setting, a growing body of clinical evidence has reinforced the association between elevated SUA and incident hypertension in humans. Epidemiological studies across diverse populations and age groups consistently demonstrate that SUA is an independent predictor of future increases in blood pressure, even after adjustment for traditional CV risk factors such as obesity, smoking, dyslipidemia, alcohol intake, and type 2 diabetes mellitus (T2DM) [7,8]. For instance, longitudinal data from the Normative Aging Study found a linear relationship between baseline SUA and the development of hypertension, a pattern confirmed even after controlling for renal function and other potential confounders [9]. Similar trends have been reported in adolescents and young adults, indicating that the pathogenic influence of UA on blood pressure may begin early in life. A growing body of evidence supports the notion that elevated SUA is associated with higher blood pressure even during childhood and adolescence. Prospective data from the Bogalusa Heart Study demonstrated that SUA levels measured in childhood, as well as their trajectory over time, were strongly predictive of both childhood and adult blood pressure levels, highlighting the long-term implications of early uric acid exposure [10]. Cross-sectional analyses conducted in diverse pediatric populations reinforce these findings. For example, data from large cohorts such as NHANES and KNHANES revealed that adolescents with SUA concentrations above 5.5 mg/dL exhibited a significantly higher prevalence of elevated systolic and diastolic blood pressure [11–13]. Notably, this association appeared robust across different demographic groups and remained significant even after accounting for confounding factors such as insulin resistance, pubertal stage, and renal function [14]. Moreover, in overweight and moderately obese children, a progressive increase in both office and 24-hour systolic blood pressure was observed across ascending SUA categories, suggesting a dose-response relationship [15]. Collectively, these studies point toward a consistent and biologically plausible link between uric acid and early alterations in vascular regulation, supporting the hypothesis that SUA may act as an early modifiable risk factor in the pathogenesis of hypertension.

Meta-analytic evaluations of large prospective cohorts have confirmed a positive and independent association between SUA and new-onset hypertension. A pooled analysis of 18 studies encompassing more than 50,000 individuals revealed a dose-dependent relationship between uricemia and hypertensive risk [16], while a more recent meta-analysis involving approximately 100,000 participants corroborated these findings, further reinforcing the role of SUA as a biomarker and potential mediator of blood pressure elevation [17].

The directionality of this association has also been addressed. A modeling study examining bidirectional associations found that baseline SUA levels predicted subsequent changes in systolic and diastolic blood pressure [18]. In contrast, initial blood pressure values did not predict future SUA levels, suggesting a unidirectional, potentially causal influence of SUA on hypertension development [18].

Sex-specific differences in the SUA-hypertension relationship have been observed in several population-based studies, particularly in Asian cohorts [19]. Data from Chinese and Japanese registries indicate that the association between elevated SUA and incident hypertension is stronger in men than in women, potentially implicating sex hormones or differential metabolic regulation in modulating UA's effects [20,21]. Additionally, SUA levels of $\geq$5 mg/dL in elderly normotensive, normoglycemic middle-aged individuals were independently associated with the development of hypertension over time, suggesting that UA may serve as an early marker of subclinical vascular dysfunction before overt hypertensive disease emerges [22].

Despite the growing evidence supporting SUA as a modifiable risk factor, the efficacy of urate-lowering therapies in preventing or treating hypertension remains a subject of active debate [23]. Small, randomized trials in young patients with hyperuricemia and preserved renal function have yielded promising results, demonstrating that allopurinol or febuxostat can reduce both SUA and blood pressure in this subgroup [15]. However, larger and more heterogeneous clinical trials have failed to replicate these findings consistently [24]. Potential reasons for this discrepancy include the inclusion of individuals with normal UA levels, high dropout rates, inadequate follow-up, and variability in drug dosing and adherence [25]. These limitations complicate the interpretation of the existing trial data and suggest that future studies should focus on carefully selected high-risk populations where the pathophysiological role of SUA is most pronounced.

Further insights have been provided by vascular studies evaluating the relationship between SUA and arterial stiffness. Data from the Brisighella Heart Study indicated that patients with both poorly controlled hypertension and elevated SUA levels displayed higher values of pulse wave velocity (PWV) and augmentation index (AI), both of which are established markers of arterial stiffness and predictors of CV events [26].

These findings were recently corroborated by a large-scale analysis from the German National Cohort (NAKO), involving over 70,000 individuals [27]. The study identified a robust, positive association between SUA levels—even within the physiological range—and PWV, suggesting that UA contributes to vascular remodeling independently of overt hyperuricemia. Notably, the relationship was more pronounced in females than in males, with multivariable models estimating that an increase of 0.1 mmol/L in SUA corresponded to a biological aging effect of approximately 7 years in women and 4 years in men, in terms of arterial stiffness. A complementary machine learning analysis also ranked SUA as a key predictor of PWV in a hypothesis-free model, reinforcing the concept that UA acts as an early marker of vascular damage, particularly in women.

Overall, hyperuricemia has been increasingly recognized as a key independent contributor to the pathogenesis and maintenance of hypertension. Evidence from mechanistic, clinical, and epidemiological research consistently points to a causal association between elevated SUA, vascular injury, renal dysfunction, and impaired blood pressure regulation. While urate-lowering treatments have yielded inconsistent outcomes in clinical trials, the available data strongly support the need for further targeted studies, particularly in well-characterized, high-risk populations.

2. Uric Acid and coronary artery disease: marker, mediator, or mere bystander?

A substantial body of research has established a strong association between SUA levels and coronary artery disease (CAD), implicating both direct atherogenic mechanisms and synergistic interactions with traditional CV risk factors. Elevated SUA concentrations are more frequently observed in individuals diagnosed with CAD than in those without, and regression analyses consistently demonstrate a significant correlation between SUA and both the presence and severity of coronary pathology across sexes [28]. Mechanistically, several interrelated pathways may explain how elevated SUA worsens CAD presence and severity — notably oxidative stress, inflammation, and microvascular dysfunction — as illustrated in Fig. 1.

Furthermore, hyperuricemia is independently associated with an increased incidence of myocardial infarction (MI) and CV disease, with reported hazard ratios of 1.87 and 1.68, respectively [29]. Meta-analytical evidence reinforces this relationship, indicating that each 1 mg/dL increment in SUA is linked to a 12 % increase in CAD-related mortality, regardless of conventional risk factor burden. Additionally, individuals in the highest tertile of SUA display a 10 % greater 10-year CAD risk, even after adjustment for potential confounders [30]. Furthermore, asymptomatic hyperuricemia has been linked to increased coronary lesion complexity and higher SYNTAX

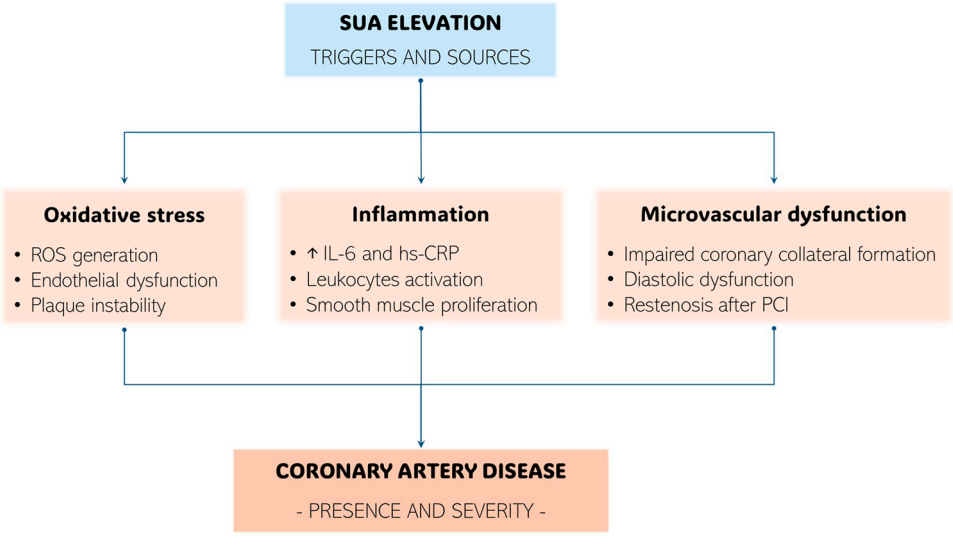

Fig. 1. Proposed mechanisms linking elevated serum uric acid to greater presence and severity of coronary artery disease. Hyperuricemia promotes oxidative stress, inflammation, and microvascular dysfunction, which synergistically drive atherogenesis, accelerate plaque progression, and exacerbate coronary disease burden.

scores, reflecting greater coronary involvement in patients with elevated SUA [31]. As far as the threshold level of serum UA responsible for an increased risk of CAD, the URRAH investigators identified a specific SUA cutoff associated with fatal MI (>5.70 mg/dL overall, >5.26 mg/dL in women), and demonstrated a significant risk increase for fatal events in women (HR, 1.514, $p < 0.01$) but not in men [32]. This sex-specific prognostic threshold reinforces the importance of personalized SUA interpretation.

The relationship appears particularly pronounced in women. A meta-analysis involving over 450,000 individuals showed that women with hyperuricemia have a significantly higher risk of CAD, with a relative risk of 1.206 (confidence interval [CI]: 1.066–1.364) compared to normouricemic counterparts [33]. Longitudinal observations highlight the prognostic importance of early SUA control, as early and cumulative exposure to elevated SUA predicts future MI and all-cause mortality more accurately than later increases [34]. In post-MI populations, persistent hyperuricemia is associated with worse long-term outcomes, potentially due to its contribution to atherosclerotic plaque vulnerability, increased thrombotic activity, and impaired coronary perfusion [35]. SUA has also been identified as an independent predictor of impaired coronary collateral circulation (CCC) in patients with stable CAD, suggesting that higher SUA levels may inhibit adaptive vascular responses [36].

Mechanistically, SUA exerts detrimental effects on the vasculature through the induction of oxidative stress and inflammation, promoting endothelial injury and accelerating atherogenesis [4]. SUA levels above 7.11 mg/dL are associated with significantly increased cardiac mortality, and a J-shaped association has been observed, with the lowest mortality risk noted at SUA levels ranging from 5.17 to 6.76 mg/dL [37]. A similar U-shaped pattern has been reported in relation to all-cause mortality among CAD patients, indicating that both excessively high and low SUA levels may be deleterious [38]. Beyond absolute values, temporal variability in SUA has emerged as an independent risk factor; individuals with greater fluctuations in SUA levels exhibit higher incidence rates of MI, HF, and cardiac death [39].

Among younger individuals with early-onset CAD, SUA levels exceeding 8 mg/dL have been independently linked to more advanced disease manifestations, including triple-vessel disease, left ventricular dysfunction, and HF [40]. These findings suggest that SUA may play a central role not only in disease onset but also in determining its anatomical and functional severity in younger populations. However, despite the strength of observational associations, the causal relationship between SUA and CAD remains controversial. Mendelian randomization (MR) analyses conducted in diabetic populations [41] and in Mexican cohorts [42] have failed to establish a direct causal link between genetically elevated SUA and CAD, suggesting that SUA may primarily serve as a promoting risk marker rather than a causative agent or may play a causative role in the early phases of coronary artery disease. In patients with T2DM, higher SUA concentrations are strongly associated with increased CAD risk when considered alongside markers of oxidative stress and inflammation [43]. In these patients, SUA may act as a surrogate for the pro-oxidative and inflammatory state that characterizes diabetic vascular dysfunction. Conversely, in patients with chronic coronary syndrome (CCS), SUA levels have not been shown to significantly correlate with coronary plaque burden or with measures of left ventricular diastolic dysfunction, implying that SUA may play a more critical role during the earlier stages of disease development, while its predictive capacity diminishes in the context of extensive myocardial injury or revascularization [44].

In the setting of chronic kidney disease (CKD), SUA has been investigated as a potential biomarker of coronary artery calcification (CAC). Evidence from predialysis cohorts shows that SUA is significantly associated with CAC during early CKD stages, though this association tends to dissipate with the progressive decline in renal function [45]. This suggests a stage-dependent effect, possibly modulated by changes in urate excretion, inflammation, or vascular calcification pathways.

In this context, emerging data from the URic acid Right for heArt Health (URRAH) study have provided valuable insights into the prognostic significance of the SUA-to-serum creatinine ratio (SUA/sCr) that can better explain the renal-adjusted role of hyperuricemia. A large cohort analysis (>20,000 individuals) identified a cutoff value of 5.35 for SUA/sCr, above which the risk of CV events (including CAD) significantly increased, particularly in the highest quintiles (HR up to 1.642; $p < 0.0001$) [46].

From the cardiometabolic point of view, hypertension and T2DM, both common in CAD populations, further complicate the SUA-CAD interplay. Elevated SUA levels are correlated with higher concentrations of inflammatory cytokines such as interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) in hypertensive diabetic patients, potentially contributing to adverse CV outcomes through sustained vascular inflammation [47]. In the context of percutaneous coronary intervention (PCI), SUA has been associated with in-stent restenosis (ISR), and the UA-to-albumin ratio (UAR) has emerged as a potential predictor of ISR through its reflection of oxidative and

inflammatory status [48].

Another dimension of the SUA-CAD connection involves sleep-disordered breathing (SDB). Patients with SDB experience nocturnal increases in SUA, with the magnitude of overnight SUA elevation correlating with SDB severity [49]. These findings suggest that intermittent hypoxia may stimulate purine metabolism and xanthine oxidase activity and enhance SUA production contributing to vascular injury through oxidative pathways [49].

Overall, SUA appears to be a significant marker of CV risk and disease severity in CAD patients, with associations supported by large epidemiological datasets and mechanistic plausibility. However, its role as a direct causal factor remains uncertain, particularly in light of genetic studies that fail to confirm a unidirectional link. The utility of SUA may therefore lie primarily in its ability to reflect underlying metabolic and inflammatory states that contribute to CAD pathophysiology. Given its associations with disease extent, progression, and outcomes—particularly in high-risk subgroups such as women, younger patients, and individuals with T2DM or CKD—SUA remains a valuable component of CV risk assessment. Future directions may include the incorporation of validated thresholds such as SUA >5.70 mg/dL or SUA/sCr >5.35 into integrated CV risk algorithms, as proposed by the URRAH initiative [50]. This could aid in identifying individuals most likely to benefit from SUA-lowering or anti-inflammatory strategies.

In addition to its metabolic and oxidative effects, UA plays a key role in triggering innate immune responses through activation of the NLRP3 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3) inflammasome [51]. This pathway leads to the release of IL-1β and IL-18, cytokines that contribute to atherogenesis, plaque instability, and adverse cardiac remodeling [52]. While monosodium urate (MSU) crystals can directly activate the inflammasome, a second inflammatory "hit"—such as elevated free fatty acids or microbial-derived products—is often necessary to unleash the full inflammatory cascade [53]. This mechanism explains why not all hyperuricemic individuals develop gout but may still exhibit increased CV risk [53].

Against this backdrop, colchicine—a long-standing therapy for gout flares—has gained renewed attention for its CV benefits [54,55]. Through microtubule inhibition, colchicine prevents inflammasome assembly and IL-1β release, potentially mitigating inflammation-driven CV complications [55]. Observational data have linked colchicine use in gout patients to a reduced risk of CV events, and recent large-scale studies suggest that colchicine prophylaxis during urate-lowering therapy is associated with fewer incident CV events [56]. The beneficial effect of colchicine has not been confirmed in the general post-MI population [57] suggesting the importance of hyperuricemia as causative risk factor. These findings support the concept that targeting downstream inflammatory mediators, in addition to lowering SUA itself, may offer a broader strategy for CV risk reduction in hyperuricemic populations [56].

These inflammatory insights complement the growing body of evidence positioning SUA as both a marker and a modifiable contributor to CVD, particularly in high-risk subgroups. The integration of SUA and SUA/sCr thresholds into CV prevention frameworks may refine individualized risk stratification and therapeutic decisions.

3. Uric Acid in heart failure: pathogenic link or prognostic red flag?

Elevated SUA levels are commonly observed in patients with HF, a phenomenon traditionally attributed to impaired renal function and the extensive use of loop diuretics [58]. However, these factors only partially explain the high prevalence of hyperuricemia observed in this population, prompting investigations into the prognostic and pathophysiological implications of SUA in HF [59]. Multiple studies have shown that SUA levels correlate closely with several clinical and surrogate markers of HF severity, including New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), exercise tolerance, and overall hospitalization risk [58,60]. Notably, the risk of adverse outcomes, including mortality and sudden cardiac death, increases significantly in patients with elevated SUA, irrespective of LVEF status [59,61].

Pathophysiologically, increased purine metabolism due to systemic hypoxia in HF leads to elevated activity of xanthine oxidase reductase (XOR), an enzyme responsible for converting xanthine to UA [62,63]. This enzymatic pathway generates reactive oxygen species (ROS), which contribute to endothelial dysfunction, inflammation, and subsequent ventricular remodeling [64]. Hypoxia-induced purine turnover has been directly linked to elevated SUA levels, with a strong inverse correlation noted between mixed venous oxygen saturation and SUA ($P < 0.001$), suggesting that SUA may serve as a surrogate marker for systemic oxygen deficit in HF [64]. Beyond reflecting oxygen imbalance, elevated SUA is implicated in several interrelated mechanisms that can actively drive disease progression — notably inflammation, endothelial dysfunction, and neurohormonal activation — as illustrated in Fig. 2.

These findings underscore the potential for SUA not only as a biomarker but also as a contributor to HF pathogenesis through oxidative stress mechanisms.

Large-scale retrospective studies have confirmed that SUA is an independent predictor of poor prognosis in chronic HF (CHF). In a cohort of 297 CHF patients, those with SUA levels ≥462 μmol/L had a 2.625-fold increased risk of poor outcomes (hazard ratio [HR], 2.625; 95 % confidence interval [CI]: 1.631–4.228; $P < 0.001$). Additionally, serum creatinine and blood urea nitrogen (BUN) were also found to be prognostically relevant, suggesting a close interplay between renal dysfunction and hyperuricemia in HF [65]. Subgroup analysis in the

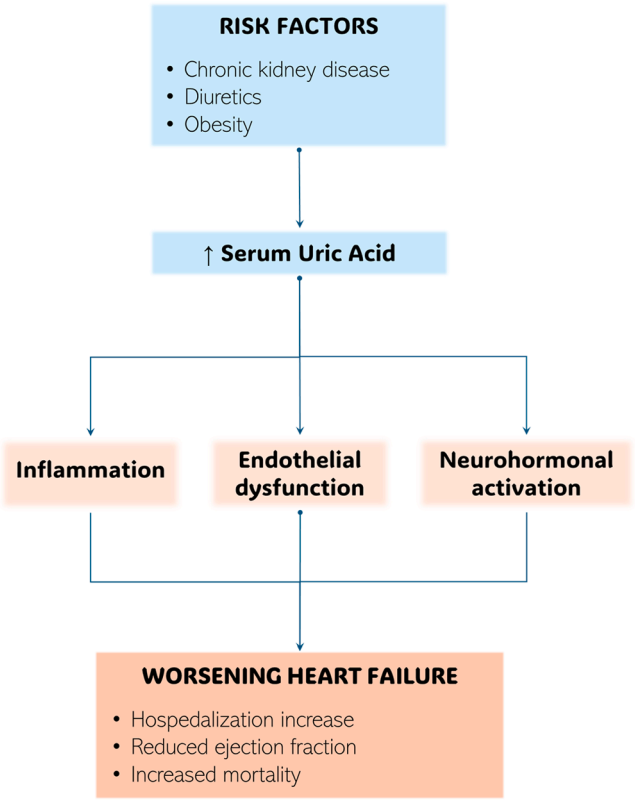

Fig. 2. Mechanisms by which hyperuricemia may worsen heart failure. Elevated serum uric acid, resulting from systemic hypoxia and increased xanthine oxidase activity, promotes inflammation, endothelial dysfunction, and neurohormonal activation. These pathophysiological processes contribute to reduced left ventricular ejection fraction, increased hospitalization risk, and higher mortality in patients with heart failure.

same study revealed that the male sex and advancing age were further associated with worse outcomes, with male patients experiencing a disproportionately higher risk (OR: 2.424; $P < 0.001$) [65].

This association extends to patients with HF with mildly reduced ejection fraction (HFmrEF). In a large retrospective study involving 1419 HFmrEF patients, both elevated and low SUA levels were significantly associated with increased all-cause mortality over a 30-month follow-up (high SUA: 42 %; low SUA: 43 %; vs. normal SUA: 27 %), even after adjustment for confounders (HR for high vs. normal = 1.230, $p = 0.046$; HR for low vs. normal = 1.915, $p = 0.001$) [66].

Machine learning analyses of acute HF (AHF) patients have highlighted SUA as a key variable in prognostic modeling. In a study involving 908 AHF patients, SUA, in combination with other parameters such as BUN, systolic blood pressure, and serum electrolytes, improved risk stratification in the emergency department setting. This reinforces the idea that SUA is more than a metabolic byproduct; it is an actionable biomarker that could aid in early triage decisions and ICU admissions [67].

These prognostic insights are corroborated by large-scale population studies. The URRAH study, involving over 21,000 Italian individuals, identified SUA as an independent predictor of both all HF (HR, 1.29; $p < 0.0001$) and fatal HF (HR, 1.268; $p < 0.0001$) after adjustment for major confounders. Importantly, this study proposed specific prognostic cut-off values: SUA >5.34 mg/dL for all HF, and >4.89 mg/dL for fatal HF, both of which retained statistical significance in multivariate analysis [68].

Beyond observational data, recent genetic studies employing MR have attempted to clarify whether elevated SUA levels are causative or merely associative in HF pathogenesis. Findings suggest a causal relationship, particularly among patients with preexisting CVD. This adds a layer of credibility to therapeutic strategies aimed at lowering SUA as a means of modulating HF risk [59].

Urate-lowering therapies, especially xanthine oxidase inhibitors like allopurinol and febuxostat, have been studied extensively in this context. The results, however, remain inconclusive.

The CARES trial reported an increased risk of CV and all-cause mortality with febuxostat compared to allopurinol, raising concerns about the CV safety of some xanthine oxidase inhibitors (XOIs) [69]. However, a careful review of CARES study has revealed several methodological limitations that make highly unrealistic any conclusion beyond the primary endpoint of a comparable efficacy of febuxostat and allopurinol in patients with gout and high CV risk [70]. Moreover, the results of a recent UK survey comparing over 300.000 patients with gout in primary practice, did not report any excess in cardiovascular disease in patients treated with febuxostat when compared to allopurinol or no treatment [71].

In contrast, the FAST trial later suggested that febuxostat was non-inferior to allopurinol in terms of CV safety and was even associated with lower all-cause mortality, offering reassurance about its use in appropriately selected patients [59].

However, more recent real-world evidence has highlighted the importance of clinical context. A retrospective cohort study including nearly 1000 hospitalized patients with heart failure and asymptomatic hyperuricemia found that febuxostat significantly reduced SUA levels but did not improve clinical outcomes [72]. Over a median follow-up of 16 months, there were no significant differences in the composite endpoint of CV death, recurrent hospitalization, or emergency department visits, nor in surrogate measures such as left ventricular ejection fraction, six-minute walk distance, or quality-of-life scores (KCCQ). Interestingly, the study identified a SUA/sCr ≥5.35 as an independent predictor of worse CV outcomes, suggesting potential utility in risk stratification. These findings support the growing consensus that urate-lowering therapy in heart failure should be applied selectively, particularly avoiding overtreatment in asymptomatic individuals, and reinforce the need for personalized strategies based on individual risk profiles.

Recent evidence has brought sodium-glucose cotransporter 2 (SGLT2) inhibitors into the spotlight for their dual role in managing HF and lowering SUA. Trials such as EMPEROR-Preserved and DAPA-HF have demonstrated that SGLT2 inhibitors like empagliflozin and dapagliflozin not only improve clinical outcomes in patients with HF with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) respectively, but also are associated with a robust reduction of SUA levels [73,74]. In the EMPEROR-Preserved trial, empagliflozin led to a meaningful reduction in SUA and fewer gout-related events, independent of baseline SUA levels [65]. Similarly, dapagliflozin has been associated with decreased CV mortality and reduced hospitalizations, particularly in hyperuricemic patients [65,75].

Sex differences in the prognostic significance of SUA have also been explored. Elevated SUA seem to be strongly associated with increased all-cause and CV mortality in men with HFpEF but not in women, suggesting that sex-specific biological factors may influence the clinical impact of SUA [61,76]. This finding has implications for personalized medicine, indicating that risk stratification and treatment decisions involving SUA should consider gender-specific responses.

The relationship between hyperuricemia and other CVDs further complicates the landscape. A meta-analysis of 22 studies indicated that patients with gout had a significantly higher risk of developing MI (risk ratio [RR], 4.60; 95 % CI: 4.39–4.82; $P < 0.001$) and HF (RR, 2.71; 95 % CI: 2.61–2.82; $P < 0.001$). Notably, the risk persisted across both genders, although women with gout had a slightly higher relative risk compared to men (RR = 1.70 vs. RR = 1.98) [77]. This underscores the systemic nature of hyperuricemia and its widespread impact on CV morbidity.

In patients with CAD, SUA has shown strong predictive value for the onset and progression of HF. In a retrospective analysis of 342 CAD patients, those who developed HF, particularly HFrEF, had significantly higher SUA levels. Multivariate regression identified SUA as an independent predictor of HF progression, surpassing other common markers like aspartate aminotransferase (AST) and creatine kinase-myoglobin binding (CK-MB) in predictive power. SUA also correlated positively with Gensini scores, linking it directly to the severity of coronary atherosclerosis [78].

Taken together, these findings establish SUA as a multifaceted biomarker in HF, with implications spanning risk prediction, disease progression, and therapeutic monitoring. Its elevation reflects complex pathophysiological processes involving renal function, oxidative stress, and systemic inflammation. While urate-lowering therapies remain under scrutiny due to mixed clinical trial results, SGLT2 inhibitors offer a promising alternative with a favorable safety profile and demonstrated efficacy in both lowering SUA and improving HF outcomes.

Nonetheless, the exact role of SUA in the pathophysiology of HF continues to be debated. Is hyperuricemia a mediator of HF progression, or merely a marker of disease severity? Current evidence supports both interpretations. Elevated SUA is clearly associated with worse outcomes, but whether lowering SUA translates into better survival or quality of life remains uncertain. Personalized treatment approaches, incorporating patient-specific factors such as sex, renal function, and comorbid conditions, are likely to yield the most benefit.

Future research should focus on resolving the inconsistencies surrounding XOIs, optimizing the integration of SUA into existing HF risk scores, and expanding the role of SGLT2 inhibitors in hyperuricemic populations. Large, multicenter randomized controlled trials with clearly defined endpoints are needed to determine whether targeted SUA reduction can alter the clinical course of HF. Moreover, exploration into novel biomarkers and machine learning-based predictive models may help delineate the complex interactions between SUA and CVD, potentially leading to more nuanced and effective therapeutic strategies [59,67].

In conclusion, SUA stands at the intersection of metabolic dysfunction and CVD, acting as both a warning signal and a possible agent of harm in HF. While lowering SUA alone may not suffice to reverse the

trajectory of HF, it remains a valuable component of the broader clinical picture. The integration of SUA assessment into routine HF management—particularly through the use of SGLT2 inhibitors and risk stratification tools—could enhance our ability to identify high-risk patients and tailor interventions accordingly. Continued investigation into the mechanisms, consequences, and therapeutic implications of hyperuricemia in HF is warranted to fully unlock its prognostic and therapeutic potential.

4. Uric Acid and stroke: A double-edged sword in cerebrovascular disease

Growing evidence suggests that elevated SUA levels are linked to an increased risk of stroke, with numerous studies highlighting its complex role in both the incidence and outcomes of cerebrovascular events. In particular, several large-scale cohort studies and meta-analyses have underscored a potentially detrimental effect of hyperuricemia on stroke development, although findings related to prognosis and recovery remain inconsistent across different populations and study designs.

One of the most notable investigations in this area is the Rotterdam Study, which followed over 4000 individuals over time [29]. The results indicated that those in the highest quintile of SUA exhibited a significantly elevated risk for total stroke (HR, 1.57; 95 % CI: 1.11–2.22) and for ischemic stroke specifically (HR, 1.77; 95 % CI: 1.10–2.83) [29]. This suggests that elevated SUA may play a contributory role in atherothrombotic processes or in promoting vascular dysfunction, thereby predisposing individuals to ischemic events.

This evidence is further reinforced by a comprehensive meta-analysis encompassing over 1 million participants across multiple prospective studies [79]. This large-scale synthesis reported a modest but statistically significant association between hyperuricemia and increased stroke incidence (RR, 1.22; 95 % CI: 1.02–1.46), as well as stroke-related mortality (RR, 1.33; 95 % CI: 1.24–1.43) [79]. These findings point to SUA as a potential modifiable risk factor, which, if addressed, might reduce stroke burden on a population level.

Consistent with this evidence, a nationwide cohort analysis from the URRAH study identified a prognostic SUA cut-off value of >4.79 mg/dL (284.91 μmol/L), above which the risk of fatal and non-fatal cerebrovascular events significantly increased (HR, 1.249; 95 % CI: 1.041–1.497; $p = 0.016$) [80]. This association remained robust after multivariable adjustment for major confounders including age, sex, blood pressure, diabetes, chronic kidney disease, smoking, low density lipoprotein cholesterol (LDL-C), body mass index (BMI), and diuretic use. These findings support the inclusion of SUA >4.79 mg/dL as a plausible prognostic threshold in the stratification of cerebrovascular risk.

However, more nuanced insights are emerging when considering SUA in relation to kidney function. A cross-sectional analysis using NHANES data (1999–2018) examined SUA/sCr and found an inverse association with stroke risk. Specifically, individuals in the highest quartile of SUA/sCr had a 53 % lower risk of stroke compared to those in the lowest quartile (odd ratio [OR], 0.47, 95 % CI: 0.31–0.71). Restricted cubic spline analysis confirmed a nonlinear relationship, with stroke risk decreasing as SUA/sCr rose up to a threshold of 6.33, beyond which the protective effect plateaued [81].

Similar findings were reported in a Chinese cohort of 1932 patients with acute ischemic stroke and impaired renal function. Each unit increase in SUA/sCr was associated with a 17 % reduction in the risk of 1-year stroke recurrence (hazard ratio [HR], 0.83; 95 % CI: 0.73–0.96). Subgroup analysis revealed an even stronger protective effect in patients with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, where those in the highest quartile had an 81 % lower recurrence risk than those in the lowest quartile [82].

In the context of stroke outcomes, the literature remains divided. Some investigations suggest that higher SUA levels may confer neuroprotective benefits. A meta-analysis of 13 cohort studies reported that elevated SUA was linked to reduced risks of poor functional outcomes, hemorrhagic transformation, and post-stroke depression, although it had no significant association with overall mortality [83].

Supporting this neuroprotective potential, a major preclinical study within the Stroke Preclinical Assessment Network (SPAN) found that intravenous UA (16 mg/kg) administered during reperfusion significantly improved neurological outcomes and survival in rodents subjected to ischemic stroke. The beneficial effects were consistent across sexes, age groups, and comorbidities such as obesity, hypertension, and T2DM (primary outcome: $P = 0.006$; survival HR,1.41, 95 % CI: 1.08–1.83) [84]. This preclinical evidence is further supported by clinical data showing that higher endogenous serum UA levels are associated with improved outcomes in patients undergoing thrombolysis for acute ischemic stroke. In a prospective registry of 317 consecutive patients treated with reperfusion therapies, elevated UA levels were independently associated with a greater likelihood of achieving an excellent functional outcome (modified Rankin Scale (mRS) <2 at 90 days; OR, 1.23; 95 % CI, 1.03–1.49; $p = 0.025$), as well as a shift toward better functional outcomes across the mRS spectrum (OR, 1.19; 95 % CI, 1.04–1.38; $p = 0.014$) [85]. Furthermore, UA levels inversely correlated with final infarct volume ($r = -0.216$; $P < 0.001$), even after adjustment for age, sex, and baseline stroke severity [85]. Notably, patients with malignant MCA infarction or post-thrombolysis parenchymal hemorrhage exhibited significantly lower UA levels, further suggesting a neuroprotective role of UA in the clinical setting [85].

Conversely, other studies raise caution about potential risks. An NHANES-based analysis of 1382 stroke survivors revealed that the ratio of UA to HDL cholesterol (UHR) was significantly associated with all-cause mortality (HR, 1.05, 95 % CI: 1.01–1.08). An inverted U-shaped relationship was observed with CV mortality: below a threshold of 14.42 %, increases in UHR raised the risk of CVD mortality (HR, 1.27), while above this threshold, higher UHR was slightly protective (HR, 0.89) [86].

Adding another dimension, a nomogram for predicting post-stroke depression identified SUA as one of five significant predictors, alongside activities of daily living (ADL), instrumental activities of daily living (IADL), sleep duration, and TyG-BMI (triglyceride glucose-BMI) index. The predictive model demonstrated good accuracy, with AUC (area under the curve) values of 0.751 and 0.723 in training and testing datasets, respectively. These findings suggest that SUA may also influence psychological recovery and could be included in broader clinical tools to assess post-stroke risk profiles [87].

Despite promising observational and experimental data, questions remain about causality. A triangulated analysis employing cohort data, meta-analysis, and MR found no evidence supporting a direct causal effect of SUA on 3-month post-stroke functional outcome [88]. Likewise, studies in younger patients with ischemic stroke showed no long-term prognostic value of SUA, though higher levels correlated with less severe initial presentations [89].

Moreover, SUA does not appear to be a reliable biomarker for post-stroke cognitive impairment. A recent meta-analysis concluded that SUA levels did not differ significantly between patients with or without post-stroke cognitive decline [90].

Taken together, current findings present a dualistic picture of SUA in stroke: elevated levels appear to increase stroke incidence and mortality in some populations yet may offer functional and neuroprotective benefits in the context of acute management and recovery—especially when adjusted for kidney function. The identification of inflection points in SUA/sCr and UHR ratios may help define therapeutic windows and risk thresholds.

As such, SUA may serve as a valuable, albeit complex, biomarker in stroke research. It interacts with metabolic, renal, and vascular factors, and its interpretation must be contextualized accordingly. Further large-scale prospective and randomized studies are needed to validate its utility and to assess whether modulating SUA can improve clinical outcomes without unintended harm.

5. Uric Acid in peripheral artery disease: from biomarker to risk stratifier

Recent investigations have increasingly focused on the connection between UA and peripheral artery disease (PAD), although the precise clinical significance of this relationship remains to be fully delineated. Notably, one randomized controlled trial assessed the therapeutic impact of allopurinol—a xanthine oxidase inhibitor—on patients with PAD, hypothesizing potential benefits in alleviating claudication symptoms. Despite a notable reduction in SUA levels following allopurinol treatment, the study did not report any improvements in either pain-free walking time or maximum walking distance, suggesting that UA reduction alone may not translate into tangible functional gains for PAD patients [91].

Parallel to this, attention has turned to novel composite biomarkers involving UA. Among these, UAR has emerged as a candidate with significant diagnostic and prognostic value. In a cohort study involving 243 individuals diagnosed with PAD and categorized using the TASC (TransAtlantic Inter-Society Consensus) classification, UAR was found to be significantly elevated in those with more advanced disease (TASC II stages C and D). Furthermore, elevated UAR values correlated with worse clinical outcomes. The predictive power of UAR for identifying severe PAD was demonstrated with a sensitivity of 57.9 % and a specificity of 78.8 %, indicating its potential utility as a non-invasive indicator of disease severity and a possible aid in clinical decision-making [92].

The prognostic relevance of UAR has also been demonstrated in the context of endovascular procedures for PAD. A recent study including 663 patients undergoing lower extremity percutaneous intervention evaluated the association between UAR and the development of contrast-induced nephropathy (CIN)—a complication known to increase morbidity and mortality in this setting. While multiple factors such as male sex, T2DM, contrast volume, CAD, and elevated CRP were associated with CIN in univariate analysis, multivariate logistic regression identified UAR as the sole independent predictor of CIN occurrence, with an odds ratio of 3.426 (95 % CI: 1.059–11.079; $P = 0.040$). These results highlight UAR's potential as a simple, cost-effective, and clinically applicable tool to predict adverse renal outcomes in PAD patients undergoing interventional procedures [93].

Population-level evidence further supports the relationship between SUA levels and PAD, with notable variations observed across sex. In a large-scale epidemiological study involving 9839 Chinese adults diagnosed with essential hypertension, elevated SUA concentrations were associated with an increased prevalence of PAD, particularly in male participants. Stratified analysis revealed that men in the highest SUA tertile exhibited a significantly elevated odds ratio for PAD. Interestingly, this association was not observed in female participants, pointing to a possible sex-specific pathophysiological response to hyperuricemia in the development of PAD [94].

The impact of UA on PAD outcomes appears even more pronounced in the context of T2DM, particularly among patients with diabetic foot ulcers (DFUs). One study focusing on Chinese individuals with DFUs found that higher UA levels were significantly linked to an increased risk of amputation. This association persisted after adjusting for other relevant clinical parameters, including BMI, ulcer duration, and triglyceride levels. These findings underscore the prognostic implications of SUA in patients with diabetic PAD and suggest that UA may serve as a marker for disease progression in this high-risk subgroup [95].

Beyond amputation risk, the presence and extent of arterial stenosis in PAD have also been associated with UA levels. Evidence shows that SUA and systemic inflammatory markers correlate positively with both the number and severity of stenotic lesions, reinforcing the hypothesis that UA contributes to vascular pathology not only through metabolic mechanisms but also via inflammation-mediated vascular remodeling [96].

In line with these observations, gout—characterized by chronic hyperuricemia—has been associated with poor PAD outcomes, particularly the risk of lower extremity amputation (LEA). A population-based study demonstrated that individuals with gout had a higher likelihood of undergoing LEA compared to non-gout counterparts, even after adjusting for confounding variables such as T2DM and peripheral vascular disease. More importantly, patients with poorly controlled SUA exhibited a greater risk of amputation, suggesting that effective urate management might mitigate severe PAD-related complications in this population [97].

Taken together, these findings suggest a nuanced and multifactorial relationship between UA and PAD. While pharmacologically lowering SUA may not directly improve functional parameters such as walking capacity, as evidenced by the lack of benefit from allopurinol treatment, elevated UA and derived ratios such as UAR appear to hold significant diagnostic and prognostic value. They may serve as biomarkers for assessing PAD severity, identifying high-risk patients, and guiding therapeutic strategies. Moreover, the influence of UA appears to vary across subpopulations, with sex, comorbid T2DM, and gout status all contributing to differential risk profiles. For instance, hyperuricemia in men and diabetic patients seems particularly deleterious, contributing to increased PAD prevalence and higher rates of amputation. Additionally, SUA may contribute to the pathogenesis of PAD through mechanisms related to oxidative stress, endothelial dysfunction, and low-grade chronic inflammation.

Despite this growing body of evidence, several gaps remain. The predictive capacity of UA and UAR in PAD needs further validation in large, prospective cohorts. Likewise, whether interventions targeting UA can confer vascular protective effects beyond SUA reduction—potentially through anti-inflammatory or antioxidant pathways—warrants additional investigation. Future studies should also explore the role of SUA and UAR in treatment stratification, particularly in tailoring management plans for PAD patients with complex comorbidity profiles. Overall, while UA is unlikely to be a direct therapeutic target for improving exercise capacity or reversing arterial stenosis, it holds promise as a biomarker for disease burden and outcome prediction in PAD.

6. Targeting Uric acid: pharmacological strategies and clinical gaps

The treatment of hyperuricemia in gout patients is well-established and primarily relies on XOIs and uricosuric agents. The primary objective is to lower serum urate levels to below 6 mg/dL, or to 5 mg/dL in patients with severe tophaceous gout, recurrent acute attacks, or early-onset disease (before the age of 40) [98]. A recent position paper published by the European League Against Rheumatism (EULAR) [99] underscores the importance of reducing circulating urate levels not only to manage gout but also to mitigate the risk of CV complications. This aligns with gout's recognition as a significant risk factor for CVD and supports the recent decision by the European Society of Hypertension (ESH) and the International Society of Hypertension (ISH) to classify it as an additional CV risk factor in patients with hypertension and a high-risk CV profile [100].

In contrast, asymptomatic hyperuricemic patients, who exhibit elevated SUA levels without any signs or symptoms of MSU crystal deposition (such as gout or nephrolithiasis), do not require pharmacologic intervention. Instead, lifestyle and dietary modifications remain the mainstay of management for these individuals. While a comprehensive review of SUA-lowering therapies is beyond the scope of this article, we will focus on the key therapeutic strategies. These therapies can be broadly categorized based on their mechanism of action: (a) inhibitors of SUA synthesis, (b) agents promoting urate excretion, and (c) agents facilitating the hydrolysis of UA.

Allopurinol, a well-known synthesis inhibitor, works by inhibiting XOR, thereby reducing UA production. This, in turn, leads to increased nucleic acid synthesis and the inhibition of purine metabolism [101].

However, a key drawback of allopurinol is the potential for hypersensitivity reactions, which can range from mild to severe. Alternatively, febuxostat, another XOIs, offers a similar effect in lowering SUA levels but does so without interfering with purine and pyrimidine metabolism, which may make it a preferable option for some patients. A third option, topiroxostat, shares the same mechanism of action as febuxostat.

On the other hand, uricosuric agents such as probenecid and benzbromarone help reduce tubular urate reabsorption, thus promoting the excretion of UA through the kidneys. Rasburicase, a recombinant form of uricase, catalyzes the conversion of UA to allantoin, providing a rapid and powerful means of lowering SUA levels. Rasburicase is especially beneficial for patients at risk of acute renal failure and other complications associated with tumor lysis syndrome (TLS), although its role in TLS prophylaxis remains an area of ongoing research.

Long-term clinical trials have provided strong evidence that XOIs, such as allopurinol and febuxostat, are generally well-tolerated and effective in most patients. These medications have shown a favorable balance between efficacy and safety, even among individuals with multiple comorbidities, including elderly patients, those with HF, and cancer patients. As a result, XOIs are widely regarded as the first-line treatment for chronic hyperuricemia [102,103]. However, recent findings have brought attention to significant disparities in clinical trial participation [104]. Women and racial minorities remain markedly underrepresented in trials investigating SUA-lowering therapies [104]. Over time, the mean proportion of female participants has significantly declined (r = –0.43, P = 0.02), ranging from just 0.8 % in dotinurad trials to 71.1 % in studies of rasburicase. Similarly, the inclusion of racial minorities dropped from 8.7 % to 2.2 % over a 10-year period. When compared to their prevalence in the target populations, women were notably underrepresented—both among those with asymptomatic hyperuricemia (participation-to-prevalence ratio [PPR] = 0.34) and those with gout (PPR = 0.69). This underrepresentation was consistent across drug classes, including XOIs (PPR = 0.38 for asymptomatic hyperuricemia; 0.69 for gout) and uricosurics (PPR = 0.29 and 0.68, respectively) [104]. Only a few agents, such as rasburicase, pegloticase, and topiroxostat, demonstrated more balanced representation [104]. These findings underscore the need for greater inclusivity in clinical research to ensure that the efficacy and safety of SUA-lowering treatments are adequately assessed across diverse patient populations.

More recently, the role of sodium-glucose co-transporter 2 (SGLT-2) inhibitors in managing hyperuricemia is garnering increasing attention, particularly due to their capacity to reduce SUA levels across diverse patient populations [105]. While these agents are primarily used for glycemic control in T2DM, growing evidence underscores a secondary but clinically significant urate-lowering effect, which may contribute meaningfully to their renal and CV protective benefits.

Several comprehensive analyses have consistently demonstrated that SGLT-2 inhibitors significantly reduce SUA levels in patients with T2DM and CKD. A recent network meta-analysis evaluated eight randomized controlled trials (9367 participants) and found that SGLT-2 inhibitors produced a modest but statistically significant reduction in SUA compared with placebo (standardized mean difference [SMD], −0.22; 95 % CI: −0.42 to −0.03). Notably, dapagliflozin 10 mg and ipragliflozin 50 mg were identified as the most effective dosages in this context, with tofogliflozin also showing favorable results in subgroup analyses [106].

Empagliflozin has demonstrated a particularly strong effect in this regard. A systematic review by You et al. encompassing 12 studies and 7801 diabetic patients reported a substantial reduction in SUA with empagliflozin treatment (SMD, −1.97; 95 % CI: −3.39 to −0.55). Compared to placebo, empagliflozin continued to show superior urate-lowering activity (SMD, −1.34; 95 % CI: −2.05 to −0.63), and it also outperformed sitagliptin in head-to-head comparisons (SMD, −1.00; 95 % CI: −1.78 to −0.22) [107].

Mechanistically, these effects are supported by physiological studies. Suijk et al. showed that both dapagliflozin and empagliflozin significantly increased fractional UA excretion, with dapagliflozin reducing plasma SUA by up to 1.0 mg/dL during hyperinsulinemic-euglycemic states and increasing fractional UA excretion by 3.0 % ±2.1 %. These effects were closely linked to urinary glucose excretion (r = 0.35, P = 0.02) and were attenuated by pharmacologic blockade of urate transporter 1 (URAT1), indicating a tubular mechanism of action that includes enhanced UA clearance [108].

Further supporting these findings, another network meta-analysis including 4218 Asian patients with T2DM demonstrated that all SGLT-2 inhibitors studied significantly reduced SUA levels compared to controls (SMD, −0.965; 95 % CI: −1.029 to −0.901). Among these, luseogliflozin (1 and 10 mg) and dapagliflozin (5 mg) were found to be the most effective, suggesting a potential dose-response relationship and highlighting certain agents as superior choices for managing hyperuricemia [105].

In conclusion, SGLT-2 inhibitors consistently demonstrate a clinically meaningful reduction in SUA levels through mechanisms involving increased renal urate excretion and potential modulation of urate transporters. While the magnitude of SUA reduction varies among agents, the cumulative evidence suggests that these drugs may account for approximately 20–25 % of the total cardiorenal benefits seen in clinical trials, positioning them as valuable adjuncts in the treatment of hyperuricemia, especially in patients with comorbid diabetes or CKD.

6.1. *Uric Acid level–lowering drugs and hypertension*

Recent studies have increasingly suggested that SUA-lowering therapies may play a significant role in reducing blood pressure in hyperuricemic patients with concomitant hypertension. A notable Cochrane Review sought to evaluate the effect of SUA-lowering drugs on blood pressure reduction. This meta-analysis included three randomized controlled trials, involving a total of 211 participants with hypertension or prehypertension and elevated SUA levels. Despite its comprehensive nature, the review found inconclusive results regarding the effect of these treatments on 24-hour ambulatory systolic and diastolic blood pressure. The authors concluded that, at present, the available data do not provide a robust foundation for assessing the blood pressure-lowering potential of SUA-lowering agents [109].

However, more recently, a large meta-analysis published in Hypertension presented compelling evidence of a significant reduction in both systolic and diastolic blood pressure in response to urate-lowering treatment. Notably, the extent of the blood pressure reduction was directly correlated with baseline SUA levels. Patients with higher pre-treatment SUA concentrations exhibited a more pronounced decrease in blood pressure, thus reinforcing the hypothesis that hyperuricemia is a critical contributor to the pathophysiology of hypertension in this cohort. These findings further substantiate the potential role of SUA in the onset and progression of elevated blood pressure, underscoring its relevance as a modifiable risk factor in hypertensive patients [110].

Taken together, these studies suggest that urate-lowering therapies may offer a promising adjunctive strategy not only for the management of gout but also for blood pressure control, particularly in patients with hyperuricemia. Nevertheless, while the results are promising, they highlight the necessity for further rigorous and well-designed clinical trials to delineate the precise mechanisms by which UA influences blood pressure and to clarify the long-term benefits of such treatments in hypertensive patients.

6.2. *Uric Acid lowering drugs and cardiovascular prevention*

The role of SUA-lowering therapies in influencing CV outcomes in patients with hyperuricemia, both with and without concomitant gout, remains an area of considerable debate within the scientific community [111]. A comprehensive meta-analysis of 26 studies recently aimed to assess this relationship, with a focus on the efficacy of urate-lowering treatments, particularly allopurinol. The analysis revealed a trend

towards a reduction in the risk of major CV events (HR, 0.72; 95 % CI: 0.48–1.09), although the results did not reach statistical significance. This lack of significance was likely influenced by the relatively small sample sizes and substantial heterogeneity between the included studies, which are common limitations in clinical meta-analyses [110]. Despite this, the study provided valuable insights, suggesting that urate-lowering treatment may still offer CV benefits, especially in specific patient populations.

Of particular interest were the findings within the subgroup of patients with a history of CVD, where the effects of urate-lowering treatment achieved statistical significance (HR, 0.40; 95 % CI: 0.21–0.73) [110]. This suggests that, in patients with pre-existing CV conditions, reducing serum urate levels may provide an important therapeutic benefit, potentially mitigating the adverse CV consequences of hyperuricemia. These findings highlight the need for a more refined and personalized approach to the treatment of hyperuricemia, where the presence of comorbidities such as CVD plays a critical role in determining the potential benefits of urate-lowering interventions.

These data emphasize the necessity of judiciously selecting patients with elevated SUA levels for treatment. In particular, the identification of individuals at high CV risk, even in the absence of overt gout, is crucial to optimize treatment outcomes. A more precise selection could be achieved through the use of advanced clinical tools, such as the SUA to serum creatinine ratio or other indirect markers of UA overproduction, which may help identify those who are more likely to benefit from urate-lowering therapies. Such a strategy could not only improve clinical outcomes but also prevent the unnecessary treatment of patients who have a low probability of responding to therapy. In doing so, it would maximize the clinical efficacy of urate-lowering treatments and minimize the potential risks associated with their use, enhancing overall patient care.

7. From Waste product to therapeutic target: rethinking uric acid in cardiovascular medicine

The evidence presented throughout this second installment of our two-part review supports a fundamental reappraisal of UA, moving beyond its historical role as a metabolic waste product to recognize it as a biologically active molecule with significant implications in CV and renal disease [112,113]. Across diverse clinical contexts—hypertension, CAD, HF, stroke, and PAD—SUA emerges not only as a marker of increased risk, but in many cases, as a potential mediator of disease processes [114].

Mechanistic studies provide a compelling rationale for this shift. UA has been shown to induce endothelial dysfunction, oxidative stress, and inflammatory activation, all of which contribute to vascular remodeling and organ damage [115]. These pathophysiological pathways are mirrored in epidemiological data, where elevated SUA—sometimes even within the so-called "normal" range—predicts adverse outcomes with surprising consistency. Importantly, several studies report U- or J-shaped relationships, indicating that both excessive and excessively low SUA levels may be detrimental, and suggesting a complex homeostatic role for UA that demands careful clinical interpretation [116,117]. Emerging data also implicate obstructive sleep apnea syndrome (OSAS) as a major and underrecognized contributor to hyperuricemia, through hypoxia-induced purine catabolism and acidosis-driven urate precipitation, especially during sleep [118].

This evolving understanding has begun to shape clinical guidance. As summarized in Table 1, several national and international guidelines have now incorporated SUA as an additional CV risk factor, particularly in patients with hypertension.

While this trend reflects growing awareness of UA's role in CV pathophysiology, notable discrepancies remain: the most recent ESC guidelines, for instance, omit any reference to SUA, even where its mention would be clinically relevant. This inconsistency underscores the need for harmonization across guidelines and for further high-quality evidence to support stronger recommendations.

Table 1
- Recognition of uric acid as a cardiovascular risk factor in major hypertension guidelines.

International Guidelines (year)	Recommendations
ESH/ESC (2018) [119]	Uric acid as a risk factor for CV risk in hypertension
ISH (2020) [120]	Uric acid additional risk factor for CVD in hypertension
ESH (2023) [121]	Uric acid and gout as risk factors for CV risk in hypertension
CHL (2024) [122]	Uric acid as a risk factor for CV risk in hypertension
ESH (2024) [123]	Uric acid as a risk factor for CV risk in hypertension
ESC (2024) [124]	No reference is made, not even where it is warranted.
LASH (2024) [125]	Uric acid as a risk factor for CV risk in hypertension

CV= Cardiovascular; CVD= Cardiovascular disease; ESH= European society of Hypertension; ESC= European Society of Cardiology; ISH= International Society of Hypertension; CHL= Chinese Hypertension League; LASH= Latin American Society of Hypertension.

Therapeutically, urate-lowering interventions have produced mixed results [126–128]. While XOIs have shown benefit in specific patient subsets—such as young hypertensive individuals or those with early HF—their broader efficacy remains uncertain. Moreover, recent data reinforce the need for individualized targets rather than a universal threshold. Composite biomarkers such as the SUA/sCr ratio or UAR may offer more refined tools for risk stratification and treatment selection [48,50].

In this context, selective uricosuric agents such as dotinurad—an inhibitor of urate transporter 1 (URAT1)—have shown promise extending beyond mere urate lowering. A recent long-term study in Japanese patients with asymptomatic hyperuricemia demonstrated that dotinurad not only reduced SUA and increased urinary excretion, but also improved metabolic parameters including body weight, hepatic steatosis, serum lipids, and albuminuria, without impairing renal function [129]. Notably, unlike XOIs, dotinurad does not inhibit ATP-binding cassette subfamily G member 2 (ABCG2), a key transporter involved in UA and uremic toxin excretion, which may offer nephroprotective advantages.

Given the strong epidemiological link between OSAS and hyperuricemia—even in non-obese individuals—sleep studies may be warranted in patients with gout or unexplained SUA elevations, both to prevent flares and to reduce systemic CV risk [130].

Of particular interest are the pleiotropic effects of SGLT2 inhibitors, which reduce SUA levels while simultaneously improving CV and renal outcomes [65,73–75]. These agents may help bridge the gap between metabolic modulation and clinical benefit, positioning UA as both a therapeutic target and a surrogate marker of treatment response.

Equally crucial is the recognition of population heterogeneity. Sex differences, renal function, and comorbidities like diabetes or chronic kidney disease significantly influence the impact of SUA on disease risk and therapeutic response [131]. OSA-related hyperuricemia adds another layer of complexity, underscoring the importance of addressing sleep health alongside traditional risk factors. These nuances highlight the limitations of a one-size-fits-all approach and emphasize the value of a personalized strategy that integrates biochemical, clinical, and demographic factors.

While the question of causality remains partly unresolved, the convergence of mechanistic, observational, and interventional evidence points to SUA as an actionable component of CV risk—particularly in high-risk groups. Future research should aim to clarify optimal SUA ranges, better identify treatment responders, and further explore the interactions between UA metabolism, systemic inflammation, and cardiometabolic health.

Declaration of interests

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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