Progress of uric acid in cardiovascular disease

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Due to the global prevalence of hyperuricemia (HUA), there is growing interest in research on uric acid (UA). HUA is a common condition that has various adverse consequences, including gout and kidney disease. However, recent studies have also implicated UA in the development of cardiovascular diseases (CVD) such as atrial fibrillation (AF) and coronary heart disease (CHD). Experimental and clinical research has extensively demonstrated the detrimental effects of elevated serum UA levels on cardiovascular health. Furthermore, serum UA levels have been identified as predictors of CVD outcomes following percutaneous coronary intervention (PCI) and catheter ablation. Additionally, the use of UA-lowering therapy holds important implications for the management of CVD. This review aims to consolidate the current evidence on the relationship between serum UA and CVD. *Cardiovasc Endocrinol Metab* **13: 1–7**

Cardiovascular Endocrinology & Metabolism 2024, **13**:1–7

Keywords: atrial fibrillation, cardiovascular disease, coronary heart disease, hyperuricemia, uric acid

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Received 6 January 2024 **Accepted** 10 March 2024.

Introduction

Uric acid (UA) is formed through the breakdown of purine nucleotides, both from internal sources and from the diet. Hyperuricemia (HUA) occurs when there is an excessive production of UA or impaired renal clearance. It is defined as an elevated level of UA in the blood, with a solubility of urate in plasma at 37 °C greater than 0.42 mmol/L (7.0 mg/dl) for men or greater than 0.36 mmol/L (6.0 mg/dl) for women. Although the relation between gout and kidney disease has long been recognized, recent research has indicated that raised serum UA (SUA) levels are also related to cardiovascular disease (CVD). This poses a significant risk for cardiovascular mortality, which can greatly affect a person's quality of life and even survival. Epidemiological evidence indicates a rising global prevalence of HUA and gout. Understanding the connection between UA and CVD is crucial in managing and preventing the adverse cardiovascular outcomes associated with HUA [1,2]. Therefore, it is imperative to investigate the relation between SUA levels and CVD. Measuring SUA levels can also assist in risk stratification [3]. Multiple studies in the Uric Acid Right for Heart Health (URRAH) programme have shown that HUA combined with left ventricular hypertrophy (LVH) is a marker for CV mortality [4]. Additionally, SUA also predicts mortality in cardiometabolic patients with undiagnosed CVD [5]. In combination with other metrics, UA can also be a factor. For instance, an SUA/sCr ratio greater than 5.35 is a marker of CV risk [6]. Furthermore, research related to the Brisighella Heart Study has indicated that SUA is a predictor of electrocardiogram-diagnosed myocardial infarction (MI), LVH, and tachyarrhythmias [7]. Maintaining control of SUA has a beneficial effect on the age-related worsening of SBP and fasting blood glucose [8]. Understanding the relation between SUA levels and CVD results is essential for predicting CVD risk and improving patient prognosis. However, the exact relation between SUA levels and CVD is still unknown. This article aims to review the relation between SUA levels and atrial fibrillation (AF) and coronary heart disease (CHD), as well as the impact of SUA levels on percutaneous coronary intervention (PCI) and catheter ablation (CA). Furthermore, the advancements in UA-lowering therapy (ULT) will be discussed (Fig. 1).

UA and AF

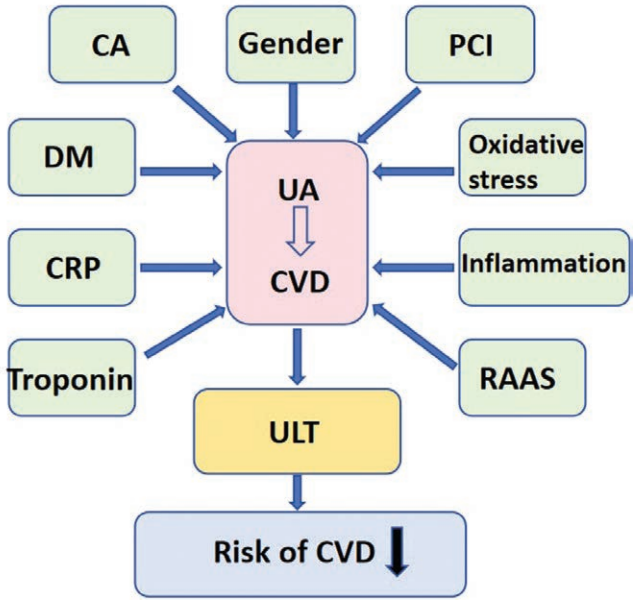
The role of UA in the onset and development of AF

HUA is strongly related to an elevated risk of AF and serves as an independently competing risk factor for AF. Additionally, HUA is often prevalent among the elderly population [9–11]. Recent research has shown that an elevation of SUA levels by 1 mg/dl is related to a 21% rise in the incidence of AF. Furthermore, SUA levels exceeding 5.0 mg/dl significantly elevate the risk of AF, indicating a positive linear dose-exposure relation between SUA and AF [12]. Therefore, addressing HUA or gout may offer potential benefits to patients with AF [13].

Mechanisms between UA and AF

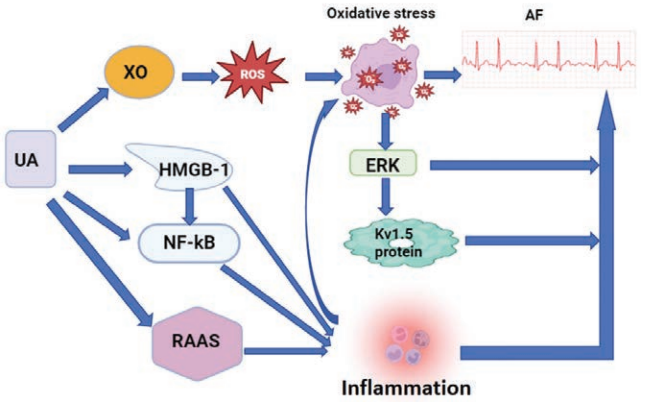
The process by which SUA promotes the development of AF is complex and involves multiple mechanisms (Fig. 2).

Fig. 1



Relationship between UA and CVD. CRP, c-reactive protein; CVD, cardiovascular disease; DM, diabetes; PCI, percutaneous coronary intervention; RAAS, renin angiotensin aldosterone system; UA, uric acid; ULT, uric acid-lowering therapy.

Fig. 2



Mechanisms of AF promotion by UA. AF, atrial fibrillation; ERK, extracellular signal-regulated kinase; HMGB-1, high-mobility group box-1 protein; NF-kB, nuclear factor kappa-B; RAAS, renin angiotensin aldosterone system; ROS, reactive oxygen species; UA, uric acid; XO, xanthine oxidase.

Oxidative stress

Oxidative stress plays a significant role in the development of AF induced by SUA. This complex pathological process presents potential strategies for therapeutic intervention and has been extensively studied in the prevention and treatment of AF. Research has established the crucial involvement of reactive oxygen species (ROS) in oxidative stress and their close association with UA-induced AF. Studies indicate that elevated UA levels are linked to increased xanthine oxidase (XO) activity, which leads to ROS production. Accumulated ROS can impair nitric oxide clearance, cause endothelial dysfunction, and induce detrimental metabolic, functional, and immunological effects [14]. The increased oxidative stress triggered by ROS can also contribute to cardiac arrhythmias, implicating UA in arrhythmogenesis under oxidative stress conditions. Therefore, it is essential to identify therapeutic strategies that target upstream events, such as reducing ROS production or attenuating oxidative stress caused by ROS, inhibiting XO-derived ROS, or inhibiting XO activity, to prevent arrhythmic complications in individuals with elevated UA levels [15].

However, clinical trials targeting common antioxidants have not yielded the anticipated therapeutic effects. To develop more effective antioxidant therapy, it may be necessary to target specific sources of ROS. Potential targets for AF treatment include mitochondria and NADPH oxidase, both of which contribute to ROS production in the heart. It is worth noting that mitochondria are a vital source of ROS in myocytes. Therefore, interventions that specifically target mitochondria with antioxidants may prove most effective in treating arrhythmias. To achieve better control of oxidative stress, it is necessary to simultaneously inhibit ROS production from multiple sources due to the positive feedback loops between them. Furthermore, by identifying downstream targets of ROS that contribute to arrhythmogenesis, such as c-Src and CaMK II, it may be possible to develop effective antiarrhythmic therapies, even if these interventions do not directly reduce ROS levels [16,17].

It has also been observed that the extracellular signal-regulated kinase (ERK) pathway is closely associated with UA-induced AF. HUA can impede cardiomyocyte function through the oxidative stress pathway in the ERK/p38 pathway, offering a new possible mechanism for HUA-related CVD. However, further exploration is required to understand the mechanisms linking HUA to cardiomyocyte damage and its relevance to heart disease [18]. Additionally, urate can enter cells via the UA transporter protein, leading to increased expression of the Kv1.5 protein. This action is facilitated by NADPH oxidase-dependent oxidative stress and activation of the ERK pathway. Atrial tissue with elevated Kv1.5 currents is more susceptible to AF. Therefore, the application of UA transporter protein inhibitors and antioxidants that prevent endocytosis may be of therapeutic benefit in the prevention of AF in individuals with HUA [19].

Inflammation

Inflammation plays a pivotal role in UA-induced AF, presenting new possibilities for therapeutic interventions

in the clinical setting. Hypersensitive C-reactive protein (hs-CRP) is a plasma protein that is elevated during inflammation and following tissue injury. Research has demonstrated that raised levels of SUA and an elevation of SUA over time are related to an elevated risk of AF. Moreover, individuals with high levels of both SUA and hs-CRP have a markedly elevated risk of developing AF [20]. Therefore, reducing elevated SUA and hs-CRP levels may help prevent AF in patients. One study suggests that SLC17A1 can induce inflammation, leading to increased UA levels and a heightened risk of AF [21]. Animal models have shown that UA induces inflammatory cell infiltration and production of inflammatory mediators in hyperuricemic mice. These pro-inflammatory effects may be mediated through the activity of the nuclear factor kappa-B (NF-κB) pathway, which may be a possible therapeutic goal [22].

Furthermore, UA activates endothelial cells, resulting in the acetylation of nuclear high-mobility group box-1 protein (HMGB-1), facilitating its translocation and release. The translocation and release of HMGB-1 induced by UA depend on calcium mobilization and the activation of the MAP/ERK signaling pathway. Released HMGB-1 can act as an autocrine and paracrine agent, stimulating further HMGB-1 acetylation and release. Additionally, it activates NF-κB activity, upregulates ANG2 expression and release, and triggers a feedback loop mechanism that leads to the activation of various pro-inflammatory and pro-repair mediators locally and systemically. These findings provide potential explanations for the systemic inflammatory response following local injury and hold implications for therapeutic interventions [23].

Renin-angiotensin-aldosterone system

Activation of the renin-angiotensin-aldosterone system (RAAS) by SUA has been implicated in oxidative stress and the inflammatory reaction that leads to the development of AF. Concurrently, oxidative stress and the inflammatory reaction may themselves contribute to the development of AF, creating a detrimental cycle that perpetuates the progression of AF. Recent research has identified the immune subunit PSMB10 as a novel modulator of angiotensin II (Ang II)-induced AF. Inhibition of PSMB10 has been demonstrated to prevent Ang II-induced AF, fibrosis, inflammation, and oxidative stress. Therefore, inhibiting PSMB10 holds considerable potential as a therapeutic approach for the treatment of AF [24].

In addition, UA serves as a marker for risk factors related to coronary artery disease (CAD) and activates the RAAS, leading to elevated Ang II production, cell proliferation and ROS production. The detrimental effects of UA can be attenuated by RAS blockers, including ACE inhibitors and AT1 receptor blockers [25]. Elevated UA levels may trigger RAAS overactivation, exacerbate oxidative stress and contribute to atrial remodeling, thereby promoting the initiation and persistence of AF [26]. It is evident that oxidative stress, inflammation and the RAAS are intricately intertwined and intimately involved in the pathophysiological process of UA-induced AF. These three factors have the potential to interact and collectively promote the development and progression of UA-induced AF.

Association between UA and AF differs by gender

Gender differences play a considerable role in the risk of developing AF in relation to SUA levels. Notably, SUA levels show a stronger correlation with CVD in women compared to men [27]. The relation between elevated UA levels and AF risk is more pronounced in women as well [28]. Furthermore, higher SUA levels in women are associated with a higher prevalence of AF [29]. In women, the prevalence of AF increases with higher baseline UA levels. Significantly, baseline UA levels ≥6.5 mg/dl in men and ≥4.9 mg/dl in women were linked to a higher incidence of AF [30]. However, it is noteworthy that a study found that SUA levels had moderate predictive value for non-valvular AF in women but not in men [31]. Although the specific gender-specific mechanism remains incompletely understood, it highlights the importance of conducting more comprehensive studies. Consequently, the need for gender stratification in studies examining UA should be emphasized.

The relationship between UA and AF in patients with diabetes

Diabetes is recognized as a potential contributor to the progression of UA-induced AF. Research has demonstrated that raised levels of SUA may raise the risk of type 2 diabetes [32]. Moreover, HUA is independently related to a higher incidence of AF in individuals with type 2 diabetes, even after adjustment for multiple risk factors and possible confounders [33]. Additionally, this research observed a significantly related relation between SUA and AF across different levels of fasting blood glucose. Elevated SUA, which plays a critical role in regulating glucolipid metabolism, may be contributing to the complicated inflammatory and oxidative stress processes associated with AF. Therefore, monitoring of SUA levels is recommended not only in individuals with diabetes, but also in those with impaired fasting glucose and normal blood glucose levels [34]. Collectively, the above studies provide robust evidence for the close relation between diabetes and the progression to UA-induced AF.

UA and CA of AF

SUA levels have emerged as potential predictors of AF recurrence after CA. The UA/creatinine ratio (UCR) has been proposed as a new biomarker that better reflects endogenous UA levels by eliminating the influence of renal function. Raised preoperative UCR is closely

related to AF recurrence after CA, suggesting its utility as a predictive marker [35]. Similarly, the UA to albumin ratio (UAR) has shown an association with AF recurrence after CA, with higher UAR related to increased recurrence frequency [36]. In individuals who have undergone successfully cryoballoon-based AF ablation, SUA levels have been shown to be a reliable and independent marker of AF recurrence. In addition, the pre-procedural pro-inflammatory and pro-oxidative microenvironment plays a significant role in AF recurrence after CA. Thus, SUA serves as an accessible and affordable marker of inflammation and oxidative stress, making it a potential tool for predicting AF recurrence after cryoablation [37]. However, it should be noted that some research has reported conflicting findings. One study found no relation between elevated SUA and an elevated risk of AF recurrence after CA [38], whereas another study found a strong relation between SUA levels and postoperative recurrence [39]. Further exploration is required to fully elucidate the mechanism underlying the relationship between SUA levels and AF recurrence after CA. Despite the ongoing debate, it is important to recognize that SUA levels are intimately linked to the development of CVD after CA. Therefore, further investigations are needed to explore the specific mechanisms by which SUA affects the occurrence of AF recurrence in CA patients. The main meta-analyses (Table 1) summarize the relation between SUA and AF outcomes.

UA and CHD

The role of UA in the development and progression of CHD

SUA exhibits a close association with the development of CHD, providing valuable insights for preventive and control strategies. Research has highlighted the strong relation between SUA levels and the occurrence of acute coronary syndrome (ACS) in individuals with essential hypertension. Higher SUA levels are correlated with an elevated incidence of ACS, with a 62% higher risk for SUA levels above 452.63 umol/L compared to levels below 310.43 umol/L. The risk of ACS increases significantly with elevated SUA levels [40]. Furthermore, SUA levels above 8.0 mg/dl have been identified as a significant marker for cardiac death within 2 years. This may be partly due to the worrying effect of accumulating SUA on plaque morphology in ACS individuals [41].

Elevated SUA levels also exhibit unfavorable short-, medium-, and long-term prognoses in individuals with non-ST-elevation ACS (NSTE-ACS). Individuals with higher levels of SUA have an elevated risk of hospitalization, death and stroke compared with those with lower levels [42]. UA has also been related to the severity of CAD and atherosclerosis [43,44]. In addition, in individuals with ACS, higher levels of SUA may reduce the likelihood of myocardial revascularisation, even in those with raised levels of lipoprotein(a) (Lp(a)) and low-density lipoprotein cholesterol (LDL-c). It is worth noting that elevated SUA may have a protective effect during the acute phase of ACS, although further research is necessary to confirm this hypothesis [45].

Table 1 Relationship between SUA and AF outcomes in meta-analyses

Relationship between SUA and AF outcomes in meta-analyses	
Zhang *et al.* [12] 2020	The incidence of AF increased by 21% for every 1 mg/dl increase in SUA levels. Moreover, SUA levels above 5.0 mg/dl significantly increased the risk of AF.
Gao *et al.* [13] 2022	Patients with hyperuricemia were easier to suffer from AF.
Zhao *et al.* [38] 2016	Elevated SUA is not associated with increased risk of AF recurrence after CA.
Chen *et al.* [39] 2022	Patients with high SUA levels have a higher risk of recurrence after CA.

The impact of gender on UA and CHD

The impact of SUA levels on CHD exhibits significant gender variations. UA shows a noteworthy association with the severity of CHD, particularly in women, while the correlation is not as pronounced in men [46]. Moreover, SUA levels undergo substantial changes with age. In women, SUA levels and the prevalence of HUA rise significantly with age, while the opposite trend is observed in men. Recognizing the gender and age differences in the relationship between UA and CHD is crucial [47]. Specifically, the correlation between UA, HUA, and CHD is primarily observed in women, particularly in those aged 80 years or older, while such an association is not prominent in men [47]. Moreover, elevated UA levels exhibit a stronger correlation with major adverse cardiovascular events (MACE) in women with ACS compared to men [48]. Overall, studies have indicated varying outcomes and prognoses regarding UA and CHD, emphasizing the importance of considering gender-specific implications.

Troponin and CRP in relation to UA and CHD

In hyperuricemic ACS patients, troponin I (cTnI) has been identified as a predictor of SUA levels [49]. Furthermore, ACS patients with elevated SUA levels also have elevated levels of CRP and biomarkers related to myocardial necrosis, such as troponin (cTn) and creatine kinase isoenzyme (CK-MB) [50]. However, further comprehensive research is required to fully understand the application and underlying mechanisms of troponin and CRP in relation to UA and CHD, as limited research has been conducted on this specific topic.

UA and PCI

Elevated SUA levels have been demonstrated to be a risk factor for MACE after PCI. Moreover, SUA is clinically relevant for prognostic assessment and risk stratification.

SUA levels have been recognized as one of the most valid prediction of CV events after PCI, with raised levels having a detrimental effect on prevention [51]. Recent studies have shown that hyperuricemic individuals with chronic coronary syndrome (CCS) complications undergoing PCI have twice the incidence of MACE compared to non-hyperuricemic patients, highlighting HUA as a potential predictor of MACE after PCI [52]. Furthermore, HUA has been shown to be an independently relevant risk marker for increased mortality after elective PCI in elderly patients with CAD. This suggested that HUA has the possibility to serve as a novel marker for prognostic estimation and risk stratification in this specific population [53].

In individuals with chronic total occlusion (CTO) undergoing PCI, high SUA levels have been demonstrated to be an independently marker of all-cause mortality, suggesting the potential incorporation of SUA into the risk estimation of CTO patients [54]. In addition, SUA has been demonstrated to be an independently related marker for an elevated risk of stent restenosis after PCI. When combined with diabetes, hypercholesterolemia, hs-CRP and lesions in multiple target regions, SUA can form a prediction model for the risk of in-stent restenosis in individuals with CAD undergoing PCI [55]. Likewise, SUA has been demonstrated to be an independently predictive risk marker for MACE and the presence of multiple coronary lesions 1–3 years after PCI in individuals with ACS and hypertension [56]. In addition, elevated SUA levels have been related to elevated short- and long-term mortality rates and a more serious post-reperfusion inflammatory reaction in individuals with ST-segment elevation MI (STEMI) undergoing direct PCI. SUA serves as a readily available biomarker that may contribute to the stratification of short- and long-term prognosis in STEMI individuals treated with PCI [57]. A 'J-shaped' relationship has been observed between admission UA levels and all-cause mortality in ACS individuals treated with PCI [58]. High variability in UA levels may increase the risk of future CV events, highlighting the necessity of maintaining steady SUA levels and avoiding significant fluctuations after PCI in individuals with CAD [59]. In addition, a major clinical trial reported that elevated UA on admission markedly raised the risk of in-hospital heart failure in individuals with acute MI undergoing PCI [60]. Taken together, these studies demonstrate the value of SUA in predicting risk after PCI. Although more research is necessary to fully elucidate the mechanisms underlying the role of SUA in the occurrence of MACE after PCI for CVD, recent research has reaffirmed the value of exploring the relation between SUA and CVD.

Effect of ULT on CVD

XO inhibitors

Chronic administration of UA-lowering drugs that inhibit XO for a duration of 4 weeks has been shown to lead to a decrease in sympathetic innervation and a reduction in post-MI arrhythmias. These findings suggest that therapeutic approaches aimed at reducing XO activation could potentially serve as a novel option for preventing post-MI arrhythmias [61,62].

Allopurinol, an XO inhibitor, has shown promising effects in the prevention and treatment of AF in various animal models [63]. It inhibits electrical and structural remodeling of the atrium, thereby reducing susceptibility to AF. These protective effects are related to a decrease in ROS generation, factors associated with atrial fibrosis and abnormalities in calcium homeostasis [64]. Allopurinol also improves atrial electrical remodeling by inhibiting CaMK II activity and reducing NCX protein expression. These findings highlight the potential value of allopurinol as an effective treatment for AF by reducing oxidative stress and improving atrial electrical remodeling [65]. Notably, allopurinol has been related to a reduced risk of AF in older individuals, with a more pronounced effect observed after longer periods of use, such as 6 months or 2 years [66].

Febuxostat has been shown to significantly reduce SUA levels compared with lifestyle changes alone and is related to a reduced risk of CV events [67]. However, there are concerns about the potential risk of arrhythmias related to the use of febuxostat. Studies suggest that febuxostat may disrupt calcium dynamics, leading to increased arrhythmogenic events through activation of JNK phosphorylation. Inhibition of JNK phosphorylation could potentially attenuate these arrhythmogenic effects [68]. It is noteworthy that the usage of febuxostat has been related to a higher risk of adverse CV events compared to allopurinol, especially at higher doses of febuxostat [69]. However, more research is needed to assess the long-term CV prognosis of individuals receiving various ULT drugs. One study found no significant variation in the risk of AF in individuals with gout treated with febuxostat, allopurinol or benzbromarone [70].

Benzbromarone

In an animal study, hyperuricemic rats exhibited increased susceptibility to AF due to atrial collagen deposition, atrial myocyte apoptosis, and sympathetic over-innervation. These findings suggest that AF in hyperuricemic rats primarily occurs through the induction of atrial remodeling. Conversely, treatment with benzbromarone significantly inhibited atrial electrical, structural, and sympathetic remodeling, effectively suppressing the development of AF. Therefore, benzbromarone may serve as a possible treatment option to reduce the incidence of AF [71]. Additionally, benzbromarone has been demonstrated to decrease CV risk and improve mortality in individuals with gout. In contrast, the use of allopurinol increased the risk of CV events and all-cause mortality compared with benzbromarone [72].

Summary

SUA levels have strong associations with the incidence, progression and outcomes of AF and CHD. Additionally, SUA levels play an essential predictive function for the occurrence of MACE after PCI and CA. SUA levels may serve as a novel biological marker for prognostic assessment in CVD, enabling risk stratification and providing valuable clinical insights. However, the precise effects of SUA levels on AF, CHD, PCI, CA and ULTs as well as their detailed mechanisms are not yet completely known. Therefore, there is a need for future research studies that focus on exploring the relation between SUA levels and CVDs, such as AF and CHD, as well as potential treatment approaches.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (Grant No. 82160077), the Self-Funded Scientific Research Project of Guangxi Health Department (Grant No. Z20211177), the General Program of Natural Science Foundation of Guangxi Province of China (Grant No. 2017GXNSFAA198129) and the Key Project of Scientific Research and Technology Development of Qingxiu District of Nanning, Guangxi government (Grant No. 2017027).

Conflicts of interest

There are no conflicts of interest.

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