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**Authors:** Claudio Borghi, Justyna Domienik-Karłowicz, Andrzej Tykarski, Krzysztof J. Filipiak, Miłosz J. Jaguszewski, Krzysztof Narkiewicz, Marcin Barylski, Artur Mamcarz, Jacek Wolf, Giuseppe Mancía

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## **Expert consensus for the diagnosis and treatment of patients with hyperuricemia and high cardiovascular risk. 2023 update**

Claudio Borghi et al., Hyperuricemia and high cardiovascular risk

Claudio Borghi<sup>1\*</sup>, Justyna Domienik-Karłowicz<sup>2\*</sup>, Andrzej Tykarski<sup>3</sup>, Krzysztof J. Filipiak<sup>3, 5</sup>,  
Milesz J. Jaguszewski<sup>5</sup>, Krzysztof Narkiewicz<sup>6</sup>, Marcin Barylski<sup>7</sup>, Artur Mamcarz<sup>8</sup>, Jacek  
Wolf<sup>6</sup>, Giuseppe Mancina<sup>9</sup>

<sup>1</sup>Department of Medical and Surgical Sciences, University of Bologna, Italy

<sup>2</sup>Department of Internal Medicine and Cardiology with the Center for Diagnosis and Treatment of Venous Thromboembolism, Medical University of Warsaw, Poland

<sup>3</sup>Department of Hypertensiology, Angiology and Internal Medicine, University of Medical Sciences, Poznan, Poland

<sup>4</sup>Institute of Clinical Science, Maria Skłodowska-Curie Medical Academy, Warsaw, Poland

<sup>5</sup>1<sup>st</sup> Department of Cardiology, Medical University of Gdansk, Poland

<sup>6</sup>Department of Hypertension and Diabetology, Medical University of Gdansk, Poland

<sup>7</sup>Department of Internal Medicine and Cardiac Rehabilitation, Medical University of Lodz, Poland

<sup>8</sup>3<sup>rd</sup> Department of Internal Medicine and Cardiology, Medical University of Warsaw, Poland

<sup>9</sup>Università Milano-Bicocca, Milan, Italy

Address for correspondence: Dr. Justyna Domienik-Karłowicz, Department of Internal Medicine and Cardiology with the Center for Diagnosis and Treatment of Venous Thromboembolism, Medical University of Warsaw, ul. Lindleya 4, 02–005 Warszawa, Poland, tel: +48 22 502 1144, e-mail: jdomienik@tlen.pl

\*Equal contribution.

This document updates previous documents [1, 2] and provides a condensed overview of the existing information. It aims to support healthcare professionals in developing optimal approaches to managing patients struggling with hyperuricemia (HU) and its related health conditions. The intention is to enhance the decision-making process for healthcare professionals in their daily clinical activities. However, it is important to note that the

responsible healthcare provider should make the final decisions regarding patient care, considering what is most appropriate in the given context. Particular attention will be given to the latest advancements in this field. First, the focus herein, was on:

- pointing to the need to standardize the definition of HU;
- paying attention to HU in patients with chronic kidney disease;
- paying attention to HU values associated with the risk of various cardiovascular diseases (CVD);
- focusing on new medications supporting HU treatment with allopurinol in patients at increased cardiovascular risk.

### **Definition and epidemiology: The growing importance of hyperuricemia despite varying definitions and limited epidemiological data**

Unfortunately, the definition of HU and the threshold for diseases of the cardiovascular system are still not clearly defined. This means that data on HU and the relationship between uric acid (UA) concentration and other diseases are often difficult to interpret and inconsistent in many publications. Undoubtedly, UA is the end product of purine metabolism. Its concentration in blood can increase in humans, great apes, and Dalmatian dogs as a consequence of a genetic mutation that occurred millions of years ago and contributed to human evolution from less evolved species [3]. Increased UA levels in the blood result from nearly three separate mechanisms, regulated by genetics and involving UA production, renal excretion, and intestinal absorption. Under normal circumstances, the body balances UA production and elimination. When this balance is disrupted, it results in HU [4]. Generally, uric acid levels exceeding 7 mg/dL (420  $\mu\text{mol/L}$ ) in males and 6 mg/dL (360  $\mu\text{mol/L}$ ) in females are classified as HU.

The latest scientific data [5, 6] suggest that the average serum UA (sUA) levels have consistently risen in various populations, in addition to concurrent illnesses. The frequency of HU escalates with advancing age. It is more pronounced in males compared to premenopausal females, attributable to the beneficial impact of estrogen on the elimination of UA by the kidneys [5]. Based on the information at hand, the occurrence of HU varies, spanning from 6% in individuals without health issues to 14% in those with hypertension and notably rising

to 23% among patients affected by acute coronary syndrome (ACS) and chronic coronary syndrome (CCS) [7–9].

We are eagerly awaiting the publication of the results from the UVID registry collecting UA concentration values in a group of over 30,000 Polish patients.

It is crucial to highlight significant variations in UA-related conditions based on the chosen threshold. When HU is defined using the traditional criterion ( $> 7.0$  mg/dL in men and  $> 6.0$  mg/dL in women), it was found in 6.3% of the entire population (7.3% in males, 2.8% in females). However, when considering the more recently established threshold (5.6 mg/dL for both sexes), the presence of HU was observed in a larger proportion, affecting 28.2% of the total population (37.3% in males, 4.7% in females) [9]. In a Chinese epidemiological study, the overall prevalence of HU was recorded at 15.1%. This prevalence was higher in specific subgroups such as males, current smokers, individuals with higher body mass index (BMI), those engaging in lower levels of physical activity, and those with noninfectious chronic diseases. Notably, a higher prevalence of HU was observed in subgroups following the non-vegetarian diets, having inadequate vegetable consumption and consuming excessive amounts of red meat and alcohol. Upon inclusion of all variables in the survey-logistic regression analysis, age and physical activity acted as protective factors against HU, while BMI emerged as a risk factor for its occurrence. Diseases such as hypertension and dyslipidemia were linked to an increased risk of HU, while diabetes mellitus demonstrated a negative association [10]. Subsequently, we should not forget about the findings from the United States National Health and Nutrition Examination Survey (NHANES) conducted from 2007 to 2016, which revealed that the prevalence of HU was 20.2% among men and 20.0% among women. To put it simply, 1 out of every 5 men and 1 out of every 5 women are affected by HU. Additionally, sUA levels exceeding 6.0 mg/dL were recorded at 32.3% in the general population, with figures of 49.5% among men and 16.4% among women. The collective average sUA level was measured at 5.39 mg/dL (95% confidence interval [CI] 5.34–5.45), while the specific average sUA levels were 6.04 mg/dL for men and 4.79 mg/dL for women. Moreover, the prevalence rates of HU remained consistent over the period between 2007 and 2016 ( $p$  for trend  $> 0.05$ ) [6]. Based on the information at hand, the occurrence of HU varies, spanning from 6% in individuals without health issues to 14% in those with hypertension and notably rising to 23% among patients affected by ACS and CCS.

Of note, the prevalence of HU increased significantly with worsening renal function, from 12.2% in patients with estimated glomerular filtration rate (eGFR)  $> 90$  mL/min to 63.9% in patients with eGFR  $< 15$  mL/min [11].

Huang highlighted the prevalence of HU in the group of patients with chronic kidney disease, and they revealed that an elevated UA level was strongly linked to a more pronounced deterioration in kidney function and an increased likelihood of advancing to kidney failure. A total of 739 patients were included in the analysis. In the comprehensive adjusted model, individuals with an initial UA level of  $\geq 6$  mg/dL experienced a more significant decrease in eGFR (with a  $\beta$  coefficient of  $-9.6$  and a 95% CI of  $-16.1$  to  $-3.1$ ) when compared to those with a UA level below 6 mg/dL. Upon categorizing patients into four groups based on UA levels, all three groups with HU (UA levels of 6–8, 8–10, and  $\geq 10$  mg/dL) displayed a greater reduction in eGFR over the observation period. This effect exhibited a dose-response pattern, with higher UA levels correlating with more pronounced eGFR decline than the group with the lowest UA levels. The risk of advancing to renal failure escalated by 7% (with a hazard ratio [HR] of 1.07 and a 95% CI of 1.00 to 1.14) for each 1 mg/dL increase in baseline UA level [12].

### **Hyperuricemia values associated with the risk of various CVDs**

In 2018 European Guidelines on Arterial Hypertension formally integrated the assessment of UA as one of the cardiovascular risk factors that should be considered for risk stratification in patients [13, 14]. Uric acid has been extensively studied and has been shown to predict not only overall and cardiovascular-related mortality independently but also incidents of myocardial infarction (MI), stroke, and heart failure (HF), among others. Despite numerous studies on this matter, a crucial unanswered question remains: determining the specific UA level at which it becomes a cardiovascular risk factor. The existing HU threshold ( $> 6$  mg/dL in women and 7 mg/dL in men) is mainly based on the saturation point of UA. Still, previous evidence indicates that adverse cardiovascular effects might also occur at lower levels [1, 2, 15, 16]. Expert consensus on HU suggests a value of 5 mg/dL in patients with a strictly defined elevated cardiovascular risk.

Addressing this issue, the Working Group on uric acid and cardiovascular risk of the Italian Society of Hypertension introduced the Uric acid Right for heArt Health (URRAH) project. The central goal of this initiative is to establish the UA concentration above which the independent risk of CVD significantly rises. Details are presented in Table 1 [17–20].

### ***Overall- and cardiovascular mortality***

In multivariate Cox regression analyses, the URRAH study demonstrated an independent connection between sUA and overall mortality (HR 1.53; 95% CI 1.21–1.93) and cardiovascular mortality (HR 2.08; 95% CI 1.146–2.97;  $p < 0.001$ ). Serum UA values that effectively distinguish between total- and cardiovascular mortality were determined to be 4.7 mg/dL and 5.6 mg/dL, respectively. Including sUA data resulted in a substantial improvement in net reclassification by 0.26 and 0.27 in relation to the Heart Score risk chart for overall mortality and cardiovascular mortality, respectively [16].

Moreover, URRAH supplementary analysis revealed that across the entire study population, sUA emerged as a predictor for both all-cause mortality (ACM) and cardiovascular mortality (CVM). This association held true when stratifying according to triglyceride (TG) levels: ACM predictions in individuals with normal TG levels and hypertriglyceridemia and CVM predictions in those with normal TG levels and hypertriglyceridemia. Therefore, the study reveals that sUA can anticipate all-cause mortality and CVM among individuals with cardiometabolic profiles without established CVD, independently of TG levels [21].

### ***Heart failure***

In Cox regression analyses, when considering sUA as a continuous measure, it emerged as a significant predictor for both overall- and fatal incident HF. Receiver operating characteristic curves were employed across the entire dataset to identify threshold values of sUA that could distinguish between the presence and absence of all HF and fatal HF. Specifically, a sUA level higher than 5.34 mg/dL (CI 4.37–5.6, sensitivity 52.32%, specificity 63.96%,  $p < 0.0001$ ) was established as the univariate prognostic threshold for all HF, while a sUA level exceeding 4.89 mg/dL (CI 4.78–5.78, sensitivity 68.29%, specificity 49.11%,  $p < 0.0001$ ) was identified as the univariate prognostic threshold for fatal HF [17].

### ***Myocardial infarction***

Receiver operating characteristic curves were utilized to pinpoint cut-off values of sUA that effectively distinguish MI status. These values were identified across the entire dataset ( $> 5.70$  mg/dL), specifically for women ( $> 5.26$  mg/dL) and separately for men ( $> 5.49$  mg/dL). Through multivariate Cox regression analyses that were adjusted for various confounding factors (including age, arterial hypertension, diabetes, chronic kidney disease,

smoking habit, ethanol intake, BMI, hematocrit, low density lipoprotein cholesterol, and diuretic use), an independent relationship between sUA and fatal MI was determined. Moreover, in the overall dataset, there was an identified HR of 1.381 (with 95% CIs spanning from 1.096 to 1.758 and a p value of 0.006) for this association with fatal MI. Similarly, in the case of women, the HR was found to be 1.514 (with CIs of 1.105–2.075 and a p value below 0.01), signifying a notable independent link with fatal MI. However, this independent association was not evident among men [22].

### ***Cerebrovascular events***

Using a receiver operating characteristic curve, a predictive threshold value for sUA that effectively distinguishes combined cerebrovascular (CBV) events ( $> 4.79$  mg/dL or  $> 284.91$   $\mu\text{mol/L}$ ) was identified within the entire dataset. After accounting for confounding factors such as age, sex, arterial hypertension, diabetes, chronic kidney disease, smoking habit, ethanol intake, BMI, low-density lipoprotein cholesterol, and diuretic usage, multivariate Cox regression analysis unveiled an autonomous link between sUA and the occurrence of combined CBV events across the entire dataset. This independent association with combined CBV events was quantified as a HR of 1.249, with a 95% CI ranging from 1.041 to 1.497 and a significance level of p of 0.016. The findings of this study validate sUA as a distinct risk indicator for combined CBV events, even after adjusting for potential confounding variables, including arterial hypertension. Furthermore, the research confirms that the  $> 4.79$  mg/dL threshold is a reliable predictive cut-off value for these events [23].

### **Risk models**

Although many studies are helping us to understand the concepts of the relationship between HU and CVD, the independent association of sUA with CVD remains controversial as sUA is not currently included as one of the risk factors that increase the risk in both the Systematic COronary Risk Evaluation 2 (SCORE2) model and atherosclerotic cardiovascular disease risk (ASCVD-PCE), as per the most recent guidelines [24–26]. Hence, Moshkovits et al. [27] presented a study to assess how sUA affects the precision of modern 10-year ASCVD-PCE and SCORE2 risk classification models. They assessed 19,769 individuals aged 40–79 without CVD or diabetes who self-referred for screening in a preventive healthcare setting. The primary endpoint was the composite of death, ACS, or stroke, excluding those diagnosed with metastatic cancer during follow-up. The average age was  $50 \pm 8$  years (69% men). Over a median follow-up of 6 years, 8% (1658 subjects) reached the endpoint. In a multivariable

model, both ASCVD PCE and SCORE2, along with high sUA, independently correlated with the study endpoint ( $p < 0.001$  for all). When high sUA was added to either ASCVD PCE or SCORE2, continuous net reclassification improvement analysis showed a 13% enhancement in classification accuracy ( $p < 0.001$  for both). In conclusion, sUA notably boosts the accuracy of ASCVD PCE and SCORE2 models, particularly among normal-weight and low-risk individuals [27].

Most recent observational data further support integrating sUA in the cardiovascular-risk assessment, especially in subpopulations where cardiovascular prognosis was either only partly explored or/and difficult to estimate precisely. In multivariate analysis, Obrycki et al. [28] showed that in the non-obese adolescent population with spurious hypertension, the main factor capable of predicting disadvantageous hemodynamic outcome (rise in central blood pressure after 1 year of non-pharmacological treatment) was sUA alterations. The clinical significance of their finding is that sUA alterations serve as a reasonable proxy and are much more accessible and easier to follow than central blood pressure monitoring.

Adults diagnosed with obstructive sleep apnea (OSA) constitute a group of high cardiovascular-risk patients where the treatment-resultant prognosis is difficult to predict, mainly due to low OSA-specific treatment adherence (nasal continuous positive airway pressure). Symptomatic therapy of OSA may reduce blood pressure, and it supports device-based strategies to address difficult-to-control hypertension in OSA. However, its role in cardiovascular outcomes remains obscure [14, 29]. Recent analyses of OSA cohorts, including patients after MI, strongly suggest that higher/lower sUA levels dichotomize patients concerning their clinical outcomes [30]. This phenomenon adds to our understanding of why long-term continuous positive airway pressure therapy produces inconsistent clinical effects, especially as OSA-OSA-symptomatic treatment appears to have minimal, if any, impact on sUA [31].

### **Recent studies connecting elevated uric acid levels with chronic kidney disease and CVD** ***Hyperuricemia and chronic kidney disease***

Elevated sUA levels often arise from impaired kidney function, even though some prior studies have disregarded the impact of renal health on sUA levels. Consequently, a new biomarker called renal function-normalized sUA, denoted as the ratio of sUA to serum creatinine (sUA/sCr), has emerged. This marker is considered a more accurate indicator of net sUA production. Multiple investigations have indicated significant links between sUA/sCr



and a range of metabolic disorders, various cardiometabolic factors, as well as mortality. Wang et al. [32] confirmed that sUA/sCr and CVD are positively associated. In their study, they enrolled 96,378 participants from the Kailuan study who did not have a history of stroke or MI at the baseline in 2006. Over an average follow-up period of 11.01 years, 6,315 (6.55%) individuals experienced new-onset CVD. The study revealed that individuals in the highest quartile of sUA/sCr had the highest risk of developing CVD (HR 1.15; 95% CI 1.07–1.23), stroke (HR 1.16; 95% CI 1.07–1.26), ischemic stroke (HR 1.12; 95% CI 1.02–1.22), and hemorrhagic stroke (HR 1.36; 95% CI 1.11–1.65). However, there was no significant association with MI (HR 1.07; 95% CI 0.92–1.25). Furthermore, they found that the link between elevated sUA/sCr and CVD was partially mediated by several factors, including TGs, BMI, total cholesterol, high-sensitivity C-reactive protein, diastolic blood pressure, and fasting glucose [32].

### **Hyperuricemia and ischemic heart disease**

Unfortunately, the exact pathophysiological mechanisms leading to an increased risk of coronary artery disease in patients with elevated UA levels are still unknown. It has been postulated that HU leads to endothelial dysfunction, oxidative metabolic processes, and platelet adhesion and aggregation, ultimately resulting in coronary artery disease [33].

Several new studies have explored the potential connection between HU and the risk of developing ischemic heart disease. The outcomes were anticipated of the ALL-HEART study, a controlled and prospective trial conducted across multiple centers. This study utilized randomization and examined the impacts of allopurinol (up to 600 mg daily) compared to no treatment on cardiovascular outcomes (such as non-fatal heart attacks, non-fatal strokes, or cardiovascular-related deaths) in patients with coronary artery disease. The study also aimed to assess the cost-effectiveness of adding allopurinol to standard therapy, evaluate whether allopurinol enhances the patient's quality of life, and gauge the safety and tolerability of administering allopurinol to individuals with ischemic heart disease (excluding those with a history of gout). The primary criteria for inclusion were individuals aged 60 years and above with ischemic heart disease. In contrast, exclusion criteria involved a history of gout, eGFR below 30 mL/min, and moderate-to-severe HF, as well as significant hepatic disease [34].

The analysis, conducted on treatment-specific subgroups, was modified as per the intention-to-treat approach (mITT-analysis), encompassed 5721 randomized patients, out of whom 2853 were in the allopurinol arm, and 2868 were in the standard care arm

(conventional treatment under general practitioner care). The mean observation time amounted to 4.8 years. There was no difference between the groups in the frequency of the primary endpoint, which occurred in 314 (11.0%) participants in the allopurinol arm (2.47 events per 100 patient-years) and 325 (11.3%) in the standard care arm (2.37 events per 100 patient-years; (HR 1.04; 95% CI 0.89–1.21;  $p = 0.65$ ).

Furthermore, no differences were observed between the groups in any of the secondary outcomes involving time to events, which included non-fatal MI, non-fatal stroke, cardiovascular-related death, all-cause mortality, hospitalization due to ACS, coronary revascularization, hospitalization due to HF, and all cardiovascular-related hospitalizations. A total of 288 (10.1%) patients in the allopurinol arm died, compared to 303 (10.6%) patients in the standard care arm, yielding an HR of 1.02 (95% CI 0.87–1.20;  $p = 0.77$ ).

Moreover, some aspects of the study are worth paying attention to. Firstly, many patients discontinued treatment during the study, yet they were still considered in the final results according to the modified ITT analysis methodology. In the allopurinol group, a very high percentage of patients discontinued allopurinol treatment during the study. This is a substantial proportion: 57.4% (1637 individuals out of 2805 enrolled through randomization). These patients did not take the medication (we do not know precisely when they discontinued treatment), yet they were assessed in the allopurinol arm, which could have had an impact on the outcome. Secondly, the average age was 72 years, and the average observation period was 4.8 years. By the end of the observation, this was already a quite advanced-age group, from which outstanding effects are difficult to anticipate. It is important to note that in the United Kingdom, medications for this group are fully subsidized. The aim was not to exclude individuals who cannot afford medication for financial reasons. These patients also had well-controlled arterial hypertension and metabolic parameters. 90% of them were using statins, and 87% in both groups were on antiplatelet drugs.

The study did not present which statins and dosages were used in which groups or which antihypertensive drugs were used. As we know, both statins and angiotensin converting enzyme inhibitor, as well as angiotensin receptor blockers, influence oxidative stress, vascular inflammation, and, consequently, the development of atherosclerosis and cardiovascular complications. Based on this alone, it is difficult to determine whether both groups were truly homogeneous in terms of the “baseline level of oxidative stress” in the vessels.

Additionally, there was no information about the level of low density lipoprotein; finally, this patient group had a very low baseline uric acid level. Namely, 5.7 mg/dL (standard deviation: 1.3) initially decreased to 3.02 at 6 weeks in the allopurinol arm. These are surprisingly low uric acid levels, considering the prevalence of HU in the population. This might stem from the fact that patients with gout were initially excluded (long history of HU, higher likelihood of gout); patients taking uric acid-lowering medications were excluded as well, so those likely diagnosed with HU were excluded. In any case, the conclusion is that the study was conducted in a group that does not have HU. Therefore, it is challenging to draw conclusions regarding the treatment of patients with HU and a high risk of serum uric acid elevation [35].

In this extensive and widespread observational cohort study conducted by the CLIDAS Research Group, it was revealed that hyperuricemic individuals with CCS following percutaneous coronary intervention (PCI) experienced double the incidence of major adverse cardiovascular events (MACE) compared to those without HU over a median follow-up period of 910 days. Even after making multiple adjustments, HU was found to be independently linked to a heightened risk of MACE (Model 1: HR 1.52; Model 2: HR 1.31; Model 3: HR 1.33). Further analyses considering various adjustments indicated that HU was autonomously associated with an increased likelihood of hospitalization due to HF (Model 1: HR 2.19; Model 2: HR 1.76; Model 3: HR 1.71), while not significantly correlated with cardiovascular death and MI. These findings suggest that HU among patients with CCS following PCI might serve as a predictive factor for heightened risks of MACE, particularly concerning HF [36]. This aligns with a previous prospective observational study conducted across multiple centers. It was reported that an elevated sUA level served as an autonomous predictor of both cardiovascular events and mortality due to all causes among patients with coronary artery stenosis of at least 75% in one branch of the coronary arteries, as confirmed by coronary angiography. Over a follow-up period of 3 years, the highest quartile of sUA (sUA levels  $\geq 6.8$  mg/dL) exhibited a HR of 1.25 (with a 95% CI of 1.07 to 1.45) for all-encompassing events, encompassing both cardiovascular events and mortality from any cause. These findings remained consistent even after adjusting for other confounding factors. While the specific components of the combined endpoint in this study slightly differed from those in the present investigation, the overarching theme was that elevated sUA levels correlated with heightened rates of adverse events [37].

## ***Hyperuricemia and hypertension***

A significant body of evidence widely acknowledges that the association between an increased relative risk of hypertension and elevated levels of sUA remains unaltered by conventional risk factors [15, 38–45]. HU has long been acknowledged as having an association with an elevated cardiovascular risk, encompassing the susceptibility to develop hypertension. Epidemiological observations indicate this association is particularly pronounced among the younger demographic, specifically children and adolescents. UA is a potent extracellular antioxidant; however, its intracellular presence is linked to pro-inflammatory effects. Prolonged periods of HU are known to give rise to a chronic phase characterized by microvascular damage. This phenomenon is postulated to contribute to a condition known as afferent arteriopathy, potentially leading to a persistent elevation of blood pressure that may eventually become unresponsive to therapies aimed at lowering UA levels. The establishment of a direct causal relationship between HU and hypertension has proven challenging in scientific investigations due to a multitude of confounding factors.

As it stands, the available evidence to endorse the effectiveness of uric acid-lowering treatments in attenuating the risk of hypertension remains limited. Nonetheless, it is important to recall a PAMELA (Pressioni Arteriose Monitorate e Loro Associazioni) study which validated that an increase in sUA by 1 mg/dL was linked to a notable elevation in the likelihood of developing new-onset home and ambulatory hypertension (odds ratio 1.34, 95% CI 1.06–1.7,  $p = 0.015$ ; odds ratio 1.29, 95% CI 1.05–1.57,  $p = 0.014$ , respectively) [15].

## **Hyperuricemia treatment and cardiovascular outcomes: Allopurinol continues to be the preferred initial choice for uric acid-lowering therapy**

In a comprehensive analysis of 24 guidance documents, most of them, specifically 19, outlined recommended target levels for long-term sUA control. The predominant target level suggested was 6.0 mg/dL (or 360  $\mu\text{mol/L}$ ), although it is worth noting that the South African guidelines deviated from this consensus by recommending a lower threshold of 5.0 mg/dL (300  $\mu\text{mol/L}$ ). However, it is important to highlight that the definition of HU varies significantly among different clinical trials, resulting in a wide range of interpretations. This variability makes it challenging to maintain consistency and comparability in epidemiological reports.

Xanthine-oxidase inhibitors (XOI), particularly allopurinol, are the preferred and recommended first-line uric acid-lowering therapy (ULT) approach. However, it is crucial to acknowledge that further research is required to fully understand the implications of using febuxostat, another XOI [46–48].

### ***Febuxostat — Other significant studies are eagerly awaited***

Febuxostat is an alternative to allopurinol for patients who do not respond well or cannot tolerate allopurinol, and it is suitable for chronic kidney disease stages 1–3 without dose adjustments. It is a potent XOI with stronger uric acid-lowering effects than standard allopurinol doses. However, a 2017 Food and Drug Administration alert raised concerns about a potential cardiac risk associated with febuxostat, especially in high cardiovascular-risk patients, (this is based on the CARES studies). On the other hand, the Febuxostat versus Allopurinol Streamlined Trial (FAST), mandated by the European Medicines Agency (EMA) and published in the *Lancet*, does not corroborate the increased cardiovascular risk associated with febuxostat. This conclusion comes despite the trial's use of higher dosages approved by EMA, in contrast to those used in the CARES trial. In a study of 6128 patients with a history of CVD, the incidence of the primary endpoint showed that febuxostat (172 patients [1.72 events per 100 patient-years]) was not inferior to allopurinol (241 patients [2.05 events per 100 patient-years]; adjusted HR 0.85; 95% CI 0.70–1.03;  $p < 0.0001$ ). Bardin and Richette [47] noted in their editorial comments that the CARES study participants had more advanced gout compared to those in the FAST study, and all CARES participants had a history of CVD, unlike only 2046 (33.4%) out of 6128 in the FAST study. No significant increase in death rates was noted in this subgroup in the FAST trial. However, they pointed out the possibility that the sample size might not be large enough to comprehensively evaluate the risk of febuxostat in patients with severe CVD. Bardin and Richette [47] analyzed 20 randomized controlled trials. The follow-up averaged  $69.7 \pm 81.5$  weeks, with febuxostat doses ranging from 10 to 240 mg, most commonly at 80 mg. Quality concerns were noted in 65% of these studies. MACE were defined in 35% of the trials, showing varied reporting of cardiovascular outcomes. Overall, the cardiovascular safety data for febuxostat appeared reassuring. However, additional clinical trials are necessary to resolve this matter [47–51].

**Management strategies: Revised recommendations comprising five-step suggestions for managing patients with elevated serum uric acid levels (Fig. 2)**

### ***STEP 1: Assess serum uric acid level and uric acid-to-GFR ratio***

Assess sUA level and UA-to-GFR ratio. Experts from the European Society of Cardiology and the European Society of Hypertension recommend measuring sUA concentration as part of screening for patients with heart conditions or hypertension [46]. The advice remains consistent: the ideal objective for sUA levels should be 6 mg/dL (360  $\mu$ mol/L). It's essential to regularly monitor sUA levels and ensure they are maintained below 6 mg/dL. However, even though there is a lack of randomized controlled trials, it is advisable to contemplate an sUA target of less than 5 mg/dL for patients with an increased cardiovascular risk, which includes having at least two of the following conditions: hypertension, diabetes, dyslipidemia, recent stroke, MI, or chronic kidney disease. Considering the new knowledge, in patients with kidney disease, the assessment of the UA-to-GFR ratio can provide insights into how well the kidneys are handling UA excretion. It can help healthcare professionals monitor kidney health and make informed decisions about managing kidney disease progression.

### **STEP 2: Assess existing medical conditions and ongoing therapies, and discontinue using medications that impact serum uric acid levels**

Assess existing medical conditions and ongoing therapies, and discontinue using medications that impact SUA levels. Suitable approaches need to be identified and executed for individuals with elevated UA, involving more proactive management of concurrent risk factors and the utilization of medications that indirectly impact UA levels. Effectively addressing concurrent conditions, depicted in Figure 1, that influence sUA levels should be the preferred course of action [52–56].

In clinical situations, practical modifications should be contemplated when the potential advantages outweigh the potential disadvantages, especially in the case of the drugs presented in the Table 2.

Forming interdisciplinary groups to achieve the best possible diagnostic and treatment approaches, along with accurately assessing the importance of elevated UA (HU), is imperative. Enhancing adherence to established clinical practice recommendations, increasing understanding of HU and its related coexisting conditions, and encouraging more rigorous and precise monitoring of these conditions are crucial.

### **STEP 3: Suggested modifications to patients' lifestyle**

Among the most significant lifestyle changes are:

- following a nutritionally balanced dietary regimen with controlled intake of purine-rich foods;
- hydration emphasis, ensuring adequate water intake;
- limiting alcohol — reducing alcohol consumption, particularly beer and spirits;
- weight management — maintaining a healthy weight through proper diet and exercise;
- reduced sugar intake — minimizing high-fructose corn syrup and sugary foods;
- moderate protein — opting for lean protein sources and moderate consumption;
- adding coffee, dairy products, cherries and ascorbic acid [57–62].

**STEP 4: Administer xanthine oxidase inhibitors as the initial treatment choice, adjusting the dosage to attain the desired serum uric acid target**

Allopurinol, classified as a XOI, is advised as the primary choice for ULT. As outlined in the Summary of Product Characteristics (SmPC) for allopurinol, the suggested starting dosage ranges from 100 to 200 mg daily for mild cases, 300 to 600 mg daily for moderate cases, and 700 to 900 mg daily for severe conditions. The dosage should be incrementally adjusted to attain the target sUA level [63]. Hence, in cases of advanced chronic kidney disease, it might be suitable to consider doses lower than 100 mg per day or to administer singular 100 mg doses at extended intervals exceeding one day. In specific circumstances and with the availability of suitable instrumentation, dosages should be fine-tuned to ensure that plasma oxypurinol concentrations remain below 100  $\mu\text{mol/L}$  (15.2 mg/L). When allopurinol is employed for patients undergoing dialysis, a 300–400 mg dose is recommended immediately after dialysis, abstaining from additional doses on alternate days [63].

**STEP 5: Reach the desired serum uric acid concentrations, avoid discontinuing the treatment, and maintain twice-a-year serum uric acid level assessments. In specific circumstances, contemplate the potential for combined therapy**

*Allopurinol*

Only 40% of patients with HU successfully achieved the targeted sUA level with this therapy. If reaching the sUA goal proves difficult, the dosage should be gradually increased under supervision, reaching a maximum of 900 mg of allopurinol, or the patient's treatment could be switched to benzbromarone. Alternatively, a combined therapy approach involving benzbromarone and allopurinol (STEP 5) could be considered, excluding patients with an eGFR below 30 mL/min. However, these dose escalations should be undertaken cautiously to avoid adverse effects in patients who are intolerant to allopurinol. Another XOI, febuxostat, can be considered.

*SGLT2*

The exact mechanism of sUA reduction by sodium-glucose transport protein 2 (SGLT2) inhibitors remains uncertain, but most researchers suggest that it occurs through increased urinary excretion of UA. While clinical evidence is limited, animal and in vitro studies have shed some light on this effect. Notably, studies in healthy subjects receiving luseogliflozin demonstrated a reduction in sUA after a single dose, with a negative correlation between sUA and urinary excretion of UA. Urinary excretion of UA was also positively associated with urinary d-glucose excretion and SGLT2 inhibitors concentration. The most significant sUA reduction occurred on day 1 of a multiple-dose study, and urinary excretion of uric acid remained elevated for 7 days. In type 2 diabetes mellitus patients treated with tofogliflozin, sUA reached its lowest point after 4 weeks, plateauing thereafter. Empagliflozin and luseogliflozin seem to have the highest sUA lowering effects among flozins, and some experts connect it to their highest SGLT2/SGLT1 selectivity [64].

*Lesinurad*

Lesinurad is an oral selective inhibitor of the renal transporters URAT1 and OAT4. Impeding UA reabsorption enhances renal UA excretion, leading to decreased sUA levels. When patients fail to achieve treatment goals, a recommended dose of 200 mg daily of lesinurad can be combined with XOIs. This combination helps achieve therapeutic goals, amplifies the efficacy of XOIs (compared to monotherapy) and avoids the necessity for



maximal XOI dosages. To emphasize, the usage of lesinurad alongside allopurinol presents a fresh approach for managing HU in adults afflicted with gout, especially when their desired sUA levels remain unattained solely with allopurinol treatment (STEP 5). After reaching the consistent sUA target, the dose of ULT should be perpetually upheld, accompanied by biannual sUA level assessments (STEP 5) [65–68].

### **Many unresolved questions still remain: Areas in need of further study**

Primarily, it might be necessary to reconsider the desired treatment target for UA, particularly in light of recent findings from the URRAH study, which have illuminated novel cardiovascular thresholds and enhanced algorithms for the comprehensive evaluation of overall cardiovascular risk. This emerging data highlights the ongoing need to refine treatment approaches to ensure the best possible patient outcomes.

Furthermore, the presence of chronic kidney disease and the potential elevation of serum creatinine levels introduce additional complexities to the management of HU. Given the frequent coexistence of chronic kidney disease and HU, a customized approach becomes indispensable. Deliberate attention must be devoted to selecting the appropriate ULT and determining suitable dosages to mitigate potential adverse effects on renal function. Vigilant monitoring of serum creatinine levels and renal function becomes imperative in this context, as safeguarding kidney health takes precedence.

While the well-established effectiveness of ULT in relieving symptoms associated with asymptomatic HU is widely acknowledged, an expanding body of evidence is illuminating the favourable influence of these interventions on cardiovascular outcomes. Despite the absence of overt clinical symptoms, the potential advantages of ULT in mitigating the risk of cardiovascular events should not be understated.

In summary, the dynamic landscape of HU management mandates a comprehensive reevaluation of treatment objectives and methodologies. Incorporating the latest cardiovascular risk benchmarks, addressing the complexities associated with chronic kidney disease, and acknowledging the potential cardiovascular merits of ULT collectively underscore the pivotal role of evidence-based decision-making within the clinical routine.

### **Most relevant recommendations: The take home message for clinical practitioners**

Summarizing our viewpoints for clinical practitioners managing patients with HU and increased cardiovascular risk, we present the following key recommendations:

1. Prevalence and awareness:

— hyperuricemia affects at least 20% of patients, and its prevalence continues to rise;

— patients with HU should receive comprehensive education about the environmental and pharmacological factors influencing HU and associated comorbidities and cardiovascular risk factors;

— immediate implementation of lifestyle adjustments, dietary modifications, and weight reduction when needed, along with consistent adherence to recommended treatments, is essential.

2. Uric acid management:

— both patients and healthcare professionals across specialities, particularly primary care physicians, cardiologists, and nephrologists, should work collaboratively to achieve and sustain sUA levels consistently below 6 mg/dL;

— the target sUA level should be maintained at 5 mg/dL for patients at increased cardiovascular risk.

3. Choice of initial treatment:

— as previously mentioned, allopurinol, classified as a XOI, is endorsed as the primary ULT option;

— referring to the Summary of Product Characteristics (SmPC) for allopurinol, the recommended starting dose varies from 100 mg to 200 mg daily for mild cases, 300 to 600 mg daily for moderate patients, and 700 to 900 mg daily for severe conditions.

4. Caution with febuxostat:

— due to concerns regarding cardiovascular risk, it is advisable to be cautious when considering febuxostat for patients with a high cardiovascular risk profile.

## 5. Individualized dosage and monitoring:

- titration of XOI dosages is imperative to achieve the desired sUA target level;
- post-achievement, twice-a-year monitoring of sUA levels ensures the maintenance of appropriate sUA levels.

## 6. Combining therapies:

- in cases where XOI therapy is either poorly tolerated or the target sUA levels remain unachievable, combination therapy involving allopurinol with uricosuric agents, lesinurad, or febuxostat should be considered as a next step;
- the role of SGLT2 in managing HU is growing, but it still requires further research.

In summary, effective management of HU necessitates a multidisciplinary approach, with an emphasis on patient education, personalized treatment strategies, and continuous monitoring to achieve.

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**Table 1.** Key findings from Uric acid Right for heArt Health (URRAH) studies.

Title	Aim	Results	sUA level	References
Serum UA and LVMI independently predict CV mortality: The UA right for heart health	To examine the link between sUA and LVMI, as well as to determine if either sUA, LVMI or their combination can forecast the occurrence of CV mortality	A noteworthy correlation between sUA and LVMI was evident through multi-regression analysis for both men (beta 0.095, F 5.47, $p < 0.001$ ) and women (beta 0.069, F 4.36, $p < 0.001$ ). Over the follow-up period, 319 CV fatalities occurred. Kaplan-Meier plots demonstrated a considerably lower survival rate among individuals with elevated sUA levels (> 5.6 mg/dL in men and 5.1 mg/dL in women) and LVH (log-rank chi-square 298.105; $p < 0.0001$ )	> 5.6 mg/dL in men, > 5.1 mg/dL in women	[18]
Serum UA levels threshold for mortality in diabetic individuals: URRAH project	To confirm the threshold levels of sUA that can predict overall mortality at 4.7 mg/dL and CV mortality at 5.6 mg/dL among individuals with diabetes	In the analysis involving multiple factors in the Cox regression model, accounting for various influencing variables, individuals with sUA levels of 5.6 mg/dL or higher demonstrated an elevated risk of both overall mortality (HR 1.23, 95% CI 1.04–1.47) and CV mortality (HR 1.31, 95% CI 1.03–1.66) when compared to those with sUA levels below 5.6 mg/dL. While an increased risk of mortality from any cause was observed in participants with sUA levels of 4.7 mg/dL or higher in comparison to those with levels below 4.7 mg/dL, this difference was not statistically significant after accounting for all the potential influencing factors		[19]
The association of UA with mortality modifies at old age: data from URRAH study	To explore the connection between sUA levels and the occurrence of both overall mortality and CV mortality	In individuals aged 65–74, a multivariate Cox regression analysis that accounted for CV risk factors and concurrent health conditions revealed an independent connection between sUA levels and both overall mortality (HR 1.169, 95% CI 1.107–1.235) and CV mortality (HR 1.146, 95% CI	4.8 mg/dL	[20]

	in elderly individuals (aged over 65 years) enrolled in the extensive multicenter observational study known as Uric Acid Right for Heart Health (URRAH)	1.064–1.235). The threshold value of 4.8 mg/dL accurately distinguished the mortality status. For participants aged 75 and older, a curving pattern in the relationship between sUA levels and both overall and CV mortality, where the risk increased at extremely high and low sUA levels		
Serum UA predicts HF in a large Italian cohort: search for a cut-off value URRAH study	To determine the specific threshold levels of sUA that can predict the occurrence of severe and fatal HF	<p>In the Cox analyses, when examining sUA as a continuous measure, it was found to be a significant predictor for both overall HF (with a HR of 1.29; 95% CI 1.23–1.359, and a p-value less than 0.0001) and fatal HF (with a HR of 1.268; 95% CI 1.121–1.35, and a p-value less than 0.0001)</p> <p>The identified threshold value for all HF was sUA levels above 5.34 mg/dL (with a CI of 4.37–5.6). This value exhibited a sensitivity of 52.32%, a specificity of 63.96%, and a p-value below 0.0001. Correspondingly, for fatal HF, the established cut-off value was sUA levels exceeding 4.89 mg/dL (with a CI of 4.78–5.78). This value demonstrated a sensitivity of 68.29%, a specificity of 49.11%, and a p-value below 0.0001</p>	For all HF — sUA levels > 5.34 mg/dL; for fatal HF — 4.89 mg/dL	[17]

CI — confidence interval; CV — cardiovascular; HF — heart failure; HR — hazard ratio; UA — uric acid; LVH — left ventricular hypertrophy LVMI — left ventricular mass index; sUA — serum uric acid

**Table 2.** Medications requiring special attention during the treatment of hyperuricemia.

Medication	Drug class	Potential mechanism
Loop diuretics, thiazide diuretics and thiazide-like diuretics	Diuretics	Interaction with renal urate transporters
Low-dose ASA	NSAID	Acting as an exchange substrate to facilitate urate reabsorption
Niacin (nicotinic acid)	Vitamin B-vitamin	Decreases urinary excretion of UA
Cyclosporine	Immunosuppressant	Increase of proximal UA reabsorption,

		decrease in glomerular filtration rate secondary to afferent arteriolar vasoconstriction
Tacrolimus	Immunosuppressant	Not known
Levodopa	Antiparkinsonian	Not known
Ethambutol	Anti-tubercular drugs	Reduction in the fractional excretion of UA
Pyrazinamide	Anti-tubercular drugs	Causing the reabsorption of urate from the luminal side into tubular cells; interferes with OAT2 and OAT10
Cytotoxic chemotherapy	Chemotherapy	Massive disruption of tumor cells

ASA — acetylsalicylic acid; NSAID — nonsteroidal anti-inflammatory drug; UA — uric acid

**Figure 1.** Concurrent conditions, that influence serum uric acid (sUA) levels.



**Figure 2.** Five-step ladder of hyperuricemia treatment.

**5-STEP LADDER OF HIPERURICEMIA TREATMENT**

ACHIEVE TARGET OF TREATMENT. DO NOT DISCONTINUE TREATMENT CONTINUE AND MONITOR SUA LEVEL TWICE EACH YEAR IN SPECIAL CASES, CONSIDER A COMBINATION THERAPIES**	05
CONSIDER STARTING ALLOPURINOL 100–200 mg DAILY, THEN TITRATE TO 300–600 mg DAILY TO REACH TARGETS OF <b>&lt; 6 mg/dL OR &lt; 5 mg/dL IN HIGH CV RISK</b> AND IN SPECIAL CASES, CONSIDER MAXIMUM DOSE 900 mg DAILY	04
EDUCATE PATIENTS ABOUT THE DISEASE, LIFESTYLE AND PHYSICAL ACTIVITY ENSURE ADHERENCE TO LONG-TERM TREATMENT	03
VERIFY COMORBIDITIES AND CURRENT TREATMENT IF POSSIBLE, DISCONTINUE DRUGS WHICH INCREASE SUA LEVEL	02
ASSESS SUA LEVEL CONSIDER AS HIGH LEVEL OF $\geq 6$ mg/dL OR $\geq 5$ mg/dL IN HIGH CV RISK*	01

\*At least two of the following are presented: hypertension, diabetes, dyslipidemia, organ target organ damage or previous CV events  
\*\*If treatment target is not reached, consider a strategy of allopurinol + uricosuric/lesinurad

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