European Journal of Internal Medicine 146 (2026) 106727

Contents lists available at ScienceDirect

European Journal of Internal Medicine

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

Practice Guidelines

Expert consensus for the diagnosis and treatment of patients with hyperuricemia and high cardiovascular risk: 2025 update

ARTICLE INFO

Keywords:
Uric acid
Hyperuricemia
Gout
Cardiovascular disease
Cardiovascular risk factors

ABSTRACT

Background: Hyperuricemia has traditionally been viewed primarily as a cause of gout; however, accumulating evidence indicates that elevated serum uric acid (sUA) is also associated with increased cardiovascular and renal risk. Recent epidemiological studies suggest that adverse outcomes may occur at sUA levels well below the classic crystal-based thresholds, particularly in patients with high cardiovascular risk.

Methods: This expert consensus document was developed by a multidisciplinary European panel of cardiology, internal medicine, nephrology, and hypertension specialists. The recommendations are based on a critical narrative review of the literature published, including large cohort studies, meta-analyses, randomized controlled trials, and contemporary European guidelines (ESC, ESH, KDIGO, EULAR). Particular emphasis was placed on outcome-driven serum urate thresholds and clinically applicable risk stratification.

Results: Hyperuricemia is common and increasingly prevalent, especially among individuals with hypertension, chronic kidney disease, obesity, diabetes, and established cardiovascular disease. Elevated sUA is independently associated with cardiovascular mortality, heart failure, stroke, and faster progression of chronic kidney disease. However, randomized trials have not shown clear cardiovascular or renal benefit from routine urate-lowering therapy in patients with asymptomatic hyperuricemia. Based on current evidence, this consensus proposes a risk-based, individualized approach to hyperuricemia management and presents a pragmatic six-rung therapeutic ladder integrating lifestyle measures, optimization of comorbidities, and pharmacological urate-lowering therapy when clinically indicated.

Conclusions: Hyperuricemia should be recognized as a relevant cardiovascular and renal risk factor rather than a benign biochemical finding. Serum urate measurement can improve risk stratification in selected high-risk populations. While routine treatment of asymptomatic hyperuricemia cannot be universally recommended, targeted urate-lowering strategies may be appropriate in patients with high cardiovascular risk, symptomatic disease, or very high sUA levels. Future randomized trials are needed to define whether urate-lowering therapy can improve hard cardiovascular and renal outcomes in these populations.

Hyperuricemia, long considered chiefly in the context of gout, has recently gained recognition as a significant cardiovascular and renal risk factor [1]. Elevated serum uric acid (sUA) levels are increasingly prevalent worldwide and often coexist with hypertension, chronic kidney disease (CKD), type 2 diabetes, obesity and other components of metabolic syndrome [1–3]. Unlike traditional approaches focusing primarily on gout flares, this expert consensus document emphasizes hyperuricemia as a modifiable risk factor for cardiovascular (CV) and renal disease. Following the editorial conventions of the European Society of Cardiology (ESC) and European Alliance of Associations for Rheumatology (EULAR), we offer brief sections on definition, epidemiology, pathophysiology, risk stratification, and a pragmatic step-wise scheme for treatment. Our goal is to support clinicians in evidence-based decision-making for hyperuricemia in cardiology and internal medicine, harmonizing current evidence (2022–2025) with European guidelines (ESC, KDIGO, etc.). We highlight the need for a harmonized definition of hyperuricemia, acknowledge its role as an independent risk factor, and present an six-rung ladder for urate-lowering therapy. Above all, once again, we urge clinicians to manage hyperuricemia proactively, looking well beyond its link with gout, so that cardiovascular and renal complications can be minimized through early recognition and timely treatment [4–6]

Key areas of focus are:

1. A multidimensional approach to standardizing the definition of hyperuricemia.
2. Identifying serum-urate levels linked to various cardiovascular risks.
3. Addressing hyperuricemia in chronic kidney disease.
4. Integrating novel agents that enhance allopurinol in patients at high cardiovascular risk.
5. Examining the relationship between hyperuricemia and metabolic syndrome.
6. Assessing the impact of the global obesity epidemic on rising urate levels.

https://doi.org/10.1016/j.ejim.2026.106727
Received 14 December 2025; Accepted 19 January 2026
Available online 4 March 2026

7. Evaluating the urate-lowering and cardiometabolic benefits of GLP-1 receptor agonists and sodium–glucose cotransporter-2 inhibitors ("flozins").

1. Definition and epidemiology –The growing importance of hyperuricemia despite varying definitions and limited epidemiological data

Hyperuricemia (HU) is generally defined as an abnormally high serum uric acid (sUA) concentration in the blood. Traditionally, the diagnostic threshold has been set at ≥7.0 mg/dL (420 μmol/L) in adult men and ≥6.0 mg/dL (360 μmol/L) in adult women, reflecting the approximate limit of urate solubility [6]. These conventional cut-offs correspond to the saturation point at which monosodium urate crystals may form in peripheral tissues, leading to gout. However, recent evidence demonstrates that adverse cardiovascular and renal effects of uric acid may occur at substantially lower levels. The URic acid Right for heArt Health (URRAH) project has shown that, particularly in high cardiovascular risk populations, a sUA level of around 5.0 mg/dL (297 μmol/L) is a more clinically relevant threshold for predicting cardiovascular mortality than the traditional 7 mg/dL [7,8]. The same threshold has been reported by Tian et al in a paper including a large population of patients without additional risk factors [9]. Therefore, while this consensus maintains the classical definition for general use (≥7 mg/dL in men, ≥6 mg/dL in women), it strongly emphasizes that a threshold of 5.0 mg/dL should be considered the critical upper limit for patients at elevated cardiovascular risk (see Risk Stratification below) [10–14,15–18].

2. Physiology and metabolism

Uric acid (UA) represents the terminal metabolite of purine degradation in man. Owing to an ancient evolutionary mutation, humans (and, incidentally, the great apes) lack hepatic uricase (urate oxidase). Consequently, baseline urate concentrations in our species are appreciably higher than in most mammals. Chemically speaking, UA is a weak acid that, at physiological pH, circulates chiefly in the form of monosodium urate [19,20].

Biosynthesis proceeds predominantly in the liver and, to a lesser extent, in the intestinal mucosa under the catalytic influence of xanthine oxidase. Roughly seventy per cent of the daily urate load is eliminated by the kidneys, while the remainder leaves the body via the gastrointestinal tract. Hyperuricemia thus develops whenever production exceeds excretory capacity. Overproduction may follow an excessive intake of purine-rich foods, fructose or alcohol, may accompany obesity (with its accelerated purine turnover), over-expression of the xanthine oxidase activity or may arise in clinical states characterized by high cell-turnover rates, for example tumor lysis syndrome. Far more commonly, however, the problem lies in underexcretion, attributable either to germline variants of renal urate transporters or to secondary influences such as impaired renal function and certain drugs (notably diuretics or cyclosporin). In everyday conditions, uric acid acts as an important antioxidant in the bloodstream, neutralizing harmful reactive oxygen species and providing a large share of the blood's total antioxidant defense. Paradoxically, once urate penetrates the intracellular environment or accumulates within the vascular wall, it may assume prooxidant and proinflammatory properties, encouraging endothelial dysfunction and tissue injury. This dualistic behavior shows clearly that uric acid can be both protective and damaging, a point of real clinical importance [20–22].

3. Pathophysiology of hyperuricemia

Pathophysiological connections with cardiovascular and renal disease. Elevated serum urate, aside from forming crystals in the joints, harms both the heart and the kidneys through multiple pathways. Experimental and clinical work has uncovered a number of underlying mechanisms (see Fig. 1):

- **Endothelial Dysfunction**: High urate impairs endothelial nitric oxide bioavailability, promoting oxidative stress and vasoconstriction. Xanthine oxidase activity, which generates UA, produces reactive oxygen species that can directly damage endothelium. Hyperuricemia is associated with reduced endothelial-dependent vasodilation, an early step in atherogenesis [23,24].
- **Inflammation:** Monosodium-urate crystals, by activating the NLRP3 inflammasome, set off the classical gouty inflammatory cascade. Importantly, even in the absence of crystals, soluble urate itself can tip the balance toward inflammation: it stimulates cytokine release, encourages proliferation of vascular smooth-muscle cells, and attracts immune cells into vessel walls and the renal parenchyma. Such persistent, low-grade inflammation accompanying hyperuricemia may accelerate atherosclerosis and adverse remodeling of the heart [25]
- **Renin–Angiotensin–Aldosterone System (RAAS) Activation:** Uric acid has been shown to stimulate the RAAS, raising blood pressure and causing renal arteriolopathy. In animal models, hyperuricemia can induce hypertension by renal microvascular damage and sodium retention. In adolescent humans, urate elevation correlates with new-onset primary hypertension. Small clinical trials have even demonstrated blood pressure reduction with urate-lowering therapy in youths, suggesting a causal role [26].
- **Oxidative Stress in Myocardium:** In chronic heart failure (HF), high urate often reflects xanthine oxidase upregulation under chronic hypoxia and oxidative stress. Elevated sUA in HF patients correlates with worse functional class and outcomes, presumably via amplification of oxidative injury in the myocardium and vasculature. Hyperuricemia also impairs mitochondrial function in cardiomyocytes, although clinical trials with xanthine-oxidase inhibitors in heart failure have produced rather inconsistent results, as discussed later [27].
- **Prothrombotic Effects:** Hyperuricemia is linked with platelet activation and impaired fibrinolysis. It may promote a prothrombotic state, contributing to the risk of myocardial infarction and stroke in individuals with hyperuricemia [28].
- **Renal Damage:** In the kidney, urate can crystallize in tubules causing microinjury, but even soluble urate is associated with nephrosclerosis. Hyperuricemia induces afferent arteriolar thickening and glomerular hypertension, accelerating CKD progression. It also impairs nitric oxide in renal vessels and stimulates inflammation and fibrosis in the kidney interstitium [29].

In summary, hyperuricaemia is not merely a biochemical bystander; it actively contributes to pathophysiological processes seen in major cardiovascular and renal diseases. These insights provide a rationale for treating hyperuricaemia not only to prevent gout, but also to mitigate cardiovascular and kidney risk [7,14].

4. Updates on epidemiology of hyperuricemia

Global and European Trends: The prevalence of hyperuricemia has risen in many populations, paralleling changes in diet and the increasing burden of obesity and metabolic syndrome. Contemporary data affirm that average serum urate levels are climbing worldwide. Globally, reported prevalence ranges widely (approx. 3–36 % of adults), reflecting demographic and lifestyle differences. In the United States, about 20 % of adults have hyperuricemia by traditional criteria. European countries show variable rates. For example, recent studies reported prevalence about 25 % in Ireland (virtually equal in men and women) and as high as 48 % in parts of Finland (60 % of men, 31 % of women). In Poland, hyperuricemia was observed in up to 23 % of those with acute or chronic

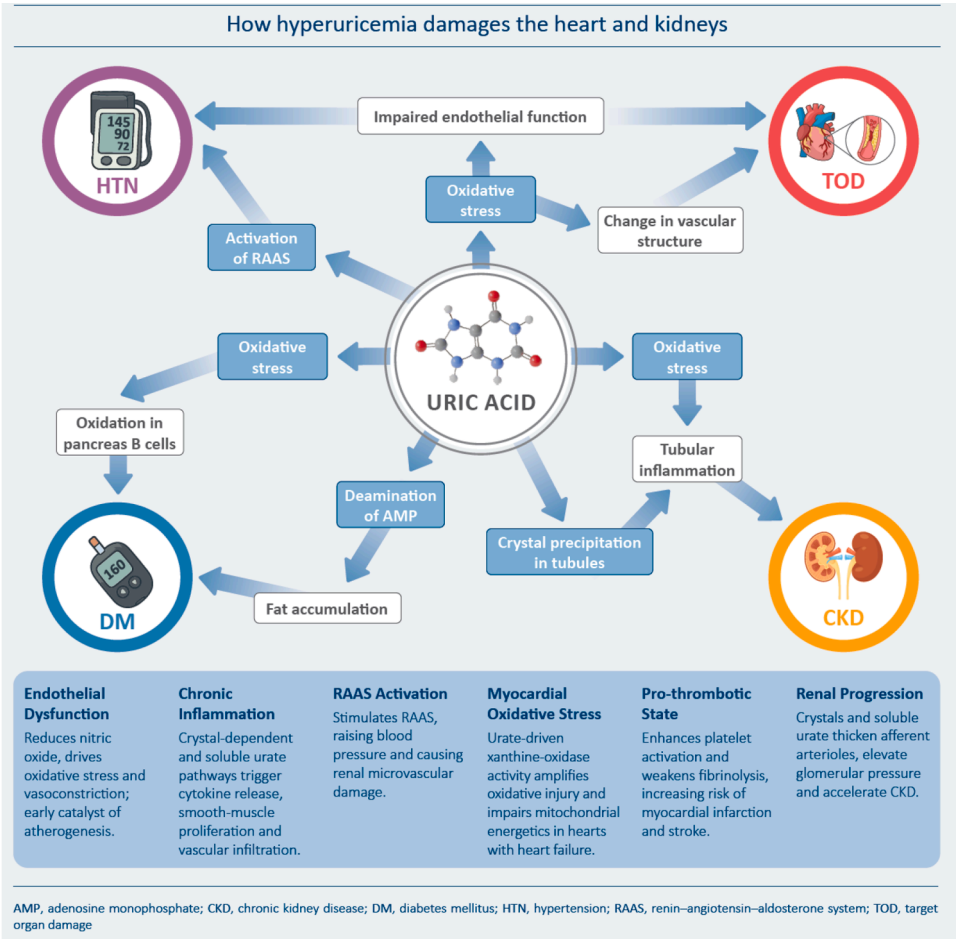

Fig. 1. Pathophysiological mechanisms linking uric acid metabolism with cardiovascular disease.

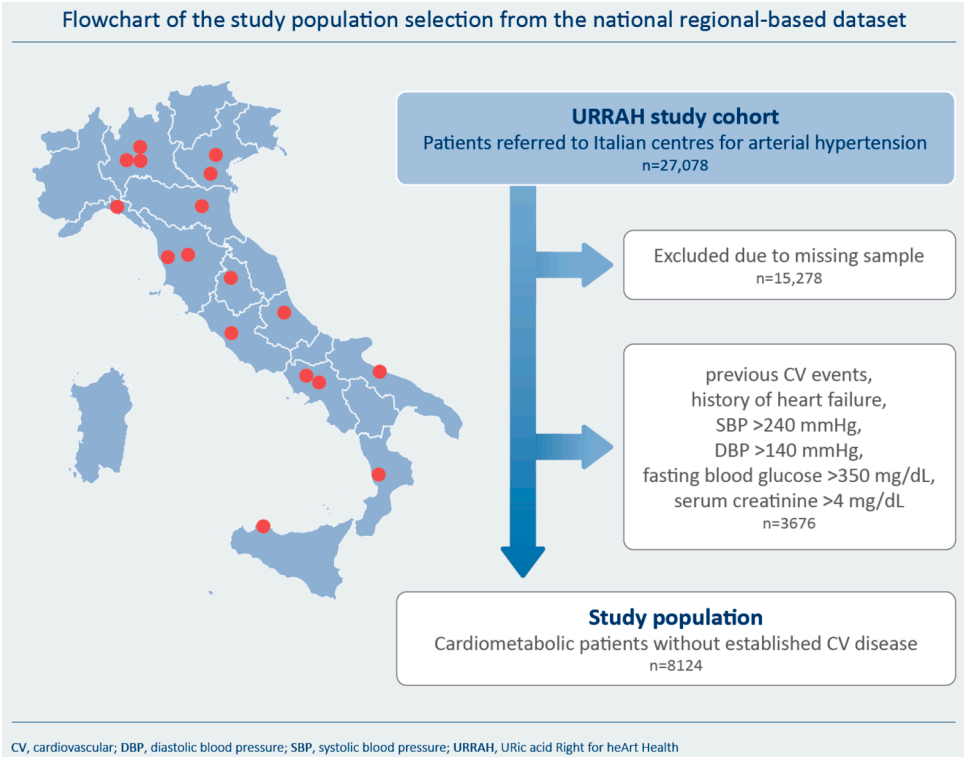

Fig. 2. Flowchart of the study population selection from the national regional-based dataset.

coronary syndromes. These figures underscore that 1 in 5 European adults may have elevated urate, especially among those with comorbid conditions [30,31].

Importantly, the detected prevalence of hyperuricemia depends on the threshold applied. Using the traditional sex-specific cut-offs (>7 mg/dL in men (420 μmol/L) , >6 mg/dL in women (360 μmol/L)), a general European cohort might show single-digit prevalence. However, if a single cut-off of 5.6 mg/dL (333 μmol/L), proposed by URRAH as the risk threshold, is applied to men and women alike, the recorded prevalence in the same population can rise four-fold. One study showed that such a definition would label 28 % of adults as hyperuricaemic, including 37 % of men and 5 % of women. This gap underlines an important issue: many people who appear to have a normal urate level under older criteria move into a high-risk category when newer limits are used. It also mirrors biological differences between the sexes [32]. Premenopausal women generally present with lower urate values because oestrogen enhances renal urate clearance. After the menopause, women's urate concentrations tend to match those seen in men, and the difference in hyperuricaemia rates between the sexes becomes much smaller [8].(see Fig. 2):

5. Risk factors and comorbidities

Hyperuricemia often coexists with other risk factors. Its frequency rises steadily with advancing age in both sexes yet remains consistently higher in men than in premenopausal women. Dietary patterns contribute – high consumption of red meat, seafood, alcohol (especially beer and spirits), and sugar-sweetened beverages (fructose) are associated with higher urate levels. A Chinese national survey (2015-2017) confirmed higher hyperuricemia rates in those with purine-rich diets, excessive red meat intake, low dairy and vegetable intake, and heavy alcohol use [33]. Obesity and metabolic syndrome are strongly linked, each 5 kg/m^2 increase in body mass index raises HU risk substantially, and insulin resistance can reduce renal urate clearance [34]. Hypertension and dyslipidemia correlate with higher urate, whereas interestingly, some studies observe that patients with longstanding type 2 diabetes have slightly lower sUA (possibly due to uricosuric effects of glycosuria or certain medications) [35,36]. Nevertheless, in general, hyperuricemia correlates positively with risk of developing hypertension, CKD, and cardiovascular disease (discussed in the next section). Ethnic and genetic factors also play a role. For instance, certain ethnic groups, e.g. Pacific Islanders, have particularly high prevalence of hyperuricemia as high as about 50–70 % in some Pacific populations, partly due to genetic predisposition and diet [37]. See Table 2.

6. Pediatric and adolescent trends

In children, hyperuricemia is uncommon when defined by adult thresholds, but urate levels rise notably through adolescence. Population studies in China show that the mean uric acid in healthy children is about 4.5 mg/dL (≈268 μmol/L) at age 8, increasing after age 10, especially in boys. By ages 12–15, mean sUA reaches about 5.8 mg/dL (≈345 μmol/L) in boys and about 5.1 mg/dL (≈303 μmol/L) in girls [38]. Using adult cut-offs such as 7 mg/dL (420 μmol/L), the prevalence of "hyperuricemia" in a pediatric cohort was only about 3 %. However, if a lower cut-off of 5.5 mg/dL (327μmol/L) is applied, which is closer to pediatric 95th percentile in some age groups, the overall prevalence increases to about 15 %, and in pubertal boys it exceeds even 60 %. This indicates that many adolescents have urate levels that would be considered high by stringent criteria yet may be normal for their developmental stage. Pediatric reference ranges for urate are age and sex dependent. Clinically, asymptomatic hyperuricemia in children has drawn attention for its potential link to obesity and blood pressure. Cross-sectional data have shown uric acid correlates with pediatric hypertension and even cognitive function in youth at risk for hypertension. Symptomatic gout is almost never seen in childhood, except in rare genetic disorders or during tumor lysis after chemotherapy. Nevertheless, an HU in an overweight child may signal that metabolic syndrome and arterial hypertension will surface earlier than usual. This observation underlines the importance of prompt lifestyle measures in children and adolescents who are at risk. Routine sUA testing in pediatrics is limited to clearly defined clinical situations. Whenever HU is identified in a child, the value should be interpreted with age-specific reference ranges to avoid inappropriate classification [38].

7. Geriatric considerations in epidemiology

In the elderly, hyperuricemia becomes more prevalent due to reduced renal clearance, comorbidities, and polypharmacy. The PolSenior study in Poland found a hyperuricemia prevalence of 48 % in individuals ≥65 when using >6 mg/dL(360 μmol/L) as the cut-off [31]. An intriguing finding from URRAH: in those over 75, the relationship between uric acid and mortality appears U-shaped – extremely high and very low urate levels both associated with increased mortality. This suggests that in frail elderly patients, very low uric acid might reflect malnutrition or cachexia, whereas HU is associated with the expected cardiovascular risk. Therefore, in epidemiologic terms, optimal sUA in advanced age is narrow, with both very older adults often coexists with chronic kidney disease and heart failure, circumstances that complicate day-to-day management and call for careful individualization of therapy (see Special Populations below) [39,40].

In summary, hyperuricemia is common, and its prevalence continues to increase, especially in individuals at cardiovascular risk. Epidemiological data collected between 2022 and 2025 make it clear that the numerical threshold we choose to define "elevated urate" profoundly affects the proportion of patients classified as hyperuricaemic. An appreciation of age-, sex- and risk-specific patterns allows clinicians to focus testing where it matters most. Current European guidelines, for instance, now advises routine sUA measurement in adults with hypertension, chronic kidney disease, obesity or metabolic syndrome. The following sections examine the prognostic weight of hyperuricemia and the serum-urate cut-offs that is associated closely with cardiovascular and renal events [30].

8. Hyperuricemia as a risk factor for cardiovascular disease

Elevated uric acid has been studied extensively as an independent risk factor for cardiovascular disease (CVD) [30]. A growing body of evidence (including large cohort studies and meta-analyses) links hyperuricemia with increased risk of all-cause mortality, cardiovascular mortality, coronary artery disease, stroke, and heart failure [4,41–43]. While hyperuricemia often accompanies other risk factors such as hypertension, type 2 diabetes, etc., modern multivariate analyses attempt to isolate uric acid's contribution to risk [30]. See Fig. 3:

9. Integration into risk stratification

The 2018 ESC/ESH Hypertension Guidelines formally added sUA assessment as part of CV risk evaluation in hypertensive patients [44]. The same approach is suggested also in ESH guideline published in 2023 and this should be included. This was a notable change signaling that managing high urate might have merit beyond gout prevention. However, a key unanswered question has been: At what level does uric acid become a cardiovascular risk factor? The traditional threshold for hyperuricemia (6 mg/dL (360 μmol/L)in women, 7 mg/dL(420 μmol/L) in men) was based on crystal saturation, not on outcome data. Observational evidence suggests adverse CV effects may start at lower levels. To address this, the URRAH project, a series of Italian cohort analyses, identified specific urate cut-offs associated with elevated CV risk [4]:

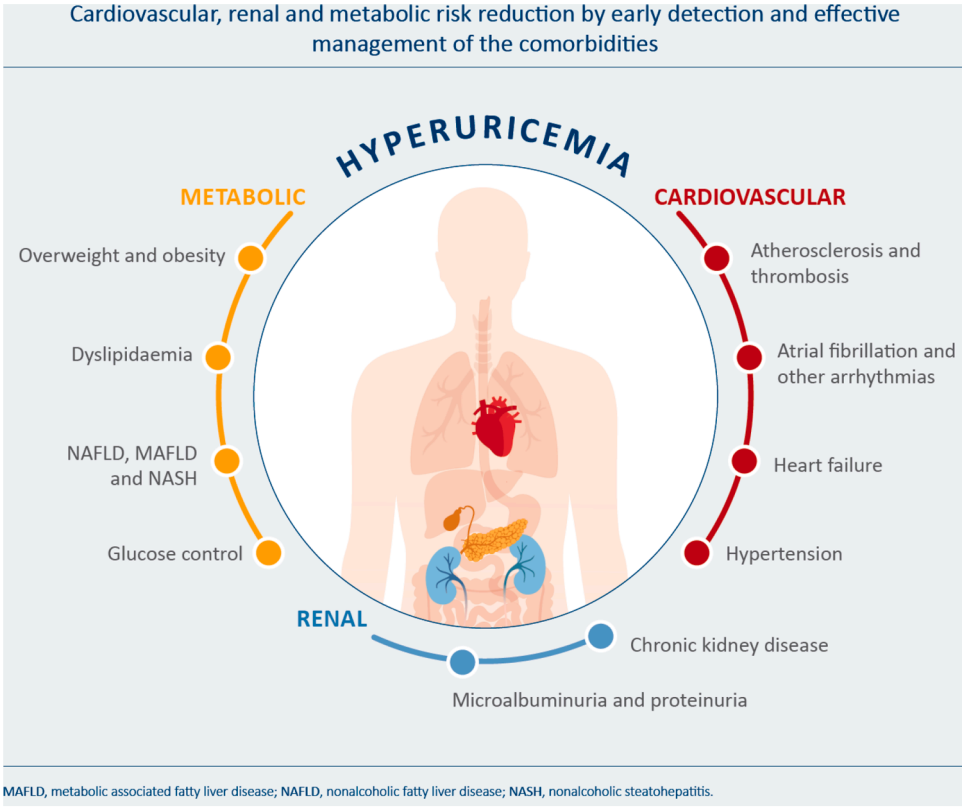

Fig. 3. Proposed mechanisms of hypertension, renal damage, and atherosclerosis in hyperuricemia.

10. Mortality risk thresholds

In the main URRAH cohort (over 23,000 adults) a serum-urate level above 5.6 mg/dL (≈333 μmol/L) in men and 5.1 mg/dL (≈303 μmol/L) in women was linked to poorer survival during an 8-year follow-up. Multivariable Cox analysis confirmed sUA as an independent predictor of cardiovascular death, with a hazard ratio close to 2.0 for the highest versus lowest category. Adding these cut-offs to the standard Heart SCORE chart improved risk reclassification, resulting in a net reclassification index of about 0.26. In the URRAH Diabetes study, Masulli et al. confirmed that a threshold of 5.6 mg/dL (≈333 μmol/L) predicted both overall and cardiovascular mortality, with an adjusted hazard ratio near 1.3 for cardiovascular death above this value. Interestingly, in diabetic patients a lower cut-off of 4.7 mg/dL (≈280 μmol/L) was associated with higher all-cause mortality in unadjusted analysis, although this association did not remain significant after full adjustments [45–48].

11. Age-specific effects

URRAH investigators found that in adults aged 65–74, a urate >4.8 mg/dL best discriminated mortality risk. However, in those ≥75, the relationship of uricemia to Ymortality was nonlinear – both low and high urate carried risk (a J-shaped curve). Thus, the optimal uric acid level might shift with age. For risk stratification in *younger* elderly [65–74], keeping urate < about 5 mg/dL could be beneficial, whereas in the very old, aggressive urate lowering to below 5 mg/dL should be weighed against potential downsides (like frailty or medication interactions) [49].

12. Heart failure

Hyperuricemia has long been noted in heart failure patients, and recent data confirmed its prognostic value. In a large Italian cohort, each 1 mg/dL (≈59 μmol/L) increase in sUA was associated with a 29 % higher risk of incident HF (HR 1.29) and a similar increase in risk of HF-related mortality. URRAH identified cut-offs of 5.34 mg/dL (≈318 μmol/L) for predicting any new-onset HF and 4.89 mg/dL (≈291 μmol/L) for predicting fatal HF, with modest sensitivity/specificity but high statistical significance. These values again are well below the classic 7 mg/dL (≈420 μmol/L) mark, underscoring that even mid-range urate levels can matter in populations at risk. Hyperuricemia in HF may reflect xanthine oxidase activity and oxidative stress, contributing to myocardial dysfunction. Clinically, sUA can be seen as a marker of severity, and possibly a therapeutic target (xanthine oxidase inhibitors have been tested in HF to improve outcomes, though results like the EXACT-HF trial were neutral) [48,50]. See Fig. 4:

13. Coronary artery disease and myocardial infarction

For myocardial infarction (MI), evidence indicates hyperuricemia correlates with risk of acute coronary events, especially in women. The URRAH analysis on fatal MI found a prognostic urate cut-off of about 5.7 mg/dL (with sex-specific thresholds about 5.3 mg/dL for women and about 5.5 mg/dL for men) that distinguished those at higher risk. In fully adjusted models controlling for age, blood pressure, diabetes, CKD, lipids, and diuretic use, higher sUA remained independently associated with greater risk of fatal MI (for example, women with sUA ≥5.26 had an about 50 % higher risk of MI death) [51]. Supporting this, a meta-analysis and numerous cohort studies over the past decade have linked elevated urate with incident coronary disease. A recent nationwide Japanese registry of over 6,000 patients with chronic coronary syndrome post-PCI found that hyperuricemia (defined by Japanese criteria >7 mg/dL) predicted increased composite CV events; notably, even patients with "intermediate" urate (6–7 mg/dL) had more events than those <6. This aligns with the notion that risk increases in a gradated fashion rather than a sharp threshold [48,51–53].

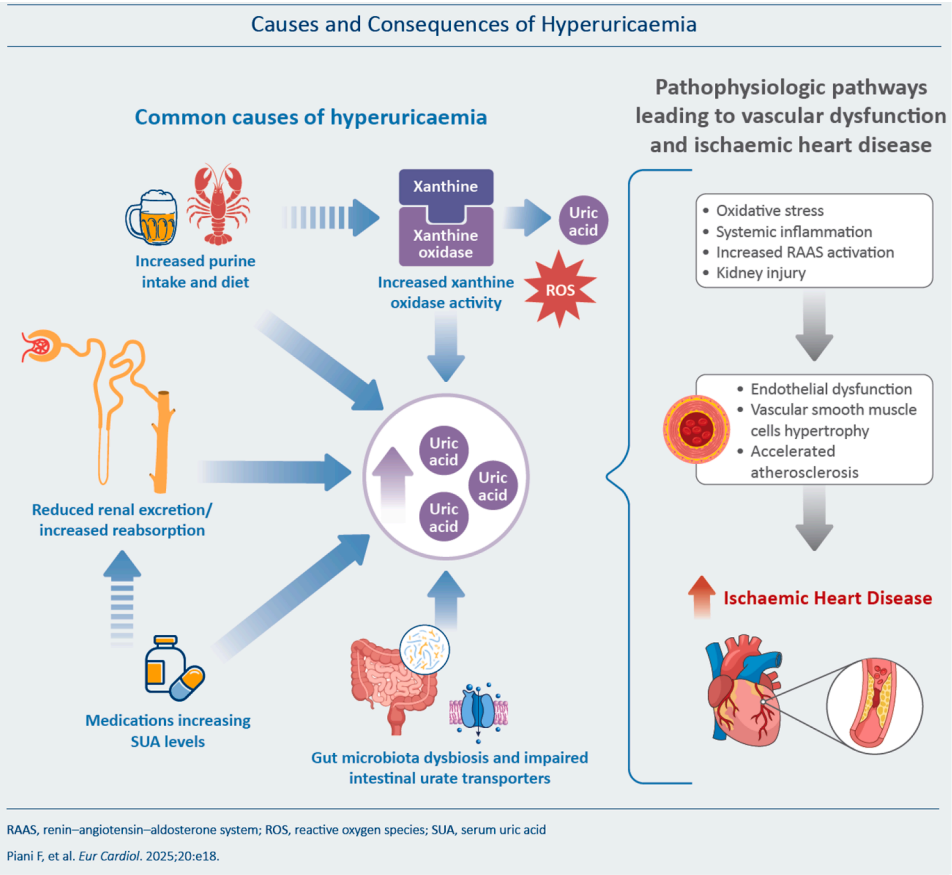

Fig. 4. Cardiovascular, renal and metabolic risk reduction by early detection and effective management of the comorbidities.

14. Stroke

Hyperuricemia's relationship with stroke is also documented. In the URRAH cohort, a cut-off about 5.3 mg/dL was identified for stroke risk stratification [54]. Other large studies found that sUA above about 5.6 mg/dL associated with greater risk of stroke incidence over long-term follow-up. Potential mechanisms include urate-induced hypertension and atherosclerosis in cerebral vessels. However, some confounding exists. Hyperuricemia often coexists with stroke risk factors like metabolic syndrome, so careful multivariable adjustment is needed. In a Chinese cohort, people in the top quartile of urate had significantly higher risk of stroke (HR 1.16), especially hemorrhagic stroke (possibly via small vessel disease potentiation) [54–56].

15. Causality vs Marker debate

It is important to note that while hyperuricemia is consistently associated with CV outcomes, proving causality has been challenging. Mendelian randomization studies have yielded mixed results – some suggest urate itself (independent of other factors) has a causal role in hypertension and CKD progression, while others question if urate is merely a risk marker or bystander. Clinical trials of urate-lowering therapy (ULT) for cardiovascular prevention have been pivotal in this debate [57,58].

The ALL-HEART trial (UK, 2022) tested allopurinol (up to 600 mg daily) vs standard care in over 5,700 patients with chronic ischemic heart disease (but no gout) to see if ULT reduces major CV events. After a median 4.8 years, allopurinol had no significant impact on outcomes – the primary composite endpoint occurred in 11.0 % of allopurinol vs 11.3 % of controls (HR 1.04, $p = 0.65$). All-cause mortality was also similar. Interestingly, allopurinol did lower sUA dramatically (from mean about 5.7 to 3.0 mg/dL within 6 weeks), yet this did not translate into CV benefit. The neutral result suggests that simply reducing urate may not reverse established CV risk in such patients – or that any benefit is too small to detect given the sample size and follow-up [59].

The FEATHER and CKD-FIX trials in CKD patients without gout also showed that lowering urate (with febuxostat or allopurinol) did not significantly slow renal function decline or prevent CV events compared to placebo [60,61]. These and ALL-HEART highlight that treating asymptomatic hyperuricemia has not yet demonstrated clear improvements in "hard" outcomes, despite the epidemiologic links.

On the other hand, in gout patients, who often have very high urate levels, treating with ULT is known to reduce gout flares and resolve tophi, but randomized data on CV event reduction are inconclusive. The CARES trial raised concern about febuxostat's CV safety, though the subsequent FAST trial found febuxostat non-inferior to allopurinol in CV outcomes over 3 years. These results relate to medication choice rather than the concept of lowering urate per se [62,63]. See Fig. 5:

In summary, hyperuricemia correlates with adverse cardiovascular outcomes, and a sUA level above about 5–6 mg/dL may be considered a marker of elevated CV risk. European experts now recognize hyperuricemia as a modifiable risk factor – particularly in patients with hypertension, coronary disease, or HF – and recommend checking urate levels in such patients. However, whether aggressively treating asymptomatic hyperuricemia improves cardiovascular prognosis remains an area of active research. This consensus adopts a balanced view: recognizing hyperuricemia as a CV risk factor (and advocating risk-factor modification and judicious urate-lowering in high-risk scenarios), while also noting that treatment decisions should be individualized [57].

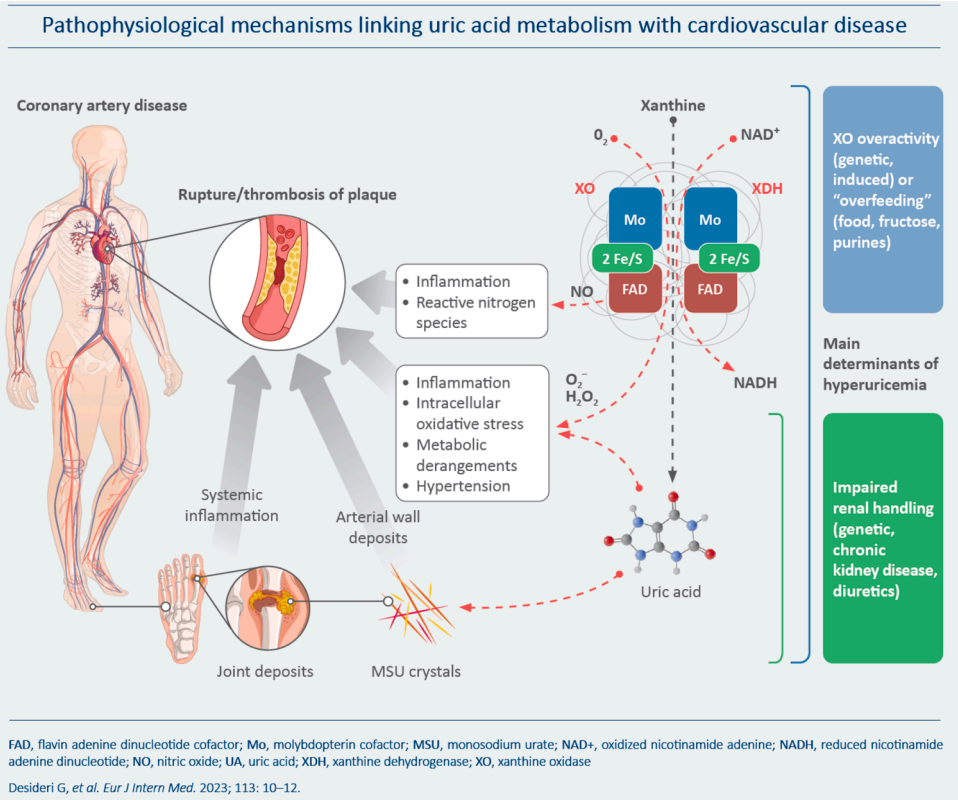

Fig. 5. Causes and consequences of Hyperuricaemia.

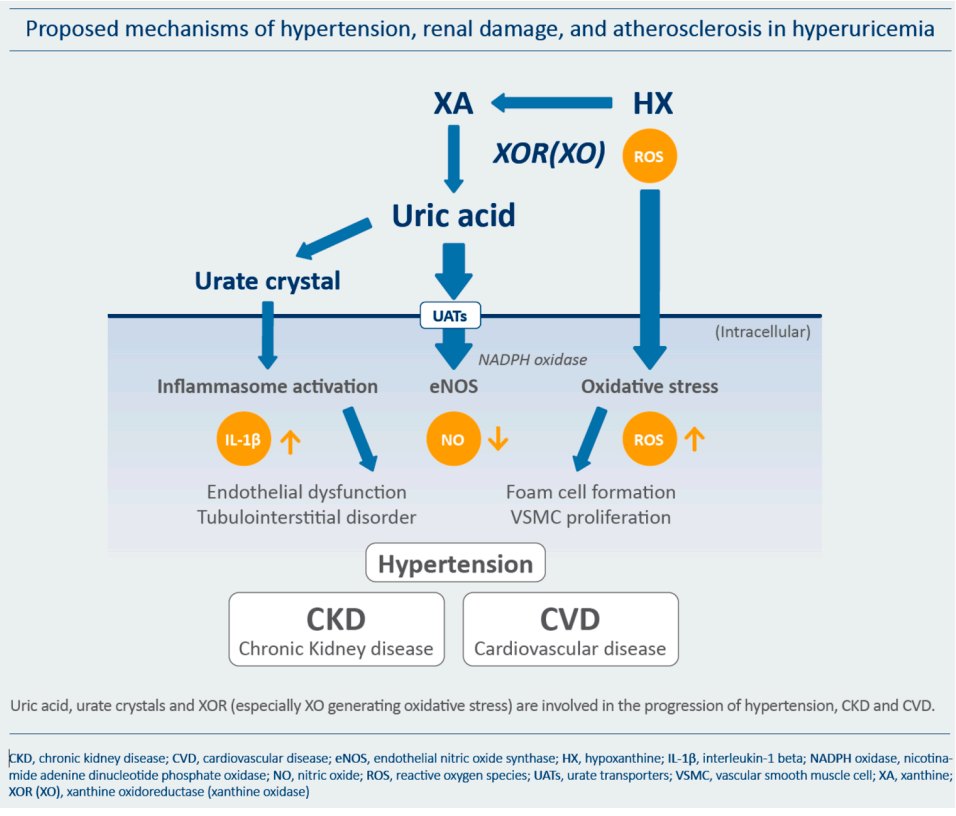

Fig. 6. Factors influencing uric acid levels.

16. Hyperuricemia and renal disease

There is a bidirectional relationship between serum uric acid and kidney health. The kidneys are responsible for the majority of urate excretion, so renal impairment leads to hyperuricemia. Conversely, experimental and clinical evidence suggests that hyperuricemia can contribute to kidney disease progression. This section examines hyperuricemia in CKD and its renal consequences [64,65]. See Fig. 6.

17. Prevalence in CKD

Hyperuricemia is extremely common in CKD patients. As glomerular filtration rate (GFR) declines, urate clearance decreases, and sUA rises. In one cohort, the prevalence of hyperuricemia jumped from about 12 % in patients with eGFR >90 mL/min (normal kidney function) to 64 % in those with eGFR <15 mL/min (end-stage renal disease). Essentially, nearly two-thirds of advanced CKD patients have hyperuricemia. Even mild reductions in GFR show an effect: CKD stage 3 (eGFR about 30–59) often features hyperuricemia in >40 % of patients in some studies. This correlation is intuitive given urate's renal handling, but it also means CKD populations are enriched with hyperuricemia, complicating management (since some ULT drugs need dose adjustment in CKD) [65–67].

18. Impact of hyperuricemia on kidney outcomes

A longstanding hypothesis is that hyperuricemia is not just a result of CKD but also a cause or accelerant. Prospective evidence supports this view. For example, Tsai et al. followed 739 CKD patients over time: those with baseline sUA ≥6 mg/dL had significantly faster annual eGFR decline than those with sUA <6. The difference was around 9.6 mL/min per 1.73 m^2 greater eGFR loss in the high-urate group over the study period, even after multivariable adjustment. Moreover, the risk of progressing to end-stage kidney failure rose by about 7 % for each 1 mg/dL increase in baseline uric acid. A dose-response pattern was observed: patients stratified into sUA categories 6–8, 8–10, and ≥10 mg/dL all had incrementally greater declines in kidney function compared to those <6. These findings, echoed by other cohorts, suggest hyperuricemia independently predicts faster CKD progression [65,68].

Uric acid can induce renal injury through multiple pathways: it causes arteriolopathy of pre-glomerular vessels (impairing autoregulation), promotes renal inflammation and oxidative stress, and can precipitate in renal tubules causing microobstruction. Hyperuricemia is also associated with higher incidence of nephrolithiasis (urate stones) which can damage the kidney. Taken together, there is biological likelihood that high sUA is nephrotoxic [69].

19. Asymptomatic hyperuricemia treatment in CKD – Controversy

Given the above, one might expect that decreasing sUA could preserve kidney function. However, clinical trials to date have not conclusively shown that treating asymptomatic hyperuricemia prevents the progression of chronic kidney disease. Several RCTs (e.g. PERL in diabetic CKD using allopurinol, CKD-FIX, and smaller Japanese trials) largely failed to meet primary endpoints in slowing GFR decline versus placebo. A 2023 KDIGO guideline explicitly recommends against routine urate-lowering therapy in CKD patients with asymptomatic hyperuricemia solely for the purpose of delaying CKD progression. By contrast, it strongly endorses treating gout in subjects with CKD. The message is that current evidence remains controversial whether using ULT as kidney-protective therapy in the absence of gout, except perhaps in research settings or specific scenarios. The message is that current evidence does not support using ULT as kidney-protective therapy in the absence of gout, except perhaps in research settings or specific scenarios (e.g. very high urate more than 9 mg/dL where urate crystal deposition in the kidney is a concern) [61,70].

20. CKD and cardiovascular synergy

It should be noted that in CKD patients, hyperuricemia may be associated with especially high cardiovascular risk. Many CKD patients die of CV causes before reaching dialysis, and high urate could contribute to that risk profile (e.g. via exacerbating hypertension or endothelial dysfunction). Some observational studies of CKD cohorts found hyperuricemia associated with higher rates of coronary disease and death. Thus, even if urate-lowering does not clearly slow CKD, it might still be justified to reduce CV risk in CKD – a hypothesis requiring further trials.

21. Urate in dialysis and transplant

End-stage renal disease (ESRD) presents special cases. Patients on dialysis often have near-normal sUA levels due to clearance during dialysis, but fluctuations occur. Interestingly, some ESRD patients can still get HU. ULT (allopurinol or febuxostat) can be used in dialysis with appropriate timing (e.g. giving allopurinol post-dialysis as per consensus: 300–400 mg after dialysis, none on non-dialysis days). Kidney transplant recipients frequently develop HU due to cyclosporine/tacrolimus-induced hyperuricemia; managing sUA is important in that population to avoid gouty damage to transplanted joints and possibly to improve blood pressure control. Allopurinol and febuxostat can be used with caution in transplant patients (avoiding xanthine oxidase inhibitors with azathioprine, for example, due to dangerous interactions).

In summary, hyperuricemia is nearly inevitable as CKD progresses and is an independent predictor of faster renal decline. However, routine urate-lowering in asymptomatic CKD remains controversial due to lack of proven benefit on hard outcomes. This consensus suggests an individualized approach: consider ULT in CKD patients with high urate especially if they have other indications (recurrent gout, urate stones, or high CV risk), but be mindful of the limited evidence for renal protection. The risk factor interplay between hyperuricemia, CKD, and CVD means these patients require multifactorial management [71–73].

22. Diagnostic evaluation and risk stratification

22.1. When to measure uric acid?

It is now recommended to measure serum uric acid as part of the work-up in patients with cardiovascular diseases or risk factors. The ESC and ESH experts advocate screening sUA in those with hypertension, obesity, established heart disease, or CKD [44]. In practice, a simple blood test for uric acid can be done along with routine metabolic labs. Not all individuals need screening but the threshold to check sUA should be low in cardiology and internal medicine clinics given the high co-prevalence discussed. If hyperuricemia is found incidentally, further evaluation is necessary.

22.2. Baseline evaluation

A patient with confirmed elevated uric acid should be assessed for:

- Symptoms and History of Gout or Stones: Even if the focus is CV risk, ask about any history of gout flares (joint pain, swelling, especially at night in the great toe) or kidney stones. Asymptomatic hyperuricemia by definition means no gout attacks have occurred, but mild symptoms might be overlooked by patients. Chronic tophaceous gout can exist with surprisingly few acute flares, so a careful joint exam for tophi (urate crystal deposits) can be revealing in longstanding hyperuricemia.
- Cardio-Renal Risk Profile: Document blood pressure, metabolic parameters (glucose, lipids), kidney function (eGFR), and whether the patient has heart failure, coronary or cerebrovascular disease. This helps stratify how aggressive management should be. For instance,

an asymptomatic individual with low urate and no other risks might be managed with lifestyle alone, whereas the same urate in a patient with coronary disease and hypertension might prompt pharmacotherapy in light of URRAH findings.

- Secondary Causes: Review medications and comorbidities that contribute to hyperuricemia. Common drugs raising sUA include thiazide and loop diuretics, low-dose aspirin, niacin, cyclosporine and tacrolimus, pyrazinamide, and ethambutol. If feasible, alternative medications should be considered. Comorbidities like hypothyroidism, psoriasis, hemolytic anemia, or lead exposure can also elevate urate and may need specific management.

Risk Stratification: We propose stratifying hyperuricemic patients into risk categories to guide therapy intensity:

- **Low Risk:** Asymptomatic hyperuricemia with sUA just above normal (e.g. 6–7 mg/dL), no history of gout or stones, and no significant CV or renal comorbidities. These patients have hyperuricemia largely as a lab finding, often due to lifestyle factors. Management can be conservative (dietary advice, weight loss, ULT at low doses) and observation.
- **Intermediate Risk:** Patients with hyperuricemia (often moderate, e.g. 7–9 mg/dL) who have some concomitant risk factors – such as hypertension, mild CKD (stage 2–3), or overweight status – but no overt CVD. They might also include individuals with a single gout flare in the past or a small tophus incidentally noted. In this group, hyperuricemia might be contributing to risk and should be addressed more proactively (aggressive lifestyle modifications and ULT with up-titration depending on sUA level and trajectory of sUA). See Fig. 7.
- **High Risk:** Hyperuricemia (which may even be mild by itself) in the presence of established cardiovascular disease, HF, recurrent gout, stage ≥3 CKD, or multiple metabolic syndrome features. For example, a patient with sUA 5.5 mg/dL but who has coronary artery disease and hypertension falls here – because evidence suggests target sUA <5–6 mg/dL might improve outcomes in such high CV risk individuals. Another example is a diabetic with CKD stage 3 and urate 6 mg/dL – relatively "normal" urate, yet studies indicate even ≥6 is associated with faster kidney function decline. High-risk patients merit close follow-up and a low threshold to initiate pharmacotherapy to achieve a low-normal urate level (below the risk thresholds identified by URRAH, i.e. ideally <5–6 mg/dL) [48].
- **Severe Hyperuricemia:** This special sub-category refers to very high urate levels (e.g. >9–10 mg/dL) regardless of comorbidities. At these levels, the absolute risk of crystal complications (gout, urolithiasis, urate nephropathy) rises sharply. Some guidelines (e.g. Japanese Society of Gout) consider treatment for any sUA > 9 mg/dL due to the risk of urate deposition. In a CV context, extremely high sUA might reflect an advanced metabolic disturbance or tumor lysis in malignancy. Such patients should be evaluated for possible causes (myeloproliferative disorders, for example) and always require urate-lowering therapy even if asymptomatic, to prevent end-organ deposition.

Laboratory and Imaging Aids: While serum uric acid is the primary diagnostic test, other evaluations can support risk stratification:

- **Urinary Uric Acid excretion:** In recurrent stone formers, a 24-hour urine uric acid can identify those with uric acid over-excretion, guiding use of uricosurics or alkalinization therapy. In gout patients, urinary urate helps classify as "over-producer" vs "under-excreter," but this distinction is less critical for asymptomatic hyperuricemia management.
- **Renal function indices:** An emerging concept is the **urate-to-creatinine ratio** or **urate-to-GFR** ratio. A high sUA relative to kidney function may indicate urate retention beyond expected and could flag patients at risk of gout or nephropathy. The consensus suggests that calculating the sUA/eGFR ratio might provide insight into renal handling of urate, though its clinical utility needs more validation.
- **Imaging for Urate Deposits:** In asymptomatic hyperuricemia, imaging is not routine. However, dual-energy CT can detect urate crystal deposits in joints, and ultrasound may show urate crystal deposition (e.g. the "double contour sign" on cartilage). These are primarily research tools or used in difficult gout diagnosis, but if one visualizes crystal deposition in an ostensibly asymptomatic patient,

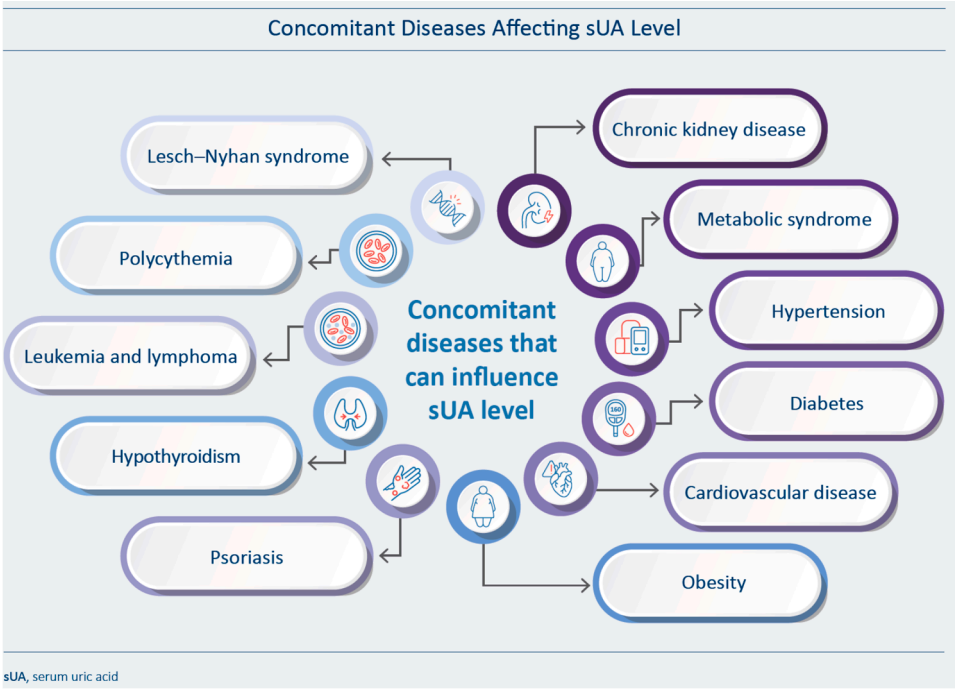

Fig. 7. Concomitant diseases affecting sUA Level.

that patient actually has subclinical gout and might benefit from treatment.

22.3. Diagnostic thresholds (URRAH and others)

As discussed earlier, risk stratification may employ different urate cut-offs than the lab normal range. Table 1 below summarizes key threshold values from recent studies that may inform clinical judgement. The table illustrates that while 6–7 mg/dL is the lab definition of hyperuricemia, adverse outcomes often correlate with lower thresholds (~5–6 mg/dL) in susceptible groups. For example, an asymptomatic man with sUA 6.5 mg/dL traditionally might not be labeled "hyperuricemic," but if he has CV risk factors, this level could be considered above the desirable target. Clinicians should thus interpret urate levels in the context of the individual patient's risk profile.

In summary, proper evaluation of a hyperuricemic patient includes confirming persistent elevation, identifying contributing factors, and assessing overall cardiovascular and renal risk. This sets the stage for rational management – detailed in the next section – which ranges from lifestyle-only approaches to pharmacologic therapy, guided by an six-step ladder of escalating intervention.

23. Management of hyperuricemia: an six-rung therapeutic ladder

Management strategy for hyperuricemia should be tailored to the patient's risk category, current sUA level, and presence of symptoms or comorbidities. We present here an updated six-rung therapeutic ladder for urate-lowering therapy (ULT), starting from general measures and progressing to advanced interventions. This schema is adapted from contemporary guidelines and consensus recommendations, emphasizing a treat-to-target approach for high-risk patients while avoiding over-treatment in low-risk cases [4].

Table 1
Diagnostic thresholds and risk associations for serum uric acid.

Context	Proposed sUA Threshold	Associated Risk (adjusted)	Source (Year)
Classical definition (men)	>7.0 mg/dL (420 μmol/L)	Crystal saturation; gout risk increases	Historical standard
Classical definition (women)	>6.0 mg/dL (360 μmol/L)	Crystal saturation; gout risk increases	Historical standard
High CV risk (ESC Consensus)	<5.0 mg/dL recommended target	Lower CV mortality and events in high-risk patients (e.g. ≥2 risk factors)	ESC Expert Consensus 2023
URRAH CV mortality (men)	>5.6 mg/dL	Higher CV mortality (HR ~2.0 vs <5.6)	URRAH (Virdis et al. 2020)
URRAH CV mortality (women)	>5.1 mg/dL	Higher CV mortality (noted with LVH)	URRAH (2023)
URRAH all-cause mort. (diabetes)	≥5.6 mg/dL	HR 1.31 for CV death vs <5.6	Masulli et al. 2022
URRAH elderly (65–74 y)	>4.8 mg/dL	Higher total/CV mortality (threshold)	Ungar et al. 2022
Heart Failure incidence (URRAH)	>5.34 mg/dL (for any HF)	HR 1.29 for incident HF	Muiesan et al. 2021
Heart Failure mortality (URRAH)	>4.89 mg/dL (for fatal HF)	HR ~1.27 for HF death	Muiesan et al. 2021
Stroke incidence (URRAH)	~5.3 mg/dL	Higher stroke risk identified	Tikhonoff et al. 2022
Gout flare risk	>9–10 mg/dL	Very high; consider ULT even if asymptomatic	Clinical observation
Uric acid stone risk (urine)	Urine UA >1100 mg/24h	High risk of uric acid nephrolithiasis	–

Rung 1. Patient Assessment and Threshold to Treat – *"Who needs urate-lowering intervention?"*

The first step is to verify the diagnosis of hyperuricemia and decide if treatment is indicated. This involves repeating the sUA measurement under standardized conditions (fasting sample, off acute illness). If sUA remains elevated, consider the context:

- Begin with lifestyle advice (Rung 3). Provide education on the implications of high urate as a risk factor.
- If sUA is markedly elevated, urate-lowering therapy is generally indicated.
- Patients with sUA above the risk thresholds discussed (≈5.5–6 mg/dL) *and* significant CV/renal comorbidities should be considered for earlier intervention. In other words, treat hyperuricemia as you would other risk factors: more aggressively if the overall risk is high.
- Establish a target sUA for therapy as 5 in patients with high CV risk and 6 n other situations. European consensus advises a target <6 mg/dL (360 μmol/L) for most situations, and <5 mg/dL (300 μmol/L) in patients with high CV risk or severe gout. These targets are derived from crystal solubility and observational risk data.

Additionally, at this stage calculate the patient's sUA-to-GFR ratio if CKD is present; an abnormally high ratio may reinforce the need for intervention or nephrology referral. This ratio (sUA divided by eGFR) is not yet a standard metric, but research suggests it might correlate with renal urate under-excretion.

Rung 2. Address Contributing Factors and Comorbid Conditions – *"Optimize the background."*

Before initiating specific urate-lowering medications, mitigate factors that may be causing or worsening hyperuricemia:

- **Review Medication List:** If the patient is on diuretics for hypertension, could an alternative be used? Thiazides and loop diuretics significantly increase urate by reducing renal excretion. Options include switching hydrochlorothiazide to an ACE inhibitor or calcium channel blocker, or if a diuretic is needed, consider SGLT2 inhibitors in diabetics (which also promote urate excretion). Low-dose aspirin (75–100 mg) causes net urate retention; if appropriate, one might stop prophylactic aspirin in a primary prevention setting to help urate levels. Immunosuppressants like cyclosporine and tacrolimus are often indispensable (e.g. in transplant), but one should be aware they cause hyperuricemia via reduced GFR and altered tubular handling. Manage accordingly (e.g. ensure adequate hydration, use allopurinol if gout develops in transplant patients).
- **Treat Comorbidities:** Good control of coexistent conditions will indirectly benefit urate metabolism. Optimal glycemic control in diabetes and aggressive lipid management may reduce vascular inflammation and urate production. Treating obesity (weight loss) is particularly impactful (see Rung 3). Hypertension treatment is interestingly closely associated: some antihypertensives raise sUA (diuretics, beta-blockers somewhat), while others lower it (calcium antagonists slightly). If a hypertensive patient has hyperuricemia, preferring a calcium blocker (amlodipine) can both control blood pressure and assist in sUA control.
- **Interdisciplinary Approach:** In complex cases, involve relevant specialists. A rheumatologist might co-manage a patient with gout; a cardiologist should be part of the plan if the patient had recent

Table 2
Individualized urate-lowering therapy planning by comorbidity.
pharmacologic management by comorbidity.

Comorbidity	Preferred Urate-Lowering Therapy & Adjustments	Avoid or Use with Caution	Dose Adjustments / Special Notes
Cardiovascular disease (e.g. coronary artery disease, heart failure, stroke)	**First-line:** Allopurinol (extensive safety data in CV patients; some studies suggest long-term allopurinol may even lower stroke risk) **Alternative:** Febuxostat if allopurinol is contraindicated or ineffective. Early data (CARES trial) raised concern of higher CV mortality with febuxostat, so guidelines prefer allopurinol in patients with significant CV history. However, a large 2020 trial (FAST) showed febuxostat was *non-inferior* to allopurinol in preventing CV events and did **not** increase overall or CV mortality	**Caution/Avoid:** Febuxostat in patients with recent unstable cardiovascular disease (FDA recommends caution in those with severe CV disease due to prior signals).	No specific ULT dose reduction is required solely for CV disease. Treat to serum urate target <6 mg/dL to reduce gout flares and systemic inflammation (which may benefit CV health). Optimize concomitant medications: if patient is on a thiazide diuretic (raises urate), consider switching to an ARB like losartan, which has mild uricosuric effects. Low-dose aspirin may raise urate slightly but **should not** be stopped if indicated for CV protection – instead manage gout with ULT.
Chronic Kidney Disease (CKD) (renal impairment)	**First-line:** Allopurinol (even in CKD, per guidelines) started at a low dose. Initiate at 100 mg daily (lower end for CKD stage ≥3) and titrate slowly to target urate. Allopurinol is effective in CKD but requires cautious dosing and monitoring for toxicity. **Alternative:** Febuxostat (metabolized partly in liver) can be used in CKD without major dose reduction until very advanced stages; studies show febuxostat remains effective even in moderate-severe CKD. KDIGO 2024 strongly recommends that CKD patients with gout (symptomatic hyperuricemia) receive urate-lowering therapy. Pegloticase (i.v. uricase) is an option for refractory gout in CKD (not renally cleared).	**Avoid:** Uricosuric agents (e.g. probenecid, lesinurad) in advanced CKD – they are ineffective when GFR is low and can cause drug accumulation or nephrolithiasis. NSAIDs should be avoided or minimized in CKD (risk of further renal damage), so controlling gout with ULT is crucial. **Caution:** Allopurinol hypersensitivity syndrome risk is higher in CKD; consider HLA-B*58:01 screening in high-risk ethnic groups (e.g. Han Chinese, Thai, Korean, or African ancestry) before starting allopurinol.	**Dose Adjustments:** Allopurinol dose **must** be adjusted to kidney function. Start at 100 mg daily if CrCl <30 mL/min and uptitrate by 100 mg every 2-4 weeks to reach target urate. Do not arbitrarily limit allopurinol dose in CKD if needed for urate control – careful titration with monitoring is preferred over under-dosing (monitor for rash or liver/renal labs). Febuxostat requires no dose adjustment for mild-moderate CKD; for CrCl <30, max 40 mg daily is often recommended (limited data in end-stage renal disease). **Special:** KDIGO guidelines advise **against** urate-lowering therapy in asymptomatic hyperuricemia solely to slow CKD progression, as RCTs have not shown kidney benefit, but they **do** recommend treating gout in CKD to prevent gout complications. Provide gout flare prophylaxis (e.g. low-dose colchicine <– use reduced dose in CKD–> or low-dose steroids) when starting ULT to prevent flare-ups.
Liver disease (e.g. cirrhosis, chronic hepatitis, fatty liver)	**Preferred:** Allopurinol is generally preferred in moderate-to-severe hepatic impairment, since it is primarily renally excreted. It can be used in patients with liver disease, but monitor liver function tests (rare idiosyncratic hepatotoxicity can occur). **Alternative:** Febuxostat in patients with mild liver disease or fatty liver– no dose adjustment is needed in mild-moderate hepatic impairment (Child-Pugh A or B), and trials indicate febuxostat's liver safety is comparable to allopurinol. In patients with NAFLD (non-alcoholic fatty liver), both allopurinol and febuxostat have been used safely.	**Avoid/Caution:** Avoid febuxostat in **severe** hepatic impairment (Child-Pugh C), as it has not been studied and could accumulate. Uricosurics (benzbromarone) are contraindicated if there is active liver disease or transaminase elevation, due to risk of serious hepatotoxicity. Benzbromarone should be avoided or used only with extreme caution and close LFT monitoring in any patient with liver disease. Monitor allopurinol patients for signs of DRESS/allopurinol hypersensitivity (which can involve the liver) especially in those also on other hepatotoxic drugs. Limit acetaminophen use to safe doses if used for pain (to avoid compounding liver injury).	**Dose Adjustments:** No specific allopurinol dose adjustment is required in hepatic impairment (dosing is based on renal function), but be vigilant with titration and LFT monitoring. Febuxostat: in mild-moderate liver disease, standard doses (40–80 mg) are acceptable; in severe disease, febuxostat is **not recommended** (lack of data – if absolutely needed, use minimal dose with caution). If liver disease coexists with CKD, dosing should follow the more restrictive organ's requirement (usually CKD). **Special:** Consider avoiding alcohol-containing formulations and other hepatotoxic medications. In patients with fatty liver and metabolic syndrome, urate lowering might incidentally improve liver inflammation (some experimental data), but primary therapy for NAFLD remains diet and weight loss. Ensure hepatitis viral statuses are considered (allopurinol/febuxostat have no direct antiviral interactions).
Solid organ transplant (renal, cardiac, etc., on immunosuppressants)	**Preferred:** Xanthine oxidase inhibitors (XOIs) are effective for lowering urate in transplant patients, *if* immunosuppressant regimen allows. Allopurinol or febuxostat can be used to reach urate goals **provided** they are **not** given alongside azathioprine. In transplant recipients not on azathioprine (e.g. those on mycophenolate mofetil instead), allopurinol is first-line (dose per renal function) and has been shown to control gout post-transplant. Febuxostat is an alternative if allopurinol is not tolerated; both have been used successfully in kidney transplant gout management. If XOIs are contraindicated due to drug interactions, consider a uricosuric (if renal function is adequate): **Benzbromarone** is used in some cases in Europe for transplant patients with gout, as it remains effective at low-moderate GFR (effective if CrCl >25 mL/min). Pegloticase is a last-resort option for	**Avoid: Allopurinol or febuxostat with azathioprine** – this combination is contraindicated due to severe, potentially fatal bone marrow toxicity (XOIs inhibit azathioprine metabolism). If a transplant patient is on azathioprine, **do not start XOIs** without adjusting immunosuppressive therapy (the transplant team may switch azathioprine to mycophenolate to allow ULT). **Caution:** Colchicine for gout flares in transplant – colchicine used with calcineurin inhibitors (e.g. cyclosporine) can cause serious neuromyopathy; reduce dose or use steroids for flares. NSAIDs are generally avoided in transplant patients (nephrotoxic with calcineurin inhibitors), so ensure adequate ULT to minimize flare frequency. Also use caution with probenecid in kidney transplant patients – often ineffective if graft	**Dose Adjustments:** Adjust allopurinol dose to the transplanted organ's function (e.g. in kidney transplant with CKD stage 3, start at 50-100 mg and titrate). Febuxostat usually can be given at standard doses post-transplant (assuming liver and renal function of the graft are adequate), but in renal transplant patients with low GFR, use lower doses (40 mg). **Special:** Co-manage with transplant specialists. The European transplant guidelines advise avoiding allopurinol+azathioprine entirely. If azathioprine must be continued, one strategy is to reduce azathioprine to ~25 % dose and closely monitor blood counts if allopurinol is absolutely needed – but this is high risk and not preferred. Ideally, switch azathioprine to another agent before ULT. Optimize other medications: for hypertension in transplant patients, use calcium-channel blockers (amlodipine) instead of diuretics – amlodipine not only spare renal

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Table 2 (*continued*)

Comorbidity	Preferred Urate-Lowering Therapy & Adjustments	Avoid or Use with Caution	Dose Adjustments / Special Notes
	refractory tophaceous gout in transplant patients and can be particularly effective in this population (immunosuppression may reduce anti-drug antibody formation).	GFR <30 and it can increase levels of other drugs.	function but also lower urate levels slightly. Avoid niacin for dyslipidemia (raises urate). Transplant patients often have metabolic syndrome from steroids & calcineurin inhibitors – aggressive management of weight, blood sugar, and lipids will complement gout therapy.
Diabetes mellitus (and metabolic syndrome)	**Preferred:** Allopurinol (first-line) and febuxostat (alternative) are both appropriate in diabetics – diabetes per se does not contraindicate any ULT. The choice should be guided by renal function and comorbidities (many diabetics have CKD or CV disease, so see those sections for modifications). Treat-to-target urate <6 mg/dL is recommended to reduce gout flares, which can worsen glycemic control during flares (due to inflammation/stress). Notably, allopurinol might confer vascular benefits in diabetes by reducing oxidative stress (research is ongoing). Febuxostat is also effective; just use caution if the patient has cardiovascular disease (common in diabetes).	**Avoid/Caution:** No urate-lowering drug is absolutely contraindicated solely due to diabetes. However, avoid medications that worsen metabolic control or interact: e.g. avoid thiazide and loop diuretics for hypertension in gouty diabetics if possible (they increase uric acid and insulin resistance) – use ACE inhibitors instead. Similarly, avoid high-dose niacin for dyslipidemia in gout patients (niacin raises uric acid significantly). Fenofibrate (often used for high triglycerides in diabetes) actually **lowers** serum urate, so it can be beneficial – but do not add fenofibrate purely for gout without a lipid indication. Low-dose aspirin for cardioprotection in diabetes is acceptable; do not stop it due to gout (just manage urate appropriately).	**Dose Adjustments:** No dose changes of ULT are required for diabetes itself. Dose adjustments should be made if the patient has diabetic nephropathy (CKD) – follow CKD dosing guidelines for allopurinol/febuxostat. **Special:** Emphasize that lifestyle modifications (weight loss, dietary changes) will improve both diabetes and gout. Some anti-diabetic drugs have urate effects: SGLT2 inhibitors modestly reduce serum urate, which can help gout; whereas insulin resistance elevates urate. Improving glycemic control and reducing insulin levels (through diet, metformin, etc.) can aid uric acid reduction. Monitor for drug interactions (e.g. allopurinol can increase risk of hypoglycemia if combined with oral sulfonylureas in rare cases). Overall, standard gout management principles apply, integrated into the patient's diabetes care plan.
Neurological disorders (stroke, dementia, Parkinson's disease, etc.)	**Preferred:** Standard ULT (allopurinol first-line; febuxostat as alternate) – neurological conditions do not change the first-line choice of urate-lowering therapy. If gout is present, it should be treated to target to prevent joint damage and pain that could further impair mobility or rehabilitation in neurologic patients. Allopurinol is well-tolerated; interestingly, observational studies noted that patients with hyperuricemia or gout had lower risk of some neurodegenerative diseases (e.g. Parkinson's), though causality is unproven. This **does not** preclude treating gout, but one should avoid driving uric acid to **below-normal** levels. Febuxostat can be used if allopurinol is not suitable (no direct neuro-specific contraindications).	**Avoid/Caution:** Generally no specific ULT contraindications solely for neurological disease. **Caution** with concomitant medications: if patient is on **azathioprine** for a neurologic condition (e.g. some use in multiple sclerosis or myasthenia gravis), the same contraindication with XOIs applies as in transplant (avoid allopurinol/febuxostat with azathioprine). If on **lithium** (for bipolar disorder), avoid probenecid – probenecid can dangerously increase lithium levels by reducing its excretion. Likewise, monitor for sedation or cognitive side effects (rare) of allopurinol; some patients report drowsiness – advise taking it in the evening if so. Colchicine neurotoxicity is a concern in frail or CKD patients – use low doses for prophylaxis to avoid neuromuscular side effects.	**Dose Adjustments:** No adjustments needed based on neurological diagnosis alone. Dose according to kidney and liver function as usual. **Special:** In patients with a history of stroke or TIA, allopurinol (titrated to urate target) may have ancillary benefits – some data suggest fewer recurrent strokes with long-term allopurinol use, possibly from improved endothelial function. Nevertheless, this is an added benefit; the primary goal is gout control. **Important:** Avoid excessive urate lowering (serum urate <3 mg/dL) long-term, as uric acid is a neuroprotective antioxidant in the CNS – guidelines (EULAR) advise against chronic urate <3 mg/dL to be safe. Ensure patients with cognitive impairment have support: involve caregivers to administer medications and dietary guidance, since adherence to daily ULT is crucial (inconsistent use can trigger flares). If physical disability (e.g. post-stroke) limits mobility, coordinate with physiatrists – effective ULT can reduce gout flares that would hinder rehab progress.
Age – Elderly patients (e.g. >65–70 years)	**Preferred:** Allopurinol remains first-line in the elderly, but start at a very low dose (50 mg or 100 mg) and titrate slowly. Older patients often have reduced GFR and multiple comorbidities, so the "start low, go slow" approach is critical to avoid adverse effects. Febuxostat is an acceptable alternative in elderly patients who cannot tolerate allopurinol or in whom allopurinol is contraindicated. Note that many elderly have cardiovascular disease – if so, use febuxostat cautiously or only if necessary (consider the latest evidence like FAST trial in decision-making). Uricosurics (probenecid, benzbromarone) are second-line in elderly only if renal function is sufficient and other options are unsuitable; they are less commonly used in older adults.	**Avoid/Caution:** Avoid under-treating gout in the elderly. Do **not** withhold ULT simply due to age – tophaceous gout can be very destructive in older patients, and effective therapy exists. That said, use caution with polypharmacy: check for drug interactions (e.g. allopurinol with warfarin can increase INR; allopurinol with ACE-inhibitors may increase hypersensitivity risk). **Avoid** uricosurics in patients with a history of kidney stones (not uncommon in older gout patients) or very low GFR. Use colchicine carefully in the elderly (even at prophylactic doses) – age-related renal decline and concurrent medications (e.g. statins) raise the risk of colchicine toxicity (neuromyopathy). If needed, low-dose colchicine (0.3–0.6 mg daily) can be used for flare prophylaxis, or consider low-dose prednisone as an alternative prophylactic in those who can't take colchicine or NSAIDs.	**Dose Adjustments:** Adjust ULT doses for renal function (many elderly have CKD even if mild). Allopurinol should be uptitrated more gradually in the elderly (e.g. every 4-6 weeks rather than every 2 weeks) while monitoring for rash or other reactions. Febuxostat dosing in older adults is the same as in younger, but consider starting at 40 mg and assessing response before increasing, especially if any frailty. **Special:** Educate elderly patients and caregivers that gout is curable with proper therapy – this helps with adherence. Ensure they maintain hydration (elderly individuals may chronically under-hydrate, contributing to urate stone risk and acute gout). Nutritional status is important: avoid crash diets or excessive restrictions that could cause malnutrition; focus on moderation (protein purine restriction yields only modest urate reductions ~1 mg/dL). Monitor for adverse effects at each visit (e.g. check CBC, liver enzymes periodically for allopurinol in older patients). HLA-B*58:01 testing should be considered in ethnically at-risk elderly patients starting allopurinol, just as in younger patients.
Age – Pediatric patients (children and adolescents)	**Preferred:** Identify the cause of hyperuricemia. True gout is rare in children, so persistent hyperuricemia usually has an underlying cause (genetic or hematologic). **Allopurinol** is the first-line urate-lowering	**Avoid/Caution:** Many urate-lowering drugs lack pediatric approval. **Avoid febuxostat in very young children** – safety and efficacy are not established under ~18 years. Uricosurics (probenecid) can be used in older	**Dose Adjustments:** Pediatric dosing generally starts low and is titrated to maintain uric acid in the normal range for age. Allopurinol: typical max ~300 mg/day in teens, but higher doses (up to 600–800 mg) have been used in teenagers with

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Table 2 (*continued*)

Comorbidity	Preferred Urate-Lowering Therapy & Adjustments	Avoid or Use with Caution	Dose Adjustments / Special Notes
	drug in pediatric hyperuricemic conditions – e.g. Lesch-Nyhan syndrome (HPRT deficiency) or tumor lysis syndrome prophylaxis. Allopurinol dosing in children is weight-based (commonly 5–10 mg/kg/day up to 300 mg/day, divided if higher doses). **Recombinant uricase (Rasburicase)** is often the drug of choice in acute pediatric hyperuricemia (tumor lysis syndrome) – it rapidly breaks down uric acid. Rasburicase is used in hospital settings for high-risk leukemia/lymphoma patients to prevent urate nephropathy. **Febuxostat:** not routinely used in young children (limited data), but has been used off-label in adolescents with gout or hyperuricemia when allopurinol was inadequate. If an adolescent presents with true gout (e.g. obesity-related early onset gout), allopurinol is started as in adults (begin low dose, 100 mg, and titrate).	children or teens, but require caution: ensure high fluid intake and an ability to adhere to regimen. Do **not** use uricase (rasburicase) in patients with G6PD deficiency (risk of hemolytic anemia). In Lesch-Nyhan syndrome, allopurinol is standard; febuxostat has been tried in a few cases but data are sparse – so use febuxostat cautiously in HPRT deficiency and only if allopurinol fails. Monitor for rash or liver enzyme changes with allopurinol in pediatric use as well.	severe tophaceous gout or genetic urate overproduction (under specialist supervision). If the child has any renal impairment, adjust doses as in CKD (e.g. cut starting dose in half). **Special:** Emphasize lifestyle and dietary education to parents and child. Encourage **hydration** – children should drink plenty of fluids to reduce risk of uric acid stone formation (especially important if on uricosuric therapy or if they have a high urate load from tumor lysis). Advise a balanced diet: avoid excessive consumption of high-purine foods (organ meats, certain seafood) and **eliminate sugary drinks (fructose-rich sodas)** which are a known contributor to hyperuricemia and childhood obesity. Weight management is key if the child is overweight. In hereditary conditions (Lesch-Nyhan), purine production is endogenous and diet has limited effect – still, moderate purine restriction can help a bit, and maintaining hydration/alkaline urine can prevent kidney stones. Pediatric cases should ideally be co-managed with a specialist (pediatric rheumatologist or metabolic specialist) given the rarity of gout in children and the need for family counseling.

CV events and now has high urate. Similarly, nephrologists should be involved early if CKD is advanced. Multidisciplinary care improves adherence and outcomes.

By removing exacerbating factors in Rung 2, one can sometimes achieve a drop in urate without pharmacotherapy (e.g. stopping a diuretic may lower sUA by 1–2 mg/dL in some individuals). Even if not, this step prevents counterproductive influences once ULT is started.

Rung 3. **Lifestyle and Dietary Modification** – *"Non-pharmacologic urate lowering."*

Lifestyle interventions are the cornerstone of managing hyperuricemia (as with other CV risk factors). Key measures, supported by evidence, include:

- Weight Management: Achieve and maintain a healthy body weight. Obesity is strongly linked to hyperuricemia; weight loss can lower sUA significantly (often ~1–2 mg/dL with substantial loss). A prospective study showed that bariatric surgery patients experienced profound urate reductions along with decreased gout flares. Even modest weight loss helps.
- Dietary Changes: Adopt a balanced diet with restricted purine-rich foods. Limit red meat (beef, organ meats like liver) and seafood (shellfish, sardines) which are high in purines. High-fructose corn syrup and sugary drinks uniquely raise urate by increasing ATP turnover – these should be minimized. Encourage low-fat dairy intake (which is associated with lower urate and gout risk). Intake of purine-rich vegetables (e.g. beans, spinach) is less problematic than meats, so those can be limited moderately but not eliminated.
- Alcohol: Curb alcohol consumption, especially beer and spirits. Beer contains guanosine (a purine) and promotes urate production, and alcohol (ethanol) in general reduces renal urate excretion. Advise at most moderate intake (e.g. $\leq$1–2 drinks/day) or abstinence in those with severe hyperuricemia. Wine in moderate amounts has less effect than beer/spirits, but excess wine can also raise urate.
- Hydration: Emphasize good hydration (e.g. 2–3 l of water per day if not contraindicated). This helps prevent uric acid crystal precipitation in kidneys (kidney stones) and may increase urate excretion slightly by diluting urine.
- Specific Foods/Supplements: Certain foods and supplements may provide benefit. Coffee consumption (regular coffee, not sugary sodas) is associated with lower gout risk and modestly lower urate, possibly via polyphenols and increased clearance. Vitamin C (ascorbic acid) at supplemental doses (~500 mg/day) has a mild uricosuric effect and can lower sUA by ~0.5–0.7 mg/dL. Cherries or cherry extract have been reported in some studies to reduce sUA and may lower urate slightly, though data are not definitive. These adjuncts are generally safe: patients can be advised to eat cherries, consider a vitamin C supplement, and drink coffee if tolerated, as part of lifestyle management.
- Exercise: Regular exercise is encouraged for overall health and weight control. While acute intense exercise can transiently raise urate (due to ATP breakdown), habitual moderate exercise is beneficial for metabolic health and likely outweighs any temporary urate changes. There's no direct proof that exercise lowers urate, but it contributes to weight loss and improved insulin sensitivity, which in turn lower sUA.

Lifestyle modifications not only lower urate but also help control blood pressure, blood sugar, and cholesterol, giving broad health benefits. Adherence is crucial – involve dietitians if needed, and set realistic goals. Notably, lifestyle alone may be enough for many low-risk hyperuricemic individuals to avoid pharmacotherapy. Even when drugs are used, continuing these measures maximizes effectiveness (and possibly allows lower dosing).

Rung 4. **Initiation of Urate-Lowering Pharmacotherapy (Xanthine Oxidase Inhibitors)** – *"Start medication if needed – first-line allopurinol."*

If sUA is above target, pharmacologic urate-lowering therapy (ULT) should be initiated. The first-line drugs are xanthine oxidase inhibitors (XOIs), which reduce uric acid production:

- **Allopurinol:** A purine analog that inhibits xanthine oxidase, allopurinol has been used for decades and is recommended as the initial ULT of choice. Start at a low dose to reduce risk of hypersensitivity – typically **100 or 200 mg daily** (especially in patients

with CKD or those of Southeast Asian descent who might have HLA-B*58:01 allele predisposing to allopurinol hypersensitivity). In mild hyperuricemia, 100–300 mg/day may suffice; moderate cases often need 300–600 mg/day, and severe cases up to the max of 800–900 mg/day, as tolerated. Dosing should be titrated every few weeks based on sUA levels, aiming for target <6 mg/dL (or <5 if indicated – in cases with high cardiovascular risk). According to product info and consensus, doses can be raised by 100 mg increments every 2–4 weeks until target is achieved or maximum dose reached. In CKD, initial doses should be lower (e.g. 50–100 mg) and titration slower, but **do not under-dose** indefinitely – many CKD patients can tolerate moderate allopurinol doses. Allopurinol's active metabolite (oxypurinol) is renally excreted; in advanced CKD, dosing frequency may be reduced (e.g. 100 mg every other day). In dialysis patients, an effective regimen is 300–400 mg given after each dialysis session, since dialysis clears the drug. Allopurinol is generally well-tolerated, but watch for rash or hypersensitivity (see Rung 6 for allele screening).

- **Febuxostat:** A non-purine XOI that can be used if allopurinol is contraindicated or not tolerated, in patients at low cardiovascular risk. Febuxostat (typically 40–80 mg daily, up to 120 mg in some cases) does not require dose adjustment in mild-to-moderate renal impairment, which is an advantage. It may lower urate more potently in some patients and achieve target when allopurinol at max dose fails. However, febuxostat's use in cardiovascular patients has been contentious due to initial reports of increased CV mortality (CARES trial) [62]. The 2020 FAST trial in Europe found no excess CV risk with febuxostat compared to allopurinol [63]. In a cardiology context, one should still be cautious using febuxostat in patients with unstable cardiovascular disease; if used, ensure risk factors are well-controlled. Febuxostat is particularly useful in CKD stage 3–4 where allopurinol dose is limited.

When starting ULT, **patient education** is vital. Explain that ULT is usually lifelong if started.

Rung 5. Titration to Target and Maintenance – *"Treat-to-target: reach goal sUA and stay there."*

Merely starting ULT is not enough – the therapy must be adjusted to achieve and maintain the urate target. This step encompasses titration, monitoring, and adherence:

- **Dose Escalation:** For allopurinol, increase the dose every few weeks until sUA falls below the target (e.g. <6 mg/dL or < 5 mg/dL in patients at high cardiovascular risk). Check urate levels about 4 weeks after each dose adjustment. If the patient is tolerating well (no rash, normal liver enzymes), push toward maximum dose if needed. Studies show only ~40 % of patients on allopurinol actually reach target at standard doses – often due to under-dosing. Do not hesitate to use 600–900 mg/day in severe hyperuricemia if renal function allows. If nearing 900 mg with inadequate response, it's reasonable to then add or switch therapy (see Rung 6 and 7).
- **Febuxostat Titration:** If on febuxostat 40 mg and sUA is above goal after 2–4 weeks, increase to 80 mg. Monitor liver function tests periodically as febuxostat can rarely cause hepatic enzyme elevations.
- **Monitoring:** Once at goal, check sUA every ~6 months to ensure it remains at target. More frequent checks early on or if adjusting therapy. Also monitor renal function and liver function annually (more often if on febuxostat or higher allopurinol doses). For patients on diuretics or with metabolic syndrome, periodic metabolic panels are useful.
- **Avoiding Interruption:** Emphasize adherence – stopping ULT can lead sUA to rebound, negating benefits. The consensus advises against discontinuing treatment once target is reached. Unlike hypertension or diabetes meds, where dose might be reduced if levels normalize, with ULT the "normalization" is entirely due to the drug; stopping will usually return sUA to baseline. Thus, maintenance is usually for life or long-term as long as risk persists. An exception might be if a reversible cause of hyperuricemia was fixed (e.g. weight loss of 30 kg or cure of hematologic disease) – then one could attempt a careful withdrawal.
- **Patient Engagement:** Educate patients that ULT is preventive – they may not "feel" any different, so adherence can wane. If asymptomatic, stress that controlling urate is akin to controlling cholesterol or blood pressure in preventing future problems.

At this rung, if targets are stubbornly not achieved, re-evaluate secondary causes and adherence (check if the patient is taking the medication regularly). If despite full-dose XOI the sUA is still above goal, move to combination or second-line therapy.

Rung 6. Second-Line and Special Pharmacologic Considerations – *"Switch or check for issues if first-line is inadequate or not tolerated."*

If the patient cannot tolerate first-line XOI therapy or has contraindications, or if target is not reached at max doses, consider the following:

- **Allopurinol Intolerance or Contraindication:** The most serious concern is **allopurinol hypersensitivity syndrome (AHS)** – a rare but life-threatening reaction (severe rash, liver/renal failure, eosinophilia). Risk factors for AHS include the HLA-B58:01 allele, particularly prevalent in certain Asian populations (e.g. Han Chinese, Thai, Korean) and in individuals with CKD. In those high-risk groups, genetic screening for HLA-B58:01 is recommended before starting allopurinol, per EULAR and ACR guidelines, as a positive test is a contraindication. If a patient develops even minor hypersensitivity signs (rash, fever) on allopurinol, stop it immediately. Other reasons to avoid allopurinol might be prior severe liver disease or significant cytopenia (though allopurinol is usually safe in liver disease at adjusted doses). In such cases, Febuxostat becomes the next option (assuming no active CV instability). Use febuxostat cautiously if the patient has known CV disease – weigh risks/benefits and ensure they are on cardioprotective therapies as appropriate.
- **Febuxostat Intolerance:** Febuxostat can cause minor side effects like nausea or abnormal liver tests; significant liver injury is rare. If febuxostat cannot be used (or fails to reach goal at max dose and combination therapy is undesired), an old alternative is oxipurinol (the active metabolite of allopurinol) available in some countries, or newer agents in trial phases. But practically, one might at this point move to a uricosuric agent (next rung).
- **SGLT2 Inhibitors:** Although not a classical hyperuricemia drug, sodium–glucose cotransporter-2 inhibitors used for type 2 diabetes (e.g. dapagliflozin, empagliflozin) have a mild uricosuric effect. They lower sUA by ~0.5–1.0 mg/dL on average by increasing glycosuria (glucose in urine competes with urate reabsorption). If a diabetic patient with hyperuricemia is not already on an SGLT2 inhibitor and has no contraindications, starting one can both improve diabetes outcomes (CV and renal protection) and incidentally reduce urate. Some guidelines now note this as a pleiotropic benefit. However, SGLT2i are not approved specifically for hyperuricemia, so consider it a bonus. Postulated mechanism of uricosuric SGLT2 inhibitor actions are described elsewhere, together with class effect discussion in this area [74,75]. See Table 3:

Table 3
Key Findings on Uric Acid / Gout based on the newest studies.

Author / Year	Study Type	Population	Key Findings on Uric Acid / Gout
Zhang et al., 2025	Meta-analysis (RCTs)	T2DM patients on SGLT2i vs placebo	Significant reduction in serum uric acid (up to –1.1 mg/dL), empagliflozin strongest effect
Zhao et al., 2024	Meta-analysis	>20,000 T2DM patients	Mean sUA reduction ~0.6 mg/dL across SGLT2i
Neal et al., 2021	Cohort analysis from RCTs (CANVAS, EMPA-REG)	T2DM with high CV risk	SGLT2i use lowered risk of incident gout by ~34 % (HR 0.66; 95 % CI 0.57–0.76)
Wiviott et al., 2021	RCT (DECLARE-TIMI 58, dapagliflozin)	T2DM, n=17,160	Dapagliflozin reduced sUA by –0.84 mg/dL vs placebo; fewer gout flares reported
Lee et al., 2023	Nationwide cohort (Korea)	T2DM with/ without SGLT2i	SGLT2i use associated with lower recurrent gout risk and all-cause mortality
Kohan et al., 2014	RCT (empagliflozin, dapagliflozin)	T2DM, phase III trials	Increased fractional excretion of uric acid (FE-UA); mechanism: glycosuria competes with urate reabsorption (GLUT9 pathway)

- **Fenofibrate:** These non-purposed medications can be leveraged if appropriate. Fenofibrate also decreases sUA significantly (~20 % reduction) by increasing renal clearance of urate. If a patient has indication for these (e.g. high TGs, or hypertension), using them can aid urate control. They are not standalone urate therapies but can be considered part of the regimen [76–78].

By the end of Rung 6, one should have either achieved target or identified refractory hyperuricemia that requires combination therapy. For example, a patient on allopurinol 900 mg with sUA still 7 mg/dL despite adherence is a candidate for add-on therapy.

Combination Urate-Lowering Therapy (XOI + Uricosuric) – *"Dual therapy to hit the target."*

When monotherapy with a XOI at maximal dose fails to reach target urate, or is contraindicated to escalate further, adding a uricosuric agent is an effective strategy. Uricosurics increase renal excretion of urate by inhibiting reabsorption in the proximal tubule:

- **Benzbromarone:** A powerful uricosuric widely used in Europe. Typical dose is 50–200 mg daily. Benzbromarone can dramatically reduce sUA, even in patients with moderate CKD (though it's not recommended if eGFR <30 mL/min). It was withdrawn in some markets due to rare hepatotoxicity; liver enzymes should be monitored. In combination with allopurinol, benzbromarone has shown synergy in lowering urate. The consensus suggests considering allopurinol + benzbromarone therapy if monotherapy is insufficient (with caution in CKD). This should be avoided if eGFR <30 or a history of urolithiasis.
- **Probenecid:** A traditional uricosuric, dose 500 mg twice daily up-titrated to 1–2 g/day. Probenecid is effective in patients with good renal function; ineffective if GFR <50–60. It can be used in combination with allopurinol and was historically combined as "probenecid-allopurinol" therapy before benzbromarone or newer agents. It shares the risk of urate stones; prophylactic hydration and sometimes bicarbonate or citrate supplements are used to keep urine pH >6.0.
- **Lesinurad:** A selective URAT1 inhibitor that was approved in Europe a few years ago as an add-on for gout patients not reaching target on XOIs. Dose was 200 mg daily. Lesinurad effectively lowers sUA in combination (monotherapy was associated with renal toxicity so it's only used with XOIs). However, the manufacturer withdrew it from the market for commercial reasons, so it's largely unavailable as of mid-2020s. It is worth mentioning historically – some patients might have been on it. There are ongoing developments of similar URAT1 inhibitors that might reintroduce this class in the future.

Combining an XOI with a uricosuric often enables patients with refractory hyperuricemia to finally reach <6 mg/dL or < 5 mg/dL adequately. For instance, adding benzbromarone 100 mg to allopurinol 300 mg can drop sUA by several mg/dL further. Monitor such patients closely for side effects (liver tests for benzbromarone, risk of kidney stones for any uricosuric). Also, ensure good hydration and possibly urine alkalinization during combination therapy to mitigate stone risk, as large urate excretion can acidify urine and precipitate uric acid crystals.

Advanced and Adjunct Therapies (Refractory Hyperuricemia) – *"Last resorts: pegloticase and beyond."*

In rare cases of truly refractory hyperuricemia where oral combination therapy fails or is contraindicated, intravenous urate-lowering therapy can be employed:

- **Pegloticase:** A recombinant porcine-like uricase enzyme given IV (usually 8 mg every 2 weeks) that converts uric acid to allantoin (highly soluble). Pegloticase can dramatically lower sUA to undetectable levels. While highly effective biochemically, it has significant drawbacks: cost is very high, infusions can cause allergic reactions (nearly 5 % risk of anaphylaxis, thus infusions require monitoring and often pre-medication), and efficacy may wane as the body develops antibodies to the enzyme. Pegloticase is usually managed by rheumatologists in specialized centers. For CV risk management, pegloticase would practically **never** be used solely for asymptomatic hyperuricemia – it's reserved for severe gout that is unresponsive to conventional treatment. Its mention here is for completeness of the urate-lowering ladder.
- **Adjuncts in Acute Settings:** In acute tumor lysis syndrome (TLS) causing hyperuricemia, **rasburicase** (another uricase enzyme) is used to rapidly break down urate and prevent renal failure. TLS is a hematology emergency rather than a chronic management issue, but clinicians should be aware if encountering extreme hyperuricemia (>15–20 mg/dL) in that context.
- **Investigational Treatments:** New agents under research include oral uricase therapies, URAT1 inhibitors like dotinurad (approved in Japan 2020), and other pathway modifiers (e.g. a novel xanthine oxidase inhibitor topiroxostat, available in Asia). While not yet in European practice, these could expand options in coming years, especially for patients who cannot tolerate current drugs. See Fig. 8.

Finally, **adjunctive measures** throughout therapy should be addressed: management of comorbid hypertension, diabetes, etc., as part of an overall CV risk reduction plan. It's worth noting that treating hyperuricemia in isolation is not a panacea – it should be one component of comprehensive risk factor control (including aggressive lipid and blood pressure management per ESC guidelines, and use of anti-platelet or RAAS blocker therapy when indicated by comorbid conditions).

This ladder provides a structured approach to hyperuricemia management, escalating therapy intensity as needed. Not every patient will require progression through all steps – many will be managed within the first few rungs. For example, a mildly hyperuricemic hypertensive patient might normalize urate with diuretic cessation and diet alone. The overarching principle is treat-to-target in those who warrant treatment: get urate below the crystalline and risk thresholds and keep it there to

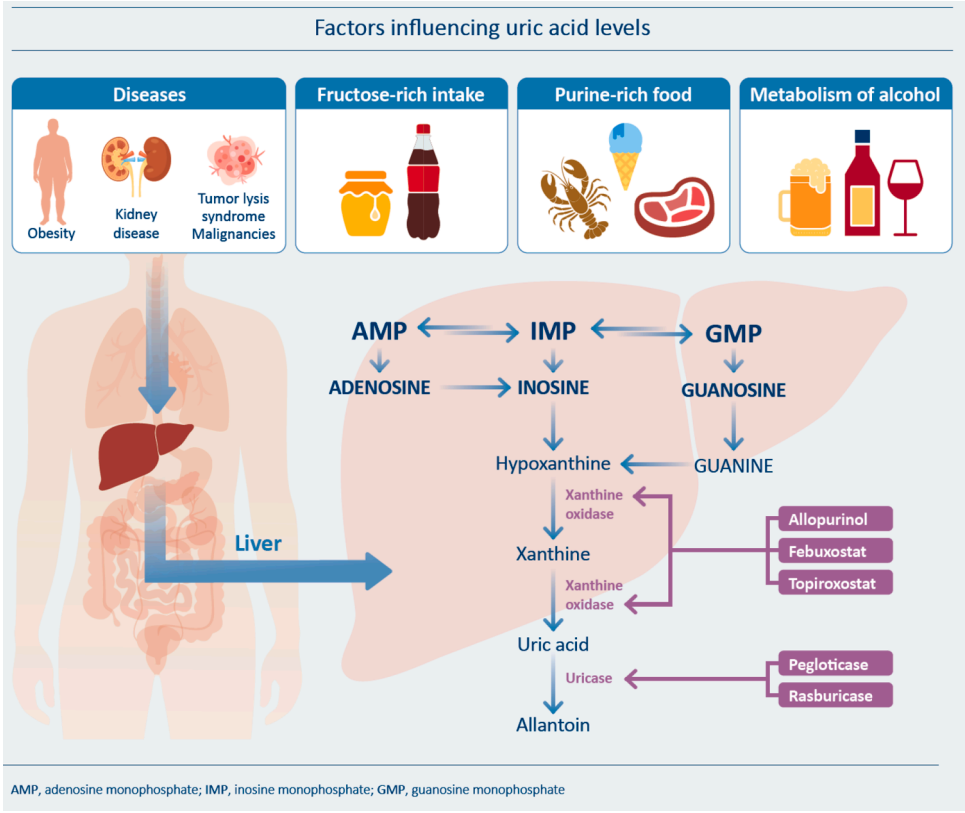

Fig. 8. How hyperuricemia damages the heart and kidneys.

potentially improve cardiovascular and renal outcomes. See Fig. 9.

24. Special populations and considerations

24.1. Hyperuricemia in pediatric patients

Pediatric hyperuricemia is relatively uncommon, but its presence may signal underlying issues or future risk. Reference ranges for uricemia in children are lower than in adults and depend on age and sex. Puberty is a turning point – urate levels rise in boys during adolescence (due to increased muscle mass and hormonal changes affecting renal urate handling). A teenage boy may have a urate of 7 mg/dL and still be within age-norms. Thus, pediatric hyperuricemia should be defined using age-specific percentiles (e.g. >95th percentile for age/gender) rather than adult cut-offs to avoid overdiagnosis.

Causes in Children: Primary gout is extremely rare before adulthood (except in certain genetic disorders like Lesch-Nyhan syndrome or familial juvenile gouty nephropathy). Common causes of high urate in kids include:

- **Obesity and Metabolic Syndrome:** Increasingly, overweight adolescents have elevated uric acid, often associated with insulin resistance. Uric acid may even mediate some hypertension development in obese youth.
- **High Purine Turnover Conditions:** Hematologic malignancies or hemolytic anemias can raise urate. Leukemia or lymphoma patients may present with hyperuricemia, especially during chemotherapy (tumor lysis syndrome).
- **Renal Conditions:** Some hereditary kidney tubule disorders (e.g. familial juvenile hyperuricemic nephropathy, UMOD gene mutations) cause reduced urate excretion and early-onset hyperuricemia with CKD. Also, children with reduced GFR from any cause will accumulate urate.
- **Dietary Excess:** While rare, excessive intake of high-fructose drinks or high-purine foods in a child can contribute, especially if coupled with low fluid intake leading to uric acid crystalluria.

Management in Children: There are no extensive trials of ULT in asymptomatic hyperuricemic children. General guidance:

- Emphasize **dietary measures and weight control**. Given the strong link between obesity and urate, focus on healthy lifestyle (which will benefit their long-term CV risk enormously). Limit sugary drinks and junk food, encourage physical activity.
- Treat underlying disorders (e.g. if a child is a cancer patient or has hemolysis, manage that primary condition; use rasburicase prophylactically in chemo per oncology protocols).
- ULT medications are not commonly used in pediatric patients unless they have significant issues. Allopurinol can be used in pediatric dosing (10 mg/kg/day divided, up to ~300 mg) for specific cases (such as Lesch-Nyhan or prophylaxis in tumor lysis).
- An interesting area is **adolescent pre-hypertension**: small studies showed allopurinol or febuxostat can lower blood pressure in obese adolescents with high urate, suggesting a pathogenic role of urate in early hypertension. However, this is not standard care yet; lifestyle modification remains first-line for these youths, reserving ULT for trial contexts or exceptional cases [79].

Overall, hyperuricemia in a child or teen should prompt a careful evaluation for secondary causes and an aggressive lifestyle intervention. Whether lowering urate pharmacologically will prevent adult hypertension or metabolic disease is still under investigation. For now, pediatricians typically do not treat asymptomatic hyperuricemia with drugs, except in special scenarios, focusing instead on dietary and weight management.

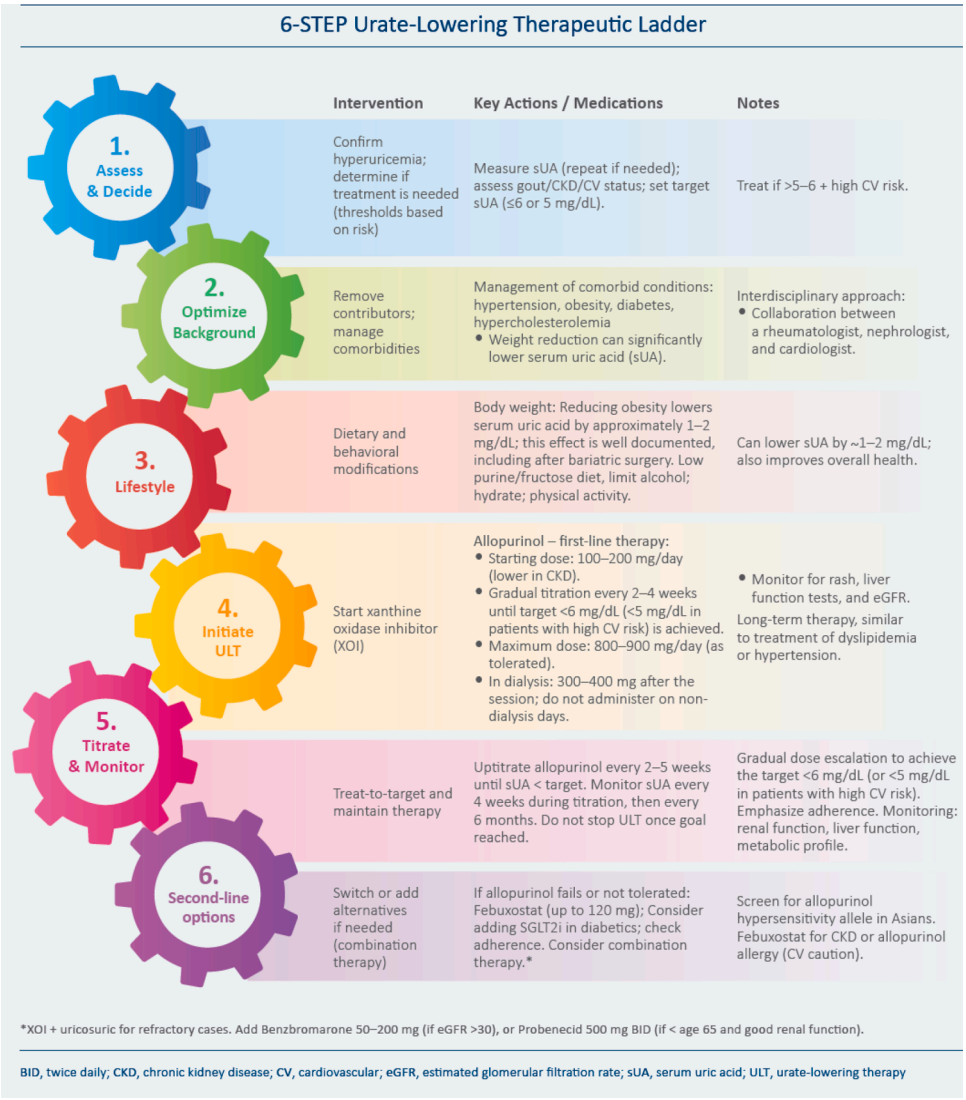

Fig. 9. 6-STEP Urate-Lowering Therapeutic Ladder 3.

25. Hyperuricemia in geriatric patients

Elderly patients (age >65–70) often have multiple comorbidities that interact with hyperuricemia. Key considerations:

- **Higher Prevalence:** As noted, nearly half of older adults might meet hyperuricemia criteria, especially men. Polypharmacy (diuretics, etc.) and reduced renal function contribute. It's common to find sUA ~7–8 mg/dL in an older patient with no gout history. One must weigh whether to intervene or simply monitor in such cases, considering life expectancy and comorbid burden.
- **Gout in the Elderly:** Gout can first present in the 70s or 80s. It may present atypically (e.g. as chronic hand osteoarthritis with superimposed urate crystals) and can be mistaken for osteoarthritis or rheumatoid nodules. Tophaceous gout in elderly women (post-menopausal, often with CKD and diuretics) is an important entity – these patients absolutely benefit from ULT to resolve painful tophi and prevent joint damage.
- **Pharmacotherapy Cautions:** Allopurinol dosing in the elderly should start low (even 50 mg in very old or CKD patients) and titrate slowly, because they may be more prone to hypersensitivity. Renal function must be accounted for. Febuxostat can be used if allopurinol is not tolerated; interestingly, FAST trial median age was 71, showing febuxostat was as safe as allopurinol in that older cohort. Uricosurics are less useful in the elderly if CKD is present (probenecid ineffective if low GFR; benzbromarone could still work but careful with livers). Also, older patients may already be on many meds, so check for interactions (allopurinol increases azathioprine effect – relevant if an older patient had a transplant or is on low-dose AZA for another condition; colchicine interaction with clarithromycin can be deadly – caution in gout flare prophylaxis).
- **Comorbid Conditions:** Elderly hyperuricemic patients often have coronary disease, HF, or stroke history. While hyperuricemia is a marker of risk, their overall management should prioritize proven therapies (antiplatelets, statins, RAAS blockers). Treating urate is secondary and should not conflict with primary CV therapies. Fortunately, most ULT don't adversely affect other conditions (though diuretic changes for urate might conflict with HF management – coordinate with cardiology if considering stopping a diuretic in an HF patient; sometimes gout prophylaxis needs to be balanced with loop diuretic need).
- **Goals of Care:** The URRAH data suggesting a J-shaped mortality curve in >75 age group (with lowest mortality around sUA ~5–6 mg/dL and higher mortality if much lower or much higher) raises

an interesting point: in very old or frail patients, aggressively driving urate below 4 mg/dL might be unnecessary or even harmful (perhaps very low urate correlates with malnutrition). Thus, for geriatric patients, a reasonable urate target might be a bit more relaxed, focusing on preventing gout attacks and avoiding extreme hyperuricemia, rather than hitting <5 in everyone. Some experts might accept sUA ~6–7 mg/dL in an asymptomatic 85-year-old if that avoids polypharmacy, whereas a 50-year-old with the same level but multiple risks would be treated.

- **Cognitive Impact:** There is emerging research on urate's relationship with neurodegenerative diseases. Interestingly, higher urate has been associated with lower risk of Parkinson's disease (perhaps due to antioxidant properties). This is observational and not a basis to keep urate high, but it adds to the complexity of risk-benefit in the elderly. If a patient has a condition like Parkinson's, one might not rush to push urate too low given this potential link, though evidence is not strong enough to formally alter targets.

In summary, management of hyperuricemia in older adults should be individualized. One should consider life expectancy, comorbidities, fall risk (gout flares causing falls), and polypharmacy. When gout causes pain and disability, treat it regardless of age. If hyperuricemia is asymptomatic and mild, with limited life expectancy, it may be reasonable to forgo additional medications and focus on comfort and simplicity.

26. Sex differences and women's health

Men have higher urate levels than premenopausal women, but after menopause women catch up. Hyperuricemia in premenopausal women is less common; if present, consider secondary causes (e.g. renal issues, genetic predisposition). When treating women of childbearing potential, note that allopurinol and febuxostat are category C (risk not ruled out) – they should be avoided in pregnancy. Hyperuricemia itself is associated with preeclampsia (high urate is a marker of disease severity in pre-eclampsia), but ULT is not used in pregnancy. In postmenopausal women, treat similarly to men. One nuance: diuretic-induced hyperuricemia is common in elderly women (since diuretics are often used for hypertension); managing that as per our ladder applies equally.

27. Hyperuricemia and other comorbidities

A few additional notes on overlapping conditions:

- **Metabolic Syndrome & Diabetes:** Uric acid correlates strongly with metabolic syndrome traits. It may be both a cause and effect of insulin resistance. In diabetic patients, SGLT2 inhibitors and possibly GLP-1 agonists might modestly reduce urate. No diabetes-specific urate target exists, but given URRAH data in diabetes (CV mortality risk above 5.6 mg/dL), it's sensible to keep diabetic patients' urate in the low-normal range if possible.
- **Hypertension:** Hyperuricemia is an independent predictor of developing hypertension. Trials of urate-lowering in early hypertension (teens, young adults) have shown BP reductions, implying causality. In practice, for a hypertensive patient with urate ~7+, especially if young, treating the urate might help BP control as adjunct (besides choosing antihypertensives that don't raise urate). The 2023 ESH Hypertension Guidelines acknowledge urate as a risk factor but stopped short of recommending ULT just to treat hypertension due to lack of outcome trials. However, they do recommend avoiding diuretics if possible in a hyperuricemic hypertensive.
- **Heart Failure:** Many HF patients have elevated urate due to reduced renal perfusion and use of diuretics. While hyperuricemia in HF is a bad prognostic sign, trials (e.g. ALL-HEART, EXACT-HF) have not proven that lowering urate improves HF outcomes. Therefore, treat hyperuricemia in HF if gout is present or urate is extremely high, but routine ULT for all hyperuricemic HF patients is not yet evidence-based. Xanthine oxidase inhibitors were hypothesized to improve endothelial function in HF – ongoing trials like EXACT-HF did not show improved exercise capacity or outcomes. Febuxostat/allopurinol can still be used safely in HF (febuxostat had no worse outcomes than allopurinol in HF subgroup in FAST).
- **Chronic Kidney Disease:** Already discussed in detail; special case where asymptomatic hyperuricemia treatment is debated. KDIGO suggests not treating solely to slow CKD (Grade 2D), though some nephrologists will treat if urate is very high or progressive CKD without other explanation. Certainly, treat if gout or urate stones occur in CKD patients (even more important to prevent further kidney insult from crystal deposition).

28. Alignment with current guidelines

This consensus draws upon and aims to harmonize recommendations from various European and international guidelines:

- **ESC Perspectives:** The ESC (and European Society of Hypertension, ESH) in 2018 recognized hyperuricemia as a cardiovascular risk factor to consider in hypertension management. The new 2023 ESH Hypertension Guidelines continue to list high uric acid as a factor that can modulate risk stratification.
- **KDIGO 2023 CKD Guideline:** KDIGO recommends treating hyperuricemia in CKD only if symptomatic. They advise against ULT purely to slow kidney disease (as trials have not shown benefit). Our consensus respects this, highlighting lifestyle and risk factor control as primary in CKD patients with asymptomatic hyperuricemia, and considering ULT on a case-by-case basis for high CV risk or extremely high urate. If ULT is used in CKD, KDIGO suggests allopurinol or febuxostat can be used with appropriate dose adjustments.
- **European Society of Cardiology (ESC) Heart Failure Guideline 2021:** It mentions that elevated uric acid is common in HF and is associated with worse outcomes, but it stops short of recommending urate-lowering therapy for HF patients without gout, given lack of proven benefit. It cites the neutral results of allopurinol trials in HF. Thus, our consensus does not contradict ESC HF guidelines – we do not advocate ULT solely for HF outcome improvement, focusing rather on gout management in HF or using urate as a prognostic marker.

In conclusion, our consensus is in concordance with mentioned documents highligts hyperuricemia's role in CV risk.

29. Clinical recommendations (2025)

Based on the reviewed evidence and consensus deliberation, the following key recommendations are proposed for the diagnosis and management of hyperuricemia as a cardiovascular and renal risk factor in clinical practice:

1. **Routine Uric Acid Assessment in At-Risk Patients:** Measure serum uric acid as part of cardiovascular risk assessment in patients with hypertension, chronic kidney disease, heart failure, or established atherosclerotic disease. Recognizing hyperuricemia can improve risk stratification and guide holistic risk factor management.
2. **Definition of Hyperuricemia:** Define hyperuricemia traditionally as sUA >7 mg/dL (420 μmol/L) in men or >6 mg/dL (360 μmol/L)in women. However, acknowledge that adverse

outcomes may occur at lower urate levels (≈5 mg/dL; (300 μmol/L)), especially in high cardiovascular risk patients. Consider 5.0 mg/dL (300 μmol/L)as a desirable target range for such patients (see Recommendation 6).

3. **Lifestyle-First Approach:** In all patients with hyperuricemia, initiate comprehensive lifestyle modifications: dietary purine/fructose restriction, weight loss, alcohol moderation, and increased hydration as first-line therapy. Lifestyle changes can significantly reduce sUA and confer broad cardiometabolic benefits.
4. **Manage Reversible Causes:** Identify and address secondary contributors to hyperuricemia. Avoid or substitute medications that raise urate (e.g. thiazide/loop diuretics, cyclosporine) when feasible. Optimize blood pressure, glycemic control, and weight, which indirectly help urate control.
5. **Indications for Pharmacotherapy:** Initiate urate-lowering medication in the following scenario. Asymptomatic hyperuricemia in patients with high cardiovascular risk or organ damage (e.g. concomitant coronary artery disease, stroke, heart failure, or CKD ≥ stage 3), particularly if sUA exceeds ~5.5–6 mg/dL. These patients may be considered for ULT to achieve a prophylactic sUA <5–6 mg/dL (300-360 μmol/L), after weighing risks and benefits on an individual basis (expert consensus).
6. **Urate Target Levels:** Employ a treat-to-target strategy for urate lowering:
   - Target **<6 mg/dL (360 μmol/L)** for most patients requiring ULT.
   - Target **≤5 mg/dL (300 μmol/L)** for patients high CV risk and organ damage. This lower target is associated with possibly greater CV risk reduction, although not yet proven in trials
   - In frail elderly patients, avoid urate <3 mg/dL; extremely low levels are unnecessary and possibly associated with other risks.
7. **Pharmacologic Therapy – First Line Xanthine Oxidase Inhibition:** Start **Allopurinol** as first-line ULT in indication-positive patients (initial dose 100 -200 mg daily, titrated to max 900 mg as needed). Titrate gradually (every 2–4 weeks) to reach target sUA, with dose adjustments for CKD if needed (but pursue target sUA even in CKD by slow uptitration).
   - Perform **HLA-B*58:01 genetic testing** prior to starting allopurinol in patients of Southeast Asian or African ancestry with CKD or those with personal/family history suggestive of prior severe cutaneous reactions.– If positive, avoid allopurinol (risk of AHS).
   - Use **Febuxostat** as an alternative first-line agent if allopurinol is contraindicated or not tolerated (40 mg up-titrated to 80 mg daily). Be cautious in patients with severe cardiovascular disease; monitor for any signs of cardiac events, although recent evidence (FAST trial) supports CV safety comparable to allopurinol.
8. **Monitoring and Follow-up:** Once ULT is initiated, monitor sUA every 2–5 weeks during titration and every 6 months once stable. Adjust doses to maintain target sUA persistently. Monitor renal function and liver enzymes periodically (especially with febuxostat). Educate patients that ULT is a long-term therapy; do **not discontinue** ULT when sUA reaches target, as continuous therapy is required to sustain urate control and prevent relapse.
9. **Combination Therapy for Refractory Cases:** If target sUA is not achieved on optimized XOI monotherapy, consider adding a uricosuric agent. Options include Benzbromarone (50–200 mg daily) or Probenecid (500 mg BID, up to 1.5–2 g) in patients without contraindications. Ensure adequate hydration and prophylaxis against uric acid stones (alkalinize urine if high urinary urate). Combination XOI + uricosuric therapy is effective and indicated in resistant hyperuricemia except in severe CKD (avoid uricosurics if eGFR <30). Lesinurad, if available, can be combined with an XOI at 200 mg/day (not to be used alone) – note that its availability is limited as of 2025.
10. **Special Situations:**
    - In **tumor lysis syndrome** or very acute urate load scenarios, use Rasburicase IV as per oncology protocols
    - **Pediatric hyperuricemia:** Focus on lifestyle; avoid pharmacotherapy unless there is an on-target cause (e.g. chemotherapy-induced, inborn error). Any ULT use in children should be under specialist guidance.
    - **Geriatric patients:** Use ULT judiciously. Treat hiperuricemia in the elderly the same as in younger (allopurinol still first-line), but start low and go slow.
    - **During cardiovascular hospitalization:** If a patient is hospitalized for MI or stroke and found to have high urate, address it after acute phase. Do not initiate ULT in the immediate post-MI period (no evidence of short-term benefit, focus on proven therapies first). Rather, ensure follow-up for hyperuricemia outpatient. One exception: in acute HF with very high urate and diuretic use, starting low-dose allopurinol in hospital might help tolerability of diuretics, but this is optional.
11. **Patient Education and Multidisciplinary Care:** Educate patients about hyperuricemia's implications –explain its link to kidney and heart health in simple terms to encourage adherence (e.g. "uric acid is like cholesterol – too much can cause long-term harm even if you don't feel it now"). (Good practice point) Engage dietitians, pharmacists, and where appropriate, rheumatologists or nephrologists for co-management. Improving patient understanding has been shown to enhance therapy adherence in gout.
12. **Research and Future Directions:** Recognize that treatment of asymptomatic hyperuricemia for CV/renal protection remains an area of active research. Clinicians should stay updated on emerging evidence (e.g. results of RCTs on ULT in CKD progression or CV outcomes). We recommend enrollment of eligible patients into clinical trials examining whether aggressive urate lowering can reduce cardiovascular events or CKD progression. (Good practice point)

By following these recommendations, clinicians can ensure a comprehensive approach to hyperuricemia that addresses both the classical concerns (gout) and the broader implications for cardiovascular and renal health. Individualization of therapy is crucial – consider urate as one piece of the complex risk puzzle and manage it alongside other risk factors for maximal patient benefit.

Declaration of competing interest

No conflicts to disclose.

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