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# Cardiological and rheumatological expert statement on the management of asymptomatic hyperuricemia in patients at high cardiovascular risk

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## DEFINITION AND EPIDEMIOLOGY OF HYPERURICEMIA — A GLOBAL HEALTH HAZARD

Uric acid (UA) is the end product of the metabolism of purines (both endogenous and exogenous). In most animals, UA is further broken down into allantoin, urea or ammonia, and excreted from the body. The enzyme that plays a crucial role in these reactions is uricase (UO, urate oxidase). UO is not present in humans, great apes and Dalmatian dogs because the gene coding UO has lost its function as a result of mutations [1]. In physiological conditions, UA synthesis and excretion are balanced out, and its concentration in the blood is affected by the number of dietary purines in food, biosynthesis of endogenous purines and renal uric acid clearance [2]. When such equilibrium is disturbed, hyperuricemia (HU) will develop. The definition of HU has not yet been precisely formulated and varies from study to study. However, most publications describe HU as serum uric acid (sUA) concentration > 7 mg/dl (420 μmol/l) in men and > 6 mg/dl (360 μmol/l) in women.

The prevalence of HU depends on gender, age and race, and is the highest in persons aged 80 or over (up to 10% in men and 6% in women) [3]. Unlike the US and Western European countries, the incidence rate of HU in developing countries does not exceed 1% of the total population. These values, however, may be understated due to insufficient epidemiological data, e.g. a very high share of HU patients (41%) in the small population of Taiwan [4]. The epidemiological data point to a steady rise in HU and gout in recent decades. Its underlying causes include rapid economic development, changes in lifestyles and eating habits [5, 6]. Furthermore, sUA level is higher in high cardiovascular (CV) risk patients, postmenopausal women (positive impact of oestrogens on renal urate excretion), dark-skinned individuals, and patients with hypertension and chronic kidney disease (CKD) [7]. NHANES (National Health and Nutrition Examination Survey), the nationally representative survey of American men and women from 2007 to 2016, found that the HU prevalence rate in persons aged ≥ 20 was 20.2% for men (22.8 million)

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and 20% for women (24.4 million). Put simply, it meant that 1 in 5 men and 1 in 5 women had elevated sUA levels. Uric acid concentration > 6 mg/dl was found in 32.3% of the total population (75.8 million), of whom 49.5% were men (55.8 million) and 16.4% were women (20.0 million) [8]. The recently published data from the Irish healthcare system indicate that in the period between 2006 and 2014 the prevalence of HU increased from 19.7% to 25.0% in men and from 20.5% to 24.1% in women ( $p < 0.001$ ). What is more, the incidence of age-dependent HU was on the rise in all the groups, with similar rates of increase for each age group. Uric acid levels also increased as the kidney function deteriorated, from 12.2% in patients with estimated glomerular filtration rate (eGFR) > 90 ml/min, to 63.9% patients with eGFR < 15 ml/min [9].

### HYPERURICEMIA AND GOUT — THE CAUSE-AND-EFFECT RELATIONSHIP

Gout is a chronic form of arthritis that is caused by the deposition of monosodium urate (MSU) crystals in or around the joints during long-term hyperuricemia [3]. At the temperature of 37°C and pH = 7, MSU crystallization *in vitro* takes place at sUA ≥ 6.8 mg/dl, and at 35°C — at sUA > 6.0 mg/dl. This process can also begin at a lower sUA level in a more acidic environment or at a lower temperature prevailing in poorly vascularized or peripherally located structures: tendons, ligaments, auricles, foot joints, knees, shoulders, elbows, and finger joints. Urate depositions begin to dissolve at sUA < 5 mg/dl [10].

The linear relationship between sUA level and the risk of gout has been demonstrated in many published studies and large-sample registry trials. It is estimated that in Western European countries gout occurs in 3–6% of men and 1–2% of women [11]. Even though HU is a necessary precondition for crystal deposition, only some HU patients develop gout; it is rarely found in people with low sUA levels [12, 13]. Four stages can be identified in the development of gout: 1) HU without symptoms of MSU crystal accumulation and gout symptoms; 2) MSU crystal deposition without gout symptoms; 3) MSU crystal deposition with gout attacks; 4) advanced gout with tophi, chronic arthritis and irreversible joint changes. If no adequate treatment is initiated, gout will progress to the advanced stage on average 10 years after the first attack.

Gout attacks typically involve distal leg joints (e.g. first metatarsophalangeal joint). In the absence of proper treatment, gout attacks will come more and more frequently and affect more and more joints.

High sUA levels are mostly caused by excretion disorders (90%) or overproduction (10%) of uric acid. Therefore, the goal of therapy is to dissolve and prevent further deposition of MSU crystals. The significance of the relationship between HU, CKD and CVD (cardiovascular diseases) has also been long emphasized.

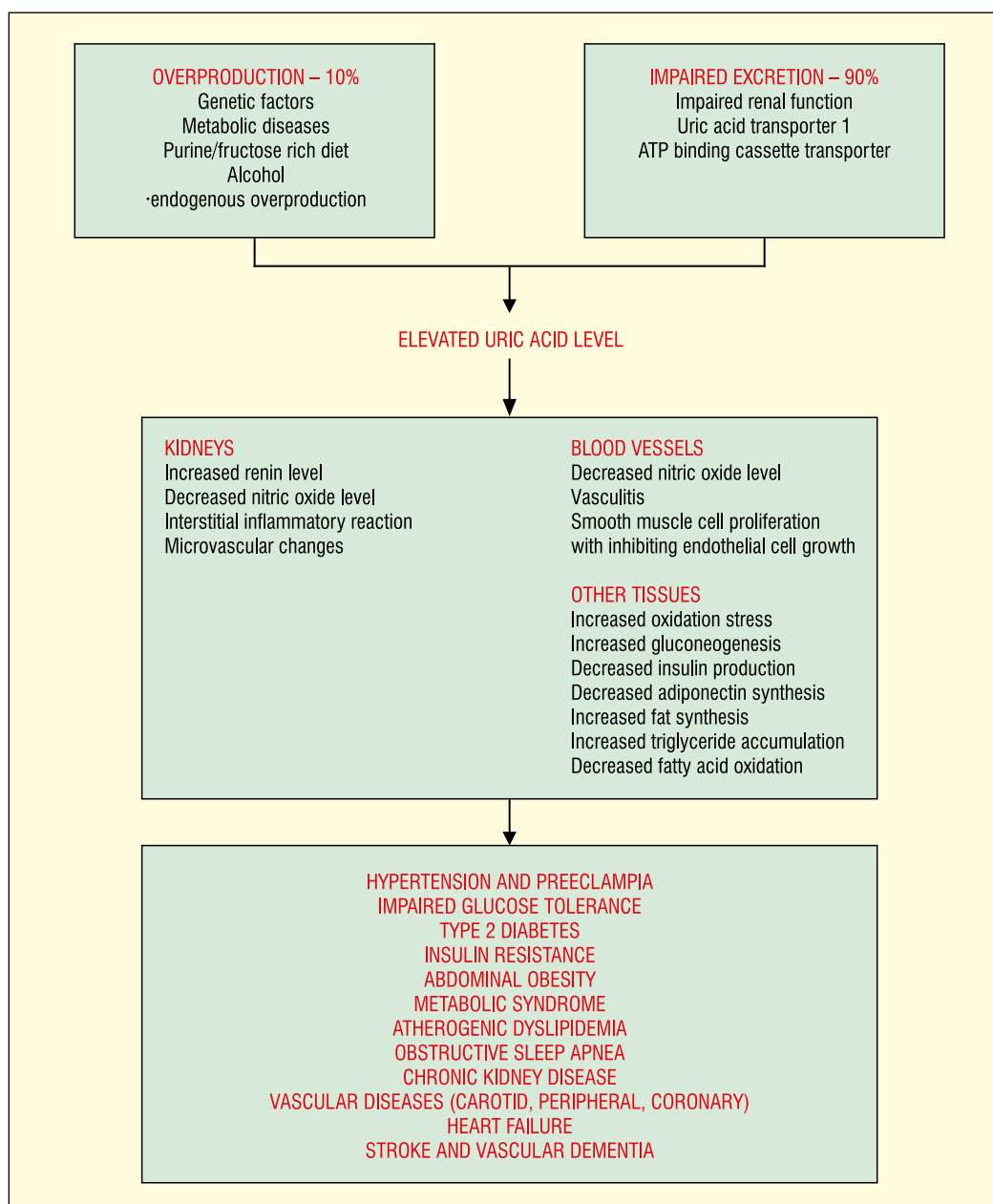
### ADVERSE EFFECTS OF HYPERURICEMIA ON THE CARDIOVASCULAR AND RENAL SYSTEMS — PATHOPHYSIOLOGICAL ASPECTS

Elevated sUA levels are caused by a diet rich in purines/fructose (high consumption of red meat, giblets, seafood, sweetened beverages, desserts with glucose-fructose syrup, beer), genetic and environmental factors, metabolic disorders, as well as endogenous overproduction or, in most cases, impaired uric acid excretion. It is also very important to know what drugs can affect uric acid levels in the serum (Table 1).

Xanthine oxidase (XO), an enzyme that plays a crucial role in the metabolism of purines, and catalyses the conversion of hypoxanthine to xanthine and xanthine to uric acid, uses molecular oxygen as an electron recipient to produce superoxide anions and other active forms of oxygen as by-products; this can impair the endothelial function (e.g. reduce endothe-

**Table 1.** Impact of selected drugs on serum uric acid levels

Acetylsalicylic acid	↑ (small doses), ↓ (large doses)
Clopidogrel	↔
Ticagrelor	↑
Beta-adrenolytics (regardless of cardioselectivity)	↑
Thiazide, thiazide-like, loop diuretics	↑
Calcium antagonists	↔
Aldosterone antagonists	↔
Alfa-adrenolytics	↔
ACE inhibitors/sartans	↔ or ↓
Fibrates	↓
Atorvastatin	↓
Rosuvastatin	↓
SGLT2 inhibitors (flozins)	↓



**Figure 1.** Pathophysiological aspects of hyperuricemia and its effect on cardiovascular and renal diseases

lial production of nitric oxide [NO]) and in effect can lead to the development of hypertension and end-organ complications.

Oxidation stress caused by increased XO activity has a strong negative effect on vascular endothelium, also in the coronary arteries [14, 15]. Elevated sUA levels impair oxygen metabolism, stimulate the renin-angiotensin-aldosterone system and inhibit endothelial NO secretion. This can lead to microvascular complications in the afferent arterioles, renal vasospasm and persistent, salt-sensitive hypertension [16, 17]. Long-term renal vasospasm may induce increased vascular stiffness and stimu-

late the development of primary hypertension. Apart from hypertension, elevated UA levels stimulate the proliferation of vascular smooth muscle cells (VSMC) by affecting endothelial cells, thus leading to renal microangiopathy, microalbuminuria, and renal dysfunctions [18–23]. The findings from preclinical trials also suggest that endothelial dysfunctions, inflammatory response and oxidation stress in fat cells play a key role in the development of obesity and metabolic syndrome [24]. The pathophysiological aspects of hyperuricemia and its impact on cardiovascular and renal diseases are shown in Figure 1.

**Table 2.** Hyperuricemia-related conditions that require more frequent monitoring of patients and appropriate therapeutic interventions

Hypertension
Overweight, obesity
Dyslipidaemia
Metabolic syndrome
Type 2 diabetes
Atherosclerosis
Chronic renal disease
Hyperthyroidism/hypothyroidism
Excessive consumption of alcohol (especially beer)
Purine-rich diet
Psoriasis
Using drugs increasing uric acid levels
Male gender
Postmenopausal women
Advanced age
Genetic predisposition
Oncological diseases

## **HYPERURICEMIA AND CARDIOVASCULAR AND RENAL RISKS**

Hyperuricemia is regarded as an independent risk factor in the development of many micro- and macrovascular disorders, including hypertension [25], metabolic syndrome [26, 27], chronic coronary syndrome (CCS) [28], diabetes [29], cerebrovascular disease [30, 31], CKD [32] or other CVDs [33, 34]. In parallel, the presence of any of these diseases increases HU prevalence [35].

HU or gout patients require systematic screening for diseases which are potentially linked to high sUA levels. There is ample evidence demonstrating that the presence of HU worsens the prognosis of CVD, diabetes, dyslipidaemia and renal disease, which corroborates the role of elevated sUA levels as a new CV risk factor [36–40]. For this reason, appropriate monitoring and potential HU therapy should form an integral part of the management strategy in the aforementioned conditions (Table 2) [35, 41–43].

## **HYPERURICEMIA AND HYPERTENSION RISK**

There is extensive evidence suggesting that the relationship between an increase in the relative risk of hypertension and high sUA levels is independent of traditional risk factors [44–52]. A large meta-analysis comprising 18 clinical trials showed an increase in the incidence rate of newly diagnosed hypertension cases by 13% per every 1% of sUA increase [46]. In turn, the PAMELA (Pressio-

ni Arteriose Monitorate e Loro Associazioni) study found that an increase in sUA level by 1 mg/dl was associated with a significantly increased risk of developing hypertension based on home or outpatient measurements (OR [odds ratio]: 1.34; 95% CI [confidence interval]: 1.06–1.7;  $p = 0.015$ ; OR: 1.29; 95% CI: 1.05–1.57;  $p = 0.014$ , respectively) [47].

## **HYPERURICEMIA AND THE HEART ATTACK AND STROKE RISK**

In the Rotterdam Study involving 4385 subjects, high sUA levels in patients without a history of myocardial infarction (MI) or stroke were associated with a remote MI and stroke risk; the risk coefficients adjusted for age and gender (95% CI) for the highest and the lowest quintile of sUA concentration were as follows: 1.68 (1.24–2.27) for CVD; 1.87 (1.12–3.13) for MI; 1.57 (1.11–2.22) for stroke; 1.77 (1.10–2.83) for ischaemic stroke, and 1.68 (0.68–4.15) for haemorrhagic stroke [53]. Another research study suggested that there is an independent relationship between HU (defined as sUA > 6.0 mg/dl in women and > 7.0 mg/dl in men) and a remote major adverse cardiovascular event (MACE), including death caused by CV, MI and stroke, in patients with acute coronary syndrome undergoing percutaneous coronary intervention. HU patients were characterized by 1.6 times higher risk of death from cardiovascular causes ( $p = 0.005$ ) and by a 1.5 times higher risk of MI ( $p = 0.032$ ) [54]. A large Swedish registry study involving 417,734 patients undergoing regular checkups suggested that moderate sUA levels were linked to increased incidence of MI, strokes and congestive heart failure (HF) in middle-aged individuals with no history of CVD [55]. Ultimately, sUA showed a positive correlation with the presence, number, size and location of lacunar infarcts (LI) in the basal ganglia, deep white matter (DWM) and pons, morphologically characterized by atherosclerosis. Interestingly, LI incidence has been rising from sUA as low as 5.7 mg/dl. The authors suggest that the presence of HU can considerably increase the risk of stroke and poses an independent risk factor for its occurrence [56]. The meta-analysis by Kim et al. also found an association between HU and much higher risk for both types of strokes (relative risk [RR]: 1.41), and mortality (RR: 1.36) [57]. Zhong et al. also confirmed that elevated sUA levels showed a significant correlation with an

increased risk of stroke both in men and women (respectively: RR: 1.10 and RR: 1.11 per 1 mg/dl of elevated sUA level) [58]. Interestingly, in the most recent CIRCUS (Circulatory Risk in Communities Study) elevated sUA was an independent stroke predictor, but only in women [59].

### **HYPERURICEMIA AND RISK OF ATRIAL FIBRILLATION**

In a large prospective cohort study (n = 123,238) conducted in 2006–2012, elevated sUA level was associated with increased risk of atrial fibrillation (AF) (adjusted HR [hazard ratio]: 1.91; 95% CI: 1.32–2.76; p = 0.001). This correlation was even higher in persons with a high hs-CRP (high-sensitivity C-reactive protein) level (adjusted HR: 2.63; 95% CI: 1.63–4.23) [60]. Hong et al. also corroborated the correlation between sUA concentration and AF risk (p = 0.001) [61].

### **HYPERURICEMIA AND RISK OF CHRONIC KIDNEY DISEASE**

The initial observations concerning the potential causal role of sUA in CKD were corroborated in large clinical trials, including NHANES and GKCD (German Chronic Kidney Disease) [62, 63]. The results of the meta-analysis comprising 18 prospective studies (n = 431,000) confirmed that HU is a predictor of developing CKD and reducing GFR [64]. Moreover, HU plays a key role in the development and progression of CKD. It is also an independent factor for CKD progression even after adjustment for all typical comorbidities such as hypertension, proteinuria, and dyslipidaemia. This correlation has been confirmed in patients with IgA nephropathy, diabetic nephropathy, those after organ transplants and autosomal dominant polycystic kidney disease [65–68]. It is worth noting that a correlation between sUA and probable eGFR reduction was observed in persons with normal blood pressure and normal renal function. This effect could be observed at sUA level > 5.5 mg/dl in men and > 5.0 mg/dl in women [69].

### **HYPERURICEMIA AND TOTAL AND CARDIOVASCULAR MORTALITY — CAN THE CUT-OFF VALUE OF URIC ACID CONCENTRATION BE DETERMINED?**

The NHANES study demonstrated that there was an increased risk of total and car-

diovascular mortality in patients with elevated sUA levels. This correlation remained significant after its adjustment for several factors, including demographics and comorbidities [70]. The analysis of data from the PAMELA study suggests the cut-off value of sUA level at **5.4 mg/dl**, as it offers the best sensitivity to specificity ratio in predicting the risk of cardiovascular mortality, and at **4.9 mg/dl** for total mortality [47]. Based on the PreCIS (Preventive Cardiology Information System) data, it was demonstrated that each increase in sUA level by 1 mg/dl corresponds to a 39% increase in the risk of death. After data adjustment for most basic factors (e.g. age, gender, smoking, alcohol consumption, body mass, BMI, waist circumference, blood pressure, CVD burden, eGFR, cholesterol fraction values, glucose level), sUA level remained a significant death risk factor (HR: 1.26; 95% CI: 1.15–1.38; p < 0.001) [71]. In the prospective HPFS (Health Professionals Follow-Up Study), in a group of 51,297 men, higher total mortality risk was linked to the presence of gout. Interestingly, in men with no history of coronary artery disease, increased mortality risk was primarily associated with increased risk of death from cardiovascular causes. Moreover, men with diagnosed gout showed a higher risk of non-fatal MI (RR: 1.59; 95% CI: 1.04–2.41) [72].

The Working Group on Uric Acid and Cardiovascular Risk of the Italian Society of Hypertension designed URRAH (Uric Acid Right for Heart Health), a study in a group of 22,714 subjects aimed to determine the UA level above which the risk of death significantly increases. The predictive cut-off values for all-cause deaths were  $\geq 4.7$  mg/dl, and  $\geq 5.6$  mg/dl for cardiovascular deaths. In terms of the patients' gender, the sUA cut-off value for mortality from any cause was  $\geq 5.4$  mg/dl in men and  $\geq 4.7$  mg/dl in women [73, 74]. The findings from the URRAH study are largely consistent with other observations showing a significant increase in the relative risk of serious cardiovascular events at sUA levels in the 4.5 to 5.5 mg/dl range [75–78].

The URRAH researchers also identified the cut-off sUA values for predicting heart failure morbidity and mortality: sUA > 5.34 mg/dl (sensitivity 52.32%; specificity 63.96%; p < 0.0001) was a one-dimensional cut-off value for heart failure morbidity, and sUA concentration > 4.89 mg/dl (sensitivity 68.29%; specificity 49.11%; p < 0.0001) was

a predictive cut-off value for heart failure mortality [79]. Furthermore, Huang et al. analysed 10 studies involving 12,854 patients suffering from acute heart failure and found (after adjusting for potential variables) that patients with the highest sUA levels showed an increased risk of all-cause death (RR: 1.43; 95% CI: 1.31–1.56) and combined end-point (death or re-hospitalization due to heart failure) (RR: 1.68; 95% CI: 1.33–2.13). Therefore, any increase in sUA by 1 mg/dl increases the risk of all-cause death, or death and re-hospitalization due to heart failure, by 11% and 12%, respectively [80].

### ALLOPURINOL — A SPECIAL PREPARATION AMONG DRUGS REDUCING URIC ACID CONCENTRATION, PARTICULARLY IN THE CONTEXT OF CARDIOVASCULAR RISK

In nearly all guidelines, xanthine oxidase inhibitors (XOI) are first-line drugs, and **allopurinol** is recommended as a **first-line drug** in urate-lowering therapy (ULT). Because comorbidities can increase HU incidence, therapy should also include their effective treatment. In addition to allopurinol, febuxostat is another XOI preparation currently available in Poland (Fig. 2). Both these drugs belong to the same therapeutic group, but differ e.g. in the clinical experiences regarding their use (allopurinol was synthesized in 1956, febuxostat in 1998).

The two drugs also differ in the way they affect the cardiovascular system. Since the very beginning of its global sale, objections were raised concerning febuxostat and its cardiovascular safety. In 2017, the US FDA (Food and Drug Administration) issued a special alert, quoting the research results indicating an increased risk of CV events with febuxostat compared to allopurinol [81]. The manufacturer was obliged to continue follow-up studies and conduct safety studies in that regard, even though he had been required to collect such data since 2009 when the drug was first registered internationally. It was because initial clinical studies already pointed to a higher risk of CV events in patients treated with febuxostat vs. those treated with allopurinol (cumulative events including CV deaths, heart attacks and strokes). The additional study commissioned by the FDA did not find a higher risk of such events in the febuxostat group; however, additional analyses re-

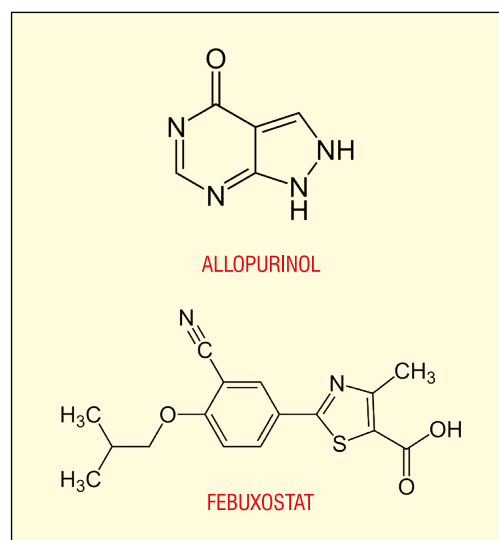


Figure 2. Structural formulae of allopurinol and febuxostat

vealed a somewhat higher risk of CV deaths and total mortality in the febuxostat group vs. the allopurinol group [81].

On the one hand, the most recent comparative meta-analyses of allopurinol and febuxostat do not corroborate such data [82–84]. On the other, however, single meta-analyses still report results showing a marginally higher risk of CV events when using febuxostat, with no such risk being observed with allopurinol. One of such meta-analyses reported a nearly 10% increase in cardiovascular risk for febuxostat, which — although statistically insignificant — was in contrast with a definite, 39% lower CV risk when using allopurinol [85].

Therefore, it should not be surprising that cardiologists in the most recent 2021 guidelines note the advantages of allopurinol over febuxostat. For instance, the current ESC (European Society of Cardiology) guidelines concerning the diagnosis and treatment of acute and chronic heart failure emphasize that an increase in sUA level by every 1 mg/dl in HU patients is associated with an increase in total mortality by 4%, and risk of HF hospitalization by 28% [86]. These are the first guidelines which so strongly emphasize the role of allopurinol and suggest that both allopurinol and febuxostat reduce sUA levels, but only allopurinol reduces total and CV mortality, as demonstrated in the prospective, multicentre, randomized double-blind trial of 6190 patients with the median follow-up time of 32 months [87]. For this reason, allopurinol — and not febuxostat — is the first-line

**Table 3.** Comparison of the indications and pharmacological properties of allopurinol and febuxostat

Parameter	Allopurinol	Febuxostat
Therapeutic indication	<p><b>Treatment of all forms of HU not controllable by diet, including secondary HU of differing origin and in clinical complications of HU states, particularly manifest gout, urate nephropathy (e.g. during neoplasia treatment), and for the dissolution and prevention of uric acid stones</b></p> <p>Management of recurrent mixed calcium oxalate stones in concurrent HU, when fluid, dietary and similar measures have failed</p> <p>Neoplastic diseases and myeloproliferative syndromes with rapid cell turnover, in which elevated urate levels occur spontaneously or are induced by cytotoxic therapy</p> <p>Enzyme deficiency disorders leading to urate overproduction, e.g. of hypoxanthine-guanine phosphoribosyltransferase (e.g. Lesch-Nyhan syndrome), glucose-6-phosphatase (e.g. glycogen storage disease), phosphoribosyl pyrophosphate synthetase, phosphoribosyl pyrophosphate amidotransferase, adenine phosphoribosyltransferase</p>	<p><b>Treatment of chronic HU in conditions where urate deposition has already occurred</b> (including a history, or presence of, tophus and/or gouty arthritis)</p>
Mechanism of action	Xanthine oxidase inhibitor	Xanthine oxidase inhibitor
Experience with the drug estimated by the number of scientific papers indexed by the drug name in the MEDLINE database (as of 10.03.2022)	10 953	1138
Cardiological safety according to SmPC approved in Poland	<p>No special notes; in patients with hypertension or heart failure, using e.g. diuretics or ACE inhibitors, according to the SmPC: an increased risk of hypersensitivity has been reported when allopurinol is given with ACE inhibitors, especially in the event of reduced kidney function. Concomitant use of allopurinol and captopril may increase the risk of skin reactions, especially in the event of chronic kidney failure</p> <p>Concomitant use of allopurinol and diuretics, especially thiazides, may increase the risk of hypersensitivity reaction, especially in the event of impaired renal function.</p> <p>Therefore, allopurinol should be used with caution in that group of patients</p>	<p>According to the SmPC: special warnings and precautions for use: „(...) treatment with febuxostat is not recommended in patients with myocardial ischaemia or congestive heart failure; a numerical greater incidence of CV events including CV death, non-fatal myocardial infarction, non-fatal stroke was observed in the febuxostat group compared to the allopurinol group in APEX and FACT studies, but not in the CONFIRMS study (...).</p> <p>In the long-term extension studies the incidences of investigator-reported CV events were 1.2 and 0.6 events per 100 patient-years for febuxostat and allopurinol, respectively (...)*”</p>

\*Source: [http://leki.urpl.gov.pl/files/30\\_Adenuric\\_80.pdf](http://leki.urpl.gov.pl/files/30_Adenuric_80.pdf). HU — hyperuricemia; SmPC — Summary of Product Characteristics; ACE — angiotensin-converting enzyme); CV — cardiovascular

drug in HU patients with comorbid HF. It is also worth noting that **allopurinol is found on the WHO (World Health Organization) Essential Medicines List of safest and most efficacious medicines needed for the healthcare system** [88]. Table 3 offers a comparison of the indications and pharmacological properties of both drugs.

### **ALLOPURINOL TREATMENT IN HYPERURICEMIA AND ITS EFFECT ON THE CARDIOVASCULAR SYSTEM**

The extremely favourable effect of allopurinol on the CV system, demonstrated in many clinical trials, is caused probably not only by the drug's strong potential for sUA

reduction but also by its considerable antioxidant activity due to its capacity to inhibit the production of reactive oxygen species [89, 90]. More and more evidence points to the key role of xanthine oxidase inhibition in various ischemic forms and other types of tissue and vascular damage, inflammatory processes or chronic HF [91].

The cohort study which analysed the data from 7135 patients aged  $\geq 60$  found that the frequency of CV events was 74.0 (95% CI: 61.9–66.1)/1000 person-years in the group taking 100 mg allopurinol; 69.7 (95% CI: 49.6–89.8) in the group taking 200 mg allopurinol, and 47.6 (95% CI: 38.4–56.9) in the group taking  $\geq 300$  mg allopurinol [92]. What is more, using large doses of allopurinol ( $\geq 300$  mg/day) was associated with a reduced risk of all-cause death (adjusted HR: 0.65; 95% CI: 0.42–0.99) [93, 94].

The favourable effect of allopurinol treatment on reducing mortality was corroborated in the study conducted in a population of HU patients (sUA  $> 7.0$  mg/dl [ $> 416 \mu\text{mol/l}$ ]). The study included patients aged  $\geq 40$  and compared the total death risk of patients treated with allopurinol ( $n = 2483$ ) with patients who did not use it ( $n = 7441$ ). The patients who initiated allopurinol therapy were originally more burdened with factors predictive of death, BMI and higher incidence of comorbidities. After taking the baseline sUA level into account, it was found that allopurinol treatment was linked to lower total mortality by 22% (HR: 0.78; 95% CI: 0.67–0.91) [95].

Another study analysed patients aged  $\geq 40$  with diagnosed HU (sUA  $> 6.0$  mg/dl [ $> 357 \mu\text{mol/l}$ ] in women and  $> 7.0$  mg/dl [ $> 416 \mu\text{mol/l}$ ] in men). Of 5927 patients treated with allopurinol and 5927 patients who did not use it, 654 and 718 patients, respectively, died during the follow-up period (average/median 2.9 years). This meant that treatment with allopurinol was associated with an 11% lower total mortality risk (HR: 0.89; 95% CI: 0.80–0.99) [96]. The results of these studies indirectly suggest that allopurinol therapy can improve the survival rate of HU patients.

A significant role of 6-week allopurinol treatment (600 mg/day) vs. placebo was found in a small randomized controlled trial of 65 patients aged 18–85, with angiographically documented coronary artery disease, positive exercise test, and stable angina for at least 2 months. The study found that allopurinol vs. placebo increased the time median until the ST section was reduced to 298 s ([IQR, inte-

rquartile range] 211–408) vs. 249 s (IQR: 200–375;  $p = 0.0002$ ) [97]. Similarly, the results of another, small, randomized double-blind placebo-controlled study ( $n = 65$ ) conducted in patients with coronary artery disease and left ventricular (LV) hypertrophy showed considerable reduction in the LV mass and LV systolic volume in patients receiving 600 mg allopurinol compared to placebo (respectively:  $-5.2 \pm 5.8$  g vs.  $-1.3 \pm 4.48$  g;  $p = 0.007$ , and  $-2.81 \pm 7.8$  ml vs.  $+1.3 \pm 7.22$  ml;  $p = 0.047$ ) [98]. In a systematic review and meta-analysis of 40 studies, Higgins et al. confirmed that XOI improves the endothelial function and reduces the concentration of oxidative stress markers [99]. The paper also discusses the dosage-dependent correlation between allopurinol and endothelial function and illustrates the influence of vascular oxidative stress [100].

Many studies evaluated the influence of XOI on blood pressure. According to the UK Clinical Practice Research Datalink data, the use of allopurinol is independently associated with reducing both systolic (SBP) and diastolic (DBP) blood pressure [101].

Allopurinol treatment ( $2 \times 200$  mg/day for 6 weeks) vs. placebo led to an average change in SBP ( $-6.9$  mm Hg; 95% CI: from  $-4.5$  to  $-9.3$  mm Hg vs.  $-2.0$  mm Hg; 95% CI: from  $0.3$  to  $-4.3$  mm Hg;  $p = 0.009$ ) and DBP ( $-5.1$  mm Hg; 95% CI: from  $-2.5$  to  $-7.8$  mm Hg vs.  $-2.4$  mm Hg; 95% CI: from  $0.2$  to  $-4.1$  mm Hg;  $p = 0.05$ ) values [102].

Further evidence suggesting a favourable effect of allopurinol on reducing blood pressure was offered by Agarwala et al. The meta-analysis of 10 clinical trials (738 subjects) found that SBP in the allopurinol group vs. the control group (not taking allopurinol) decreased by 3.3 mm Hg (95% CI: 1.4–5.3 mm Hg;  $p = 0.001$ ), and DBP by 1.3 mm Hg (95% CI: 0.1–2.5 mm Hg;  $p = 0.03$ ) [103]. This demonstrates that the use of allopurinol is associated with small but significant blood pressure reduction. Such effect may be used in optimizing the therapy of patients with hypertension and comorbid HU. Similar conclusions were formulated in the meta-analysis of a team from China, which showed that allopurinol can reduce SBP and DBP in HU patients [104].

It is not clear whether sUA concentration is the causal factor for increased blood pressure and impaired vascular compliance. However, there should be mentioned a study in which allopurinol administered to patients



with hypertension improved aortic compliance regardless of the antihypertensive drugs being used [105]. Such observation is consistent with the fact that in one study xanthine oxidase inhibition with allopurinol significantly decreased arterial reflection assessed by the augmentation index (arterial stiffness index) in people who had a prior stroke [106].

A study published in “Hypertension” in 2016 found that taking allopurinol by patients aged  $\geq 65$  in the follow-up period up to 10-years was associated with reducing blood pressure and lowering the risk for stroke (HR: 0.50; 95% CI: 0.32–0.80) and serious heart events (HR: 0.61; 95% CI: 0.43–0.87). Treatment with high doses, i.e.  $\geq 300$  mg/day, was associated with lower risk for stroke (HR: 0.58; 95% CI: 0.36–0.94) and serious heart events (HR: 0.65; 95% CI: 0.46–0.93) [107]. The data from the cited studies point to a potentially significant role of allopurinol in patients with hypertension and asymptotic HU, particularly in those from the high CV risk group.

Several studies also tested the hypothesis of the potential favourable impact of xanthine oxidase inhibition on HF progression. In a large follow-up study (n = 25,090) conducted for patients with HF and gout, Thanassoulis et al. showed that over 30 days of allopurinol therapy was associated with a reduced number of HF re-hospitalizations or deaths (adjusted RR: 0.69; 95% CI: 0.60–0.79;  $p < 0.001$ ) and decreased total mortality (adjusted RR: 0.74; 95% CI: 0.61–0.90;  $p < 0.001$ ) [108]. In contrast, the OPT-CHF (Oxypurinol Therapy for Congestive Heart Failure) study did not observe any clinical improvement in an unselected group of patients (n = 405) with moderate to acute HF (NYHA [New York Heart Association] Class III/IV) due to systolic dysfunction [109]. Similarly, the EXACT-HF studies (n = 253) involving patients with symptomatic HF, left ventricular ejection fraction (LVEF)  $\leq 40\%$ , taking allopurinol (600 mg/day) for 24 weeks, showed no improvement regarding LVEF and no significant improvement between allopurinol and placebo patients (deterioration: 45% vs. 46%; no change: 42% vs. 34%; improvement: 13% vs. 19%;  $p = 0,68$ ) [110]. Nonetheless, the post-hoc analysis of the OPT-CHF is quite interesting as it suggests that reduced sUA following the use of oxipurinol was correlated with favourable clinical response, and that sUA could serve as a biomarker for targeted inhibition of xanthine oxidase in congestive HF [111–114].

The favourable effect of XO1 therapy on kidney function is also worth noting [115]. A complex 2015 meta-analysis of 19 randomized trials demonstrated statistically significant improvement of eGFR and serum creatinine levels during the treatment for hyperuricemia, specifically pointing to an allopurinol-based strategy [116]. Goicoechea et al. documented slower progression of chronic kidney disease and reduction in proteinuria incidence among patients randomly assigned to the XO1 group vs. the placebo group [117]. Another meta-analysis confirmed that sUA lowering therapy reduces the risk of kidney failure and end-stage renal disease (ESRD) by 55% (RR: 0.45; 95% CI:  $0.31 \pm 0.64$ ) and 41% (RR: 0.59; 95% CI:  $0.37 \pm 0.96$ ), respectively, compared to standard treatment or placebo [118]. The meta-analysis of 12 studies conducted by Sampson et al. (n = 1187) showed improved renal function, assessed by the reduction of serum creatinine level, and increased eGFR during treatment for hyperuricemia conducted for a year in very different patient groups [119]. Another population cohort study (n = 111,992) investigating the relationship between HU and kidney disease in patients undergoing treatment for hyperuricemia with sUA  $< 6$  mg/dl found a 37% risk reduction of events defined as GFR decrease by at least 30% of ESRD [120].

## **HYPOURICEMIA MANAGEMENT PYRAMID — A MANAGEMENT STRATEGY FOR ASYMPTOMATIC HYPERURICEMIA (FIG. 3)**

### **LEVEL 1 — ASSESSING SERUM URIC ACID LEVEL AND DETERMINING ITS TARGET CONCENTRATION DEPENDING ON CARDIOVASCULAR RISK**

In a systematic review of 24 national and international guidelines published in 2003–2013, 14 documents provide comments on the ULT pharmacological option concerning asymptomatic hyperuricemia. Although most of them recommend no treatment, 3 documents suggest pharmacological therapy in patients with comorbidities or very high sUA levels (with cut-off values ranging from 8.0 mg/dl to 13.0 mg/dl). Nineteen documents also provide target levels for long-term sUA control; most of them recommend  **$< 6.0$  mg/dl** ( $< 357 \mu\text{mol/l}$ ), except the South African guidelines which recommend  $< 5.0$  mg/dl ( $< 297.5 \mu\text{mol/l}$ ) [121]. The current Polish Society of Hypertension (PTNT) guidelines from 2019 and the international expert consensus statement from



**Figure 3.** Hypouricemia management pyramid

\*SCORE  $\geq$  5%; documented cardiovascular disease; diabetes with end-organ complications (proteinuria, retinopathy, neuropathy); diabetes with at least 3 additional risk factors (age, hypertension, dyslipidaemia, smoking, obesity); diabetes lasting over  $\geq$  10 years without end-organ complications, but with an additional risk factor; type 1 diabetes with early-onset and long duration ( $>$  20 years); chronic kidney disease with eGFR  $<$  60 ml/min/1.73 m<sup>2</sup>; family hypercholesterolaemia; total cholesterol  $>$  310 mg/dl; LDL cholesterol  $>$  190 mg/dl; blood pressure  $\geq$  180/110 mm Hg; at least 2 risk factors: hypertension, diabetes, dyslipidaemia

\*\*unavailable in Poland

2021 emphasize the need to take into account CV risk in long-term sUA control and recommend a target sUA level of  $<$  5.0 mg/dl in patients with high CV risk [122, 123].

Similar recommendations can also be found in other guidelines: ACR (American College of Rheumatology) from 2012, and EULAR (European League Against Rheumatism) from 2016, which recommend sUA lowering therapy in patients with gout and set the target sUA value  $<$  6.0 mg/dl for all patients undergoing therapy, and in a more severe form  $<$  5.0 mg/dl (to enable faster dissolution of the crystals, especially with tophi, chronic arthropathy or frequent gout attacks) [124, 125].

It is worth noting here that the EULAR 2016 guidelines draw attention to the harmful influence of uric acid on the cardiovascular system, stating that:

— several studies confirm that **gout is a mortality risk factor, especially due to cardiovascular causes, and a risk factor for kidney failure;**

— delaying the initiation of sUA lowering therapy until the second or third attack **may be harmful to the cardiovascular system and kidneys;**

— recommendation to initiate sUA lowering therapy earlier is mainly based on experts' opinions, and also on the studies which indicate **cardiovascular and renal benefits of xanthine oxidase inhibitors (XOI)** [125].

The British Society for Rheumatology suggests a lower target sUA value of  $<$  5.0 mg/dl in patients with severe gout in order to facilitate faster dissolution of crystals [126].

Therefore, when analysing the existing clinical trial data, the target sUA level  $<$  5.0 mg/dl needs to be considered in patients with at least **high cardiovascular risk** (Fig. 3). The category includes the following clinical situations:

SCORE chart  $\geq$  5%;

— documented cardiovascular disease: acute coronary syndrome (myocardial infarction or unstable angina), chronic coronary syndrome, post-revascularization condition, stroke, transient ischaemic attack, periph-

- eral arterial disease, presence of significant atherosclerotic plaques confirmed by coronary angiography or CT scan (multivessel coronary artery disease > 50% stenosis of two major epicardial coronary arteries) or ultrasound of the carotid arteries;
- diabetes with end-organ complications (proteinuria, retinopathy, neuropathy);
  - diabetes with at least 3 additional risk factors (age, hypertension, dyslipidaemia, smoking, obesity);
  - diabetes lasting  $\geq 10$  years without end-organ complications, but with an additional risk factor;
  - type 1 diabetes with early-onset and long duration (> 20 years);
  - chronic kidney disease with eGFR < 60 ml/min/1,73 m<sup>2</sup>;
  - familial hypercholesterolaemia;
  - total cholesterol > 310 mg/dl;
  - LDL cholesterol > 190 mg/dl;
  - blood pressure  $\geq 180/110$  mm Hg;
  - at least 2 risk factors: hypertension, diabetes and dyslipidaemia [127].

Such a low target sUA level, identical to the one for the patient with severe gout, not only helps dissolve the existing sodium urate crystals and prevents their further formation, but also provides **more effective cardiovascular prevention**.

## LEVEL 2 — RAISING PATIENT AWARENESS ABOUT HYPERURICEMIA AND ENCOURAGING LIFESTYLE CHANGES

Raising patient awareness concerning the harmful effects of HU, the role of proper diet, weight loss and regular exercise is a major step toward an effective HU therapy. Factors which can adversely affect sUA levels include a low-sodium diet, high consumption of red meat and seafood, alcohol (especially beer), fructose and sweetened beverages. Diet components which help reduce sUA levels include coffee, dairy products, ascorbic acid and sour cherries (Table 4) [128–131].

## LEVEL 3 — MANAGEMENT OF COMORBIDITIES AND TREATMENT APPLIED, AND MODIFICATION OF PHARMACOTHERAPY IF REQUIRED

A proper management strategy needs to be adopted for HU patients, particularly regarding intensive control of concomitant risk factors and the use of drugs indirectly affect-

**Table 4.** Dietary factors affecting the onset of hyperuricemia [128–131]

Factor	Risk of hyperuricemia
Alcohol (especially beer)	Increased
Meat	Increased
Seafood	Increased
Purine-rich vegetables	No impact
Low-fat dairy products	Decreased
High-fat dairy products	No impact
Coffee	Decreased
Tea	No impact
Vitamin C	Decreased
Sweetened beverages	Increased
Beverages with a high fructose content	Increased
Fruit juices	Increased

ing sUA levels (Table 1). It is recommended to use drugs with a neutral or favourable impact on sUA levels. If possible, patients should not take acetylsalicylic acid or loop or thiazide diuretics. In hypertension therapy, preference should be given to ACE inhibitors, sartans and calcium antagonists, and atorvastatin, rosuvastatin and fenofibrate in the treatment of dyslipidaemia. The procedure of choice should also include intensive treatment of diseases that harm sUA levels, e.g.: hypertension, diabetes, metabolic syndrome, CKD and CVD [27, 32–35].

## LEVEL 4 — INITIATING THERAPY WITH ALLOPURINOL

Allopurinol is the recommended first-line drug in HU therapy. The recommended initial dose is 100–200 mg/day. It should be emphasized, however, that in most cases this dose is insufficient and needs to be gradually increased every 2–4 weeks until the target sUA concentration is achieved (the usual dose is 300–600 mg/day) [125]. This is corroborated by the WHO's so-called Defined Daily Dose (DDD), which is defined as the average prescribed daily maintenance dose in the primary indication for adults of a given drug, which in the case of allopurinol is 400 mg [132].

## LEVEL 5 — DETERMINING THE TARGET THERAPEUTIC DOSE

The following dosage is recommended: 100–200 mg/day in mild; 300–600 mg/day in

moderate; 700–900 mg/day in severe hyperuricemia. Allopurinol requires the dosage to be adjusted depending on the renal function. Allopurinol and its metabolites are excreted by the kidneys, and therefore renal function disorders may lead to the retention of the active substance and (or) its metabolites, and in effect extending their serum half-life. The dosage should be standard in CKD patients with eGFR > 20 ml/min, and the dosage with eGFR of 10–20 ml/min should be 100–200 mg/day. Allopurinol should not be administered in the dose of 100 mg/day earlier than at CKD Stage 5 and eGFR < 10 ml/min; or a 100 mg dose should be administered at intervals longer than 24 hours. It is worth noting that allopurinol and its metabolites are removed from the body by renal dialysis. If dialysis is required 2 to 3 times a week, consideration should be given to an alternative dosage schedule of 300–400 mg allopurinol after each dialysis, with no doses in the interim [133].

In case of allopurinol intolerance or ineffective therapy, using febuxostat, another XOI may be considered. It should be borne in mind, however, that special caution is required when febuxostat is used in patients with high cardiovascular risk, and it is contraindicated in patients with coronary artery disease or congestive heart failure [134].

### **LEVEL 6 — COMBINATION THERAPY (XOI + LESINURAD)**

When achieving the target sUA levels is not possible, consideration should be given to using XOI in combination with lesinurad. Lesinurad is an orally administered, selective inhibitor of URAT-1 (urate anion transporter 1) and OAT4 (organic anion transporter 4), which stimulates increased UA excretion by the kidneys, lowering the sUA level by inhibiting its reabsorption. The recommended dose is 200 mg/day in combination with an XOI in patients who have not achieved the therapeutic targets [135]. Commercial combo preparations are available on the global markets which com-

bine the better-researched XOI (allopurinol) with lesinurad. At present, however, lesinurad is not available in Poland and is also (similarly to febuxostat) registered to be used only by adult patients with urate deposits.

### **LEVEL 7 — CONTINUATION OF TREATMENT AND MONITORING OF URIC ACID LEVELS**

After the therapeutic target is achieved and sustained, the current therapeutic dose should be continued, with periodic sUA monitoring every 6 months. Such a procedure ought to be followed indefinitely.

### **SUMMARY**

According to the authors of this Statement, **general practitioners, and other medical professionals (internists, cardiologists, hypertensiologists, diabetologists, and rheumatologists) bear special responsibility concerning high-risk hyperuricemia patients and, if possible, ought to implement an appropriate procedure.** All HU patients should be effectively informed about the factors which affect sUA levels, comorbidities and CV risk factors. Patients need to be instructed about the necessary lifestyle and dietary modifications, regular, moderate exercise and, if required, the need to lose weight. In such patients, physicians should always strive to achieve and sustain indefinitely sUA < 6 mg/dl, and < 5 mg/dl in patients at high CV risk. Allopurinol is recommended as a first-line ULT drug. Consideration should be given to starting allopurinol therapy with a dose of 100–200 mg/day, to be gradually escalated to 300–900 mg/day until the therapeutic target is achieved. When the target sUA level is reached, the required XOI dose should be maintained indefinitely, while monitoring the sUA level every 6 months. Febuxostat ought to be used with special caution in patients at higher CV risk, and it is contraindicated in patients with coronary artery disease or congestive heart failure.

## **References**

1. Kratzer JT, Lanaspá MA, Murphy MN, et al. Evolutionary history and metabolic insights of ancient mammalian uricases. *Proc Natl Acad Sci U S A*. 2014; 111(10): 3763–3768, doi: [10.1073/pnas.1320393111](https://doi.org/10.1073/pnas.1320393111), indexed in Pubmed: 24550457.
2. Samborski W, Brzosko M. Dna moczanowa i inne choroby wywołane przez kryształy. In: Brzosko M, Flicięński J, Prajs K. ed. *Reumatologia praktyczna*. Wolters Kluwer Polska, Warszawa 2011.
3. Ragab G, Elshahaly M, Bardin T. Gout: An old disease in new perspective - A review. *J Adv Res*. 2017; 8(5): 495–511, doi: [10.1016/j.jare.2017.04.008](https://doi.org/10.1016/j.jare.2017.04.008), indexed in Pubmed: 28748116.
4. Bardin T, Richette P. Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. *BMC Med*. 2017; 15(1): 123, doi: [10.1186/s12916-017-0890-9](https://doi.org/10.1186/s12916-017-0890-9), indexed in Pubmed: 28669352.
5. Conen D, Wietlisbach V, Bovet P, et al. Prevalence of hyperuricemia and relation of serum uric acid with cardio-

- vascular risk factors in a developing country. *BMC Public Health*. 2004; 4: 9, doi: [10.1186/1471-2458-4-9](https://doi.org/10.1186/1471-2458-4-9), indexed in Pubmed: [15043756](https://pubmed.ncbi.nlm.nih.gov/15043756/).
6. Qiu L, Cheng Xq, Wu J, et al. Prevalence of hyperuricemia and its related risk factors in healthy adults from Northern and Northeastern Chinese provinces. *BMC Public Health*. 2013; 13: 664, doi: [10.1186/1471-2458-13-664](https://doi.org/10.1186/1471-2458-13-664), indexed in Pubmed: [23866159](https://pubmed.ncbi.nlm.nih.gov/23866159/).
  7. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. *Arthritis Rheum*. 2011; 63(10): 3136–3141, doi: [10.1002/art.30520](https://doi.org/10.1002/art.30520), indexed in Pubmed: [21800283](https://pubmed.ncbi.nlm.nih.gov/21800283/).
  8. Chen-Xu M, Yokose C, Rai SK, et al. Contemporary Prevalence of Gout and Hyperuricemia in the United States and Decadal Trends: The National Health and Nutrition Examination Survey, 2007–2016. *Arthritis Rheumatol*. 2019; 71(6): 991–999, doi: [10.1002/art.40807](https://doi.org/10.1002/art.40807), indexed in Pubmed: [30618180](https://pubmed.ncbi.nlm.nih.gov/30618180/).
  9. Kumar A U A, Browne LD, Li X, et al. Temporal trends in hyperuricaemia in the Irish health system from 2006–2014: A cohort study. *PLoS One*. 2018; 13(5): e0198197, doi: [10.1371/journal.pone.0198197](https://doi.org/10.1371/journal.pone.0198197), indexed in Pubmed: [29852506](https://pubmed.ncbi.nlm.nih.gov/29852506/).
  10. Perez-Ruiz F, Calabozo M, Pijoan JL, et al. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. *Arthritis Rheum*. 2002; 47(4): 356–360, doi: [10.1002/art.10511](https://doi.org/10.1002/art.10511), indexed in Pubmed: [12209479](https://pubmed.ncbi.nlm.nih.gov/12209479/).
  11. Kuo CF, Grainger MJ, Zhang W, et al. Global epidemiology of gout: prevalence, incidence and risk factors. *Nat Rev Rheumatol*. 2015; 11(11): 649–662, doi: [10.1038/nrrheum.2015.91](https://doi.org/10.1038/nrrheum.2015.91), indexed in Pubmed: [26150127](https://pubmed.ncbi.nlm.nih.gov/26150127/).
  12. Hall AP, Barry P, Dawber T, et al. Epidemiology of gout and hyperuricemia. *The American Journal of Medicine*. 1967; 42(1): 27–37, doi: [10.1016/0002-9343\(67\)90004-6](https://doi.org/10.1016/0002-9343(67)90004-6), indexed in Pubmed: [6016478](https://pubmed.ncbi.nlm.nih.gov/6016478/).
  13. Schlesinger N, Norquist JM, Watson DJ. Serum urate during acute gout. *J Rheumatol*. 2009; 36(6): 1287–1289, doi: [10.3899/jrheum.080938](https://doi.org/10.3899/jrheum.080938), indexed in Pubmed: [19369457](https://pubmed.ncbi.nlm.nih.gov/19369457/).
  14. Prasad M, Matteson EL, Herrmann J, et al. Uric Acid Is Associated With Inflammation, Coronary Microvascular Dysfunction, and Adverse Outcomes in Postmenopausal Women. *Hypertension*. 2017; 69(2): 236–242, doi: [10.1161/HYPERTENSIONAHA.116.08436](https://doi.org/10.1161/HYPERTENSIONAHA.116.08436), indexed in Pubmed: [27993955](https://pubmed.ncbi.nlm.nih.gov/27993955/).
  15. Farquharson CAJ, Butler R, Hill A, et al. Allopurinol improves endothelial dysfunction in chronic heart failure. *Circulation*. 2002; 106(2): 221–226, doi: [10.1161/01.cir.0000022140.61460.1d](https://doi.org/10.1161/01.cir.0000022140.61460.1d), indexed in Pubmed: [12105162](https://pubmed.ncbi.nlm.nih.gov/12105162/).
  16. Watanabe S, Kang DH, Feng L, et al. Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. *Hypertension*. 2002; 40(3): 355–360, doi: [10.1161/01.hyp.0000028589.66335.aa](https://doi.org/10.1161/01.hyp.0000028589.66335.aa), indexed in Pubmed: [12215479](https://pubmed.ncbi.nlm.nih.gov/12215479/).
  17. Lin C, Zhang Pu, Xue Y, et al. Link of renal microcirculatory dysfunction to increased coronary microcirculatory resistance in hypertensive patients. *Cardiol J*. 2017; 24(6): 623–632, doi: [10.5603/CJ.a2017.0074](https://doi.org/10.5603/CJ.a2017.0074), indexed in Pubmed: [28653312](https://pubmed.ncbi.nlm.nih.gov/28653312/).
  18. Kang DH, Park SK, Lee IK, et al. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. *J Am Soc Nephrol*. 2005; 16(12): 3553–3562, doi: [10.1681/ASN.2005050572](https://doi.org/10.1681/ASN.2005050572), indexed in Pubmed: [16251237](https://pubmed.ncbi.nlm.nih.gov/16251237/).
  19. Corry DB, Eslami P, Yamamoto K, et al. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. *J Hypertens*. 2008; 26(2): 269–275, doi: [10.1097/HJH.0b013e-3282f240bf](https://doi.org/10.1097/HJH.0b013e-3282f240bf), indexed in Pubmed: [18192841](https://pubmed.ncbi.nlm.nih.gov/18192841/).
  20. Kang DH, Han L, Ouyang X, et al. Uric acid causes vascular smooth muscle cell proliferation by entering cells via a functional urate transporter. *Am J Nephrol*. 2005; 25(5): 425–433, doi: [10.1159/000087713](https://doi.org/10.1159/000087713), indexed in Pubmed: [16113518](https://pubmed.ncbi.nlm.nih.gov/16113518/).
  21. Feig DI, Nakagawa T, Karumanchi SA, et al. Hypothesis: Uric acid, nephron number, and the pathogenesis of essential hypertension. *Kidney Int*. 2004; 66(1): 281–287, doi: [10.1111/j.1523-1755.2004.00729.x](https://doi.org/10.1111/j.1523-1755.2004.00729.x), indexed in Pubmed: [15200435](https://pubmed.ncbi.nlm.nih.gov/15200435/).
  22. Lee JE, Kim YG, Choi YH, et al. Serum uric acid is associated with microalbuminuria in prehypertension. *Hypertension*. 2006; 47(5): 962–967, doi: [10.1161/01.HYP0000210550.97398.c2](https://doi.org/10.1161/01.HYP0000210550.97398.c2), indexed in Pubmed: [16520402](https://pubmed.ncbi.nlm.nih.gov/16520402/).
  23. Iseki K, Oshiro S, Tozawa M, et al. Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. *Hypertens Res*. 2001; 24(6): 691–697, doi: [10.1291/hyres.24.691](https://doi.org/10.1291/hyres.24.691), indexed in Pubmed: [11768729](https://pubmed.ncbi.nlm.nih.gov/11768729/).
  24. Furukawa S, Fujita T, Shimabukuro M, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest*. 2004; 114(12): 1752–1761, doi: [10.1172/JCI21625](https://doi.org/10.1172/JCI21625), indexed in Pubmed: [15599400](https://pubmed.ncbi.nlm.nih.gov/15599400/).
  25. Cannon PJ, Stason WB, Demartini FE, et al. Hyperuricemia in primary and renal hypertension. *N Engl J Med*. 1966; 275(9): 457–464, doi: [10.1056/NEJM196609012750902](https://doi.org/10.1056/NEJM196609012750902), indexed in Pubmed: [5917940](https://pubmed.ncbi.nlm.nih.gov/5917940/).
  26. Ford ES, Li C, Cook S, et al. Serum concentrations of uric acid and the metabolic syndrome among US children and adolescents. *Circulation*. 2007; 115(19): 2526–2532, doi: [10.1161/CIRCULATIONAHA.106.657627](https://doi.org/10.1161/CIRCULATIONAHA.106.657627), indexed in Pubmed: [17470699](https://pubmed.ncbi.nlm.nih.gov/17470699/).
  27. Puig JG, Martínez MA. Hyperuricemia, gout and the metabolic syndrome. *Curr Opin Rheumatol*. 2008; 20(2): 187–191, doi: [10.1097/BOR.0b013e3282f4b1ed](https://doi.org/10.1097/BOR.0b013e3282f4b1ed), indexed in Pubmed: [18349749](https://pubmed.ncbi.nlm.nih.gov/18349749/).
  28. Tuttle K, Short R, Johnson R. Sex differences in uric acid and risk factors for coronary artery disease. *The American Journal of Cardiology*. 2001; 87(12): 1411–1414, doi: [10.1016/s0002-9149\(01\)01566-1](https://doi.org/10.1016/s0002-9149(01)01566-1).
  29. Dehghan A, van Hoek M, Sijbrands EJJ, et al. High serum uric acid as a novel risk factor for type 2 diabetes. *Diabetes Care*. 2008; 31(2): 361–362, doi: [10.2337/dc07-1276](https://doi.org/10.2337/dc07-1276), indexed in Pubmed: [17977935](https://pubmed.ncbi.nlm.nih.gov/17977935/).
  30. Schretlen DJ, Inscore AB, Vannorsdall TD, et al. Serum uric acid and brain ischemia in normal elderly adults. *Neurology*. 2007; 69(14): 1418–1423, doi: [10.1212/01.wnl.0000277468.10236.f1](https://doi.org/10.1212/01.wnl.0000277468.10236.f1), indexed in Pubmed: [17909154](https://pubmed.ncbi.nlm.nih.gov/17909154/).
  31. Lehto S, Niskanen L, Rönnemaa T, et al. Serum uric acid is a strong predictor of stroke in patients with non-insulin-dependent diabetes mellitus. *Stroke*. 1998; 29(3): 635–639, doi: [10.1161/01.str.29.3.635](https://doi.org/10.1161/01.str.29.3.635), indexed in Pubmed: [9506605](https://pubmed.ncbi.nlm.nih.gov/9506605/).
  32. Yu KH, Kuo CF, Luo SF, et al. Risk of end-stage renal disease associated with gout: a nationwide population study. *Arthritis Res Ther*. 2012; 14(2): R83, doi: [10.1186/ar3806](https://doi.org/10.1186/ar3806), indexed in Pubmed: [22513212](https://pubmed.ncbi.nlm.nih.gov/22513212/).
  33. Abbott RD, Brand FN, Kannel WB, et al. Characteristics and prognosis of lone atrial fibrillation. 30-year follow-up in the

- Framingham Study. *JAMA*. 1985; 254(24): 3449–3453, indexed in Pubmed: [4068186](#).
34. De Vera MA, Rahman MM, Bhole V, et al. Independent impact of gout on the risk of acute myocardial infarction among elderly women: a population-based study. *Ann Rheum Dis*. 2010; 69(6): 1162–1164, doi: [10.1136/ard.2009.122770](#), indexed in Pubmed: [20124358](#).
  35. Borghi C, Rosei EA, Bardin T, et al. Serum uric acid and the risk of cardiovascular and renal disease. *J Hypertens*. 2015; 33(9): 1729–41; discussion 1741, doi: [10.1097/HJH.0000000000000701](#), indexed in Pubmed: [26136207](#).
  36. Kleber ME, Delgado G, Grammer TB, et al. Uric Acid and Cardiovascular Events: A Mendelian Randomization Study. *J Am Soc Nephrol*. 2015; 26(11): 2831–2838, doi: [10.1681/ASN.2014070660](#), indexed in Pubmed: [25788527](#).
  37. Yan D, Wang J, Jiang F, et al. A causal relationship between uric acid and diabetic macrovascular disease in Chinese type 2 diabetes patients: A Mendelian randomization analysis. *Int J Cardiol*. 2016; 214: 194–199, doi: [10.1016/j.ijcard.2016.03.206](#), indexed in Pubmed: [27064641](#).
  38. Kuwabara M, Borghi C, Cicero AFG, et al. Elevated serum uric acid increases risks for developing high LDL cholesterol and hypertriglyceridemia: A five-year cohort study in Japan. *Int J Cardiol*. 2018; 261: 183–188, doi: [10.1016/j.ijcard.2018.03.045](#), indexed in Pubmed: [29551256](#).
  39. Borghi C, Desideri G. Urate-Lowering Drugs and Prevention of Cardiovascular Disease: The Emerging Role of Xanthine Oxidase Inhibition. *Hypertension*. 2016; 67(3): 496–498, doi: [10.1161/HYPERTENSIONAHA.115.06531](#), indexed in Pubmed: [26865197](#).
  40. Bove M, Cicero AF, Veronesi M, et al. An evidence-based review on urate-lowering treatments: implications for optimal treatment of chronic hyperuricemia. *Vasc Health Risk Manag*. 2017; 13: 23–28, doi: [10.2147/VHRM.S115080](#), indexed in Pubmed: [28223818](#).
  41. Lurbe E, Torro MI, Alvarez-Pitti J, et al. Uric acid is linked to cardiometabolic risk factors in overweight and obese youths. *J Hypertens*. 2018; 36(9): 1840–1846, doi: [10.1097/HJH.0000000000001814](#), indexed in Pubmed: [29916994](#).
  42. Jalal DI, Chonchol M, Chen W, et al. Uric acid as a target of therapy in CKD. *Am J Kidney Dis*. 2013; 61(1): 134–146, doi: [10.1053/ajkd.2012.07.021](#), indexed in Pubmed: [23058478](#).
  43. Shadick NA, Kim R, Weiss S, et al. Effect of low level lead exposure on hyperuricemia and gout among middle aged and elderly men: the normative aging study. *J Rheumatol*. 2000; 27(7): 1708–1712, indexed in Pubmed: [10914856](#).
  44. Krishnan E, Kwok CK, Schumacher HR, et al. Hyperuricemia and incidence of hypertension among men without metabolic syndrome. *Hypertension*. 2007; 49(2): 298–303, doi: [10.1161/01.HYP0000254480.64564.b6](#), indexed in Pubmed: [17190877](#).
  45. Mellen PB, Bleyer AJ, Erlinger TP, et al. Serum uric acid predicts incident hypertension in a biethnic cohort: the atherosclerosis risk in communities study. *Hypertension*. 2006; 48(6): 1037–1042, doi: [10.1161/01.HYP0000249768.26560.66](#), indexed in Pubmed: [17060502](#).
  46. Grayson PC, Kim SY, LaValley M, et al. Hyperuricemia and incident hypertension: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2011; 63(1): 102–110, doi: [10.1002/acr.20344](#), indexed in Pubmed: [20824805](#).
  47. Bombelli M, Ronchi I, Volpe M, et al. Prognostic value of serum uric acid: new-onset in and out-of-office hypertension and long-term mortality. *J Hypertens*. 2014; 32(6): 1237–1244, doi: [10.1097/HJH.0000000000000161](#), indexed in Pubmed: [24675682](#).
  48. Perlestein TS, Gumieniak O, Williams GH, et al. Uric acid and the development of hypertension: the normative aging study. *Hypertension*. 2006; 48(6): 1031–1036, doi: [10.1161/01.HYP0000248752.08807.4c](#), indexed in Pubmed: [17060508](#).
  49. Forman JP, Choi H, Curhan GC. Plasma uric acid level and risk for incident hypertension among men. *J Am Soc Nephrol*. 2007; 18(1): 287–292, doi: [10.1681/ASN.2006080865](#), indexed in Pubmed: [17167112](#).
  50. Zhang W, Sun K, Yang Y, et al. Plasma uric acid and hypertension in a Chinese community: prospective study and metaanalysis. *Clin Chem*. 2009; 55(11): 2026–2034, doi: [10.1373/clinchem.2009.124891](#), indexed in Pubmed: [19729471](#).
  51. Shankar A, Klein R, Klein BEK, et al. The association between serum uric acid level and long-term incidence of hypertension: Population-based cohort study. *J Hum Hypertens*. 2006; 20(12): 937–945, doi: [10.1038/sj.jhh.1002095](#), indexed in Pubmed: [17024135](#).
  52. Sundström J, Sullivan L, D'Agostino RB, et al. Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence. *Hypertension*. 2005; 45(1): 28–33, doi: [10.1161/01.HYP0000150784.92944.9a](#), indexed in Pubmed: [15569852](#).
  53. Bos MJ, Koudstaal PJ, Hofman A, et al. Uric acid is a risk factor for myocardial infarction and stroke: the Rotterdam study. *Stroke*. 2006; 37(6): 1503–1507, doi: [10.1161/01.STR.0000221716.55088.d4](#), indexed in Pubmed: [16675740](#).
  54. Tscharré M, Herman R, Rohla M, et al. Uric acid is associated with long-term adverse cardiovascular outcomes in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *Atherosclerosis*. 2018; 270: 173–179, doi: [10.1016/j.atherosclerosis.2018.02.003](#), indexed in Pubmed: [29432935](#).
  55. Holme I, Aastveit AH, Hammar N, et al. Uric acid and risk of myocardial infarction, stroke and congestive heart failure in 417,734 men and women in the Apolipoprotein MOrtality RiSk study (AMORIS). *J Intern Med*. 2009; 266(6): 558–570, doi: [10.1111/j.1365-2796.2009.02133.x](#), indexed in Pubmed: [19563390](#).
  56. Crosta F, Occhiuzzi U, Passalacqua G, et al. Association Between the Serum Uric Acid Levels and Lacunar Infarcts in the Elderly. *J Mol Neurosci*. 2018; 65(3): 385–390, doi: [10.1007/s12031-018-1096-0](#), indexed in Pubmed: [29974380](#).
  57. Kim SY, Guevara JP, Kim KMi, et al. Hyperuricemia and risk of stroke: a systematic review and meta-analysis. *Arthritis Rheum*. 2009; 61(7): 885–892, doi: [10.1002/art.24612](#), indexed in Pubmed: [19565556](#).
  58. Zhong C, Zhong X, Xu T, et al. Sex-Specific Relationship Between Serum Uric Acid and Risk of Stroke: A Dose-Response Meta-Analysis of Prospective Studies. *J Am Heart Assoc*. 2017; 6(4), doi: [10.1161/JAHA.116.005042](#), indexed in Pubmed: [28356280](#).
  59. Li J, Muraki I, Imano H, et al. CIRCUS investigators. Serum uric acid and risk of stroke and its types: the Circulatory Risk in Communities Study (CIRCUS). *Hypertens Res*. 2020;

- 43(4): 313–321, doi: [10.1038/s41440-019-0385-5](https://doi.org/10.1038/s41440-019-0385-5), indexed in Pubmed: [31988479](https://pubmed.ncbi.nlm.nih.gov/31988479/).
60. Li S, Cheng J, Cui L, et al. Cohort Study of Repeated Measurements of Serum Urate and Risk of Incident Atrial Fibrillation. *J Am Heart Assoc.* 2019; 8(13): e012020, doi: [10.1161/JAHA.119.012020](https://doi.org/10.1161/JAHA.119.012020), indexed in Pubmed: [31213103](https://pubmed.ncbi.nlm.nih.gov/31213103/).
  61. Hong M, Park JW, Yang PS, et al. A mendelian randomization analysis: The causal association between serum uric acid and atrial fibrillation. *Eur J Clin Invest.* 2020; 50(10): e13300, doi: [10.1111/eci.13300](https://doi.org/10.1111/eci.13300), indexed in Pubmed: [32474920](https://pubmed.ncbi.nlm.nih.gov/32474920/).
  62. Juraschek SP, Kovell LC, Miller ER, et al. Association of kidney disease with prevalent gout in the United States in 1988–1994 and 2007–2010. *Semin Arthritis Rheum.* 2013; 42(6): 551–561, doi: [10.1016/j.semarthrit.2012.09.009](https://doi.org/10.1016/j.semarthrit.2012.09.009), indexed in Pubmed: [23312548](https://pubmed.ncbi.nlm.nih.gov/23312548/).
  63. Jing J, Kielstein JT, Schultheiss UT, et al. GCKD Study Investigators. Prevalence and correlates of gout in a large cohort of patients with chronic kidney disease: the German Chronic Kidney Disease (GCKD) study. *Nephrol Dial Transplant.* 2015; 30(4): 613–621, doi: [10.1093/ndt/gfu352](https://doi.org/10.1093/ndt/gfu352), indexed in Pubmed: [25395390](https://pubmed.ncbi.nlm.nih.gov/25395390/).
  64. Johnson RJ, Nakagawa T, Jalal D, et al. Uric acid and chronic kidney disease: which is chasing which? *Nephrol Dial Transplant.* 2013; 28(9): 2221–2228, doi: [10.1093/ndt/gft029](https://doi.org/10.1093/ndt/gft029), indexed in Pubmed: [23543594](https://pubmed.ncbi.nlm.nih.gov/23543594/).
  65. Hsu Cy, Iribarren C, McCulloch CE, et al. Risk factors for end-stage renal disease: 25-year follow-up. *Arch Intern Med.* 2009; 169(4): 342–350, doi: [10.1001/archinternmed.2008.605](https://doi.org/10.1001/archinternmed.2008.605), indexed in Pubmed: [19237717](https://pubmed.ncbi.nlm.nih.gov/19237717/).
  66. Myllymäki J, Honkanen T, Syrjänen J, et al. Uric acid correlates with the severity of histopathological parameters in IgA nephropathy. *Nephrol Dial Transplant.* 2005; 20(1): 89–95, doi: [10.1093/ndt/gfh584](https://doi.org/10.1093/ndt/gfh584), indexed in Pubmed: [15572382](https://pubmed.ncbi.nlm.nih.gov/15572382/).
  67. Liu P, Chen Y, Wang B, et al. Allopurinol treatment improves renal function in patients with type 2 diabetes and asymptomatic hyperuricemia: 3-year randomized parallel-controlled study. *Clin Endocrinol (Oxf).* 2015; 83(4): 475–482, doi: [10.1111/cen.12673](https://doi.org/10.1111/cen.12673), indexed in Pubmed: [25400252](https://pubmed.ncbi.nlm.nih.gov/25400252/).
  68. Hart A, Jackson S, Kasiske BL, et al. Uric acid and allograft loss from interstitial fibrosis/tubular atrophy: post hoc analysis from the angiotensin II blockade in chronic allograft nephropathy trial. *Transplantation.* 2014; 97(10): 1066–1071, doi: [10.1097/01.TP.0000440952.29757.66](https://doi.org/10.1097/01.TP.0000440952.29757.66), indexed in Pubmed: [24503762](https://pubmed.ncbi.nlm.nih.gov/24503762/).
  69. Bellomo G, Venanzi S, Verdura C, et al. Association of uric acid with change in kidney function in healthy normotensive individuals. *Am J Kidney Dis.* 2010; 56(2): 264–272, doi: [10.1053/j.ajkd.2010.01.019](https://doi.org/10.1053/j.ajkd.2010.01.019), indexed in Pubmed: [20385436](https://pubmed.ncbi.nlm.nih.gov/20385436/).
  70. Stack AG, Hanley A, Casserly LF, et al. Independent and conjoint associations of gout and hyperuricaemia with total and cardiovascular mortality. *QJM.* 2013; 106(7): 647–658, doi: [10.1093/qjmed/hct083](https://doi.org/10.1093/qjmed/hct083), indexed in Pubmed: [23564632](https://pubmed.ncbi.nlm.nih.gov/23564632/).
  71. Ioachimescu AG, Brennan DM, Hoar BM, et al. Serum uric acid is an independent predictor of all-cause mortality in patients at high risk of cardiovascular disease: a preventive cardiology information system (PreCIS) database cohort study. *Arthritis Rheum.* 2008; 58(2): 623–630, doi: [10.1002/art.23121](https://doi.org/10.1002/art.23121), indexed in Pubmed: [18240236](https://pubmed.ncbi.nlm.nih.gov/18240236/).
  72. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. *Circulation.* 2007; 116(8): 894–900, doi: [10.1161/CIRCULATIONAHA.107.703389](https://doi.org/10.1161/CIRCULATIONAHA.107.703389), indexed in Pubmed: [17698728](https://pubmed.ncbi.nlm.nih.gov/17698728/).
  73. Desideri G, Virdis A, Casiglia E, et al. Working Group on Uric Acid and Cardiovascular Risk of the Italian Society of Hypertension. Exploration into Uric and Cardiovascular Disease: Uric Acid Right for heArt Health (URRAH) Project, A Study Protocol for a Retrospective Observational Study. *High Blood Press Cardiovasc Prev.* 2018; 25(2): 197–202, doi: [10.1007/s40292-018-0250-7](https://doi.org/10.1007/s40292-018-0250-7), indexed in Pubmed: [29427170](https://pubmed.ncbi.nlm.nih.gov/29427170/).
  74. Virdis A, Masi S, Casiglia E, et al. from the Working Group on Uric Acid and Cardiovascular Risk of the Italian Society of Hypertension. Identification of the Uric Acid Thresholds Predicting an Increased Total and Cardiovascular Mortality Over 20 Years. *Hypertension.* 2020; 75(2): 302–308, doi: [10.1161/HYPERTENSIONAHA.119.13643](https://doi.org/10.1161/HYPERTENSIONAHA.119.13643), indexed in Pubmed: [31813345](https://pubmed.ncbi.nlm.nih.gov/31813345/).
  75. Perticone M, Tripepi G, Maio R, et al. Risk reclassification ability of uric acid for cardiovascular outcomes in essential hypertension. *Int J Cardiol.* 2017; 243: 473–478, doi: [10.1016/j.ijcard.2017.05.051](https://doi.org/10.1016/j.ijcard.2017.05.051), indexed in Pubmed: [28528984](https://pubmed.ncbi.nlm.nih.gov/28528984/).
  76. Dutta A, Henley W, Pilling LC, et al. Uric acid measurement improves prediction of cardiovascular mortality in later life. *J Am Geriatr Soc.* 2013; 61(3): 319–326, doi: [10.1111/jgs.12149](https://doi.org/10.1111/jgs.12149), indexed in Pubmed: [23496291](https://pubmed.ncbi.nlm.nih.gov/23496291/).
  77. Tscharre M, Herman R, Rohla M, et al. Uric acid is associated with long-term adverse cardiovascular outcomes in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *Atherosclerosis.* 2018; 270: 173–179, doi: [10.1016/j.atherosclerosis.2018.02.003](https://doi.org/10.1016/j.atherosclerosis.2018.02.003), indexed in Pubmed: [29432935](https://pubmed.ncbi.nlm.nih.gov/29432935/).
  78. Zalawadiya SK, Veeranna V, Mallikethi-Reddy S, et al. Uric acid and cardiovascular disease risk reclassification: findings from NHANES III. *Eur J Prev Cardiol.* 2015; 22(4): 513–518, doi: [10.1177/2047487313519346](https://doi.org/10.1177/2047487313519346), indexed in Pubmed: [24431384](https://pubmed.ncbi.nlm.nih.gov/24431384/).
  79. Muesan ML, Salvetti M, Virdis A, et al. from the Working Group on Uric Acid, Cardiovascular Risk of the Italian Society of Hypertension. Serum uric acid, predicts heart failure in a large Italian cohort: search for a cut-off value the URic acid Right for heArt Health study. *J Hypertens.* 2021; 39(1): 62–69, doi: [10.1097/HJH.0000000000002589](https://doi.org/10.1097/HJH.0000000000002589), indexed in Pubmed: [32694342](https://pubmed.ncbi.nlm.nih.gov/32694342/).
  80. Huang G, Qin J, Deng X, et al. Prognostic value of serum uric acid in patients with acute heart failure: A meta-analysis. *Medicine (Baltimore).* 2019; 98(8): e14525, doi: [10.1097/MD.00000000000014525](https://doi.org/10.1097/MD.00000000000014525), indexed in Pubmed: [30813158](https://pubmed.ncbi.nlm.nih.gov/30813158/).
  81. Commissioner, Office of the “Safety Alerts for Human Medical Products — Febuxostat (Brand Name Uloric): Drug Safety Communication — FDA to Evaluate Increased Risk of Heart-related Death”. <http://www.FDA.gov> (November 17, 2017).
  82. Wang M, Zhang Yi, Zhang M, et al. The major cardiovascular events of febuxostat versus allopurinol in treating gout or asymptomatic hyperuricemia: a systematic review and meta-analysis. *Ann Palliat Med.* 2021; 10(10): 10327–10337, doi: [10.21037/apm-21-1564](https://doi.org/10.21037/apm-21-1564), indexed in Pubmed: [34498481](https://pubmed.ncbi.nlm.nih.gov/34498481/).
  83. Zhang S, Xu T, Shi Q, et al. Cardiovascular Safety of Febuxostat and Allopurinol in Hyperuricemic Patients With or Without Gout: A Network Meta-Analysis. *Front Med (Lausanne).* 2021; 8: 698437, doi: [10.3389/fmed.2021.698437](https://doi.org/10.3389/fmed.2021.698437), indexed in Pubmed: [34211992](https://pubmed.ncbi.nlm.nih.gov/34211992/).

84. Gao L, Wang B, Pan Y, et al. Cardiovascular safety of febuxostat compared to allopurinol for the treatment of gout: A systematic and meta-analysis. *Clin Cardiol.* 2021; 44(7): 907–916, doi: [10.1002/clc.23643](https://doi.org/10.1002/clc.23643), indexed in Pubmed: [34013998](https://pubmed.ncbi.nlm.nih.gov/34013998/).
85. Ying H, Yuan H, Tang X, et al. Impact of Serum Uric Acid Lowering and Contemporary Uric Acid-Lowering Therapies on Cardiovascular Outcomes: A Systematic Review and Meta-Analysis. *Front Cardiovasc Med.* 2021; 8: 641062, doi: [10.3389/fcvm.2021.641062](https://doi.org/10.3389/fcvm.2021.641062), indexed in Pubmed: [33869304](https://pubmed.ncbi.nlm.nih.gov/33869304/).
86. McDonagh TA, Metra M, Adamo M, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021; 42(36): 3599–3726, doi: [10.1093/eurheartj/ehab368](https://doi.org/10.1093/eurheartj/ehab368), indexed in Pubmed: [34447992](https://pubmed.ncbi.nlm.nih.gov/34447992/).
87. White WB, Saag KG, Becker MA, et al. CARES Investigators. Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout. *N Engl J Med.* 2018; 378(13): 1200–1210, doi: [10.1056/NEJMoa1710895](https://doi.org/10.1056/NEJMoa1710895), indexed in Pubmed: [29527974](https://pubmed.ncbi.nlm.nih.gov/29527974/).
88. World Health Organization Model List of Essential Medicines — 22nd List, 2021. Geneva: World Health Organization; 2021 (WHO/MHP/HPS/EML/2021.02). Licence: CC BY-NC-SA 3.0 IGO.
89. Richette P, Perez-Ruiz F, Doherty M, et al. Improving cardiovascular and renal outcomes in gout: what should we target? *Nat Rev Rheumatol.* 2014; 10(11): 654–661, doi: [10.1038/nrrheum.2014.124](https://doi.org/10.1038/nrrheum.2014.124), indexed in Pubmed: [25136785](https://pubmed.ncbi.nlm.nih.gov/25136785/).
90. Okafor ON, Farrington K, Gorog DA. Allopurinol as a therapeutic option in cardiovascular disease. *Pharmacol Ther.* 2017; 172: 139–150, doi: [10.1016/j.pharmthera.2016.12.004](https://doi.org/10.1016/j.pharmthera.2016.12.004), indexed in Pubmed: [27916655](https://pubmed.ncbi.nlm.nih.gov/27916655/).
91. Pacher P, Nivorozhkin A, Szabó C. Therapeutic effects of xanthine oxidase inhibitors: renaissance half a century after the discovery of allopurinol. *Pharmacol Rev.* 2006; 58(1): 87–114, doi: [10.1124/pr.58.1.6](https://doi.org/10.1124/pr.58.1.6), indexed in Pubmed: [16507884](https://pubmed.ncbi.nlm.nih.gov/16507884/).
92. Wei Li, Mackenzie IS, Chen Y, et al. Impact of allopurinol use on urate concentration and cardiovascular outcome. *Br J Clin Pharmacol.* 2011; 71(4): 600–607, doi: [10.1111/j.1365-2125.2010.03887.x](https://doi.org/10.1111/j.1365-2125.2010.03887.x), indexed in Pubmed: [21395653](https://pubmed.ncbi.nlm.nih.gov/21395653/).
93. Feig DI, Kang DH, Johnson RJ, et al. Diuretic-induced hyperuricemia does not decrease cardiovascular risk. *J Hypertens.* 2004; 22(7): 1415–1417, indexed in Pubmed: [15201561](https://pubmed.ncbi.nlm.nih.gov/15201561/).
94. Wei L, Fahey T, Struthers AD, et al. Association between allopurinol and mortality in heart failure patients: a long-term follow-up study. *Int J Clin Pract.* 2009; 63(9): 1327–1333, doi: [10.1111/j.1742-1241.2009.02118.x](https://doi.org/10.1111/j.1742-1241.2009.02118.x), indexed in Pubmed: [19691616](https://pubmed.ncbi.nlm.nih.gov/19691616/).
95. Luk AJ, Levin GP, Moore EE, et al. Allopurinol and mortality in hyperuricaemic patients. *Rheumatology (Oxford).* 2009; 48(7): 804–806, doi: [10.1093/rheumatology/kep069](https://doi.org/10.1093/rheumatology/kep069), indexed in Pubmed: [19447769](https://pubmed.ncbi.nlm.nih.gov/19447769/).
96. Dubreuil M, Zhu Y, Zhang Y, et al. Allopurinol initiation and all-cause mortality in the general population. *Ann Rheum Dis.* 2015; 74(7): 1368–1372, doi: [10.1136/annrheumdis-2014-205269](https://doi.org/10.1136/annrheumdis-2014-205269), indexed in Pubmed: [24665118](https://pubmed.ncbi.nlm.nih.gov/24665118/).
97. Norman A, Ang D, Ogston S, et al. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial. *The Lancet.* 2010; 375(9732): 2161–2167, doi: [10.1016/s0140-6736\(10\)60391-1](https://doi.org/10.1016/s0140-6736(10)60391-1).
98. Rekhraj S, Gandy SJ, Szejewski BR, et al. High-dose allopurinol reduces left ventricular mass in patients with ischemic heart disease. *J Am Coll Cardiol.* 2013; 61(9): 926–932, doi: [10.1016/j.jacc.2012.09.066](https://doi.org/10.1016/j.jacc.2012.09.066), indexed in Pubmed: [23449426](https://pubmed.ncbi.nlm.nih.gov/23449426/).
99. Higgins P, Dawson J, Lees KR, et al. Xanthine oxidase inhibition for the treatment of cardiovascular disease: a systematic review and meta-analysis. *Cardiovasc Ther.* 2012; 30(4): 217–226, doi: [10.1111/j.1755-5922.2011.00277.x](https://doi.org/10.1111/j.1755-5922.2011.00277.x), indexed in Pubmed: [22099531](https://pubmed.ncbi.nlm.nih.gov/22099531/).
100. George J, Carr E, Davies J, et al. High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. *Circulation.* 2006; 114(23): 2508–2516, doi: [10.1161/CIRCULATIONAHA.106.651117](https://doi.org/10.1161/CIRCULATIONAHA.106.651117), indexed in Pubmed: [17130343](https://pubmed.ncbi.nlm.nih.gov/17130343/).
101. Beattie CJ, Fulton RL, Higgins P, et al. Allopurinol initiation and change in blood pressure in older adults with hypertension. *Hypertension.* 2014; 64(5): 1102–1107, doi: [10.1161/HYPERTENSIONAHA.114.03953](https://doi.org/10.1161/HYPERTENSIONAHA.114.03953), indexed in Pubmed: [25135183](https://pubmed.ncbi.nlm.nih.gov/25135183/).
102. Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. *JAMA.* 2008; 300(8): 924–932, doi: [10.1001/jama.300.8.924](https://doi.org/10.1001/jama.300.8.924), indexed in Pubmed: [18728266](https://pubmed.ncbi.nlm.nih.gov/18728266/).
103. Agarwal V, Hans N, Messerli FH. Effect of allopurinol on blood pressure: a systematic review and meta-analysis. *J Clin Hypertens (Greenwich).* 2013; 15(6): 435–442, doi: [10.1111/j.1751-7176.2012.00701.x](https://doi.org/10.1111/j.1751-7176.2012.00701.x), indexed in Pubmed: [23730993](https://pubmed.ncbi.nlm.nih.gov/23730993/).
104. Qu LH, Jiang H, Chen JH. Effect of uric acid-lowering therapy on blood pressure: systematic review and meta-analysis. *Ann Med.* 2017; 49(2): 142–156, doi: [10.1080/07853890.2016.1243803](https://doi.org/10.1080/07853890.2016.1243803), indexed in Pubmed: [27689859](https://pubmed.ncbi.nlm.nih.gov/27689859/).
105. Kostka-Jeziorny K, Uruski P, Tykarski A. Effect of allopurinol on blood pressure and aortic compliance in hypertensive patients. *Blood Press.* 2011; 20(2): 104–110, doi: [10.3109/08037051.2010.532323](https://doi.org/10.3109/08037051.2010.532323), indexed in Pubmed: [21405957](https://pubmed.ncbi.nlm.nih.gov/21405957/).
106. Khan F, George J, Wong K, et al. Allopurinol treatment reduces arterial wave reflection in stroke survivors. *Cardiovasc Ther.* 2008; 26(4): 247–252, doi: [10.1111/j.1755-5922.2008.00057.x](https://doi.org/10.1111/j.1755-5922.2008.00057.x), indexed in Pubmed: [19035875](https://pubmed.ncbi.nlm.nih.gov/19035875/).
107. MacIsaac RL, Salatzki J, Higgins P, et al. Allopurinol and Cardiovascular Outcomes in Adults With Hypertension. *Hypertension.* 2016; 67(3): 535–540, doi: [10.1161/HYPERTENSIONAHA.115.06344](https://doi.org/10.1161/HYPERTENSIONAHA.115.06344), indexed in Pubmed: [26865199](https://pubmed.ncbi.nlm.nih.gov/26865199/).
108. Thanassoulis G, Brophy JM, Richard H, et al. Gout, allopurinol use, and heart failure outcomes. *Arch Intern Med.* 2010; 170(15): 1358–1364, doi: [10.1001/archinternmed.2010.198](https://doi.org/10.1001/archinternmed.2010.198), indexed in Pubmed: [20696962](https://pubmed.ncbi.nlm.nih.gov/20696962/).
109. Hare JM, Mangal B, Brown J, et al. OPT-CHF Investigators. Impact of oxypurinol in patients with symptomatic heart failure. Results of the OPT-CHF study. *J Am Coll Cardiol.* 2008; 51(24): 2301–2309, doi: [10.1016/j.jacc.2008.01.068](https://doi.org/10.1016/j.jacc.2008.01.068), indexed in Pubmed: [18549913](https://pubmed.ncbi.nlm.nih.gov/18549913/).
110. Givertz MM, Anstrom KJ, Redfield MM, et al. NHLBI Heart Failure Clinical Research Network. Effects of Xanthine Oxidase Inhibition in Hyperuricemic Heart Failure Patients: The Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) Study. *Circulation.* 2015; 131(20):



- 1763–1771, doi: [10.1161/CIRCULATIONAHA.114.014536](https://doi.org/10.1161/CIRCULATIONAHA.114.014536), indexed in Pubmed: [25986447](https://pubmed.ncbi.nlm.nih.gov/25986447/).
111. Cleland JGF, Coletta AP, Clark AL. Clinical trials update from the Heart Failure Society of America meeting: FIX-CHF-4, selective cardiac myosin activator and OPT-CHF. *Eur J Heart Fail.* 2006; 8(7): 764–766, doi: [10.1016/j.ejheart.2006.10.001](https://doi.org/10.1016/j.ejheart.2006.10.001), indexed in Pubmed: [17049305](https://pubmed.ncbi.nlm.nih.gov/17049305/).
  112. Freudenberger RS, Schwarz RP, Brown J, et al. Rationale, design and organisation of an efficacy and safety study of oxypurinol added to standard therapy in patients with NYHA class III - IV congestive heart failure. *Expert Opin Investig Drugs.* 2004; 13(11): 1509–1516, doi: [10.1517/13543784.13.11.1509](https://doi.org/10.1517/13543784.13.11.1509), indexed in Pubmed: [15500398](https://pubmed.ncbi.nlm.nih.gov/15500398/).
  113. George J, Struthers A. The OPT-CHF (Oxypurinol Therapy for Congestive Heart Failure) trial: a question of dose. *J Am Coll Cardiol.* 2009; 53(25): 2405, doi: [10.1016/j.jacc.2008.07.076](https://doi.org/10.1016/j.jacc.2008.07.076), indexed in Pubmed: [19539154](https://pubmed.ncbi.nlm.nih.gov/19539154/).
  114. Hare JM, Mangal B, Brown J, et al. OPT-CHF Investigators. Impact of oxypurinol in patients with symptomatic heart failure. Results of the OPT-CHF study. *J Am Coll Cardiol.* 2008; 51(24): 2301–2309, doi: [10.1016/j.jacc.2008.01.068](https://doi.org/10.1016/j.jacc.2008.01.068), indexed in Pubmed: [18549913](https://pubmed.ncbi.nlm.nih.gov/18549913/).
  115. Borghi C, Rosei EA, Bardin T, et al. Serum uric acid and the risk of cardiovascular and renal disease. *J Hypertens.* 2015; 33(9): 1729–41; discussion 1741, doi: [10.1097/HJH.0000000000000701](https://doi.org/10.1097/HJH.0000000000000701), indexed in Pubmed: [26136207](https://pubmed.ncbi.nlm.nih.gov/26136207/).
  116. Kanji T, Gandhi M, Clase CM, et al. Urate lowering therapy to improve renal outcomes in patients with chronic kidney disease: systematic review and meta-analysis. *BMC Nephrol.* 2015; 16: 58, doi: [10.1186/s12882-015-0047-z](https://doi.org/10.1186/s12882-015-0047-z), indexed in Pubmed: [25928556](https://pubmed.ncbi.nlm.nih.gov/25928556/).
  117. Goicoechea M, de Vinuesa SG, Verdalles U, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. *Clin J Am Soc Nephrol.* 2010; 5(8): 1388–1393, doi: [10.2215/CJN.01580210](https://doi.org/10.2215/CJN.01580210), indexed in Pubmed: [20538833](https://pubmed.ncbi.nlm.nih.gov/20538833/).
  118. Su X, Xu B, Yan B, et al. Effects of uric acid-lowering therapy in patients with chronic kidney disease: A meta-analysis. *PLoS One.* 2017; 12(11): e0187550, doi: [10.1371/journal.pone.0187550](https://doi.org/10.1371/journal.pone.0187550), indexed in Pubmed: [29095953](https://pubmed.ncbi.nlm.nih.gov/29095953/).
  119. Sampson AL, Singer RF, Walters GD. Uric acid lowering therapies for preventing or delaying the progression of chronic kidney disease. *Cochrane Database Syst Rev.* 2017; 10: CD009460, doi: [10.1002/14651858.CD009460.pub2](https://doi.org/10.1002/14651858.CD009460.pub2), indexed in Pubmed: [29084343](https://pubmed.ncbi.nlm.nih.gov/29084343/).
  120. Levy GD, Rashid N, Niu F, et al. Effect of urate-lowering therapies on renal disease progression in patients with hyperuricemia. *J Rheumatol.* 2014; 41(5): 955–962, doi: [10.3899/jrheum.131159](https://doi.org/10.3899/jrheum.131159), indexed in Pubmed: [24692523](https://pubmed.ncbi.nlm.nih.gov/24692523/).
  121. Li Q, Li X, Kwong JSW, et al. Diagnosis and treatment for hyperuricaemia and gout: a protocol for a systematic review of clinical practice guidelines and consensus statements. *BMJ Open.* 2017; 7(6): e014928, doi: [10.1136/bmjopen-2016-014928](https://doi.org/10.1136/bmjopen-2016-014928), indexed in Pubmed: [28645962](https://pubmed.ncbi.nlm.nih.gov/28645962/).
  122. Tykarski A, Filipiak KJ, Januszewicz A, et al. Zasady postępowania w nadciśnieniu tętniczym — 2019 rok. *Nadciśn Tętn Prakt.* 2019; 5(1): 1–86.
  123. Borghi C, Domienik-Karłowicz J, Tykarski A, et al. Expert consensus for the diagnosis and treatment of patient with hyperuricemia and high cardiovascular risk: 2021 update. *Cardiol J.* 2021; 28(1): 1–14, doi: [10.5603/CJ.a2021.0001](https://doi.org/10.5603/CJ.a2021.0001), indexed in Pubmed: [33438180](https://pubmed.ncbi.nlm.nih.gov/33438180/).
  124. Khanna D, Fitzgerald JD, Khanna PP, et al. American College of Rheumatology. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic non-pharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken).* 2012; 64(10): 1431–1446, doi: [10.1002/acr.21772](https://doi.org/10.1002/acr.21772), indexed in Pubmed: [23024028](https://pubmed.ncbi.nlm.nih.gov/23024028/).
  125. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis.* 2017; 76(1): 29–42, doi: [10.1136/annrheumdis-2016-209707](https://doi.org/10.1136/annrheumdis-2016-209707), indexed in Pubmed: [27457514](https://pubmed.ncbi.nlm.nih.gov/27457514/).
  126. Hui M, Carr A, Cameron S, et al. British Society for Rheumatology Standards, Audit and Guidelines Working Group. The British Society for Rheumatology Guideline for the Management of Gout. *Rheumatology (Oxford).* 2017; 56(7): e1–e20, doi: [10.1093/rheumatology/kex156](https://doi.org/10.1093/rheumatology/kex156), indexed in Pubmed: [28549177](https://pubmed.ncbi.nlm.nih.gov/28549177/).
  127. Mach F, Baigent C, Catapano AL, et al. ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2020; 41(1): 111–188, doi: [10.1093/eurheartj/ehz455](https://doi.org/10.1093/eurheartj/ehz455), indexed in Pubmed: [31504418](https://pubmed.ncbi.nlm.nih.gov/31504418/).
  128. Singh JA, Reddy SG, Kundukulam J. Risk factors for gout and prevention: a systematic review of the literature. *Curr Opin Rheumatol.* 2011; 23(2): 192–202, doi: [10.1097/BOR.0b013e3283438e13](https://doi.org/10.1097/BOR.0b013e3283438e13), indexed in Pubmed: [21285714](https://pubmed.ncbi.nlm.nih.gov/21285714/).
  129. Jacob RA, Spinozzi GM, Simon VA, et al. Consumption of cherries lowers plasma urate in healthy women. *J Nutr.* 2003; 133(6): 1826–1829, doi: [10.1093/jn/133.6.1826](https://doi.org/10.1093/jn/133.6.1826), indexed in Pubmed: [12771324](https://pubmed.ncbi.nlm.nih.gov/12771324/).
  130. Schlesinger N. Dietary factors and hyperuricaemia. *Curr Pharm Des.* 2005; 11(32): 4133–4138, doi: [10.2174/138161205774913273](https://doi.org/10.2174/138161205774913273), indexed in Pubmed: [16375734](https://pubmed.ncbi.nlm.nih.gov/16375734/).
  131. Dalbeth N, So A. Hyperuricaemia and gout: state of the art and future perspectives. *Ann Rheum Dis.* 2010; 69(10): 1738–1743, doi: [10.1136/ard.2010.136218](https://doi.org/10.1136/ard.2010.136218), indexed in Pubmed: [20858623](https://pubmed.ncbi.nlm.nih.gov/20858623/).
  132. [https://www.whocc.no/atc\\_ddd\\_index/](https://www.whocc.no/atc_ddd_index/) (February 10, 2022).
  133. Charakterystyka Produktu Leczniczego, Milurit, tabletki 100 mg. [https://leki.urpl.gov.pl/files/Milurit\\_tabl\\_100\\_300\\_allopinol.pdf](https://leki.urpl.gov.pl/files/Milurit_tabl_100_300_allopinol.pdf) (February 10, 2022).
  134. Charakterystyka Produktu Leczniczego, Denofix, tabletki 80 mg. [https://leki.urpl.gov.pl/files/48\\_Denofix\\_tabl\\_powi\\_80mg\\_25081.pdf](https://leki.urpl.gov.pl/files/48_Denofix_tabl_powi_80mg_25081.pdf) (February 10, 2022).
  135. Deeks ED. Lesinurad: A Review in Hyperuricaemia of Gout. *Drugs Aging.* 2017; 34(5): 401–410, doi: [10.1007/s40266-017-0461-y](https://doi.org/10.1007/s40266-017-0461-y), indexed in Pubmed: [28425024](https://pubmed.ncbi.nlm.nih.gov/28425024/).