

Hyperuricemia and its treatment in patients with a high cardio-vascular risk — experts opinion

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Introduction

Hyperuricemia is defined as a serum uric acid level exceeding 6.8 mg/dL (404 μmol/L). At that level we can observe a crystallization of a monosodium urate in the water solution at the physiological pH and body temperature [1–4]. The solubility of the uric acid in water and physiologic fluids is limited and depends mostly on the pH and temperature. The solubility in water reaches 6.8 mg/dL (404 μmol/L) at the temperature of 37°C. The solubility significantly decreases at low temperatures and at acidification reaching 6.0 mg/dL (360 μmol/L) at 35°C degrees, and only about 4 mg/dL (238 μmol/L) at 30°C degrees [2]. Due to this fact, the crystals of the monosodium urate firstly deposit in tissues that are less warmed and poorly vascularised (tendons, ligaments) or not vascularised (cartilages) e.g. concha, para peripheral joints regions [1]. In vivo the formation and deposition of the urate crystals depends not only on the uric acid concentration, pH and temperature, but is also regulated by the concentration of the sodium chloride and presence of some connective tissue

components (probably the fragments of proteoglycans). Moreover, it is important to mention that the solubility of the uric acid cannot be equated with the solubility of its sodium urate (forming the deposits in tissues) and depends also on the dissociation of both substances.

The uric acid is a metabolite of purines which metabolism influences the development of the hyperuricemia. The uric acid is a final product of the purines transformation in human and apes while in other animals it is further metabolised (catalysed by an uricase) to the allantoin, which has higher solubility. The evolutionary lack of the uricase promotes the development of the higher uric acid concentrations in human. Hyperuricemia may result from the increased production of purines (also caused by the intensive lysis of cells), the excessive supply (and absorption) of purines and from the impaired excretion of the uric acid. Around two thirds of the total urates pool in the organism derives from the endogenous production, while the remaining one third derives from the consumed

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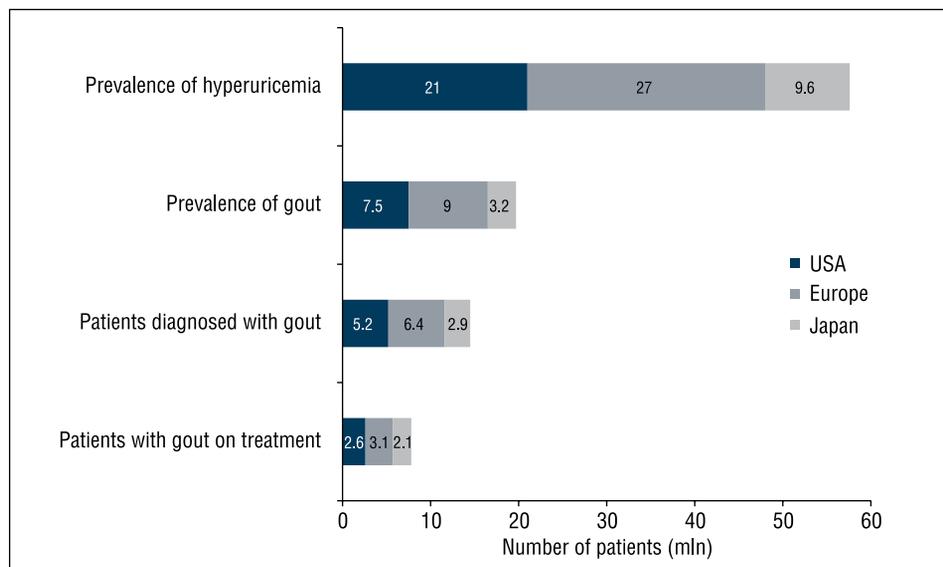


Figure 1. Prevalence of hyperuricemia in the world based on NHANES I-III reports (based on: BMC Public Health. 2004; 4: 9; BMC Public Health. 2013; 13: 664; Rheum Dis Clin North Am. 2014; 40: 155–175; Ann Rheum Dis. 2014; 73: 1470–1476)

dietary purines. About 70% of the produced urates is eliminated by the kidneys while the rest is eliminated by the alimentary tract. Hyperuricemia results from the overproduction of the uric acid (10%) or from the insufficient elimination of the uric acid (90%) [2–4].

The recent epidemiologic studies prove, that the problem of hyperuricemia and gout concerns many millions of people (Fig. 1).

In the nearest future, due to the obesity and metabolic disorders as well as the ageing of the human population, one should expect the increasing frequency of hyperuricemia [5, 6]. This phenomenon is related to the rapideconomic development and change of lifestyle of the society with higher socio-economic status [7, 8]. An increased prevalence of hyperuricemia is favoured by many common habits, such as massive consumption of purine rich food (meat, giblets, seafood), fructose, alcohol abuse, taking small doses of aspirin and thiazides. Metabolic disorders are a risk factor for hyperuricemia, and around 50% of patients with gout presents concomitantly symptoms of a metabolic syndrome. A diagnosed gout is closely connected with diabetes, obesity, coronary disease and arterial hypertension [4, 9, 10]. A schema of the main risk factors of hyperuricemia is presented in Figure 2.

An increased concentration of the uric acid is also present in the myeloproliferative and lymphoproliferative diseases, polycythaemia vera, neoplastic diseases, haemolytic anaemia and during the chemotherapy and radiotherapy treatment (so called tumour lysis syndrome) [2].

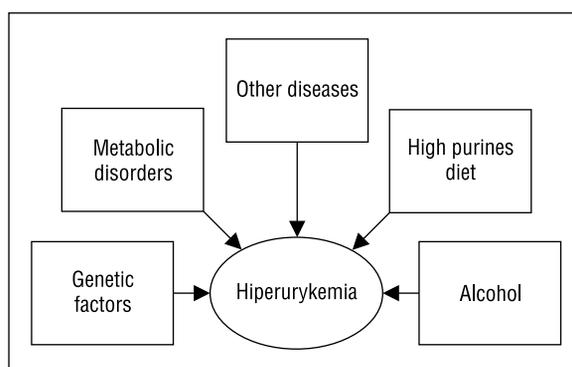


Figure 2. Schematic presentation of the main risk factors of hyperuricemia (based on: J Rheumatol. 2000; 27: 1501–1505; Int J Cardiol. 2016; 15: 8–14)

Asymptomatic hyperuricemia describes a condition of increased concentration of the uric acid [$> 6.8 \text{ mg}\%$ ($404 \mu\text{mol/L}$)] without any symptoms of the gout [3]. This condition may last for many years and only in a dozen or so percentage of patients causes the development of the gout.

The relation between hyperuricemia and the cardiovascular diseases

It has long been known that the antioxidative properties of the uric acid may prevent ageing, oxidative stress and cell damage [11–15]. However, the recent clinical and epidemiological evidence suggest a negative influence of the elevated serum concentrations of the uric acid. Hyperuricemia plays an important,

Tabla I. Diseases of a cardiovascular system and factors associated with an increased uric acid concentration (based on: Hypertension. 2006; 47: 962–967; BMC Cardiovascular Disorders. 2016; 16: 85–98; Int J Cardiol. 2016; 15: 8–14; N Engl J Med. 2008; 359: 1811–1821; J Cardiol. 2012; 59: 235–242)

Arterial hypertension and prehypertension
Kidney diseases (microalbuminuria, reduced glomerular filtration)
Metabolic syndrome
Obstructive sleep apnoea
Blood vessels diseases (of the jugular, peripheral and coronary arteries)
Stroke and vascular stupor
Pre-eclampsia
Increased levels of the acute phase reactants [C-reactive protein, tissue plasminogen activator (PAI) etc.]
Dysfunction of the endothelium
Oxidative stress
Advanced age
Male Sex

pathophysiological role in the development of the arterial hypertension, diabetes mellitus type 2 and is an independent cardiovascular risk factor [13–17]. The most common cardiovascular diseases and the factors related to the increased concentration of the uric acid are presented in Table I.

It is related to a common presence of hyperuricemia in persons with the increased cardiovascular risk: men, postmenopausal women (oestrogens fosters the renal elimination of the uric acid), persons with obesity, arterial hypertension, diabetes, dyslipidaemia [3, 18]. Moreover, in patients with arterial hypertension associated with the metabolic syndrome a positive correlation between the serum uric acid concentration and a body mass index, fasting insulin concentration and the index of the insulin-resistance HOMA-IR can be also observed [4]. Hyperuricemia is often present in patients with threshold values of the blood pressure, especially when it is associated with the proteinuria [9, 10, 19].

Lee et al. [19] demonstrated, that patients with prehypertension (systolic pressure 120–140 mmHg or diastolic pressure 80–90 mmHg) and microalbuminuria had higher concentrations of the uric acid, compared to persons with normal albuminuria [males 6.5 ± 1.1 mg/dL (387 ± 65 μ mol/L) and to 6.2 ± 1.1 mg/dL (369 ± 65 μ mol/L) respectively; $p = 0.017$; females 4.8 ± 0.9 mg/dL (286 ± 54 μ mol/L) vs. 4.4 ± 0.9 mg/dL (262 ± 54 μ mol/L); $p = 0.006$]. It was proven in the logistic regression model that, having included all cardiovascular risk factors in the group of patients with the prehypertension, the higher quadrille of the uric acid concentrations was rela-

ted to more than 2 fold higher risk of microalbuminuria occurrence compared to the lowest quadrille in both males [odds ratio (OR) 2.12; 95% confidence interval (CI) range: 1.16–3.87] and females (OR 3.36; 95% CI range: 1.17–9.69).

On the basis of the observation of the original cohort of the Framingham study, important data confirming the predictive value of the uric acid concentrations, was acquired. An increased risk of the coronary disease and cardiac infarction for patients with high serum uric acid concentrations was demonstrated in this study. The mean serum uric concentration was 5.0 mg/dL (297 μ mol/L) in males and 3.9 mg/dL (232 μ mol/L) in females [16, 20].

There is some evidence confirming that in the population of patients with a very high cardiovascular risk, the serum uric acid concentration is an independent predictor of mortality. In the study published by Ndrepepa et al. [21] a group of 5124 patients with acute coronary syndromes (1629 heart infarctions with ST segment elevation, 1332 without ST segment elevation and 2163 with unstable coronary disease) was divided into quartiles according to the serum uric acid concentrations as follows: quartile 1: 1.3–5.3 mg/dL (77–315 μ mol/L); quartile 2: 5.3–6.3 mg/dL (315–375 μ mol/L); quartile 3: 6.3–7.5 mg/dL (375–446 μ mol/L); quartile 4: from 7.5–18.4 mg/dL (446–1094 μ mol/L). After a year of observation 80 deaths were recorded in quartile 1, 77 in quartile 2, 72 in quartile 3 and 122 deaths in quartile 4 of the serum uric acid concentrations. The uncorrected mortality risk reached 3.05 (95% CI 2.54–3.67, $p < 0.001$) for the fourth quartile vs. the first quartile of the uric acid concentrations. It is worth mentioning, that the correlation between the uric acid concentration and mortality remained significant even if the common cardiovascular risk factors, kidney function and inflammatory states had been included in the analysis (by the increase of 12% of the corrected mortality risk per year for 1 mg/dL (59 μ mol/L) of the uric acid). The data is shown in Figure 3.

It was also proven that the elevated uric acid concentration is not only related to an increased risk of the cardiovascular system diseases, but also predisposes patients to a higher incidence of the cognitive disorders [22–24]. The results of the epidemiological investigation show that hyperuricemia may cause dementia [12, 24]. Ruggiero et al. [12] in the cross-sectional study of the population of the 1016 elderly people, evaluated in the multifactor logistic regression model the risk of dementia depending on the serum uric acid concentration. The study revealed that the patients with dementia had

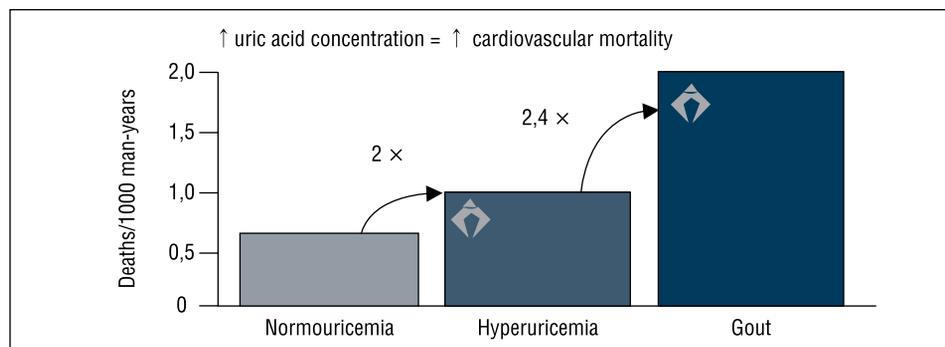


Figure 3. The increase in the uric acid concentration by 1 mg/dL = the increase of the corrected mortality risk per each year by 12% (based on: *Am J Cardiol.* 2012; 109: 1260–1265)

higher serum uric acid concentrations ($p = 0.001$). Moreover, patients with the highest uric acid concentrations had threefold (OR = 3.32; 95% CI: 1.06–10.42) higher probability to develop a syndrome compared to those who were in the lowest tertile of the concentrations.

Pathophysiologic background of the influence of hyperuricemia on the cardio-vascular system

The dysfunction of the endothelium and the systemic infection are the main two mechanisms which impact constituted a basis to explain the effects of the hyperuricemia [13, 25]. The inflammatory process has a systemic character and is initiated by the crystals of the monosodium urate which are eliminated by the phagocytes e.g. neutrophils and macrophages. The development of the inflammation is assisted by the innate immunity system. The microcrystals are coated by opsonising proteins what leads to the activation of the type 2 and 4 Toll-like receptors and initiation of the inflammatory process and activation of the inflammasome. The pro-inflammatory cytokines released by the monocytes and synoviocytes transform the local process into the systemic inflammation [26]. It is considered that the chronic systemic inflammation causes the damage of the endothelium of the blood vessels. As a result, the synthesis of the nitric oxide is stopped in the vessel wall and the vascular renin-angiotensin system is activated. This leads to the hypertrophy of the muscular membrane of the vessels (including the proliferation and migration of the myocytes) [15]. Besides, the chronic, systemic inflammatory process escalates the progress of the sclerotic changes [27].

One of the main places, in which the antioxidative effects of the uric acid occur, is a central nervous system, especially in case of coexistence of such medical

conditions as: multiple sclerosis, Parkinson disease or a stroke [28, 29]. The studies suggest that the potential role of the uric acid in prevention of the acute activation, by the oxidants, of the pro-inflammatory cells in the blood, may be a beneficial mechanism, in which the uric acid concentration presents its total antioxidative activity. On the other hand, uric acid cannot eliminate all oxygenic radicals, such as superoxides. Experiments have shown, that, depending on the concentration, uric acid may become a pro-oxidant through the activation of the intracellular production of the superoxide by the NADP oxidase. It is so called the oxidant-antioxidant paradox [30]. The uric acid, due to its degradation and aforementioned mechanisms, may form the free radicals, what causes simultaneously an inflammatory reaction and dysfunction of the endothelium [30, 31].

Pharmacological treatment of hyperuricemia

Clinical practice in the treatment of the hyperuricemia is a necessity. Another important issue is the time when the treatment should be started. The paper presents a study in which a mathematic model was constructed to evaluate two strategies of treatment: of all asymptomatic patients with use of allopurinol or to start the therapy once the symptoms occur (symptomatic treatment). In this model a hypothetical cohort of 50 year old males with different serum uric acid concentrations [6.0–6.9 mg/dL (357–410 $\mu\text{mol/L}$) and 7.0–7.9 mg/dL (416–470 $\mu\text{mol/L}$)] were simulated and observed for over 20 years. The main end-points of the model were the occurrence of the cardiovascular incident and the ratio of mortality related with it. In the group of 50 year old males with serum uric acid levels 6.0–6.9 mg/dL (357–410 $\mu\text{mol/L}$), who had received allopurinol independently of the symptoms, a 30% decrease of the mean

number of cardiovascular incidence and 39% lower mortality rate was prognosticated, in comparison to the patients treated only with gout symptoms. The authors affirmed the presented model was the most effective in the prevention of the cardiovascular incidents as long as the treatment when the serum uric acid concentration exceeds 7.0 mg/dL (416 $\mu\text{mol/L}$) in males and 5.0 mg/dL (297 $\mu\text{mol/L}$) in females [32].

Based on these data, the evaluation of the serum uric acid concentrations was included into the routine tests in the recommendations of both Polish Society of Arterial Hypertension (Polskie Towarzystwo Nadciśnienia Tętniczego, PTNT) in 2011 and 2015 and European Society Cardiology and European Society Hypertensiology (ESC/ESH) in 2013 [33–35].

In the cited recommendations the hypotensive therapy of patients with coexisting gout should include sartanes, angiotensin-converting-enzyme inhibitors and calcium antagonists. The drugs which may increase the concentration of the uric acid, mainly thiazide or thiazide-like diuretic and beta-adrenergic are not recommended.

The analysis of the Losartan Intervention for Endpoint Reduction (LIFE) study resulted in some publications concerning the uricosuric properties of losartan. These properties were due to two mechanisms: to the increase of the tubular secretion (a mechanism typical of drugs blocking the RAA system) and to the increase of the tubular secretion of the uric acid (a mechanism typical of losartan) [36]. These reports resulted in the inclusion of losartan in the PTNT 2011 recommendations, as a hypotensive drug by choice in the patients with hypertension and hyperuricemia [33]. There was no such distinction of losartan neither in the ESC/ESH nor American recommendations [34, 37]. A detailed data analysis, the evidence of the unique uricosuric activity of losartan seem to be insufficient and not confirmed by the EBM proofs. Moreover, losartan, due to its short activity time does not meet the actual criteria recommending to use the drugs with 24-hours efficacy [35].

In the PTNT 2015 guidelines the value of allopurinol was emphasized, as a first-line drug in the non-hypotensive therapy in patients with arterial hypertension and asymptomatic hyperuricemia.

“Allopurinol, which is used for long-term therapy of gout, may also be considered in hypertensives with asymptomatic hyperuricaemia, particularly those with cardiovascular disease, due to a proven beneficial effect of this drug on the improvement of endothelial function and aortic compliance” [35].

Drugs reducing the concentration of the uric acid available in Poland

Allopurinol

Allopurinol is a non-selective xanthine oxidase inhibitor, which inhibits synthesis of the uric acid depending on a dose. It is considered to be one of the strongest drugs reducing the serum concentrations of the uric acid [38]. The treatment should be initiated by a low dose of 100 mg/day and escalated by 100 mg every 2–4 weeks to the maximum dose of 900 mg/day if necessary. It can be expected, that each 100 mg of allopurinol will reduce the concentration of the uric acid by 1 mg/dL. The drug dose must be always adjusted to the creatinine clearance and to the concomitant medications used by the patient. To obtain a good therapeutic effect the appropriate dialy dosing of allopurinol should be applied, i.e. the initial dose should equal around 100–200 mg, the maintenance dose 300–600 mg and the maximum dose 700–900 mg/day [39].

A meta-analysis, comparing the allopurinol with another drugs reducing the serum concentration of uric acid, has been recently published [40]. The evidence of the comparable influence on the treatment interruption due to the adverse or severe adverse events as well as on the frequency of the severe gout attacks when allopurinol (100–600 mg/day) was compared with placebo, benzbromarone (100–200 mg/day) or febuxostate (80 mg/day). Single examinations did not report any difference in the incidence of the acute gout arthritis (“gout attacks”), when allopurinol (300 mg/day) was compared to placebo or in the regression of changes caused by the urates deposits, when allopurinol (200–300 mg/day) was compared to febuxostate (80 mg/day) [41].

Allopurinol is commonly used not only due to its ability to reduce the concentration of the uric acid, but also due to its proven protective impact on the cardiovascular system. A beneficial role of allopurinol therapy in reducing the mortality was confirmed in the study conducted in the population of patients with hyperuricemia [serum urates concentration > 7.0 mg/dL (> 416 $\mu\text{mol/L}$)]. Patients aged at least 40 years were involved in the study. The total death risk was compared between the allopurinol treated ($n = 2483$) and untreated patients ($n = 7441$). Patients in the allopurinol treated group had initially worse prognostic factors of death, were characterized by a higher body mass index and a higher frequency of the comorbidities. After including the initial uric acid concentration, it was proven that the administration of allopurinol was related to a decreased total mortality rate by 22% (risk ratio, HR 0.78; 95% CI:

0.67–0.91). The results suggesting directly that the use of allopurinol may improve the overall survival rate in patients with hyperuricemia [42].

In another study patients aged ≥ 40 year, with diagnosed hyperuricemia (serum uric acid concentration 6.0 mg/dL ($> 357 \mu\text{mol/L}$) in females and 7.0 mg/dL ($> 416 \mu\text{mol/L}$) in males. In the group of 5927 patients treated with allopurinol and 5927 untreated patients, 654 and 718 persons respectively, died during the observation period (median = 2.9 years). Allopurinol therapy was involved lower total mortality risk (HR 0.89; 95% CI: 0.80–0.99) [43].

The above-mentioned dependence seems to result from the close relation between the concentration of the uric acid and the prevalence of the cardiovascular diseases. The publication by Agarwal et al. [44] supplied some evidence of the beneficial influence of allopurinol on reducing the arterial hypertension. In the meta-analysis, including 10 clinical studies (738 participants), the systolic blood pressure was reduced by 3.3 mmHg (95% CI: 1.45–5.3; $p=0.001$) and the diastolic blood pressure was reduced by 1.3 mmHg (95% CI: 0.1–2.5 mmHg; $p = 0.03$), among patients receiving allopurinol and the control group (untreated). This fact confirms the relation between the administration of allopurinol and a small but significant reduction of the blood pressure. The effect may be potentially used to optimized the therapy in patients with arterial hypertension and coexisting hyperuricemia. Comparable conclusions were drawn from the Chinese meta-analysis in which it was proven that allopurinol reduces the systolic and diastolic blood pressure in patients with hyperuricemia [45]. Allopurinol also caused an important reduction of the systolic blood pressure in patients taking hypotensive drugs as well as in the untreated ones. The reduction of the blood pressure may be caused by the beneficial effect of allopurinol on the stiffness of the arteries and, consequently, on the reduction of the cardiovascular complications [46]. The aim of another study was to define the relation between the concentration of the uric acid and the prevalence and the severity of the coronary disease [47]. 705 patient, who had undergone coronarography, were involved in the study. All participants were evaluated in terms of the presence of the cardiovascular risk factors and the pharmacotherapy. Before the coronarography the serum uric acid concentration was measured in all patients. The severity of the coronary disease was defined by the SYNTAX scale. The mean concentration of the uric acid was 5.3 ± 1.5 mg/dL ($315 \pm 89 \mu\text{mol/L}$) in the control group; 5.6 ± 1.4 mg/dL ($333 \pm 84 \mu\text{mol/L}$) in the group with mild coronary disease; 6.2 ± 1.6 mg/dL ($369 \pm 95 \mu\text{mol/L}$) in the

group with the moderate coronary disease and 6.5 ± 1.7 mg/dL ($387 \pm 107 \mu\text{mol/L}$) in the group with severe form of the disease. The study shown that the routing biochemical evaluation of the uric acid concentration could be useful in diagnostics of the coronary disease.

Allopurinol therapy, as well as any drugs from other groups, is related to the risk of developing some side effects. The most common side effects are benign skin changes, which occurs in about 2% of patients treated by allopurinol. In 0.4% it may change into life threatening condition defined as a allopurinol hypersensitivity syndrome (AHS). This syndrome is characterized by a erythematous, exfoliating skin rash, fever, hepatitis and a tubulointerstitial nephritis and eosinophilia. The mortality rate of this syndromes reaches 25%. It should by stressed that not all the typical syndromes must be simultaneously present. That is why the occurrence of one of them e.g. deterioration of the renal function or increase of the transaminase activity should suggest the development of AHS. The concomitant use of allopurinol with such drugs as: thiazides, ampicillin and amoxicillin; is a risk factor of this potentially fatal syndrome [48, 49]. Some experts suggest that a decrease glomerular filtration in kidneys may also increase the risk of AHS occurrence. Therefore, the allopurinol dose, in this group of patients, must be adjusted to the glomerular filtration rate [50].

Febuxostat

Another drug which is a xanthine oxidase inhibitor decreasing the concentration of the serum uric acid was recently introduced in Poland [51]. According to the product characteristic, the main indication for use of febuxostat is a chronic hyperuricemia associated with diseases which already resulted in the urates deposition (including the gout tubercles and active gout inflammation or medical history).

The contraindication are:

- hypersensitivity to the active substance or to any other composite of the medication;
- patients with coronary disease or with congestive heart failure;
- children and youth under 18 years of age;
- pregnancy and breast feeding.

The concomitant use of mercaptopurine, azathioprine and theophylline is not recommended due to the risk of the increased blood levels of these substances.

The side effects of febuxostat, as well as allopurinol, are rare and have a mild course. The most severe side effects are the cases of severe anaphylaxis, including the life threatening Stevens-Johnson

Table II. Experts suggestion concerning the proposed doses of allopurinol in patients with high cardiovascular risk and initial serum uric acid concentration

Initial serum uric acid concentration [mg/dL]	Exemplary dose of allopurinol in a male with a high cardiovascular risk* [mg/day]	Exemplary dose of allopurinol in a male with a high cardiovascular risk** [mg/day]
4–4.9	Non-pharmacological treatment	Non-pharmacological treatment
5–5.9	Non-pharmacological treatment or 100	100
6–6.9	100 or 200	200
7–7.9	300	300
8–8.9	400	400
9–9.9	500	500
10–10.9	600	600
11–11.9	700	700
12–12.9	800	800
13 and higher	900	900

*patients with a high cardiovascular risk are those with hypertension, diabetes, metabolism syndrome or atherosclerosis of any vascular (including patients with coronary disease and cerebral atherosclerosis)

**the data suggests that therapeutic decisions of the administration of allopurinol should be applied rather in the cases of a lower serum uric acid concentration in females than in males

syndrome (a toxic, necrotic epithelium separation and acute anaphylactic reactions) or a drug reaction with eosinophilia and systemic syndromes (DRESS) [52].

Summary

The presented data shows that the increased concentration of the uric acid, independently of the occurrence of the gout syndromes, is associated with an increased risk of the development of many cardiovascular diseases. The administration of allopurinol significantly reduces the serum concentration of the uric acid and lowers the risk of cardiovascular disease occurrence and of the general mortality. According to this data and the unsatisfactory diagnosis and the treatment of hyperuricemia, the role of the elevated uric acid concentration should be considered as an important prognostic factor for patients, especially in the prevention of the cardiovascular diseases.

Experts who presenting this opinion suggest that the antyuricemic therapy should be administered more commonly in Poland and the drug dose adjusted to a patients' risk and initial uric acid concentration. The supplementary data concerning the selection process, taking into consideration the individualization of treatment, are presented in Table II, based on the example of the most popular antiuricemic drug — allopurinol.

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