Folia Cardiologica 2019
tom 14, nr 2, strony 129–135
DOI: 10.5603/FC.a2019.0033

ISSN 2353–7752

Prevalence of hyperuricemia in very high cardiovascular risk patients — a single centre retrospective cohort study

Występowanie hiperurykemii u pacjentów obciążonych bardzo wysokim ryzykiem sercowo-naczyniowym — jednoośrodkowe retrospektywne badanie kohortowe

Marcin Tomasz Wełnicki[1], Jakub Żółkiewicz[2], Daniel Śliż[1], Wiesława B. Duda-Król[1], Artur Mamcarz[1]

[1]Third Department of Internal Medicine and Cardiology, Medical University of Warsaw, Warsaw, Poland
[2]Student Society at the Third Department of Internal Medicine and Cardiology, Medical University of Warsaw, Warsaw, Poland

Abstract

Introduction. Asymptomatic hyperuricemia is an established independent risk factor for cardiovascular (CV) disease. However, the awareness of this fact among physicians is still insufficient. Data are also lacking on the prevalence of asymptomatic hyperuricemia in a population of patients potentially requiring drug therapy.
The aim of the study was to assess the prevalence of asymptomatic hyperuricemia in the population of patients hospitalized in an internal medicine unit and the frequency of use of uricosuric drugs in this group of patients.

Material and methods. Single centre retrospective cohort study — evaluation of medical records of patients hospitalized in an internal medicine unit in the first half of 2018. The analysis included biochemical testing results, data on patients' medical conditions and drug therapy used. Based on the collected data, a group of patients with a very high CV risk was identified in whom serum uric acid level ≥ 5 mg/dL is considered abnormal. Typical statistical methods were used including descriptive statistics, appropriate parametric and non-parametric tests to evaluate significance of differences in the values of selected parameters between the study groups, and generalized regression models. Statistically significant differences were conventionally defined as $p < 0.05$.

Results. The analysis included data from 354 patients, of whom 194 (55%) met the criteria of a very high CV risk. These patients were older (75 vs. 62 years, $p < 0.001$) and had lower glomerular filtration rate values (85 vs. 118 mL/min/1.73 m^2, $p = 0.04$) and higher mean serum uric acid level (6.6 vs. 5.5 mg/dL, $p < 0.001$) compared to the control group (non-very high CV risk patients). No significant differences in lipid levels were found between the two groups. Serum uric acid level was measured in 55% of patients in the very high CV risk group. Abnormal renal function parameters were an independent predictor of serum uric acid level above 5 mg/dL in this group ($R^2 = 0.18$, $p < 0.001$). Serum uric acid level was above 5 mg/dL in 70% of very high CV risk patients in whom it was measured. Allopurinol was used in only 25% of these patients, and the mean serum uric acid level in those receiving uricosuric treatment was 8.1 mg/dL. The most commonly used allopurinol dose was 100 mg/day. The mean serum uric acid level in patients not receiving uricosuric treatment was 6.2 mg/dL.

Conclusions. Serum uric acid level measurement is too rarely considered in the biochemical profile of patients at a very high CV risk. Serum uric acid level may be an indication for the use of uricosuric drugs in most patients at a very high CV risk. In the light of the current expert consensus, allopurinol is underused and underdosed in the very high CV risk group.

Key words: allopurinol, uric acid

Folia Cardiologica 2019; 14, 2: 129–135

Address for correspondence: dr n. med. Marcin Tomasz Wełnicki, III Klinika Chorób Wewnętrznych i Kardiologii, II Wydział Lekarski, Warszawski Uniwersytet Medyczny, ul. Bursztynowa 2, 04–749 Warszawa, Międzyleski Szpital Specjalistyczny, Poland, e-mail: welnicki.marcin@gmail.com

Introduction

Clinically, hyperuricemia has been traditionally associated with rheumatological and oncological disease. However, gout develops in only 30% of subjects with hyperuricemia, and an asymptomatic increase in serum acid level is an established but still underrated independent risk factor for cardiovascular disease [1–2]. In the general population, serum uric acid level in the range of 3–7 mg/dL (180–420 μmol/L) is considered normal, and for many years, the European League Against Rheumatism (EULAR) recommended to treat asymptomatic hyperuricemia only when serum uric acid level was > 12 mg/dL [3–6]. Currently, however, there is an expert consensus that asymptomatic hyperuricemia is associated with an increased risk of diabetes type 2, hypertension, chronic kidney disease, and cardiovascular mortality. Asymptomatic hyperuricemia becomes clinically important already at serum uric acid levels below 7 mg/dL [7–13]. Target serum uric acid level should be < 5 mg/dL in patients with at least two of the following conditions: hypertension, diabetes, dyslipidaemia, chronic kidney disease, recent myocardial infarction or stroke [13]. However, data are still lacking on the prevalence of asymptomatic hyperuricemia as defined above in patients at high cardiovascular risk, and on its effect on therapeutic decision making in the context of uricosuric drug use.

The aim of the study was to evaluate retrospectively the frequency of serum uric acid level measurements in patients admitted to an internal medicine unit. We also evaluated the relation between measured serum uric acid levels and therapeutic decisions in the context of treating hyperuricemia depending on the patient cardiovascular risk.

Material and methods

We retrospectively evaluated admissions to the Internal Medicine Unit of the Międzylesie Specialist Hospital from January 1 to June 30, 2018. The analysis did not include hospitalizations that led to a patient's death. Very high cardiovascular risk was defined as the presence of generalized atherosclerosis (based on the data from medical history and/or hospital discharge diagnoses) or concomitant presence of at least two of the following conditions: hypertension, diabetes, chronic kidney disease [glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2], ischaemic heart disease (previous myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention, stable ischemic heart disease), or previous stroke. The control group included patients who did not meet the above criteria of a very high cardiovascular risk. The two groups were compared in regard to renal function, lipid profile, serum uric acid level, age, comorbidities, and treatment with allopurinol. In case of repeated admissions, the one with serum uric acid level measurement was included in the analysis. If serum uric acid level was not measured during any of the repeated admissions, the one that provided the most of the analysed data was included in the analysis. Statistical analysis was performed using the STATISTICA 12 PL software. Significance of the differences in quantitative variables was assessed using the Student *t* test or the Mann-Whitney U test, depending on variable distribution. Significance of the differences in categorical variables was assessed using the chi-square test. Generalized linear regression models were used to evaluate variables that had an effect on the decision to measure serum uric acid level and to treat hyperuricemia in patients at a very high cardiovascular risk. For all tests, statistical significance was set at $p < 0.05$.

Results

Among 428 admissions from January 1 to June 30, 2018, 50 led to the patient's death and were not included in the analysis. Of the remaining 378 admissions, 18 patients were hospitalized more than once (range 2–5). Ultimately, data from 354 admissions were included in the analysis, with 194 (55%) patients assigned to the very high cardiovascular risk group (Group A), and the remaining 160 (45%) patients not fulfilling the very high cardiovascular risk criteria as defined in the methods (Group B). The patients in Group A were older (75 vs. 62 years, $p < 0.001$), had higher mean serum uric acid level (6.6 vs. 5.5 mg/dL, $p < 0.001$; Figure 1), and lower GFR (85 vs. 118 mL/min/1.73 m^2, $p = 0.04$). We did not find significant differences in lipid levels between the two groups (Table 1). Serum uric acid level was measured in 55% patients in Group A and 45%

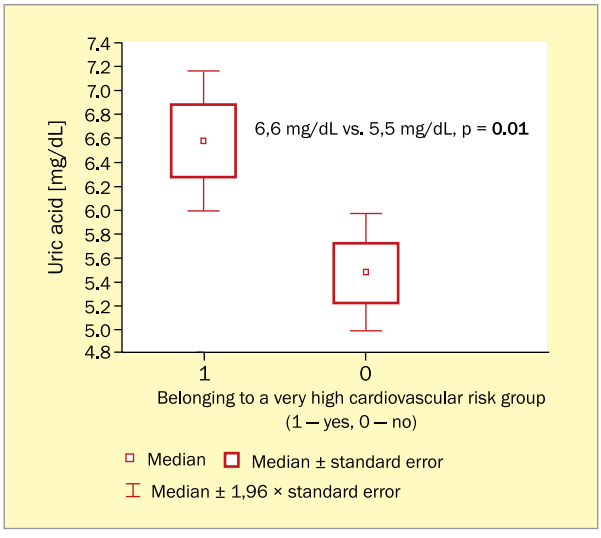

Figure 1. Box plot for serum uric acid level in the study population: very high cardiovascular risk group vs. control group

Table 1. Study population characteristics (age and biochemical testing results) in the very high cardiovascular (CV) risk group and the control group

Variable (mean ± SD)	Very high CV risk group (N = 194)	Control group (N = 160)	p
Age [years]	75.51 (± 11.9)	62.06 (± 18.6)	**< 0.001**
GFR [mL/min/1.73 m^2]	85.39 (± 43.8)	118.00 (± 51.2)	**< 0.001**
Creatinine [mg/dL]	1.24 (± 0.3)	0.77 (± 0.3)	**< 0.001**
Urea [mg/dL]	48.76 (± 28.8)	32.53 (± 19.8)	**< 0.001**
Uric acid [mg/dL]	6.57 (± 3.1)	5.48 (± 2.14)	**0.01**
Total cholesterol [mg/dL]	147.17 (± 47.6)	154.08 (± 52.9)	0.28
HDL cholesterol [mg/dL]	39.87 (± 13.5)	42.32 (± 15.9)	0.19
LDL cholesterol [mg/dL]	82.11 (± 35.7)	84.86 (± 33.2)	0.54
TG [mg/dL]	127.59 (± 73.3)	136.32 (± 155.1)	0.56

SD — standard deviation; GFR — glomerular filtration rate; HDL — high-density lipoprotein; LDL — low-density lipoprotein; TG — triglycerides

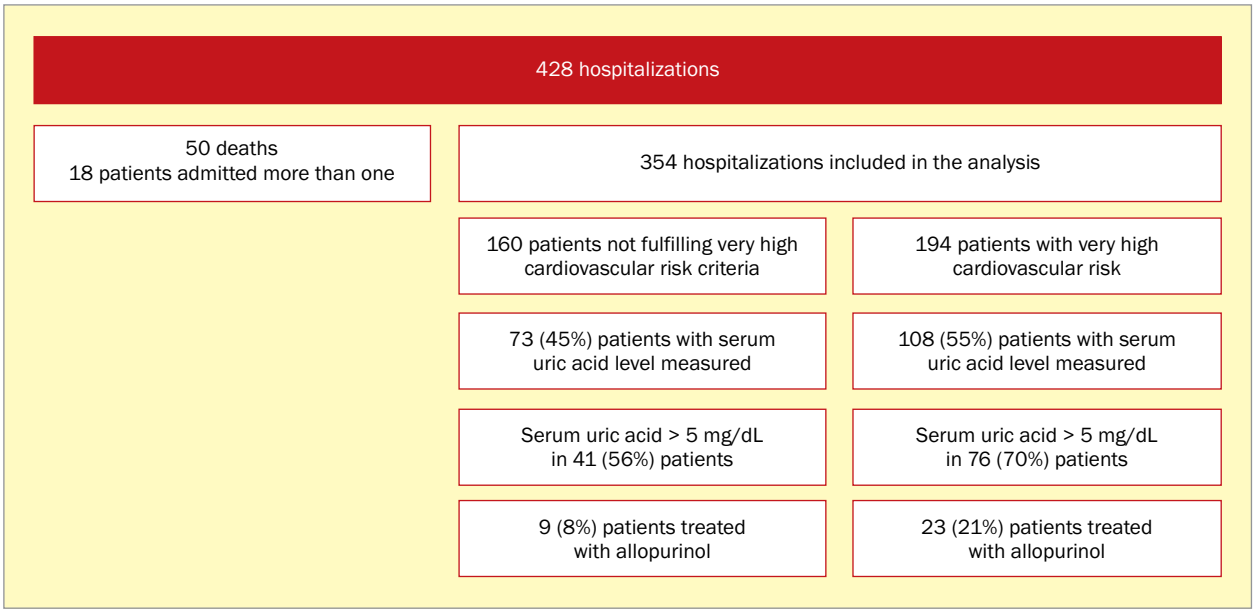

Figure 2. Patient flowchart showing serum uric acid measurements, prevalence of hyperuricemia, and allopurinol use in the study population

patients in Group B. In both groups, serum uric acid level showed a moderate but significant negative correlation with GFR ($r = -0.4$). In the very high cardiovascular risk group, a positive correlation was also seen with age ($r = 0.25$), urea level ($r = 0.45$) but not creatinine, and triglyceride level ($r = 0.25$). However, regression analysis showed that abnormal renal function was the only independent predictor of serum uric acid level > 5 mg/dl ($R^2 = 0.18$, $p < 0.001$).

In 70% of patients in Group A in whom serum uric acid level was measured, it was higher than 5 mg/dL. Allopurinol was given in only 25% of these patients (Figure 2). The mean serum uric acid level in these patients was 8.1 mg/dL compared to 6.2 mg/dL in those in whom allopurinol was not used.

Among concomitant conditions, the likelihood of serum uric acid level measurement was increased by the presence of diabetes, and concomitant chronic kidney disease affected whether allopurinol was given (Figures 3 and 4). The most commonly used allopurinol dose was 100 mg/day. No correlation was found between allopurinol dose and serum uric acid level. No difference in the mean drug dose was found between the evaluated subgroups.

Discussion

Serum uric acid level is currently considered not only an independent risk factor for cardiovascular disease but also an independent risk factor for mortality [13]. Ndrepepa et

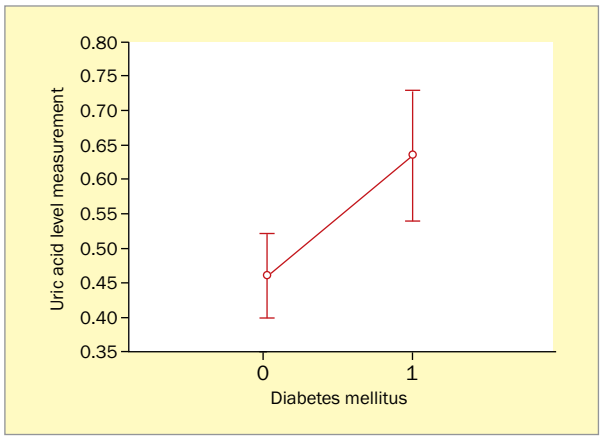

Figure 3. Main effects ANOVA. The effect of concomitant diabetes on the performance of serum uric acid level measurement. Vertical red lines indicate the 95% confidence interval. Current effect: F(1.352) = 9.1431, p = 0.003

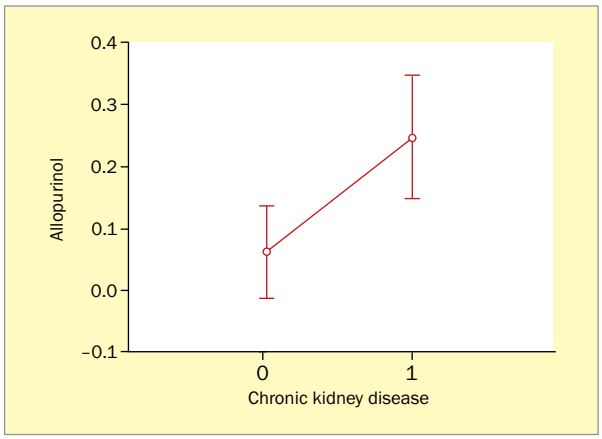

Figure 4. Main effects ANOVA. The effect of concomitant chronic kidney disease on allopurinol use. Vertical red lines indicate the 95% confidence interval. Current effect: (1.349) = 17.197, p < 0.001

al. [14] studied more than 5000 patients after an acute coronary syndrome and showed that after adjustment for conventional risk factors, each increase in serum uric acid level by 1 mg/dL was associated with an increase in the mortality risk by 12%. Korean authors reviewed medical data of more than 370,000 patients and found a U-shaped relationship between serum uric acid level and the risk of death. Serum uric acid level < 3.5 mg/dL in men and < 2.5 mg/dL in women was associated with a 58% and 80% higher mortality risk, respectively (hazard ratio [HR] 1.58, 95% confidence interval [CI] 1.18–2.1, and HR 1.8, 95% CI 1.1–2.93). For hyperuricemia, the cut-off values were > 9.5 mg/dL in men and > 8.5 mg/dL in women, associated with HR 2.39 (95% CI 1.57–3.66) and 3.77 (95% CI 1.17–12.17) for mortality risk in men and women, respectively [15]. In the PreCis study, each increase in serum uric acid level by 1 mg/dL was associated with an increase in mortality risk by 39% [16]. In the PAMELA study which evaluated cardiovascular disease risk factors in a random sample of the general population, the highest sensitivity and specificity was found for the cut-off serum uric acid level of 5.4 mg/dL for the cardiovascular mortality and 4.9 mg/dL for the overall mortality [17]. It can be thus concluded that the measurement of serum uric acid level should be included in the routine biochemical testing panel in hospitalized patients, particularly those at a very high cardiovascular risk. During our study period, however, this measurement was performed in our unit in only about half of patients at a very high cardiovascular risk. We have also shown that only the presence of diabetes independently increased the likelihood of the performance of this measurement. Paradoxically, this is justified by clinical studies but not guidelines. Liu et al. noted nephroprotective effects of allopurinol in patients with diabetes, along with a beneficial effect on insulin sensitivity and a reduction in high-sensitivity C-reactive protein (hsCRP) level and the intima-media thickness in the carotid arteries [18, 19]. However, current guidelines on the diagnosis and management of diabetes do not cover the issue of hyperuricemia at all [20]. Only the guidelines on the diagnosis and management of hypertension and rather obsolete 2013 guidelines on the management of stable coronary artery disease (new guidelines are to be published in 2019) mention the need to measure serum uric acid level and note the benefits of uricosuric drugs [21, 22]. In the guidelines on stable coronary artery disease, it has been highlighted that allopurinol has antianginal properties in subjects without gout, may reduce oxidative stress, and when used at 600 mg per day, it may prolong exercise time not only to chest pain, but also to ST segment depression [22].

In the recent years, a number of expert consensuses have been published that indicate the need for more frequent serum uric acid measurement and earlier initiation of uricosuric drugs [11, 13]. According to these documents, in patients with at least two metabolic and/or cardiovascular conditions, abnormal serum uric acid level should be defined as > 5 mg/dL in both genders [11, 13]. However, the prevalence of so defined asymptomatic hyperuricemia in the population of patients at a very high cardiovascular risk is not known. In our study, we have attempted to provide some early estimates the scope of this problem. For the purpose of our analyses, we defined the upper limit of normal values in patients at a very high cardiovascular risk as 5 mg/dl, consistent with the consensus by Borghi et al. [13]. Although a limitation of our study is its retrospective, single-centre nature, our findings indicate the need for more widespread educational efforts to promulgate the

knowledge on the importance of asymptomatic hyperuricemia and the measurement of serum uric acid level in the population of patients at cardiac and metabolic risk. Of note, we observed a tendency to use a single, lowest allopurinol dose. This is probably a result of long-held belief that uricosuric drug use is indicated only with much increased serum uric acid level and as chronic therapy in patients with a history of gout. It should also be noted that there is no consensus regarding the use of allopurinol doses exceeding 100–300 mg per day. In the expert statement of the Polish Cardiac Society Cardiovascular Pharmacotherapy Committee, the use of very high doses (600–900 mg per day) has been considered reasonable [11]. In contrast, Borghi et al. [13] stated in their consensus that the efficacy and safety of chronic use of allopurinol doses exceeding 300 mg per day requires further studies. In a study in over 7,000 patients, Wei et al. [23] showed that the cardiovascular event rate showed an inverse correlation with allopurinol dose, as it was 74.0 (95% CI 61.9–86.1) per 1,000 person-years in the 100 mg group compared to 69.7 (95% CI 49.6–99.8) per 1000 person-years in the 200 mg group and 47.6 (95% CI 38.4–56.9) per 1000 person-years in the ≥ 300 mg group. Use of allopurinol doses ≥ 300 mg/day vs. < 299 mg/day was associated with a lower risk of all-cause mortality (adjusted HR 0.65, 95% CI 0.42–0.99) [23]. Golmohammadi et al. indicated a potential nephroprotective effect of allopurinol [24]. In our study, abnormal renal function parameters were independently associated with the presence of hyperuricemia in the very high cardiovascular risk group. In the 2013 guidelines on the management of stable coronary artery disease, caution was advised when using uricosuric drugs in patients with reduced GFR. The above mentioned studies in diabetic patients and the findings of Golmohammadi et al. suggest, however, that allopurinol use should be considered in particular in these patients [18, 19, 22, 24]. At the same time Borghi et al. [25], in a study on the effects of allopurinol or probenecide in obese normotensive patients with serum uric acid level above 5 mg/dL, have questioned whether drug treatment of hyperuricemia has a protective effect on the endothelium.

Taking into account a large interest in the role of asymptomatic hyperuricemia as a contributor to the total cardiovascular risk in cardiac patients, the lack of data on the prevalence of asymptomatic hyperuricemia in this patient population in Poland, and ongoing uncertainties regarding chronic use of uricosuric drugs, a multicentre study seems warranted.

Conclusions

1. Serum uric acid level measurement is too rarely considered in the biochemical profile of patients at a very high cardiovascular risk. 2. Serum uric acid level may be an indication for the use of uricosuric drugs in most patients at a very high cardiovascular risk. 3. In the light of the current expert consensus, allopurinol is underused and underdosed in the very high cardiovascular risk group.

Conflict(s) of interest

Marcin Tomasz Wełnicki: Egis (lectures, training, opinions); Jakub Żółkiewicz: no conflicts of interest, Daniel Śliż: Egis (lectures, training, opinions); Wiesława B. Duda-Król: no conflicts of interest; Artur Mamcarz: no conflicts of interest.

Streszczenie

Wstęp. Bezobjawowa hiperurykemia jest potwierdzonym i uznanym przez ekspertów niezależnym czynnikiem ryzyka sercowo-naczyniowego (CV). Świadomość tego faktu wśród lekarzy wciąż jednak pozostaje niewystarczająca. Brakuje również danych dotyczących rozpowszechnienia bezobjawowej hiperurykemii w populacji pacjentów potencjalnie wymagających farmakoterapii.

Celem badania była ocena częstości występowania bezobjawowej hiperurykemii w populacji pacjentów hospitalizowanych na oddziale internistycznym oraz częstości stosowania leków urykozurycznych w tej grupie chorych.

Materiał i metody. Jednoośrodkowe badanie kohortowe — retrospektywna ocena dokumentacji pacjentów hospitalizowanych na oddziale internistycznym w pierwszym półroczu 2018 roku. W analizie uwzględniono wyniki badań biochemicznych, dane dotyczące chorobowości pacjentów oraz stosowanej farmakoterapii. Na podstawie zebranych danych wyodrębniono grupę pacjentów obciążonych bardzo wysokim ryzykiem CV, w odniesieniu do których za nieprawidłowe uznaje się stężenie kwasu moczowego większe lub równe 5 mg/dl. Zastosowano typowe metody statystyczne: statystyki opisowe, odpowiednie testy parametryczne i nieparametryczne w celu oceny istotności różnic wartości wybranych parametrów między badanymi grupami chorych oraz ogólne modele regresji. Przyjęto standardową wartość p poniżej 0,05 dla różnic istotnych statystycznie.

Wyniki. W analizie uwzględniono dane 354 pacjentów, spośród których 194 (55%) spełniło kryterium przynależności do grupy bardzo wysokiego ryzyka CV. Pozostali chorzy stanowili grupę kontrolną. Chorzy z grupy bardzo wysokiego ryzyka CV byli starsi (75 *v.* 62 lata; p < 0,001), wyróżniali się niższą wartością współczynnika filtracji kłębuszkowej (85 *v.* 118 ml/min/1,73 m^2; p = 0,04) oraz wyższym średnim stężeniem kwasu moczowego (6,6 *v.* 5,5 mg/dl; p < 0,001). Nie wykazano natomiast istotnych różnic w stężeniach poszczególnych frakcji lipidogramu. Stężenie kwasu moczowego oznaczono u 55% pacjentów z grupy bardzo wysokiego ryzyka CV. Niezależnym predyktorem stężenia kwasu moczowego powyżej 5 mg/dl w tej grupie były nieprawidłowe parametry nerkowe (R^2 = 0,18; p < 0,001). W przypadku 70% pacjentów z grupy bardzo wysokiego ryzyka CV, u których oznaczono stężenie kwasu moczowego, przekraczało ono 5 mg/dl. Allopurinol zastosowano jedynie u 25% tych chorych, przy czym średnie stężenie kwasu moczowego u pacjentów, u których włączono leczenie urykozuryczne, wynosiło 8,1 mg/dl. Najczęściej stosowaną dawką allopurinolu było 100 mg/dobę. Średnie stężenie kwasu moczowego u pacjentów, u których leczenia nie wdrożono, wynosiło 6,2 mg/dl.

Wnioski. Oznaczenie stężenia kwasu moczowego jest zbyt rzadko uwzględniane w profilu badań biochemicznych pacjentów obciążonych bardzo wysokim ryzykiem CV. U większości pacjentów z grupy wysokiego ryzyka mogą istnieć wskazania do stosowania leków urykozurycznych. W świetle aktualnych konsensusów ekspertów allopurinol w grupie pacjentów obciążonych bardzo wysokim ryzykiem CV stosuje się zbyt rzadko i w zbyt małej dawce.

Słowa kluczowe: allopurinol, kwas moczowy

Folia Cardiologica 2019; 14, 2: 129–135

References

1. Raciborski F, Maśliński M, Kłak A, et al. Występowanie i leczenie dny moczanowej w Polsce. Analiza, wskazania, rekomendacje. Instytut Ochrony Zdrowia, Warszawa 2015.
2. Gińdzieńska-Sieśkiewicz E, Sierakowski S, Domysławska I, et al. Dna moczanowa — aktualne spojrzenie na diagnostykę i leczenie. Reumatologia. 2010; 48(6): 425–428.
3. Zimmermann-Górska I. Komentarz do pracy Nuki G. Doherty M. Richette P. Aktualne postępowanie w dnie moczanowej. yczne wskazówki z wytycznych EULAR 2016. Med. Prakt. 2017; 5: 35–36.
4. 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 nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken). 2012; 64(10): 1431–1446, doi: 10.1002/acr.21772, indexed in Pubmed: 23024028.
5. Khanna D, Khanna PP, Fitzgerald JD, et al. American College of Rheumatology. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken). 2012; 64(10): 1447–1461, doi: 10.1002/acr.21773, indexed in Pubmed: 23024029.
6. 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, indexed in Pubmed: 27457514.
7. Gueyffier F, Boissel JP, Pocock S, et al. Identification of risk factors in hypertensive patients: contribution of randomized controlled trials through an individual patient database. Circulation. 1999; 100(18): e88–e94, indexed in Pubmed: 10545441.
8. 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, indexed in Pubmed: 5917940.
9. 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.HYP.0000150784.92944.9a, indexed in Pubmed: 15569852.
10. Kostka-Jeziorny K, Tykarski A. Związek hyperurykemii z innymi czynnikami ryzyka sercowo-naczyniowego u pacjentów z pierwotnym, nieleczonym nadciśnieniem tętniczym w populacji badania RISK. Arterial Hypertens. 2008; 12: 190–199.
11. Widecka K, Szymański FM, Filipiak KJ, et al. Stanowisko ekspertów dotyczące hiperurykemii i jej leczenia u pacjentów z wysokim ryzykiem sercowo-naczyniowym. Arterial Hypertens. 2017; 21(1): 1–9.
12. Brand FN, McGee DL, Kannel WB, et al. Hyperuricemia as a risk factor of coronary heart disease: the Framingham Study. Am J Epidemiol. 1985; 121(1): 11–18, indexed in Pubmed: 3964986.
13. Borghi C, Tykarski A, Widecka K, et al. Expert consensus for the diagnosis and treatment of patient with hyperuricemia and high cardiovascular risk. Cardiol J. 2018; 25(5): 545–563, doi: 10.5603/CJ.2018.0116, indexed in Pubmed: 30394510.
14. Ndrepepa G, Braun S, Haase HU, et al. Prognostic value of uric acid in patients with acute coronary syndromes. Am J Cardiol. 2012; 109(9): 1260–1265, doi: 10.1016/j.amjcard.2011.12.018, indexed in Pubmed: 22325088.
15. Cho SK, Chang Y, Kim I, et al. U-Shaped association between serum uric acid level and risk of mortality: a cohort study. Arthritis Rheumatol. 2018; 70(7): 1122–1132, doi: 10.1002/art.40472, indexed in Pubmed: 29694719.
16. 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, indexed in Pubmed: 18240236.
17. 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.
18. 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, indexed in Pubmed: 25400252.
19. Liu P, Wang H, Zhang F, et al. The Effects of allopurinol on the carotid intima-media thickness in patients with type 2 diabetes and asymptomatic hyperuricemia: a three-year randomized parallel-controlled study. Intern Med. 2015; 54(17): 2129–2137, doi: 10.2169/internalmedicine.54.4310, indexed in Pubmed: 26328636.
20. Araszkiewicz A, Bandurska-Stankiewicz E, Budzyński A, et al. 2019 Guidelines on the management of diabetic patients. A position of diabetes Poland. Clin Diabetol. 2019; 8(1): 1–95, doi: 10.5603/dk.2019.0001.
21. Tykarski A, Narkiewicz K, Gaciong Z, et al. Guidelines for the Management of Hypertension. Arterial Hypertens. 2015; 19(2): 53–83, doi: 10.5603/ah.2015.0010.
22. Montalescot G, Sechtem U, Achenbach S, et al. Task Force Members, ESC Committee for Practice Guidelines, Document Reviewers. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013; 34(38): 2949–3003, doi: 10.1093/eurheartj/eht296, indexed in Pubmed: 23996286.
23. Wei L, 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, indexed in Pubmed: 21395653.
24. Golmohammadi S, Almasi A, Manouchehri M, et al. Allopurinol against progression of chronic kidney disease. Iran J Kidney Dis. 2017; 11(4): 286–293, indexed in Pubmed: 28794291.
25. Borgi L, McMullan C, Wohlhueter A, et al. Effect of uric acid-lowering agents on endothelial function: a randomized, double-blind, placebo-controlled trial. Hypertension. 2017; 69(2): 243–248, doi: 10.1161/HYPERTENSIONAHA.116.08488, indexed in Pubmed: 28028194.