© Pediatr Med Rodz 2021, 17 (3), p. 221–226
DOI: 10.15557/PiMR.2021.0034

Received: 06.05.2021
Accepted: 21.05.2021
Published: 30.09.2021

Krzysztof Ozierański, Marcin Grabowski

The role of monacolin in the treatment of dyslipidaemia

Rola monakoliny w terapii dyslipidemii

1st Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland
Correspondence: Professor Marcin Grabowski, MD, PhD, 1st Chair and Department of Cardiology, Medical University of Warsaw, Banacha 1a, 02-097 Warsaw, Poland, tel.: +48 22 599 29 58, e-mail: marcin.grabowski@wum.edu.pl

Abstract

Dyslipidaemia is one of the major modifiable risk factors for cardiovascular diseases. According to the current epidemiological data, excessively high serum cholesterol levels are found in 64% of women and 70% of men aged ≥20 years in Poland. Statins are the treatment of choice in patients with high-to-very high cardiovascular risk and high low-density lipoprotein (LDL) cholesterol levels. At the other end of the spectrum, there is a group of patients with low-to-moderate cardiovascular risk and low or moderate LDL cholesterol levels, who should be put on well-planned and appropriately adjusted therapy involving lifestyle modification and, if needed, pharmacotherapy. In such cases, the current guidelines of the European Society of Cardiology make it possible to use monacolin, a nutraceutical which is a natural statin (chemically identical to lovastatin). Monacolin is found in red yeast rice and its action is based on the known mechanism of inhibition of HMG-CoA reductase, a key enzyme in endogenous cholesterol synthesis. Data on the efficacy and safety of monacolin come from many clinical trials showing a significant decrease in triglycerides, total and LDL cholesterol, resulting in a reduced number of cardiovascular events in the absence of significant adverse effects. Monacolin is likely to become an effective pharmaceutical to combat dyslipidaemia in the growing group of (relatively young) patients with low-to-moderate baseline cardiovascular risk and low-to-moderate LDL cholesterol levels, without concomitant indications for statins. This paper summarises the current knowledge on the efficacy, safety and potential indications for the use of monacolin in the treatment of dyslipidaemia.

Keywords: atherosclerosis, SCORE risk chart, cardiovascular disease, statin, nutraceutical

Streszczenie

Dyslipidemia jest jednym z głównych modyfikowalnych czynników ryzyka chorób układu sercowo-naczyniowego. Zgodnie z aktualnymi danymi epidemiologicznymi zbyt wysokie stężenie cholesterolu we krwi występuje w Polsce u 64% kobiet oraz 70% mężczyzn w wieku 20 i więcej lat. W grupach pacjentów z wysokim i bardzo wysokim ryzykiem sercowo-naczyniowym oraz wysokimi wartościami stężenia cholesterolu frakcji lipoprotein o niskiej gęstości (LDL) leczeniem z wyboru są statyny. Na drugim końcu spektrum znajduje się grupa pacjentów z niskim lub umiarkowanym ryzykiem sercowo-naczyniowym i niskimi lub pośrednimi stężeniami cholesterolu frakcji LDL, która powinna być objęta dobrze zaplanowaną i odpowiednio dostosowaną terapią obejmującą zmianę stylu życia i – jeśli to wskazane – leczenie farmakologiczne. W tej sytuacji aktualne wytyczne Europejskiego Towarzystwa Kardiologicznego dają możliwość wykorzystania nutraceutyku – monakoliny, będącej naturalną statyną (identyczną pod względem chemicznym z lowastatyną). Monakolina występuje w czerwonym ryżu drożdżowym, a jej działanie opiera się na znanym mechanizmie hamowania reduktazy HMG-CoA, enzymu kluczowego w endogennej syntezie cholesterolu. Dane dotyczące skuteczności i bezpieczeństwa monakoliny pochodzą z wielu badań klinicznych, które wykazały istotny spadek stężeń triglicerydów, cholesterolu całkowitego i cholesterolu frakcji LDL, co przekładało się na redukcję liczby incydentów sercowo-naczyniowych. W przeprowadzonych badaniach nie stwierdzono istotnych działań niepożądanych. Monakolina może być skutecznym farmaceutykiem w walce z dyslipidemią w powiększającej się grupie pacjentów (relatywnie młodych) z niskim i pośrednim wyjściowym ryzykiem sercowo-naczyniowym oraz niskimi i pośrednimi wartościami stężenia cholesterolu frakcji LDL, bez jednoczesnych wskazań do stosowania statyny. Niniejsze opracowanie podsumowuje aktualną wiedzę dotyczącą skuteczności, bezpieczeństwa i potencjalnych wskazań do stosowania monakoliny w terapii dyslipidemii.

Słowa kluczowe: miażdżyca, karta ryzyka SCORE, choroba układu sercowo-naczyniowego, statyna, nutraceutyk

INTRODUCTION

The increase in life expectancy, especially in developed countries, combined with socioeconomic and lifestyle changes in recent decades, has contributed to the role of lipid control, with a particular focus on low-density lipoprotein (LDL) cholesterol, in reducing cardiovascular risk. This role has been confirmed by epidemiological studies[1–3], controlled interventional studies to reduce LDL cholesterol levels[4], and randomised trials[5]. Dyslipidaemia is still a major problem in Poland. As shown in the WOBASZ II study, elevated blood cholesterol (>190 mg/dL) occurs in 64% of women and 70% of men aged ≥20 years in Poland[1,2].

At the same time, many studies have been published in the last few years that have deepened our understanding of the pathophysiological role of LDL cholesterol as a key factor initiating atherogenesis along with other cholesterol-rich apolipoprotein-B-containing lipoproteins that accumulate in the walls of arteries susceptible to plaque formation[6]. These changes are also reflected in the 2019 guidelines of the European Society of Cardiology (ESC), developed in cooperation with the European Atherosclerosis Society (EAS)[3], and the Third Declaration of Sopot (an interdisciplinary position of a group of experts supported by the Section of Cardiovascular Pharmacotherapy of the Polish Cardiac Society), which preceded these guidelines by a few months[7]. Based on the latest research, the ESC/EAS guidelines now recommend more stringent lipid control than before, with particular emphasis on the LDL-cholesterol fraction, which is used both as a standard/target in primary prevention, and as a therapeutic target in secondary prevention. The authors of these recommendations also suggest individualisation of the management strategy by selecting various therapeutic targets depending on SCORE (Systematic Coronary Risk Evaluation) and baseline LDL level, similarly to the regimens in the Third Declaration of Sopot (Tab. 1).

The initial estimation of the total 10-year risk of the first fatal atherosclerotic event (including myocardial infarction, stroke, or other arterial obstruction, including sudden cardiac death) in patients over 40 years of age without established cardiovascular disease (CVD) is performed using the SCORE method. The SCORE was developed for various populations, based on calculations considering the local specificity. It is also available in a version adapted to the Polish population (Pol-SCORE), which is a high cardiovascular risk population. The SCORE is used to qualify patients as low-risk (<5%), moderate-risk (5–9%) or high-risk (≥10%). The estimated total risk of a (fatal and non-fatal) cardiovascular event is approximately 3 times higher than the risk of cardiovascular death estimated from the SCORE chart. On the other hand, **patients with already diagnosed CVD are not assessed using the SCORE as their risk of death is immediately classified as very high** (Tab. 2)[8,9].

Intensified lipid-lowering treatment with the highest recommended and tolerated dose of statin is recommended in groups of patients with high-to-very high cardiovascular risk and high LDL cholesterol levels, and as secondary prevention in patients with diagnosed and proven atherosclerosis. At the other end of the spectrum, there is a group of patients with low-to-moderate cardiovascular risk and low or moderate LDL cholesterol levels, who should be put on well-planned and appropriately adjusted therapy involving lifestyle modification and, if needed, pharmacotherapy (Tab. 3)[3].

The latter group is particularly important in the context of the significant increase in the expected life expectancy in recent decades. With a sufficiently long life expectancy, even slight deviations in the lipid profile, if left untreated, will lead to atherosclerotic clinical symptoms[10]. This can be prevented by the early lifestyle modification and/or lipid lowering therapy. Therefore, it is also important to treat patients with low and moderate LDL cholesterol levels.

At the same time, studies showing a cause-and-effect relationship between cholesterol levels and the severity of atherosclerotic lesions and the associated clinical symptoms do

Risk category	The Third Declaration of Sopot	2019 ESC/EAS
Extremely high	<35 mg/dL (<0.9 mmol/L)	For patients with second cardiovascular incident within 2 years since the first incident <40 mg/dL (<1 mmol/L)
Very high	<55 mg/dL (<1.4 mmol/L)	<55 mg/dL (<1.4 mmol/L)
High	<70 mg/dL (<1.8 mmol/L)	<70 mg/dL (<1.8 mmol/L)
Moderate	<100 mg/dL (<2.6 mmol/L)	<100 mg/dL (<2.6 mmol/L)
Low	<115 mg/dL (<3.0 mmol/L)	<115 mg/dL (<3.0 mmol/L)

Tab. 1. Therapeutic targets for LDL cholesterol by cardiovascular risk category

Risk level	Risk factor
Very high	• SCORE ≥10% • Documented CVD (past myocardial infarction, acute coronary syndrome, revascularisation of coronary or peripheral arteries, stroke or transient ischaemic attack, aortic aneurysm, peripheral arterial disease, coronary or carotid plaque) • Diabetes mellitus with organ damage (proteinuria or a serious risk factor such as smoking, significant hypertension or significant hypercholesterolaemia) • Chronic kidney disease (GFR <30 mL/min/1.73 m^2)
High	• SCORE 5–9% • Chronic kidney disease (GFR 30–59 mL/min/1.73 m^2) • Diabetes mellitus (other risk factors at low or moderate levels and excluding young people with type 1 diabetes mellitus) • Significantly increased single risk factor, especially cholesterol level (>8 mmol/L) or blood pressure (≥180/110 mm Hg)
Moderate	SCORE 1–4%
Low	SCORE <1%

GFR – glomerular filtration rate.

Tab. 2. Cardiovascular risk categories. Based on[8]

DOI: 10.15557/PiMR.2021.0034 PEDIATR MED RODZ Vol. 17 No. 3, p. 221–226

Prevention	Total CV risk (SCORE) (%)	Untreated LDL cholesterol levels					
		<1.4 mmol/L (<55 mg/dL)	1.4 – <1.8 mmol/L (55 – <70 mg/dL)	1.8 – <2.6 mmol/L (70 – <100 mg/dL)	2.6 – <3.0 mmol/L (100 – <116 mg/dL)	3.0 – <4.9 mmol/L (116 – <190 mg/dL)	≥4.9 mmol/L (≥190 mg/dL)
Primary	<1, low risk	Lifestyle counselling	Lifestyle counselling	Lifestyle counselling	Lifestyle counselling	Lifestyle modification, consider pharmacotherapy for uncontrolled LDL cholesterol levels	Lifestyle modification and pharmacotherapy
	Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A	IIa/A
	From ≥1 – <5 or moderate risk	Lifestyle counselling	Lifestyle counselling	Lifestyle counselling	Lifestyle modification, consider pharmacotherapy for uncontrolled LDL cholesterol levels	Lifestyle modification, consider pharmacotherapy for uncontrolled LDL cholesterol levels	Lifestyle modification and pharmacotherapy
	Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	IIa/A	IIa/A
	From ≥5 – <10 or high risk	Lifestyle counselling	Lifestyle counselling	Lifestyle modification, consider pharmacotherapy for uncontrolled LDL cholesterol levels	Lifestyle modification and pharmacotherapy	Lifestyle modification and pharmacotherapy	Lifestyle modification and pharmacotherapy
	Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A	I/A
	≥10 or very high risk due to risk factors	Lifestyle counselling	Lifestyle modification, consider pharmacotherapy for uncontrolled LDL cholesterol levels	Lifestyle modification and pharmacotherapy	Lifestyle modification and pharmacotherapy	Lifestyle modification and pharmacotherapy	Lifestyle modification and pharmacotherapy
	Class[a]/Level[b]	IIa/B	IIa/A	I/A	I/A	I/A	I/A
Secondary	Very high risk	Lifestyle modification, consider pharmacotherapy for uncontrolled LDL cholesterol levels	Lifestyle modification and pharmacotherapy	Lifestyle modification and pharmacotherapy	Lifestyle modification and pharmacotherapy	Lifestyle modification and pharmacotherapy	Lifestyle modification and pharmacotherapy
	Class[a]/Level[b]	IIa/A	I/A	I/A	I/A	I/A	I/A

SCORE – Systematic Coronary Risk Estimation.
[a] Class (strength) of recommendation.
[b] Reliability of the data (level of evidence).

Tab. 3. Therapeutic strategies depending on LDL cholesterol level and cardiovascular risk category. The red line denotes the proposed group of patients for whom monacolin therapy should be considered. Based on[3]

not indicate a cut-off point from which this direct, positive correlation becomes undetectable[11]. This means that, contrary to the common beliefs and intuitions of many clinicians, any decrease in LDL cholesterol, even within low values, results in positive effects in the form of reduced CVD risk. Recent research confirms that the correlation between LDL cholesterol and CVD risk takes the form of a monotone curve rather than a "U" or "J" curve seen in many other parameters (e.g. heart rate)[12,13].

In the light of these studies, it is important that there is a very large group of patients with low-to-moderate risk expressed in the SCORE and increased (low or medium) levels of LDL cholesterol, which is not eligible for statin therapy. However, this group should receive planned, effective long-term treatment, following the principle of the lower the better.

Obviously, it should be remembered that each intervention is based on lifestyle modification and physical activity, but this may turn out to be insufficient (Tab. 4 shows the impact of different lifestyle modifications on lipid levels). Therefore, it is important to find a therapeutic agent that will meet the needs of this specific, wide group of patients. Such an agent should have the following characteristics:

1. proven efficacy;
2. lack of significant adverse effects;
3. long-term safety of use;
4. optimal pharmacokinetic and pharmacodynamic properties.

According to 2019 ESC/EAS guidelines, monacolin is a substance that can be used successfully in the group of patients described above.

MONACOLIN – SOURCE AND PROPERTIES

Monacolin, a nutraceutical contained in red yeast rice, although available on the market for a relatively short time, it has a long history of use in China, as evidenced by its use documented as early as 800 AD during the Tang Dynasty.

 DOI: 10.15557/PiMR.2021.0034

	Size of effect	Level of evidence
Lifestyle interventions to reduce total and LDL cholesterol levels		
Reduced intake of trans fats	+++	A
Reduced intake of saturated fats	+++	A
Increased intake of fibre	++	A
Intake of functional food enriched with phytosterols	++	A
Inclusion of dietary supplements containing red fermented rice	++	A
Reduction of excess body weight	++	A
Reduced intake of cholesterol	+	B
Increasing usual physical activity	+	B
Intake of foods containing soy protein	±	B

Tab. 4. Effects of individual lifestyle modifications on lipid levels. Based on[3,8,9]

Monacolin was used mainly in the production of wine, as a food flavour enhancer, but also for medical purposes.
Red yeast rice (RYR) fermentation yields a group of molecules, 70–83% of which is monacolin K, which is found in two forms – lactone, traditionally denoted by the letter K, and acidic, with an open ring, referred to as monacolin Ka. Both forms undergo *in vivo* transformation in both directions[14]. Monacolin is chemically identical to lovastatin, and its action is based on the already known mechanism of inhibition of HMG-CoA reductase, a key enzyme in endogenous cholesterol synthesis. For this reason, it is also sometimes referred to as a natural statin.
Monacolin K has a higher bioavailability compared to pure/synthetic lovastatin, therefore it is more effective[15].
The effects of monacolin have been assessed in many clinical trials, but their results should be interpreted with caution due to the use of various pharmaceutical forms (pure monacolin K vs. RYR extract), and the addition of supplements and additives, such as coenzyme Q10, L-arginine or ascorbic acid.

RESEARCH ON MONACOLIN

The largest randomised, single-blinded study in China, with a 4-year follow-up, was conducted in 1,445 patients treated with RYR extract known as xuezhikang, with mean monacolin content estimated at 2.5–3.2 mg[10,16]. The study showed 12.1% and 17.7% decrease in triglyceride and LDL cholesterol levels, respectively, resulting in a significant reduction in the incidence of coronary events, coronary death, and all-cause mortality by 36.9%, 31%, and 32.9%, respectively. It is worth noting, however, that CDV patients aged 65–75 years were enrolled in the study, so this data cannot be directly extrapolated to a population of younger people with a moderate SCORE risk who could be treated with monacolin. Furthermore, the dose used in this randomised clinical trial was not optimal.
The Chinese study also found a significantly lower risk of death from cancer among patients taking RYR extract. The underlying mechanism remains unknown, although it is known that ancaflavin, a compound contained in RYR, is toxic to HepG2 and A549 cancer cell lines[17]. This study was first to demonstrate this effect of monacolin, but now there are more studies suggesting that statins reduce mortality in cancer, as investigated and summarized by a 2018 meta-analysis[18].
Another multicentre, placebo-controlled randomised clinical trial compared the efficacy of monacolin K 10 mg in combination with coenzyme Q10 30 mg in a group of patients with metabolic syndrome (median age 57 years) without a history of CVD. In this study, the therapeutic efficacy in reducing both systolic and diastolic blood pressure, total and LDL cholesterol, triglycerides and glucose was found compared with the control group[19]. The levels of high-density lipoprotein (HDL) cholesterol remained unchanged. The study showed the efficacy of monacolin at a dose of 10 mg with good tolerance. The research lasted only 2 months, allowing only for the assessment of the lipid profile; therefore, it did not provide information on the risk of cardiovascular events or mortality. It should also be noted that the study was conducted in the European population, showing the efficacy of monacolin in patients living in this geographical unit.
In another study, patients aged 18–75 years with LDL cholesterol levels of 130–180 mg/dL received two treatments, each for 8 weeks with a 4-week washout period. A dietary supplement containing monacolin K, L-arginine, coenzyme Q10 and ascorbic acid, named Argicolina (A), was used and compared to commercially available product containing monacolin K and coenzyme Q10, named Normolip 5 (ESI)[20]. Both preparations contained RYR extract at a dose corresponding to 10 mg of monacolin. Two therapeutic regimens, i.e. Normolip 5 and Argicolina (A), caused 23.3% and 25.6% decrease in LDL cholesterol, respectively, as well as a significant decrease in total cholesterol.
The above studies not only assessed the effect of therapeutics on the lipid metabolism, but also investigated parameters such as alanine and aspartate aminotransferases, keratin kinase, and gamma-glutamyl transpeptidase to assess adverse effects. No significant adverse reactions were reported. It is worth noting that the first two placebo-controlled studies reported a comparable incidence of adverse effects (gastrointestinal symptoms, allergic reactions and muscle pain) for study and control groups. Furthermore, the Chinese study lasted 4 years, with no serious monacolin-related disorders developed by the patients[16].
A 2015 meta-analysis assessed the available studies on monacolin and proved its efficacy. The RYR used in the studies, containing an average of 10.4 mg of monacolin, reduced LDL cholesterol by 1.02 mmol/L. There were no significant differences in the reduction of LDL cholesterol between monacolin and other statins used in the study. The safety of this drug has been assessed as satisfactory, with rare adverse effects[21].
In 2019, a meta-analysis to assess adverse effects of monacolin therapy was published. This study also confirmed safety

DOI: 10.15557/PiMR.2021.0034

of this substance. Importantly, the meta-analysis included the latest European research, which had better methodology, which in turn increased the credibility of the analysed data and allowed to confirm the results obtained in previous years[22].

The awareness of possible adverse reactions, although rare, is particularly important in the context of the widespread opinion that monacolin supplements are less harmful and can be therefore used in patients intolerant to statins. However, it is known that the percentage of patients truly intolerant of statins is very small, and that most of adverse effects can be explained by the nocebo effect[23,24]. Since monacolin K is chemically identical to synthetic lovastatin, it seems unlikely that patients truly intolerant to statins will show good tolerance of monacolin. The greater tolerability compared with statins observed in some studies may be attributed to the lower doses used (2.5–3 mg) or the nocebo effect in the case of synthetic statins[25].

The above-mentioned publications prove, above all, the efficacy of monacolin, understood as the ability to reduce LDL cholesterol, with no significant adverse effects. At the same time, they provide data on its positive effects on mortality in risk groups, but in this case more data is needed from clinical trials, including patients with lower SCORE risk.

Despite evidence for the effects of monacolin, many issues regarding this substance are still insufficiently investigated, and the commercially available products vary in its content. One study assessed 12 commercially available products for the content of active substance and showed that the total content of monacolins in one capsule (600 mg of active substance) was 0.31–11.15 mg, the content of monacolin K was 0.10–10.09 mg and that of monacolin Ka was 0.00–2.30 mg. The authors of the study suggest the need for improved standardisation of the product[26].

The same study also assessed the content of citrinin, a mycotoxin showing nephrotoxicity in animal models. Its levels were elevated in 4/12 preparations. For this reason, it is so important to use monacolin preparations from a trusted manufacturer able to guarantee a specific dose and eliminate all substances with known toxicity.

CONCLUSIONS

Monacolin may be an effective pharmaceutical to combat dyslipidaemia in the expanding group of (relatively young) patients with low-to-moderate SCORE risk and low-to-moderate LDL cholesterol levels, without concurrent indications for statin therapy (a summary of the indications for the use of monacolin is presented in Tab. 5). It can be assumed that the demand for this substance will increase in the coming years, and with a deepened understanding of the pathophysiological role of LDL cholesterol, clinicians will more consistently strive to achieve low levels of this lipoprotein. However, patients should be carefully selected, and it should be borne in mind that monacolin, like any medicinal substance, despite proven safety, may cause potential adverse reactions. For the same reason, it is recommended that it should be used only after consulting a doctor. Also, products from trusted manufacturers should be used at the recommended dose of 10 mg. Furthermore, it should be remembered not to combine monacolin with statins, which would significantly increase the risk of adverse events. Despite the undisputable role of statins, ezetimibe or PCSK9 inhibitors in the treatment of dyslipidaemia, it should not be forgotten that medical intervention should begin much earlier and involve lifestyle advice as well as the use of nutraceuticals to stay ahead of progressive atherosclerotic changes and stop their development at an early stage, when the highest efficacy is guaranteed.

A patient with low (<1%) or moderate (1–4%) cardiovascular risk in the SCORE chart and elevated (low or moderate) LDL cholesterol levels (as shown in Tab. 3), for whom: • there are no indications for statins • lifestyle modification does not bring the expected results
Also to be considered in patients intolerant to or refusing statin therapy

Tab. 5. Summary of indications for the use of monacolin[3,27–29]

Conflict of interest

Authors do not report any financial or personal connections with other persons or organisations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

References

1. Niklas A, Marcinkowska J, Kozela M et al.: Blood pressure and cholesterol control in patients with hypertension and hypercholesterolemia: the results from the Polish multicenter national health survey WOBASZ II. Pol Arch Intern Med 2019; 129: 864–873.
2. Niklas A, Marcinkowska J, Kozela M et al.: Prevalence of cardiometabolic risk factors and selected cardiovascular diseases in hypertensive and normotensive participants in the adult Polish population: the WOBASZ II study. Medicine (Baltimore) 2020; 99: e21149.
3. 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: 111–188.
4. Cholesterol Treatment Trialists' (CTT) Collaboration; Fulcher J, O'Connell R, Voysey M et al.: Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet 2015; 385: 1397–1405.
5. Ference BA: Mendelian randomization studies: using naturally randomized genetic data to fill evidence gaps. Curr Opin Lipidol 2015; 26: 566–571.
6. Ference BA, Ginsberg HN, Graham I et al.: Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2017; 38: 2459–2472.
7. Szymański FM, Barylski M, Cybulska B et al.: Recommendation for the management of dyslipidemia in Poland – Third Declaration of Sopot. Interdisciplinary Expert Position Statement endorsed by the Polish Cardiac Society Working Group on Cardiovascular Pharmacotherapy. Cardiol J 2018; 25: 655–665.
8. Catapano AL, Graham I, De Backer G et al.: [2016 ESC/EAS guidelines for the management of dyslipidaemias]. Kardiol Pol 2016; 74: 1234–1318.

 DOI: 10.15557/PiMR.2021.0034

9. Piepoli MF, Hoes AW, Agewall S et al.: [2016 European guidelines on cardiovascular disease prevention in clinical practice]. Kardiol Pol 2016; 74: 821–936.
10. Poli A, Barbagallo CM, Cicero AFG et al.: Nutraceuticals and functional foods for the control of plasma cholesterol levels. An intersociety position paper. Pharmacol Res 2018; 134: 51–60.
11. Masana L, Girona J, Ibarretxe D et al.: Clinical and pathophysiological evidence supporting the safety of extremely low LDL levels – the zero-LDL hypothesis. J Clin Lipidol 2018; 12: 292–299.e3.
12. Rahman F, McEvoy JW: The J-shaped curve for blood pressure and cardiovascular disease risk: historical context and recent updates. Curr Atheroscler Rep 2017; 19: 34.
13. Ko DT, Alter DA, Guo H et al.: High-density lipoprotein cholesterol and cause-specific mortality in individuals without previous cardiovascular conditions: the CANHEART study. J Am Coll Cardiol 2016; 68: 2073–2083.
14. Nannoni G, Alì A, Di Pierro F: Development of a new highly standardized and granulated extract from *Monascus purpureus* with a high content of monacolin K and KA and free of inactive secondary monacolins and citrinin. Nutrafoods 2015; 14: 197–205.
15. Chen CH, Yang JC, Uang YS et al.: Improved dissolution rate and oral bioavailability of lovastatin in red yeast rice products. Int J Pharm 2013; 444: 18–24.
16. Ye P, Lu ZL, Du BM et al.; CCSPS Investigators: Effect of xuezhikang on cardiovascular events and mortality in elderly patients with a history of myocardial infarction: a subgroup analysis of elderly subjects from the China Coronary Secondary Prevention Study. J Am Geriatr Soc 2007; 55: 1015–1022.
17. Su NW, Lin YL, Lee MH et al.: Ankaflavin from *Monascus*-fermented red rice exhibits selective cytotoxic effect and induces cell death on Hep G2 cells. J Agric Food Chem 2005; 53: 1949–1954.
18. He Y, Li X, Gasevic D et al.: Statins and multiple noncardiovascular outcomes: umbrella review of meta-analyses of observational studies and randomized controlled trials. Ann Intern Med 2018; 169: 543–553.
19. Mazza A, Lenti S, Schiavon L et al.: Effect of Monacolin K and COQ10 supplementation in hypertensive and hypercholesterolemic subjects with metabolic syndrome. Biomed Pharmacother 2018; 105: 992–996.
20. Magno S, Ceccarini G, Pelosini C et al.: LDL-cholesterol lowering effect of a new dietary supplement: an open label, controlled, randomized, cross-over clinical trial in patients with mild-to-moderate hypercholesterolemia. Lipids Health Dis 2018; 17: 124.
21. Gerards MC, Terlou RJ, Yu H et al.: Traditional Chinese lipid-lowering agent red yeast rice results in significant LDL reduction but safety is uncertain – a systematic review and meta-analysis. Atherosclerosis 2015; 240: 415–423.
22. Fogacci F, Banach M, Mikhailidis DP et al.: Safety of red yeast rice supplementation: a systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 2019; 143: 1–16.
23. Stroes ES, Thompson PD, Corsini A et al.; European Atherosclerosis Society Consensus Panel: Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J 2015; 36: 1012–1022.
24. Gupta A, Thompson D, Whitehouse A et al.; ASCOT Investigators: Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. Lancet 2017; 389: 2473–2481.
25. Becker DJ, Gordon RY, Halbert SC et al.: Red yeast rice for dyslipidemia in statin-intolerant patients: a randomized trial. Ann Intern Med 2009; 150: 830–839, W147–W149.
26. Gordon RY, Cooperman T, Obermeyer W et al.: Marked variability of monacolin levels in commercial red yeast rice products: buyer beware! Arch Intern Med 2010; 170: 1722–1727.
27. Barylski M: Monakolina i atorwastatyna w prewencji zdarzeń sercowo-naczyniowych – próba pozycjonowania. Pediatr Med Rodz 2017; 13: 79–92.
28. Wożakowska-Kapłon B, Salwa P: Monakolina – pomost między prozdrowotną modyfikacją diety a farmakoterapią hipercholesterolemii. Folia Cardiol 2016; 11: 318–326.
29. Kazimierska I: Monakolina K – pomost między leczeniem behawioralnym a farmakoterapią dyslipidemii. Puls Medycyny 2019. Available from: https://pulsmedycyny.pl/monakolina-k-pomost-miedzy-leczeniem-behawioralnym-a-farmakoterapia-dyslipidemii-977058.

DOI: 10.15557/PiMR.2021.0034 PEDIATR MED RODZ Vol. 17 No. 3, p. 221–226