Atherosclerosis Supplements 39 (2019) e1–e8

Contents lists available at ScienceDirect

Atherosclerosis Supplements

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

The role of red yeast rice (RYR) supplementation in plasma cholesterol control: A review and expert opinion

Maciej Banach [a, b, c], Eric Bruckert [d, e], Olivier S. Descamps [f], Lars Ellegård [g], Marat Ezhov [h], Bernhard Föger [i, j], Zlatko Fras [k], Petri T. Kovanen [l], Gustavs Latkovskis [m, n], Winfried März [o, p, q], Demosthenes B. Panagiotakos [r], György Paragh [s], Daniel Pella [t], Angela Pirillo [u, v], Andrea Poli [w], Željko Reiner [x], Günter Silbernagel [y, z], Margus Viigimaa [aa], Michal Vrablík [ab], Alberico L. Catapano [ac, ad, *]

[a] Department of Hypertension, Chair of Nephrology and Hypertension, Medical University of Lodz, Poland
[b] Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland
[c] Cardiovascular Research Centre, University of Zielona Gora, Zielona Gora, Poland
[d] Endocrinologie Métabolisme et Prévention Cardiovasculaire, Institut E3M et IHU Cardiométabolique (ICAN), Hôpital Pitié Salpêtrière, Paris, France
[e] Sorbonne University, Paris, France
[f] Department of Internal Medicine, Centres Hospitaliers Jolimont, La Louvière and Department of Cardiology, Cliniques Universitaires Saint-Luc (UCLouvain), Bruxelles, Belgium
[g] Department of Internal medicine and clinical nutrition, Sahlgrenska Academy at the University of Gothenburg, Sahlgrenska University Hospital, Sweden
[h] National Medical Research Center of Cardiology of the Ministry of Health, Moscow, Russia
[i] Department of Internal Medicine, Medical University Innsbruck, Innsbruck, Austria
[j] Department of Internal Medicine, Landeskrankenhaus Bregenz, Austria
[k] Division of Internal Medicine, University Medical Centre Ljubljana Professor of Internal Medicine, Medical Faculty, University of Ljubljana, Slovenia
[l] Wihuri Research Institute, Helsinki, Finland
[m] Institute of Cardiology and Regenerative Medicine, Faculty of Medicine, University of Latvia, Latvia
[n] Pauls Stradins Clinical University Hospital, Riga, Latvia
[o] Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria
[p] Medical Clinic V, Medical Faculty Mannheim, University of Heidelberg, Germany
[q] SYNLAB Academy, SYNLAB Holding Deutschland GmbH, Mannheim and Augsburg, Germany
[r] Department of Nutrition – Dietetics, Harokopio University, Athens, Greece
[s] Department of Internal Medicine, University of Debrecen Faculty of Medicine, Debrecen, Hungary
[t] 2nd Department of Cardiology of the East Slovak Institute of Cardiovascular Disease and Faculty of Medicine PJ Safarik University, Kosice, Slovak Republic
[u] Center for the Study of Atherosclerosis, E. Bassini Hospital, Cinisello Balsamo, Milan, Italy
[v] IRCCS MultiMedica, Sesto S. Giovanni, Milan, Italy
[w] Nutrition Foundation of Italy (NFI), Milan, Italy
[x] Department of Internal Medicine, University Hospital Center Zagreb, School of Medicine University of Zagreb, Zagreb, Croatia
[y] Department of Cardiology, Charité Berlin (CBF), Berlin Institute of Health (BIH), And DZHK (German Research Centre for Cardiovascular Research), Partner Site Berlin, Hindenburgdamm 30, 12203, Berlin, Germany
[z] Division of Angiology, Department of Internal Medicine, Medical University of Graz, Auenbruggerplatz 15, 8036, Graz, Austria
[aa] Tallinn University of Technology, School of Information Technologies, Department of Health Technologies, Estonia
[ab] 3rd Department of Medicine, Charles University and General University Hospital, Prague, Czech Republic
[ac] Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy
[ad] Multimedica IRCCS, Milano, Italy

1. Preamble

Hypercholesterolemia is a major risk factor for atherosclerotic cardiovascular disease (ASCVD) [1]. Increased levels of low density lipoprotein cholesterol (LDL-C) are associated with an increased risk of coronary heart disease (CHD) and many clinical trials have shown that reducing LDL-C levels significantly reduced the CHD and CVD risk [2–5]. Thus LDL-C-lowering is the main approach for the management of cardiovascular disease. Current guidelines suggest LDL-C levels targets based on the individual CV risk; such targets can be achieved by several means, which include both lifestyle changes and pharmacological approaches [6], with statins being the cornerstone of cardiovascular prevention. Several statins are available and may be selected based on the individual patient needs, therapeutic goals, tolerability and response to therapy.

* Corresponding author. Department of Pharmacological and Biomolecular Sciences, University of Milan and IRCCS Multimedica, Via Balzaretti, 9, 20133, Milan, Italy.
E-mail address: alberico.catapano@unimi.it (A.L. Catapano).

https://doi.org/10.1016/j.atherosclerosissup.2019.08.023

However, statin therapy may be not sufficient to reduce significantly the CV risk in high and very-high CV, and especially ultra/extremely high risk patients [7], and consequentially there may be an indication to use a statin in combination with other non-statin lipid-lowering drugs, such as ezetimibe, acting through a different mechanism of action. The recently approved hypocholesterolemic drugs, i.e. anti-PCSK9 monoclonal antibodies, have offered the opportunity to further significantly reduce LDL-C levels and cardiovascular events in high CV risk patients already on statin therapy [4,5]. However, they are still not commonly available due to high costs of the therapy and lack of open reimbursement in most of the European countries. Finally adding ezetimibe, with the possibilities of additional 15–20% LDL-C reduction might be also not enough in those with the highest cardiovascular risk [8]. That is why there is a large unmet need to look for other agents with the potent lipid-lowering properties [9].

A large part of the population is at low-to-moderate CV risk, with LDL-C levels not far from those recommended. These subjects are usually not eligible for lipid-lowering therapies and they are generally advised with lifestyle changes, which may include dietary changes and the addition of lipid-lowering dietary supplements or nutraceuticals, such as phytosterols [6]. Among the latter groups, also red yeast rice (RYR), obtained by the fermentation of common rice with a fungus, has a hypocholesterolemic effect due to the presence of bioactive constituents (monacolins) that inhibit hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase (Fig. 1). As suggested by current guidelines, nutraceuticals containing purified RYR may be considered in subjects with CV risk not being on the LDL-C goal, but not eligible for statin treatment, or unable to tolerate statins [6]. It is also important to emphasize that nutraceuticals, including RYR, cannot replace pharmaceutical therapy, as only it is indicated.

Recently, the European Food Safety Authority (EFSA) has critically reviewed the scientific literature regarding the safety of dietary intake of monacolin K [10,11], raising uncertainties on such topic. The objective of the present expert opinion paper is to discuss all the available clinical data on the use of RYR for human health, and specifically for its cholesterol-lowering activity, to examine both *pros* and *cons*, commenting on the potential biases of published papers, and to provide a global and independent opinion on the role of RYR in the control of lipid-associated cardiovascular risk management.

2. Introduction

2.1. General considerations on RYR and monacolin K

RYR is a nutraceutical produced by the fermentation of white rice with the yeast *Monascus purpureus* mold and it has been used for centuries in Asian food and medicine. It consists of several bioactive components; among them, monacolins represent the most attractive ones, as they are inhibitors of HMG-CoA reductase (HMG-CoAR), the rate-limiting enzyme of the cholesterol biosynthesis pathway (Fig. 1) [12–15]. Monacolin K is the most abundant monacolin in RYR, being present both as a lactone and a hydroxy acid forms, at a ratio depending mainly on the pH value; at low pH, the lactone form predominates, whereas at neutral and basic pH conditions the active hydroxy acid form is predominant; the conversion of the lactone into its lipid-lowering active metabolite occurs spontaneously at neutral and basic pH and independently of the gut microbiota [16]. Cytochrome P450 (CYP450) enzymes and P-glycoprotein are involved in the metabolism of monacolin K, which suggests a potential interaction with drugs that are primarily metabolized through these pathways [17]. Furthermore, monacolin K is structurally identical to lovastatin, and this identity raised questions about the use of a "natural product" containing a molecule, which is identical to a drug. RYR contains additional compounds with potential lipid-lowering properties, including plant sterols, isoflavones and monounsaturated fatty acids, and other ingredients including fatty acids, pigments, and citrinin, a secondary toxic metabolite with the nephrotoxic properties produced during fermentation [18].

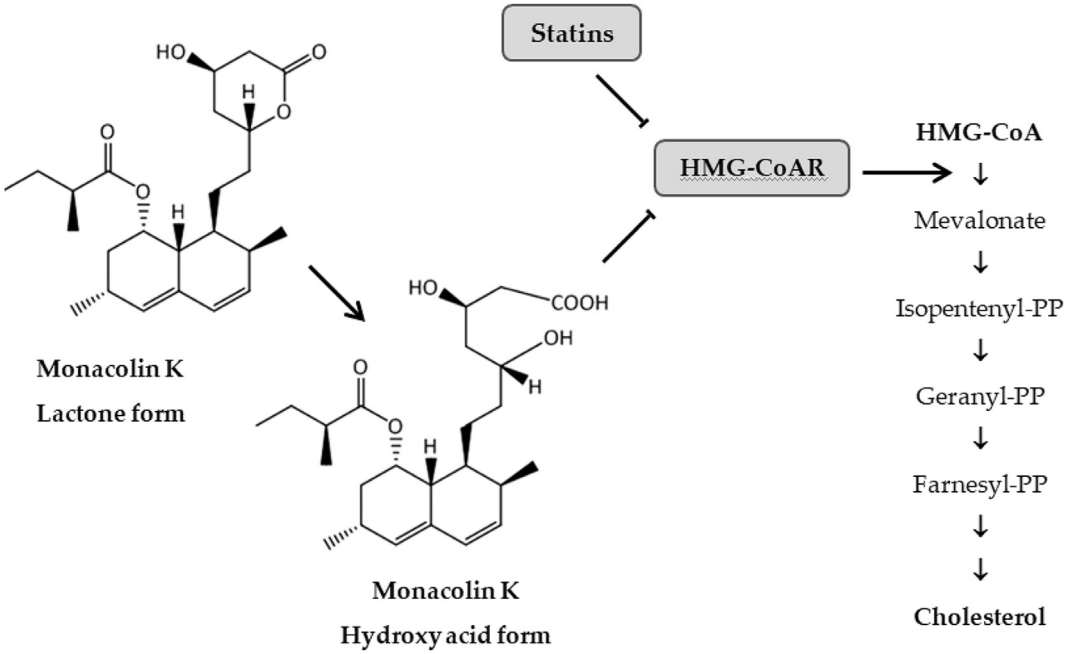

Fig. 1. Chemical structure of monacolin K and its mechanism of action. Monacolin K can be in the form of either lactone (inactive) or hydroxyl acid form (active), depending on the pH value. When in its active form, monacolin K inhibits the endogenous synthesis of cholesterol by inhibiting the activity of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. Monacolin K is structurally identical to lovastatin.

Based on human studies showing a significant hypocholesterolemic effect of RYR supplementation, in 2011 the European Food Safety Authority (EFSA) approved a health claim regarding the consumption of RYR as a food supplement containing monacolin K (10 mg) for the maintenance of normal blood LDL-cholesterol levels [10]. However, due to the identity of monacolin K with lovastatin, the EFSA recently raised safety concerns related to some side-effects commonly associated with the treatment with statins [11].

3. The EFSA Scientific Opinion on RYR: facts and gaps

In 2011, a Scientific Opinion from EFSA Panel on Dietetic Products, Nutrition and Allergies established a causal relationship between the consumption of 10 mg/day monacolin K from RYR and the reduction of blood LDL-C levels [10].

Monacolin K in its lactone form is identical to lovastatin, a hypocholesterolemic drug authorized in the European Union. Both monacolin K and lovastatin are rapidly converted to the bioactive hydroxyl acid form, which is responsible for the inhibitory activity on HMG-CoAR. While this acidic active form is naturally present in RYR (depending on pH), lovastatin is a prodrug and needs to be converted from the lactone form [19].

It has been shown that the bioavailability of lovastatin may significantly increase when taken with a standard meal. In fact, lovastatin is metabolized through the CYP3A4 isoform, and the administration together with other drugs or food ingredients, which inhibit this enzyme, may expose to higher plasma levels of statins and increase the likelihood to experience drug-related adverse events. Since CYP3A4 is also involved in the metabolism of monacolin, despite of low doses applied, there is also a risk of adverse effects due to interactions with other medicinal products and/or foods.

Monacolin K, in the range 3–11.4 mg, dose-dependently reduces LDL-C levels, from 14.8% to 26.3% [20–25]. The profile of adverse events of monacolin K is comparable to that of lovastatin at similar doses and therefore relatively safe and well-tolerated. Some case reports have described adverse effects also with the lowest dose of monacolin K, including cases of rhabdomyolysis, hepatitis and skin disorders [26], however based on this data, causality between therapy and observed symptoms cannot be confirmed.

In August 2018 another Scientific Opinion on RYR was presented by the EFSA Scientific Panel [11]. The authors identified several points of uncertainties, including a) the composition, the content and the relative abundance of monacolins (which vary widely among preparations) in food supplements containing RYR; b) the variability of the ratio between monacolin K lactone and hydroxy acid in RYR food supplements; c) the unknown bioactivity of components in RYR other than monacolin K; d) the unfeasibility to evaluate the safety of monacolins in certain groups of consumers (pregnant women, nursing women, breastfed infants); e) the possible interactions of RYR-based supplements with foods or drugs inhibiting CYP3A4; f) the unknown interactions of monacolins with other ingredient present in the supplement. This might result in health risks following RYR consumption, which may be specifically relevant to some vulnerable groups, including pregnant women, people suffering from liver, kidney and muscle disorders, persons aged over 70 years, and children and adolescents [11].

During clinical trials, several adverse effects associated with the intake of RYR-based products were reported, however they were quantitatively similar to those observed during treatment with lovastatin. In the period 2002–May 2018, 82 cases of adverse effects to RYR were reported to the World Health Organization (WHO) Vigibase; the most common ones were musculoskeletal and connective tissue disorders (39%), general disorders and administration site conditions (32.9%), and gastrointestinal disorders (18%) [11]. Between April 2002 and September 2015, the Italian Surveillance System of Natural Health Products [26] collected 52 reports (3.7 cases/per year) concerning 55 adverse events over 14 years related to the consumption of RYR, three of which were associated with a 3 mg/day dose monacolin K [11]. Causality was established for 34 (65%; 2.4 cases/per year) out of 52 clinical events. The most frequent adverse events were musculoskeletal and connective tissue disorders, gastrointestinal disorders, hepatobiliary disorders and subcutaneous tissue disorders. In 14 cases (27%), the reaction was fulfilling the criteria for seriousness, including 13 cases that required hospitalisation. The hepatic reactions reported were classified as serious (acute hepatitis) in six out of ten cases. However, sales data of all RYR-containing products were not available, leading to the impossibility of calculating the actual incidence of such adverse events. Adverse events (164 cases) following RYR consumption have been also reported by the US Food and Drug Administration (FDA) through a post-market surveillance system in the period January 2004–September 2017. The most frequent adverse effects involved the musculoskeletal and connective tissues (29.9%–38.4%). Cases of rhabdomyolysis were reported with a relatively high rank of causality. Adverse effects on the gastrointestinal system, skin and subcutaneous system, and the hepatobiliary system were also relatively frequent [11]. The Panel evidenced that the intake of RYR may be associated with other botanicals or other drugs, which may account for possible side effect(s). However, the type of reported side effects (musculoskeletal side effects with increase of creatine phosphokinase [CPK]) occurred after ingestion of monacolin K or lovastatin but not other botanicals [11].

Based on these observation and the uncertainties highlighted in this Scientific Opinion, the Panel concluded to be unable to identify a dietary intake of monacolins from RYR not giving rise to concerns about potentially harmful effects to health for the general population, and as appropriate, for vulnerable subgroups of the population [11].

It needs to be emphasized that the above mentioned numbers must be compared with the real number of individuals on RYR preparations therapy; thus the prevalence of RYR-related side effects, especially those defined as serious, is much less than 0.1‰. According to the report of one of the companies that produces RYR-based nutraceuticals, which provided the EFSA significant data of exposure to consumers on food supplements containing 3 mg of monacolin K from RYR, a global incidence of adverse events was estimated as 0.031% on the 1.613.053 exposed consumers; 0.0013% of exposed consumers experienced a serious adverse event, and only 0.0004% were confirmed as serious and only related to the specific food supplement. Moreover, it is worth noting that to date only few cases of rhabdomyolysis have been reported (one of which required hospitalization, while the other was defined by CK increase). In one case, rhabdomyolysis occurred at a daily intake of 3 mg monacolin K in a subject with previous history of rhabdomyolysis related to simvastatin treatment [26]. The other case of rhabdomyolysis occurred with a daily intake of 19.2 mg monacolin K [27]. A third case of rhabdomyolysis following the administration of a dietary supplement containing monacolin K occurred in a 70-year old woman under polytherapy including rosuvastatin and sertraline; drug interaction seems to explain this case [28]. Some individuals who experienced less severe muscle disorders following the intake of monacolin K had a previous history of muscle adverse events with statins [11]. It is well established that several risk factors or pathological conditions may predispose to an adverse reaction to statins (such as family history of muscle disorders, history of CK elevation, vitamin D deficiency, coenzyme Q10 deficiency, extensive physical exercise, renal and hepatic

impairment, previous history of muscle toxicity with another lipid-lowering therapy, untreated hypothyroidism, disorders of calcium homeostasis, alcohol abuse, Asian ethnicity, low body mass index, genetic polymorphisms), and this may also be true for RYR [29]. On the other hand, not all the adverse events described were serious, most of them were reversible, and some subjects had already experienced muscle symptoms with previous statin treatment. This suggests that patients who develop myopathy/myositis or rhabdomyolysis (extremely rarely) have generally other co-morbidities, which may predispose to such events (or drug-to-drug interactions). Finally, many reported cases were without confirmed causality, and for all such cases we need to exclude all the risk factors/conditions that might increase the risk of intolerance, so-called *drucebo effect*, as well as use all the available tools, including statin-associated muscle symptoms-clinical index (SAMS-CI) with dechallenge and rechallenge to maximally increase the chance for the reliable diagnosis of real RYR-related adverse effects [30,31]. We also wish to stress that, despite the chemical identity between monacolin K and lovastatin, the latter is administered as a single active ingredient, whereas monacolin K is only one of the multiple components present in RYR preparations, and also the ratio between the lactone and the hydroxyl acid form varies greatly among different preparations [32].

RYR is classified in Europe as a food supplement; it cannot hence claim therapeutic effects – only drugs can – and no risk/benefit ratio can be considered. The EFSA Scientific Opinion did not take into account some relevant information, which includes both clinical data (see paragraph below) and data of exposure to consumers on food supplements containing 3 mg of monacolin K.

4. Data on the safety and efficacy of RYR

The extract from red yeast Chinese rice known as Xuezhikang (XZK) has been tested in a large multicenter, randomized, double blind, placebo-controlled study conducted in 4870 Chinese patients (18–70 y) with a previous documented myocardial infarction (within 60 months prior to randomization) and increased levels of creatine kinase (CK) to evaluate the effects on cardiovascular outcomes [33]. The primary endpoint was the occurrence of a major coronary event (nonfatal myocardial infarction [MI], or coronary death, or cardiac death); secondary endpoints were total CV mortality, total all-cause mortality, coronary revascularization, and changes in lipid plasma levels. Patients enrolled received a twice-daily treatment with XZK 600 mg (300-mg capsule of XZK, corresponding to 2.5–3.2 mg monacolin K/capsule) or placebo, with an average follow-up of 4.5 years. Mean LDL-C level at baseline was 129 mg/dL. Patients who received XZK showed a significant 17.6% LDL-C level reduction compared with placebo ($p < 0.001$), and this reduction was maintained throughout the study (Table 1). Overall, the lipid profile of patients treated with XZK was significantly improved (reduction of triglycerides and increase in HDL-C levels) (Table 1) [33]. Patients treated with XZK had significant decreases in the incidence rates of cardiovascular outcomes, including nonfatal MI (risk reduction [RR] 0.38, $p < 0.0001$), coronary mortality (RR 0.69, $p = 0.005$), coronary revascularization (RR 0.64, $p = 0.004$), CV mortality, (RR 0.70, $p = 0.005$) (Table 1). Moreover, XZK significantly reduced total mortality (RR 0.67, $p = 0.0003$) and cancer mortality (RR 0.44, $p = 0.014$) (Table 1). This study did not report treatment-related serious adverse events; discontinuation rates and adverse events were similar between the two groups [33]. It is worth noting that this is the only clinical outcome trial on RYR and that the high beneficial effect of XZK might also depend on the activities of non-statin components.

Since then, a large number of clinical studies has evaluated the lipid-lowering efficacy and safety of RYR and monacolin K. A meta-analysis of 20 RCTs with 6653 participants (follow-up between 2 months and 3.5 years) in which RYR with a known content of monacolin K (dose varying from 4.8 to 24 mg per day) was compared with placebo or a statin showed that RYR supplementation reduced LDL-C levels compared with placebo (−1.02 mmol/L/−39 mg/dL); when compared to statin therapy (pravastatin 40 mg, simvastatin 10 mg, or lovastatin 20 mg) there was no difference between the interventions [34]; the incidence of liver and kidney adverse events was similar in all groups, as it was the incidence of muscle symptoms [34]. The most recent, hitherto the largest available meta-analysis on the safety of monacolin K analyzed 53 randomized controlled trials including 8535 subjects [35]. Monacolin K administration was not associated with an increased risk of muscle adverse events (odds ratio [OR] = 0.94, 95% confidence interval [CI] 0.53, 1.65) or serious adverse events (OR 0.54, 95%CI 0.46, 0.64), and a significant reduction in the risk of non-muscle-related adverse events was observed (OR 0.59, 95%CI 0.50, 0.69) [35]. We should also acknowledge a recent case of acute hepatitis 6 weeks after starting a RYR supplement and resolved after stopping the supplement [36].

Table 1
Effect of XZK, an extract from RYR, on lipid profile and coronary events in a population with previous MI.

Plasma lipids	% change (XZK vs placebo)	*p* value
Total cholesterol	−10.9%	<0.001
LDL-C	−17.6%	<0.001
HDL-C	+4.2%	<0.001
Non-HDL-C	−16.6%	<0.0001
TG	−15.2%	<0.001
Events	**risk reduction with XZK (95% CI)**	***p* value**
Nonfatal MI	0.38 (0.27–0.54)	<0.0001
Coronary disease mortality	0.69 (0.52–0.88)	0.005
Fatal MI	0.67 (0.38–1.20)	0.19
Fatal stroke	0.91 (0.42–1.99)	0.85
Coronary revascularization	0.64 (0.47–0.86)	0.004
CV mortality	0.70 (0.54–0.89)	0.005
Cancer mortality	0.44 (0.23–0.84)	0.014
Total mortality	0.67 (0.52–0.82)	0.0003

LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; TG: triglycerides; MI: myocardial infarction; CV: cardiovascular. Adapted from Lu Z. et al., *Am J Cardiol*, 2008; 101:1689–1693 [33].

5. Which patients/subjects might benefit the most from RYR?

Statins are the most commonly prescribed drugs for the treatment of hypercholesterolemia and CV risk reduction; a large number of clinical trials have indicated a high efficacy in reducing LDL-C levels and the risk of cardiovascular events. However, individuals with moderate dyslipidemia and low CV risk are not deemed for statin therapy by current guidelines and they are usually advised with lifestyle intervention [6]. Furthermore, some hypercholesterolemic patients may experience statin intolerance, which significantly reduces the adherence to therapy, limits an effective treatment and increases their CV risk [37]. Furthermore, for patients unwilling to take statins and/or other lipid-lowering drugs even when clearly indicated and recommended by their physicians, RYR might be a reasonable alternative compared to other food supplements.

We must bear in mind that patients with confirmed complete statin intolerance should not be given RYR as it contains a statin. However, a real statin intolerance affects only 3–5% of patients and only very few (<1%) develop serious side-effects such as myopathy, myositis or rhabdomyolysis (1.6 per 100,000 person-years) [29]. For most (even 95%) of those who experienced statin-associated

muscle symptoms (SAMS) it is still possible to use statins by modifying the dose and type of statin, apply alternate-day statin therapy, or alternatively a non-statin dug or specific nutraceuticals with lipid-lowering properties can be considered [38]. RYR was shown to reduce LDL-C levels by 20–30% in patients with SAMS (even by 40% with ezetimibe), with a low discontinuation rate due to recurrence of SAMS (2–7%) [39]. Since most patients have a higher probability to report adverse events than healthy subjects of the general population, a rigorous clinical assessment of statin intolerance is mandatory and must take into account the possible statin-use unrelated factors that may predispose to muscle symptoms [39].

Subjects in primary prevention with low-to-moderate hypercholesterolemia (defined as LDL-C levels mildly above the optimal level, related to the individual CV risk), and thus still without clear indications for statin therapy, as well as those with the indications however with the high risk of new onset diabetes (NODM), may be eligible for RYR use in order to reduce their LDL-C levels and CV risk. Is RYR advisable also for subjects/patients who are not willing to take a statin? We must underline that nutraceuticals, including RYR, cannot replace statin/pharmacological therapy, but may be used as add-on to non-statin lipid-lowering agents such as ezetimibe to help achieving treatment targets; thus for such patients who are unwilling to take statins they might be an important option of treatment [38].

6. Major critical points

Nutraceuticals do not require medical prescription and are freely available (although we should acknowledge that low-dose statins, i.e. simvastatin 10 mg, can be also obtained without prescription in some countries), which may give rise to some concerns.

Subjects who take RYR may be grouped into 2 categories:

- Individuals who freely buy and take RYR supplements containing monacolin K: producers should label the product with a clear indication stating that "*before taking RYR it is recommended to consult your doctor, especially if taking any other drug or food supplement*". Cannot be mandatory, but patients should inform their physician about the use of RYR for two main reasons: 1) possible interaction with food or other drugs, 2) to report potential adverse events (which may help the phytovigilance/nutrivigilance). This aspect is of special relevance when taking a product such as RYR, which can be endowed with a pharmacological effect.
- Subjects who come to the attention of the physician but are not willing to take a statin. In any case, physicians must recommend the use of a statin to lower LDL-C levels. Our recommendation is that only subjects with low CV risk, without overt characteristics of eligibility for statin therapy, or having conditions/risk factors that may predispose to an increased risk of statin-associated SAMS, may be advised to use RYR, and physicians should discuss with the patients the possible benefit as well as adverse events associated with RYR use.

Another major critical point is the assurance of a high quality of RYR containing products. To avoid the use of low quality products, companies must declare the product content (list all substances [and their doses] present in the nutraceutical), and guarantee the absence of specific harmful component (list of what must not be present at all or at least above certain levels). Citrinin is a nephrotoxic and hepatotoxic mycotoxin produced during the fermentation of rice with *Monascus*, and may be present as a contaminant in RYR preparations; an EU legal limit has been established at 2000 μg/kg, but a recent report found that this limit was exceeded in some samples among those examined [40]. This finding suggests the need of improved standardization of RYR products as well as product labelling. This Expert Panel strongly recommends using only citrinin-free RYR preparations.

In EU countries, between 2012 and 2018, 40 products have been identified as clearly stating the content of monacolin K, with recommended daily intakes ranging from 2 to 48 mg; however, for most of them, the recommended maximal intake was 10 mg, according to the 2011 indication by EFSA. Only 8 out of 40 products contained exclusively RYR preparation, whereas the others contained several additional ingredients, which may contribute to the hypocholesterolemic effect of RYR by acting via different mechanisms of action. The combination of nutraceuticals allows achieving LDL-C reductions by using lower doses of each component, and thus reduces the likelihood of adverse events related to a single component. Such products should be recommended due to their higher efficacy and safety (in comparison to those with single component at higher doses) [38,41].

6.1. Expert opinion

- From available data there is no clinical evidence of a higher incidence of side effects with RYR up to 10 mg/d than with lovastatin at the same dose. With drugs we accept to have adverse events, but nutraceuticals are not drugs; thus the question rises what matters more, safety or benefit? Benefit is important and needs to be balanced against safety; in the case of RYR safety issues need to be coped with by sincere education/detailed information on the packages.
- We must consider the overall benefit of RYR for the general population. Taking RYR would shift cholesterol levels to lower and add CV benefit, independently of starting cholesterol level (Fig. 2). Mendelian randomization studies and clinical studies indicate that this is clinically beneficial [42].
- Absolute benefit is related to the risk of the subjects. In the general population in primary prevention the relative risk reduction may be the same as high-risk population, but the absolute risk reduction is obviously lower. The absolute number of prevented events, however, may be quite relevant, because most events occur in the large low and intermediate risk population; thus, a reduction of the mean level of LDL-C will shift the whole distribution of exposure in a favourable direction (Fig. 2). In this context, RYR might represent a valuable tool with a considerable impact at the population level. It is intuitive that the adherence to RYR supplement intake is crucial to achieve the LDL-C-lowering effect, and the prescribing physician should make aware the subject that treatment will need to be followed for years, and potentially life long.
- The clinical cardiovascular benefit derives essentially from LDL-C reduction, independently of how such a reduction is achieved. However, we must emphasize that it is crucial to reduce LDL-C safely, even when the approach is by means of nutraceuticals.
- Data on the exposure to RYR (used in a combination nutraceutical, post-marketing surveillance data) have not been taken into account in the EFSA Opinion. In our view, EFSA should consider these data.
- Nutrivigilance should be applied on every commercial nutraceutical; this will allow to monitor the effects of additional components present in one RYR preparation but not in others (and will avoid the "dilution" of the effect when an overall nutrivigilance is performed on similar products). To implement the post-marketing vigilance, we may suggest that producers provide information on internet portals for side effect monitoring with the package inserts; this might be on a voluntary

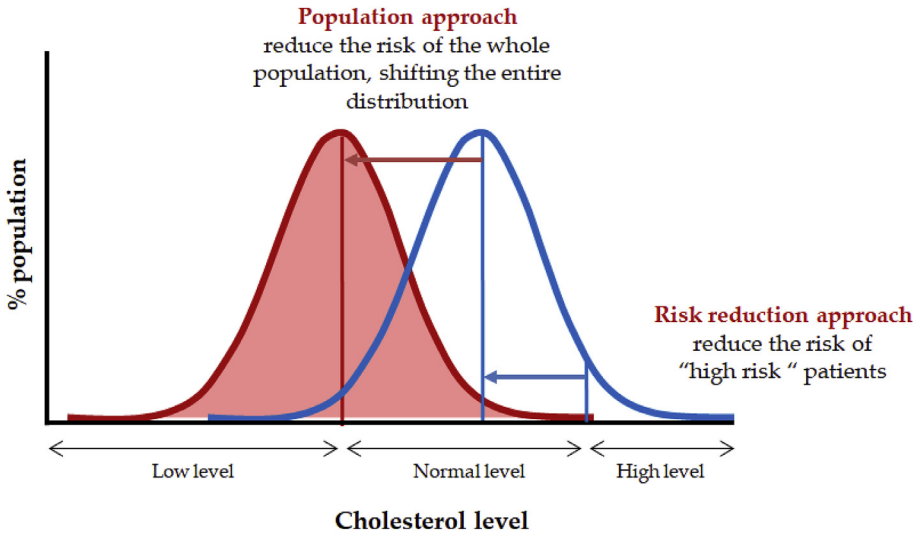

Fig. 2. A large number of subjects at low risk may translate into a higher absolute number of events than the small number of patients at high risk. Reducing the mean LDL-C level of the whole population would result in a global risk reduction (population approach); the risk reduction approach, aimed at moving high risk patients into normal range, is obtained by appropriate interventions at the individual level.

basis of the producers, with all the limits that this can imply, or better defined with formal regulations by the authorities.

- Available data suggest that the use of RYR is not associated with a higher risk of adverse side effects than the use of statins. This would raise the question on the possible indications of RYR in subjects still without clear indications for statin therapy or those with indications but having essentially higher risk of statin-related side effects (NODM, obesity, carbohydrates disturbances, SAMS) [43].
- Should individuals be informed on what monacolin K is? This is a point that requires consideration. This expert panel agrees that the patient should be informed of the content of the product, and the fact that it contains a "natural statin". In our opinion the right to be informed overcomes the fact that some subjects may not be willing to take a product with this composition; especially for people who are not willing to take statin, as well as those with the drucebo effect, the physician can address the question of whether giving the patient the information that RYR contains a natural statin might significantly reduce the adherence and compliance.
- Could the recent EFSA Scientific Opinion result in the ban of selling RYR in the EU? What might be the consequences of this banning? Mendelian randomization studies have suggested that reducing LDL-C levels independent of the approach used results in the reduction of CV risk and that lowering the plasma LDL-C level earlier than is currently recommended, if maintained over time, may result in proportionally greater reductions in the lifetime CV risk than that suggested by short-term randomized trials [1]. Patients with elevated LDL-C levels, who are not eligible for statin therapy in view of their global CV risk, likely benefit from the use of RYR, due to its cholesterol-lowering properties, allowing them to reduce their LDL-C levels and CV risk [6]. As stated above, this may lead to preventing a large number of cardiovascular events, which occur within the low-to-intermediate risk population. Another group are those with very high risk not willing to use statins/at the risk of statin intolerance/non-adherent to statin therapy. For such patients we need to reduce LDL-C, as they are at the highest risk of CVD events [44]. The banning of RYR might result in an overall increase of cardiovascular event incidence in a wide population range. It is also worth noting, on the other hand, that RYR-containing products may be bought online or at black market, which may result in an increased dissemination of low-quality products and, as a consequence, a higher risk of adverse events.
- RYR may thus be considered to reduce the overall CV risk in the general population; however, producer companies must be asked to provide unequivocal, up to date, and clear information on their products to prevent the use of low quality products.

7. Conclusions

This Expert Panel believes that RYR-based food supplements and nutraceuticals may play a role in reducing the global burden of CV disease. An increased quality of food supplements and nutraceuticals is an essential requirement to ensure safety of the product and the protection of consumers. A post-marketing surveillance must be mandatory for food supplements and nutraceuticals as it is for drugs; this will also help to collect data on long-term safety. Monacolin K at 3 mg/day appears to essentially and safely reduce LDL-C levels. (See Box 1, Box 2, Box 3)

Box 1
Recommendations to the Companies to improve the use of RYR

- *Provide clear information on the quantity of monacolin K*
- *Inform clearly on restriction of use (especially pregnant women) and risk*
- *Inform on interactions (other drugs or foods)*
- *Provide quality control data*

Box 2
Missing scientific data

- *Further specific trials in statin intolerant patients*
- *Studies to assess long-term compliance*

Box 3
Recommendations to the doctor when prescribing RYR

- *Clarify the indication of prescribing drugs or nutraceuticals containing statin in your patient. Does your patient have sufficiently high cardiovascular risk?*
- *In case of reluctance of your patient to take classical statins, clarify the exact reason: (1) adverse effect (intolerant patient), (2) specific worries about the chemical nature of a drug (the patients prefer natural medicine) or (3) worries about the statin administration in general.*
- *Based on this clarification, in cases 1 and 3, you should inform your patients on the presence of a monacolin K (= natural lovastatin) and its dose in the product.*
- *In any cases of prescription of product containing monacolin K, be careful about contraindications, advise regarding potential interactions and side effects (only if the patient accepts to be informed on this), and monitor lipid reduction and biological side effects (liver and muscles).*

Conflicts of interest

M. Banach has received research grant(s)/support from Sanofi and Valeant, and has served as a consultant for Akcea, Amgen, KRKA, MSD, Mylan, Polfarmex, Polpharma, Sanofi-Aventis, Servier, Esperion, and Resverlogix; E. Bruckert reports grants from Amgen, and personal fees from Aegerion, Genfit, MSD, Sanofi/Regeneron Pharmaceuticals Inc, AstraZeneca, Unilever, Servier and AKCEA; O. Descamps reports that his institution (Centres Hospitaliers Jolimont) received grants for his research and payment for him conducting clinical trials from Amgen, Sanofi, AstraZeneca, MSD. He received personally consulting fees and/or honoraria for delivering lectures for Amgen, Sanofi, AstraZeneca, MSD, Servier, Eurogenerics and Mylan; L. Ellegård L.E. reports no conflicts of interest; M. Ezhov reports lecture fees from Amgen, AstraZeneca, Berlin Chemie, Egis, KRKA, NovoNordisk, Pfizer, Recordati, and Sanofi; and consultant fees from Amgen, NovoNordisk, and Sanofi; B. Föger B. Föger reports personal fees and grants from Amgen, Böhringer Ingelheim, MEDA, MSD, Sanofi, and Sanova; Z. Fras; P. Kovanen reports personal fees as Company consultant and/or speaker for Aegerion, Amgen, Medaffcon, Raisio, Sanofi/Regeneron; G. Latkovskis reports grants, personal fees or non-financial support from Abbott Laboratories, Amgen, Astra-Zeneca, Bayer, Berlin-Chemie/Menarini, Boehringer Ingelheim, GlaxoSmithKline, KRKA, Mylan, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, Sanofi-Aventis, Servier, Siemens Healthcare, Zentiva; W. März reports grants and personal fees from Abbott Diagnostics, Aegerion Pharmaceuticals, Akcea Therapeutics, Alexion Pharmaceuticals, AMGEN, BASF, Berlin-Chemie, Numares AG, Sanofi, and grants from Astrazeneca, Bayer Vital GmbH, bestbion dx GmbH, Boehringer Ingelheim Pharma GmbH Co KG, Immundiagnostik GmbH, Merck Chemicals GmbH, MSD Sharp and Dohme GmbH, Novartis Pharma GmbH, Olink Proteomics, Siemens Healthineers, all outside the submitted work. W.M. is employed with SYNLAB Holding Deutschland GmbH; D.B. Panagiotakos reports no conflicts of interest; G. Paragh reports to be a Member of the Professional Advisory Board: Sanofi – Aventis Zrt., AMGEN, MSD Pharma Hungary Kft; D. Pella reports grants and personal fees from AMGEN, Boehringer Ingelheim, Krka, MSD Sharp and Dohme GmbH, Mylan, Pfizer, Sanofi-Aventis, Servier, Pfizer; A. Pirillo reports no conflict of interest; A. Poli reports to be Chairman of NFI - Nutrition Foundation of Italy, a non-profit organization partially supported by 19 food and beverage companies, some of which market food or food supplements active on plasma cholesterol levels; Ž. Reiner has received honoraria from Sanofi Aventis but there are no disclosures regarding this article; G. Silbernagel reports grants and personal fees from Sanofi, grants and personal fees from Amgen, grants from Numares, and grants and personal fees from Bayer, outside the submitted work; M Viigimaa reports grants from Amgen, and lecture honoraria from AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Servier, Sanofi and Menarini; M. Vrablík reports grants, personal fees or non-financial support from Abbott Laboratories, Amgen, Astra-Zeneca, Boehringer Ingelheim, KRKA, Mylan, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis, Servier, Zentiva outside of the submitted work; A.L. Catapano reports grants from Sanofi, Regeneron, Merck, Mediolanum, grants from SigmaTau, Menarini, Kowa, Recordati, Eli Lilly, personal fees from Merck, Sanofi, Regeneron, AstraZeneca, Amgen, Sigma Tau, Recordati, Aegerion, Kowa, Menarini, Eli Lilly, Genzyme, outside the submitted work.

Acknowledgements

This article was sponsored by the Società Italiana di Terapia Clinica e Sperimentale - SITeCS. SITeCS wishes to thank Mylan for providing an unrestricted educational grant to support the scientific consensus meeting. The grant was used in part for the publication of the present supplement. Mylan had no interference in the organization and scientific output of the meeting and had no involvement in this publication.

References

[1] Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Boren J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, van de Sluis B, Taskinen MR, Tokgozoglu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ, Catapano 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(32):2459–72.

[2] Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376(9753):1670–81.

[3] Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R, Cholesterol Treatment Trialists C. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366(9493):1267–78.

[4] Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR, Committee FS. Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376(18):1713–22.

[5] Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM, Committees OO. Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379(22):2097–107.

[6] Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Z, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL. ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the european society of cardiology (ESC) and european atherosclerosis society (EAS)developed with the special contribution of the european assocciation for cardiovascular prevention & rehabilitation (EACPR). Eur Heart J 2016;37(39):2999–3058. 2016.

[7] Banach M, Penson PE. What have we learned about lipids and cardiovascular risk from PCSK9 inhibitor outcome trials: ODYSSEY and FOURIER? Cardiovasc Res 2019;115(3):e26–31.

[8] Serban MC, Banach M, Mikhailidis DP. Clinical implications of the IMPROVE-IT trial in the light of current and future lipid-lowering treatment options. Expert Opin Pharmacother 2016;17(3):369–80.

[9] Ruscica M, Banach M, Sahebkar A, Corsini A, Sirtori CR. ETC-1002 (Bempedoic acid) for the management of hyperlipidemia: from preclinical studies to phase 3 trials. Expert Opin Pharmacother 2019;20(7):791–803.

[10] EFSA. Scientific Opinion on the substantiation of health claims related to monacolin K from red yeast rice and maintenance of normal blood LDL cholesterol concentrations (ID 1648, 1700) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA J 2011;9(7):2304.
[11] EFSA. Scientific opinion on the safety of monacolins in red yeast rice. EFSA J 2018;16:5368.
[12] Endo A. Monacolin K, a new hypocholesterolemic agent produced by a Monascus species. J Antibiot (Tokyo) 1979;32(8):852–4.
[13] Endo A, Hasumi K, Nakamura T, Kunishima M, Masuda M. Dihydromonacolin L and monacolin X, new metabolites which inhibit cholesterol biosynthesis. J Antibiot (Tokyo) 1985;38(3):321–7.
[14] Endo A, Hasumi K, Negishi S. Monacolins J and L, new inhibitors of cholesterol biosynthesis produced by Monascus ruber. J Antibiot (Tokyo) 1985;38(3):420–2.
[15] Endo A, Komagata D, Shimada H. Monacolin M, a new inhibitor of cholesterol biosynthesis. J Antibiot (Tokyo) 1986;39(12):1670–3.
[16] Beltran D, Frutos-Lison MD, Espin JC, Garcia-Villalba R. Re-examining the role of the gut microbiota in the conversion of the lipid-lowering statin monacolin K (lovastatin) into its active beta-hydroxy acid metabolite. Food Funct 2019;10(4):1787–91.
[17] Chen CH, Uang YS, Wang ST, Yang JC, Lin CJ. Interaction between red yeast rice and CYP450 enzymes/P-glycoprotein and its implication for the clinical pharmacokinetics of lovastatin. Evid Based Complement Alternat Med 2012;2012:127043.
[18] Doughari JH. The occurrence, properties and significance of citrinin mycotoxin. J Plant Pathol Micriobiol 2015;6(11):321.
[19] Song J, Luo J, Ma Z, Sun Q, Wu C, Li X. Quality and authenticity control of functional red yeast rice-A review. Molecules 2019;24(10).
[20] Heinz T, Schuchardt JP, Moller K, Hadji P, Hahn A. Low daily dose of 3 mg monacolin K from RYR reduces the concentration of LDL-C in a randomized, placebo-controlled intervention. Nutr Res 2016;36(10):1162–70.
[21] Becker DJ, Gordon RY, Halbert SC, French B, Morris PB, Rader DJ. Red yeast rice for dyslipidemia in statin-intolerant patients: a randomized trial. Ann Intern Med 2009;150(12):830–9. W147-839.
[22] Bogsrud MP, Ose L, Langslet G, Ottestad I, Strom EC, Hagve TA, Retterstol K. HypoCol (red yeast rice) lowers plasma cholesterol - a randomized placebo controlled study. Scand Cardiovasc J 2010;44(4):197–200.
[23] Heber D, Yip I, Ashley JM, Elashoff DA, Elashoff RM, Go VL. Cholesterol-lowering effects of a proprietary Chinese red-yeast-rice dietary supplement. Am J Clin Nutr 1999;69(2):231–6.
[24] Huang CF, Li TC, Lin CC, Liu CS, Shih HC, Lai MM. Efficacy of Monascus purpureus Went rice on lowering lipid ratios in hypercholesterolemic patients. Eur J Cardiovasc Prev Rehabil 2007;14(3):438–40.
[25] Lin CC, Li TC, Lai MM. Efficacy and safety of Monascus purpureus Went rice in subjects with hyperlipidemia. Eur J Endocrinol 2005;153(5):679–86.
[26] Mazzanti G, Moro PA, Raschi E, Da Cas R, Menniti-Ippolito F. Adverse reactions to dietary supplements containing red yeast rice: assessment of cases from the Italian surveillance system. Br J Clin Pharmacol 2017;83(4):894–908.
[27] Philibert C, Bres V, Jean-Pastor MJ, Guy C, Lebrun-Vignes B, Robin P, Pinzani V, Hillaire-Buys D. [Red yeast-rice-induced muscular injuries: analysis of French pharmacovigilance database and literature review. Therapie 2016. https://doi.org/10.2515/therapie/2015053. pii: S0040-5957(16)30054-3.
[28] Russo R, Gallelli L, Cannataro R, Perri M, Calignano A, Citraro R, Russo E, Gareri P, Corsonello A, Sarro GD. When nutraceuticals reinforce drugs side effects: a case report. Curr Drug Saf 2016;11(3):264–6.
[29] Banach M, Rizzo M, Toth PP, Farnier M, Davidson MH, Al-Rasadi K, Aronow WS, Athyros V, Djuric DM, Ezhov MV, Greenfield RS, Hovingh GK, Kostner K, Serban C, Lighezan D, Fras Z, Moriarty PM, Muntner P, Goudev A, Ceska R, Nicholls SJ, Broncel M, Nikolic D, Pella D, Puri R, Rysz J, Wong ND, Bajnok L, Jones SR, Ray KK, Mikhailidis DP. Statin intolerance - an attempt at a unified definition. Position paper from an International Lipid Expert Panel. Arch Med Sci 2015;11(1):1–23.
[30] Penson PE, Mancini GBJ, Toth PP, Martin SS, Watts GF, Sahebkar A, Mikhailidis DP, Banach M. Lipid, Blood Pressure Meta-Analysis Collaboration G, International Lipid Expert P. Introducing the 'Drucebo' effect in statin therapy: a systematic review of studies comparing reported rates of statin-associated muscle symptoms, under blinded and open-label conditions. J Cachexia Sarcopenia Muscle 2018;9(6):1023–33.
[31] Banach M, Mikhailidis DP. Statin intolerance: some practical hints. Cardiol Clin 2018;36(2):225–31.
[32] Cicero AFG, Colletti A, Bajraktari G, Descamps O, Djuric DM, Ezhov M, Fras Z, Katsiki N, Langlois M, Latkovskis G, Panagiotakos DB, Paragh G, Mikhailidis DP, Mitchenko O, Paulweber B, Pella D, Pitsavos C, Reiner Z, Ray KK, Rizzo M, Sahebkar A, Serban MC, Sperling LS, Toth PP, Vinereanu D, Vrablik M, Wong ND, Banach M. Lipid lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel. Arch Med Sci 2017;13(5):965–1005.
[33] Lu Z, Kou W, Du B, Wu Y, Zhao S, Brusco OA, Morgan JM, Capuzzi DM. Chinese Coronary Secondary Prevention Study G, Li S. Effect of Xuezhikang, an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction. Am J Cardiol 2008;101(12):1689–93.
[34] Gerards MC, Terlou RJ, Yu H, Koks CH, Gerdes VE. 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(2):415–23.
[35] Fogacci F, Banach M, Mikhailidis DP, Bruckert E, Toth PP, Watts GF, Reiner Z, Mancini J, Rizzo M, Mitchenko O, Pella D, Fras Z, Sahebkar A, Vrablik M, Cicero AFG. Lipid, Blood Pressure Meta-analysis Collaboration G, International Lipid Expert P. Safety of red yeast rice supplementation: a systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 2019;143:1–16.
[36] Loubser L, Weider KI, Drake SM. Acute liver injury induced by red yeast rice supplement. BMJ Case Rep 2019;12(3).
[37] Banach M, Stulc T, Dent R, Toth PP. Statin non-adherence and residual cardiovascular risk: there is need for substantial improvement. Int J Cardiol 2016;225:184–96.
[38] Banach M, Patti AM, Giglio RV, Cicero AFG, Atanasov AG, Bajraktari G, Bruckert E, Descamps O, Djuric DM, Ezhov M, Fras Z, von Haehling S, Katsiki N, Langlois M, Latkovskis G, Mancini GBJ, Mikhailidis DP, Mitchenko O, Moriarty PM, Muntner P, Nikolic D, Panagiotakos DB, Paragh G, Paulweber B, Pella D, Pitsavos C, Reiner Z, Rosano GMC, Rosenson RS, Rysz J, Sahebkar A, Serban MC, Vinereanu D, Vrablik M, Watts GF, Wong ND, Rizzo M. International lipid expert P. The role of nutraceuticals in statin intolerant patients. J Am Coll Cardiol 2018;72(1):96–118.
[39] Rosenson RS, Baker S, Banach M, Borow KM, Braun LT, Bruckert E, Brunham LR, Catapano AL, Elam MB, Mancini GBJ, Moriarty PM, Morris PB, Muntner P, Ray KK, Stroes ES, Taylor BA, Taylor VH, Watts GF, Thompson PD. Optimizing cholesterol treatment in patients with muscle complaints. J Am Coll Cardiol 2017;70(10):1290–301.
[40] Lopez-Sanchez P, de Nijs M, Spanjer M, Pietri A, Bertuzzi T, Starski A, Postupolski J, Castellari M, Hortos M. Generation of occurrence data on citrinin in food. EFSA Supporting Publications 2017;114(2):1177E.
[41] Cicero AFG, Colletti A, Bajraktari G, Descamps O, Djuric DM, Ezhov M, Fras Z, Katsiki N, Langlois M, Latkovskis G, Panagiotakos DB, Paragh G, Mikhailidis DP, Mitchenko O, Paulweber B, Pella D, Pitsavos C, Reiner Z, Ray KK, Rizzo M, Sahebkar A, Serban MC, Sperling LS, Toth PP, Vinereanu D, Vrablik M, Wong ND, Banach M. Lipid-lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel. Nutr Rev 2017;75(9):731–67.
[42] Ference BA, Majeed F, Penumetcha R, Flack JM, Brook RD. Effect of naturally random allocation to lower low-density lipoprotein cholesterol on the risk of coronary heart disease mediated by polymorphisms in NPC1L1, HMGCR, or both: a 2 x 2 factorial Mendelian randomization study. J Am Coll Cardiol 2015;65(15):1552–61.
[43] Banach M, Mikhailidis DP. Statin therapy and new-onset diabetes: an attempt at recommendations. Expert Rev Endocrinol Metab 2013;8(3):213–6.
[44] Serban MC, Colantonio LD, Manthripragada AD, Monda KL, Bittner VA, Banach M, Chen L, Huang L, Dent R, Kent ST, Muntner P, Rosenson RS. Statin intolerance and risk of coronary heart events and all-cause mortality following myocardial infarction. J Am Coll Cardiol 2017;69(11):1386–95.