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Review

Red yeast rice for dyslipidaemias and cardiovascular risk reduction: A position paper of the International Lipid Expert Panel

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ABSTRACT

The risk of atherosclerotic cardiovascular disease (ASCVD) is strongly related to lifetime exposure to low-density lipoprotein (LDL)-cholesterol in longitudinal studies. Lipid-lowering therapy (using statins, ezetimibe and PCSK9 inhibitors) substantially ameliorates the risk and is associated with long-term reduction in cardiovascular (CV) events. The robust evidence supporting these therapies supports their continued (and expanding) role in risk reduction. In addition to these 'conventional' therapeutics, while waiting for other innovative therapies, growing evidence supports the use of a range of 'nutraceuticals' (constituents of food prepared as pharmaceutical formulations) including preparations of red yeast rice (RYR), the product of yeast (Monascus purpureus) grown on rice, which is a constituent of food and is used in traditional Chinese medicine. The major active ingredient, monacolin K, is chemically identical to lovastatin. RYR preparations have been demonstrated to be safe and effective in reducing LDL-C, and CV events. However, surprisingly, RYR has received relatively little attention in international guidelines – and conventional drugs with the strongest evidence for event reduction should always be preferred in clinical practice. Nevertheless, the absence of recommendations relating to RYR may preclude the use of a product which may have clinical utility in particular groups of patients (who may anyway self-prescribe this product), what in the consequence might help to reduce population CV risk. This Position Paper of the International Lipid Expert Panel (ILEP) will use the best available evidence to give advice on the use of red-yeast rice in clinical practice.

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1. Introduction

Recent decades have seen tremendous advances in the prevention of cardiovascular diseases (CVD) – achieved as a result of pharmaceuticals (particularly lipid-lowering and antihypertensive drugs) and improvements to diet and lifestyle [1]. Dietary modifications have largely focused on the macronutrient components of diet, with strong recommendations around the reduction of the proportion of energy obtained from saturated fat being an important component of recommendations for many years [2,3]. However, micronutrients may also have an important role in modulating health and disease – particularly constituents of food with drug-like properties (physiological activity at low doses). Their role may be especially important as most of them have multidirectional beneficial properties, working not only for lipid lowering, but also decreasing blood pressure and/or arterial stiffness and/or inflammation, etc. [4] Increasing scientific and clinical knowledge relating to the safety and efficacy use of these preparations is becoming available. Many patients are more inclined to find 'natural' products acceptable than conventional medicines and self-medicate with nutraceutical products. Physicians and prescribers therefore have a need for high-quality evidence-based recommendations relating to the use of nutraceuticals, however the topic has received relatively little attention in international guidelines.

1.1. Lipids, lipoproteins, and atherosclerotic cardiovascular disease

The risk of atherosclerotic cardiovascular disease (ASCVD) is strongly related to lifetime exposure to low density lipoprotein (LDL)-cholesterol in longitudinal studies [5]. Lipid-lowering therapy (using statins, ezetimibe and PCSK9 inhibitors) substantially ameliorates the risk and is associated with long-term reduction in cardiovascular (CV) events [6–10]. The unambiguous evidence supporting these therapies supports their continued (and expanding) role in risk reduction. In addition to these 'conventional' therapeutics, growing evidence supports the use of a range of 'nutraceuticals' (constituents of food prepared as pharmaceutical formulations) [11–16]. Efficacy claims have been made for a wide range of nutraceuticals in the CVD prevention and management. The evidence has been summarised in position papers of the International Lipid Expert Panel (ILEP) [11,12,14,15,17]. Amongst the many nutraceuticals with potential lipid-lowering effects, red yeast rice (RYR) stands out as having a particularly broad evidence base, and therefore merits further detailed consideration on its role in lipid disorders management.

1.2. Red yeast rice

RYR is a natural product of yeast (Monascus purpureus) grown on white rice. It is a constituent of the diet in parts of Asia and is used in traditional Chinese medicine [17,18]. The major active ingredient is monacolin K, which (in its lactone form) is chemically identical to lovastatin, and is therefore, a naturally occurring inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMGCoA) reductase, a rate-limiting enzyme in the endogenous production of cholesterol. Importantly, RYR consumption results in reduction of circulation concentrations of atherogenic LDL-C particles [18], and studies have suggested that this is associated with a substantial reduction in the risk of cardiovascular events [19], raising the possibility that red yeast rice preparations may have a role in preventing cardiovascular disease. As expected with natural products, RYR contains a wide (and variable) range of chemical constituents, and several monacolins (M, L, J & X) may contribute in varying degrees to the lipid-lowering effect (reviewed extensively elsewhere) [20].

1.3. Organization of this International Lipid Expert Panel (ILEP) position paper

Where appropriate, the level of evidence and the strength of recommendations are categorized accordingly. While working on this Position Paper we strictly followed the ILEP scientific policy on the preparation of the recommendations (https://ilep.eu/publications/). Briefly: (1) the idea on this paper was suggested by Prof. Maciej Banach (M.B.), which was formally sent to the Steering Committee of the ILEP (see: www.ilep.eu for details) for approval. Next, (2) the selected ILEP Members - as well as external experts – recognized researchers in the field of nutraceuticals, and specifically red yeast rice were invited to be a part of the writing Committee (WC) of this paper. After establishment of the WC (3) there was the first Global Steering Committee (SC) virtual meeting, during which the most recent information on RYR efficacy, safety, aim of the paper and its main content was widely discussed. Next, (3) M.B. & Prof. Peter Penson (P.P.) started to work on the draft version of the recommendations, which were next extensively discussed with all the WC members during the 2nd SC virtual meeting, putting specially emphasis on the tables with recommendations. In case of disagreement, each recommendation was voted. In the next step (5), the final draft of recommendations was sent to all WC members for the review process and approval. Each comment and suggestion were responded and discussed.

1.4. Efficacy of Red-Yeast Rice in dyslipidaemias and cardiovascular risk reduction

Many available studies have evaluated the efficacy of RYR preparations on lipid profiles, and (to a lesser extent) CVD outcomes. The results of such studies have been summarised in several meta-analyses [18,21,22]. Beneficial effects of RYR supplementation on plasma lipid profile have been recognised for several years. A 2014 meta-analysis, including 804 participants with hypercholesterolemia across 13 randomized controlled trials (RCTs) concluded that red yeast rice supplementation (with the dose of monacolin K between 2 and 11.4 mg and follow-up from 4 to 52 weeks) significantly reduced serum total cholesterol (−0.97 mmol/L (95% confidence interval [CI]: −1.13, −0.80), triglycerides (−0.23 mmol/L (95% CI: −0.31, −0.14) and LDL-C (−0.87 mmol/L (95% CI: −1.03, −0.71) compared with placebo, without any reports of serious side effects [18]. More recently a network meta-analysis combined the results of 47 RCTs and a total of 4824 subjects who were treated with RYR-containing Chinese patent medicines with appropriate comparators (which included simvastatin). Interestingly, specific RYR preparations were found to be more effective than simvastatin in respect of the magnitude of LDL-C and total cholesterol lowering. However, the authors did suggest that owing to limitations inherent in their study, the validity of their results should be confirmed in large, well-designed, multicentre, prospective RCTs. [22].

Another recent meta-analysis of the effect of RYR preparations on major adverse cardiac events (MACE) outcomes and cardiovascular risk factors included almost 7000 participants across 30 RCTs [21]. The authors reported that RYR use was associated with impressive reductions in mortality (RR = 0.62, 95% CI [0.49, 0.78]) and MACE (RR = 0.54, 95% CI [0.43, 0.66]). These findings were accompanied and might have been a result of the significant reductions in total cholesterol (−0.74 mmol/L, 95% CI [−1.02, −0.46]), triglycerides (−0.45 mmol/L, 95% CI [−0.70, −0.21]), and LDL-C (−0.42 mmol/L, 95% CI [−0.78, −0.06]). Fasting plasma glucose (−0.46 mmol/L, 95% CI [−0.71, −0.22]), haemoglobin A1c (−0.49, 95% CI [−0.71, −0.26]), Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) (−0.93, 95% CI [−1.64, −0.21]), and blood pressure (=mean arterial pressure −3.79 mmHg, 95% CI [−5.01, −2.57]) were also reduced, with no increase in adverse reactions compared to placebo [21].

However, whilst the results of this study are impressive, and add evidence to support the efficacy and safety of RYR, there was substantial

heterogeneity in patient characteristics, and aside from a small number of notable exceptions [23–25], the trials were generally small (median 67 participants) and of relatively short duration (median follow up of 10 weeks). Therefore, a small number of larger longer trials contribute substantially to the overall results. Indeed, the mortality findings were based upon the results of only 2 studies (277 events) and the MACE findings on 3 studies (336 events). As such further long-term prospective trials of red yeast rice are warranted. The question is, which often appears, while discussing the lipid lowering efficacy of nutraceuticals/natural products, whether we really need RCTs - similarly to drugs - to investigate their impact on hard endpoints. For RYR, we have multiple studies showing its impact on lipid profile and other cardiometabolic parameters, with few studies (and meta-analyses) evaluating its role on CV outcomes, and besides omega-3 fatty acids and phytosterols, it is the 3rd nutraceutical with such impressive Evidence-Based Medicine. [26].

1.5. Safety of red-yeast rice

RYR has been shown to be very well-tolerated by patients at doses of monacolin K up to 10 mg/day [27]. In previously statin-intolerant (SI) patients, mild myalgia may be reported[20,] however data on this is inconsistent, and other analyses suggested its good tolerability even in those with SI [27]. Concerns about the safety of red yeast rice, generally relate not to the monacolin content, per se, but to batch-to-batch variability in monacolin content and especially the presence of contaminants (particularly citrinin, a nephrotoxic by-product of rice fermentation). [23] Therefore, it is so critically important to focus on the quality of production of RYR preparations, with monacolin K dose control, and with the postmarketing nutrivigilance. The largest meta-analysis on RYR safety of 53 RCTs comprising 112 treatment arms with 8535 subjects [27], published after European Food Safety Authority (EFSA) recommendations from August 2018 (based mostly on cases, without checking the production quality control – with confirmed contamination, mostly without dechallenge and rechallenge), showed that monacolin K administration was not associated with increased risk of musculoskeletal disorders (MuD; odds ratio (OR) 0.94, 95% CI 0.53, 1.65), and showed reduced risk of non-MuD (0.59, 95%CI 0.50, 0.69) and serious adverse events (0.54, 95%CI 0.46, 0.64) vs. control. Interestingly, we showed that increasing daily doses of monacolin K were negatively associated with increasing risk of non-MuD (slope: −0.10; 95%CI: −0.17, −0.03; two-tailed $p < 0.01$). [27].

In order to better understand RYR safety and efficacy and to provide reassurance about the quality of individual preparations, approaches used in the 'conventional' pharmaceutical sphere can be applied. Producing products in line with the principles of Good Manufacturing Practice (GMP), can ensure the batch-to-batch consistency of active monacolin ingredients, and the absence of toxic compounds such as citrinin. Furthermore, applying the principles of pharmacovigilance and postmarketing surveillance to nutraceuticals - 'nutrivigilance' allows for a much greater likelihood of detecting adverse effects (particularly rare symptoms) than would be possible in a RCT. [24].

A recent report was published following the monitoring of the incidence of spontaneously reported suspected adverse reactions in a brand of food supplement which contained a range of lipid-lowering nutraceuticals including RYR (200 mg, equivalent to 3 mg of monacolin K). Adverse events were reported in only 0.037% of 2287,449 exposed consumer between 2004 and 2019. Only 21 users of the product (0.0009%) reported suspected serious adverse events, and of these only six adverse events (0.0003%) were assessed by the manufacturer as serious and potentially related to exposure to the product. [24] Whilst these data are undoubtedly reassuring, the findings are only applicable to the specific product, which was evaluated, and the findings can be extrapolated to the products with confirmed content (controlled dose, lack of contamination), and quality of production.

1.6. The regulatory environment for red yeast rice preparations

In many jurisdictions, nutraceutical preparations are often marketed as 'food supplements' and therefore are not regulated in the same way as medicines (so long as manufacturers do not make any specific health-related efficacy claims about their products). Products containing RYR, however, have been the subject of greater regulatory scrutiny – particularly in regions where lovastatin is only available on a prescription - because, it has been argued that selling a product containing monacolin-K is equivalent to selling a prescription medicine. This situation presents unique challenges and opportunities. The U.S. Food and Drug Administration (FDA) determined in 1998 that red yeast rice products that contain more than trace amounts of monacolin K are unapproved new drugs and cannot be sold legally as dietary supplements. The EFSA has adopted a scientific opinion on the safety of monacolins in RYR following case reports of adverse effects linked to the use of products containing such rice [28]. Based on this scientific opinion, the EU proposes to restrict the use of monacolins from RYR to ensure this substance is used safely in foods and food supplements. The draft recommendations would not permit the sale or supply of RYR preparations which contain $\geq$ 3 mg of monacolin K[2].

Greater regulatory oversight is likely to result in greater cost of products to the patient (and therefore less widespread availability). However, greater oversight presents some opportunities with respect to the potential to use RYR more effectively in the prevention of CVD. One of the commonest concerns surrounding the use of nutraceuticals is the wide variety of quality between preparations, and the potential for contamination and batch-to-batch variation. Thus, whilst a physician or prescriber might be convinced (based upon published evidence) of the efficacy of RYR, in the absence of a locally-available quality assured product, they will be understandably reluctant to recommend red yeast rice to patients. Greater regulation is likely to result in the more widespread availability of high-quality preparations and to remove from the market substandard brands.

1.7. Red yeast rice in international guidelines

Taking into account all the information presented above, surprisingly, the European Society of Cardiology (ESC) 2021 Guidelines on cardiovascular disease prevention in clinical practice, state that red yeast rice supplements should not be recommended and warn that they may cause adverse effects [25]. The 2019 American College of Cardiology (ACC)/ American Heart Association (AHA) Guideline on the Primary Prevention of Cardiovascular Disease make no mention of red yeast rice [29], which might be also partly associated with the FDA recommendations on RYR released in 1998 that states that "RYR products that contain more than trace amounts of monacolin K are unapproved new drugs and cannot be sold legally as dietary supplements" [30]. In 2007 FDA issued a consumer warning to avoid RYR products because they may contain unauthorized drug (lovastatin) and implemented current GMP requiring that proper controls be in place by dietary supplement companies to ensure products are manufactured and processed in a consistent manner and produce high-quality products that are not adulterated with impurities or contaminants and are accurately labeled [30]. On the other hand, currently, the FDA is not regulating manufacturers of RYR products, therefore there is the large need for the action to update the FDA statement with the most updated data and suggest necessary changes, also regulatory ones. In the United Kingdom, the National Institute for Health and Care Excellence recommendations on risk reduction in cardiovascular disease (including lipid modification) are currently in the process of being updated, however the current document makes no recommendation with respect to red yeast rice. ILEP have produced several position papers, relating to the use of nutraceuticals (including red yeast rice) in clinical practice, and particularly in statin-intolerant patients [11,12,14,15,17]. Also other societies and experts' group previously attempted (before and after EFSA decision

2018) to indicate the role of RYR in the therapy of lipid disorders, indicating the groups of patients that might benefit the most from the supplementation and emphasizing the issue of safety (nutrivigilance) and quality of production (lack of contamination) [31,32].

1.8. Rationale and philosophy of the ILEP recommendations on red-yeast rice

These recommendations have been developed in the recognition that the potential use of RYR has been sparsely considered (if mentioned at all) in the major international guidelines for the reduction of cardiovascular disease. The absence of recommendations is understandable, to the extent that, compared to 'conventional' pharmaceuticals, the availability of long-term outcomes data from randomised-controlled trials for RYR is limited. Nevertheless, the current situation is entirely unsatisfactory in that prescribers, physicians and patients do not have easy access to evidence and expert opinion on a widely available product.

The authors of this ILEP position paper strongly advocate the use of therapies (statins, ezetimibe, alirocumab, evolocumab and new therapies that soon will be available and hopefully reimbursed) which have been shown to reduce the risk of cardiovascular disease in large, long-term well-designed outcomes trials wherever possible and appropriate. Furthermore, they strongly indicate the need to improve the adherence to cheap and available therapies like statins, combination therapy of statins and ezetimbe, and support the expansion of criteria for reimbursement, so that these highly effective drugs for the reduction of cardiovascular disease can be made available to all patients for whom evidence suggests are likely to derive a benefit. RYR, and other nutraceuticals [13–16,33] should be considered as supplementary or supportive agents in the armoury of lipid-modification. They should not routinely replace medicines for which a larger body of long-term efficacy and safety data exist. Nevertheless, it is recognised that the body of evidence supporting the lipid (LDL-C)-modifying effects of red yeast rice is greater than for any other nutraceutical. Therefore, in the context of patient-centred care, and in healthcare systems, which must ration the availability of costly drugs, we acknowledge that specific situations (outlined below) currently exist in which conventional therapeutics may not be indicated (or may not be appropriate) and based on available evidence red-yeast rice may be considered in the management of unmet clinical needs.

Whilst it is acknowledged that consuming red-yeast rice as part of a healthy diet might contribute to improved lipid profile and health benefits, this position paper will comment only on the use of nutraceutical preparations, prepared in accordance with the principles of Good Manufacturing Practice, in which the dose of monacolins and the composition of the product can be verified. ILEP is not in a position to provide recommendations or endorsements in respect of the quality, safety or efficacy of any specific brands or products.

1.9. Specific Recommendations

In light of the rationale described above, patient groups (adult patients; there is no indication to use RYR in children and adolescents) and situations have been identified in which nutraceutical supplementation with RYR might contribute to the management of clinical needs which are currently unmet (Section 3.1). There are also situations in which red yeast rice should not be considered (Section 3.2). Recommendations are also made relating to ensuring the safety and efficacy of red yeast rice products (Section 3.3) and relating to the provision of information and education necessary to allow patients to make an informed decision relating to the use of red yeast rice (Section 3.4).

2. Patient groups in whom red yeast rice may be considered

2.1. Patients not indicated for statin therapy owing to low CVD risk

The recognition that an individual's risk of ASCVD is strongly related to their lifetime exposure to LDL-C has led to the recognition that *'Lower is better for longer'* [34]. In younger individuals (without lipid disorders such as familial hypercholesterolaemia), optimization of diet and lifestyle are the preferred means to maintain low LDL-C. Nevertheless, a large proportion of individuals (even 75%) will not achieve ideal LDL-C through diet and lifestyle alone, leaving them with an untreated modifiable risk factor for CVD [34]. Because international guidelines generally indicate statin therapy based on 10-year cardiovascular risk (rather than LDL-C measurements), individuals with an absence of other risk factors (e.g., smoking, hypertension, diabetes, obesity) are mostly not indicated for statin therapy. In the long-term greater consideration should be given to the use of lifetime risk scores and to evaluate the benefits and harms of statins in lower risk populations than have been included in the major trials. Thus, to reduce the overall risk associated with persistently elevated LDL-C in this low-risk patients' population, the use of high-quality preparations (see Section 3.2) of red yeast rice or low dose statin, after detailed discussion with patients, should be considered [34] (Table 1).

2.2. Patients unwilling to take a statin

The provision of healthcare should be based upon the principles of patient-centred care and shared decision-making. In this light, it must be accepted that some patients eligible for statin therapy, may chose not to take a statin, but may be nevertheless willing to use a red yeast rice preparation (Table 2). When a patient is considering such a course of action, it is essential that they are provided with sufficient information regarding the relative efficacy of RYR and conventional statin therapy to allow them to make a truly informed decision about their therapy (see section 3.3.1, below). Evidence relating to the efficacy and safety of red yeast rice is summarised above (Section 1.3) and in previous position papers of ILEP. [11,12,17].

2.3. Patients with statin intolerance and the nocebo/drucebo effect

Although statin intolerance affects fewer than 10% of treated patients, it can present a difficult barrier to effective cardiovascular risk reduction [35]. RYR had been previously carefully evaluated in trials of statin-intolerant patients [11]. Even though red yeast rice contains monacolin K / lovastatin (in a very low dose), it may be tolerated in most patients and has previously been endorsed by ILEP in this situation [11]. It has been also confirmed in the clinical practice, in which we might observe lack of statin-associated muscle symptoms (SAMS) in patients treated with RYR, previously with statin intolerance (drucebo effect?) or in those that are not willing to use statins and are in favour to use RYR [36]. This use is consistent with other approaches to statin intolerance, such as using low- or alternate-day dosing of statins to minimise adverse effects whilst retaining come therapeutic benefit [36–38].

In addition to patients with true statin intolerance, a substantial proportion of patients who take statins, experience side effects due to the expectation that they will occur, the nocebo/drucebo effect [39–41] or misattribute unrelated ailments, such as musculoskeletal injury to an

Table 1
Recommendations on the RYR applications in patients not indicated for statin therapy owing to low CVD risk.

Recommendation Summary	**Class**	**Level**
Red yeast rice should be considered for patients who have a suboptimal lipid profile despite diet and lifestyle interventions.	**IIa**	**B**

Table 2
Recommendations on the RYR applications in patients who are unwilling to take statin/any lipid lowering drug.

Recommendation Summary	Class	Level
In primary prevention, in patients who (after careful education as to the benefits and risks of statin therapy) are unwilling to take a statin, RYR is recommended alone or in combination with other available lipid lowering therapies.	**I**	**C**
In primary prevention, in patients who (after careful education as to the benefits and risks of lipid lowering therapy) are unwilling to take any lipid lowering drugs, RYR is recommended.	**I**	**C**

effect of statin therapy. Comprehensive advice on the management of this patient group has been recently published by ILEP [36]. This may include the use of nutraceuticals as part of the 'MEDS' (Minimizing disruption to therapy; Educating the patient regarding the benefits of statin therapy, using Diet and nutraceuticals to complement pharmaceutical lipid-lowering, and monitoring Symptoms and biomarkers) approach to the initial management of all patients with suspected AEs on statin therapy [36] (Table 3).

3. Patient groups in whom red yeast rice should not be considered

3.1. Secondary Prevention of CVD

The lipid-lowering effects of red yeast rice are well-documented and provide a very useful supplement to diet and lifestyle in reducing lifetime exposure to LDL-C. However (particularly at a maximal dose of monacolin K of 3 mg/day) there is a clear 'ceiling' to the effectiveness of this approach. In the secondary prevention of cardiovascular disease, very substantial reductions in LDL-C are required to prevent recurrent events [7,9,10,42]. Therefore, despite data availability on the application of RYR in secondary prevention patients (and others at very high risk of first events, apart from statin intolerant patients), these individuals should wherever possible, receive high intensity statin therapy, ezetimibe, bempedoic acid and/or PCSK9 inhibitors/inclisiran as appropriate.

3.2. Contraindications unrelated to CVD indication

As with all medicines, there exist groups of patients for whom the benefit/risk ratio of red yeast rice is unlikely to be favourable, therefore the use of red yeast rice is not recommended in these patients (Table 4).

4. Products

RYR preparations used in the management of hyperlipidemia and cardiovascular risk must be produced following Good Manufacturing Practice directives. This is crucial in order to avoid batch to batch variability of the active ingredient and to ensure the absence of contaminants (particularly citrinin).

Table 3
Recommendations on the RYR applications in patients with statin intolerance and the nocebo/drucebo effect.

Recommendation Summary	Class	Level
Red yeast rice should be considered as an alternative approach to statin therapy in patients with confirmed statin intolerance* .	**IIa**	**B**
Red yeast rice may be considered as part of a supportive strategy to manage dyslipidaemias and cardiovascular risk in patients with statin-associated muscle symptoms likely to result from the nocebo/drucebo effect.	**IIb**	**C**

*Alone or in combination with ezetimibe; in those that cannot use other non-statin therapies (like bempedoic acid, PCSK9 inhibitors or inclisiran).

Table 4
Recommendations on the RYR contraindications.

Recommendation Summary	Class	Level
Red yeast rice is not recommended in patients with any of the following characteristics: 1. in patients with hypersensitivity to monacolin K/lovastatin or any of the excipients, 2. in patients with acute liver disease, 3. in patients with severe renal impairment (eGFR <30 ml/min), 4. in patients with myopathy* , 5. in women who are pregnant, breastfeeding and in women of childbearing potential not using effective contraception.	**I**	**C**

*muscle weakness, sometimes with cramping, stiffness, and soreness, with exercise intolerance and elevated creatine kinase (in most of the cases).

Red yeast rice may be presented as a single ingredient preparation or in a nutraceutical 'polypill' preparation. Compound preparations have the advantage that multiple ingredients may have additive or synergistic effects on lipid-lowering, however, each ingredient will need to be checked for suitability in light of the patient's condition and circumstances [13–16,33,43] **(**Table 5**).**

5. Provision of Information

As with all treatment and prescribing decisions, it is essential that the conversation with physician/prescriber furnishes the patient with sufficient information to make an informed decision regarding the use of red yeast rice. This includes considerations about the cost, benefits, and risks of therapy with red yeast rice in comparison to statin therapy, and no therapy.

5.1. Composition and efficacy of red yeast rice

If patients have heard of red yeast rice, it is likely to be in the context of a 'natural statin'. However, it is essential that patients are informed that whilst red yeast rice does indeed contain a natural statin molecule that the dose and potency are very low (<3 mg monacolin K/day) compared to guideline-directed statin therapy, and that owing to the variation in composition between brands of red yeast rice, and potential synergisms between different components, whose quantities can vary according to the production process, the effect obtainable by any particular product (in terms of LDL-C lowering or cardiovascular event reduction) cannot be easily predicted.

5.2. Safety of red yeast rice

Whilst adverse effects of red yeast rice are rarely reported, it is important that patients are made aware of the potential for mild muscle

Table 5
Recommendations on the required criteria of RYR products.

Recommendation Summary	Class	Level
Only recommend RYR products which fulfil the following criteria: 1. Manufactured according to principles of GMP 2. Daily dose of < 3 mg monacolins#, 3. Recommended minimum dose of citrinin (and any other possible contamination – NOAEL: ≤0.2 μg/kg b.w per day; for a 70 kg person ≤14 μg/day*) **Fixed combination of natural products is recommended, but careful consideration should be given to the benefits and potential harms of additional ingredients.**	**I**	**C**

#based on the EFSA decision 2022/860 (1st June 2022); *based on EFSA 2012 consensus panel; NOAEL - No-observed-adverse-effect-level

pain – this is particularly important in the case of patients with confirmed statin intolerance, or patients unwilling to take statins following muscle symptoms attributed to statin therapy.

5.3. Cost (to the patient) of therapy with red yeast rice

Reimbursement for red yeast rice product is likely to be unavailable in many healthcare settings. As such, the patient is likely to bear the cost of treatment (which may exceed the cost of prescription medicines, especially where these are subsidised). It is therefore essential that the patient understands the likely ongoing costs before commencing treatment. Furthermore, if the medicine is not prescribed, it may not appear in patient medication records and summary care records. Therefore, if patients elect to purchase red-yeast rice, physicians must emphasise the importance of the patient mentioning the use of red yeast rice in interactions with other healthcare professionals, such as at medicines reconciliation on admission to hospital. This will help to reduce the likelihood of iatrogenic harms owing to drug interactions or inadvertent double prescribing.

5.4. Choice of product

It is essential that patients are informed of the importance of using a product manufactured according to the principles of Good Manufacturing Practice – to ensure consistency of dose and absence of toxic contaminants, and preferably with the postmarketing nutrivigilance monitoring. Where there is any doubt that patients may not be able to distinguish such a product, it is recommended that practitioners/prescribers recommend locally available products by brand name (Table 6).

6. Conclusions

Red yeast rice preparations have been shown to be safe and effective in improving lipid profiles, and, to some extent in reducing the risk of cardiovascular events. Red yeast rice should not routinely be used in the place of conventional treatments (statins, ezetimibe and PCSK9 inhibitors) for which higher-quality long-term outcomes data exist. However, in specific situations (statin intolerance, patients with dyslipidaemia ineligible for statin therapy, strong patient preference), the use of red yeast rice may be considered. When recommending a red-yeast rice product to patients, it is important to ensure that the product has been produced according to the principles of GMP, to ensure consistency of dose of the active ingredient, and the absence of harmful contaminants.

7. Limitations and cautions

Despite the strong and established causative links between LDL-C reduction and reduced cardiovascular mortality, there is little long-term outcome data relating to the use of Red-Yeast Rice as a lipid-lowering agent. Long-term outcomes trials are unlikely to be available for RYR (as well as for other natural products) to provide answers to all the questions addressed in these recommendations. However, we strongly recommend long-term monitoring of safety and efficacy of nutraceuticals within postmarketing consumer data and real-life studies/registries. Therefore, expert consensus, based upon existing evidence, is probably the best approach to make treatment decisions. The purpose of this consensus document is to provide such recommendations. It should be noted that the regulatory status of red yeast-rice and the quality of available products (in respect of standardisation of dose and absence of contaminants) varies substantially worldwide. These recommendations presuppose the availability of high-quality contaminant free products, however ILEP cannot endorse specific product or brand. Medical professionals are encouraged to consider our recommendations when making decisions regarding the treatment of patients with lipid disorders and statin intolerance. However, the position paper does not override in any way the individual responsibility of healthcare professionals to make appropriate, accurate and patient-centred decisions, considering the patient's medical history, and in consultation with the patient and/or, where appropriate, their guardian or caretaker. It is also the responsibility of health professionals to verify the doses, rules, and regulations applicable to drugs, and devices at the time of their prescription or use. The authors of this position paper are aware that the use of recommendations depends on several judgement calls that take into account the values and preferences of the patient.

Table 6
Summary of information, which should be conveyed as part of a physician-patient's consultation.

Summary of information which should be conveyed as part of a consultation
1. Composition of RYR preparations (contains 'natural' statin)
2. Relative evidence base and efficacy of red yeast rice vs. statins
3. Duration of therapy
4. Approximate cost of therapy
5. Quality of products

CRediT authorship contribution statement

MB: speakers bureau: Amgen, Herbapol, Kogen, KRKA, Polpharma, Mylan/Viatris, Novartis, Novo-Nordisk, Sanofi-Aventis, Teva, Zentiva; consultant to Abbott Vascular, Amgen, Daichii Sankyo, Esperion, Freia Pharmaceuticals, Novartis, Polfarmex, Sanofi-Aventis; Grants from Amgen, Mylan/Viatris, Sanofi and Valeant; CMO at the Nomi Biotech Corporation; *AFGC*: has given talks, received consultancy fees and/or participated in trials sponsored by Amgen, Menarini Group, Novartis, Novo Nordisk, Pfizer, Servier, Sharper Viatris; *CE:* personal fees from Amgen, Daiichi-Sankyo, Ferrer, MSD, Novartis, Sanofi, Servier and Viatris; *BF:* speakers bureau: Mylan; *NK:* has given talks, attended conferences and participated in trials sponsored by Amgen, Astra Zeneca, Bausch Health, Boehringer Ingelheim, Elpen, Novartis, Novo Nordisk, Sanofi, Servier, Viatris, Vianex and WinMedica; *GL:* has given talks, attended conferences, received consultancy fees and participated in trials sponsored by Abbott Laboratories, Amgen, Astra-Zeneca, Berlin Chemie, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Grindex, KRKA, MSD, Mylan, Novartis, Novo Nordisk, Pfizer, Sanofi, Servier Laboratories, Siemens Laboratories, Zentiva; *PEP:* owns four shares in AstraZeneca PLC and has received honoraria and/or travel reimbursement for events sponsored by AKCEA, Amgen, AMRYT, Link Medical, Mylan, Napp, Sanofi. All other authors have nothing to declare.

None of the above-mentioned pharmaceutical companies had any role in this article, which has been written independently, without any financial or professional help, and reflects only the opinion of the authors, without any role of the industry.

Conflict of Interest

NA.

Data availability

No data was used for the research described in the article.

References

[1] R. Ferrari, T.F. Luscher, Reincarnated medicines: using out-dated drugs for novel indications, Eur. Heart J. 37 (33) (2016) 2571–2576.
[2] M. Banach, P. Burchardt, K. Chlebus, P. Dobrowolski, D. Dudek, K. Dyrbuś, M. Gąsior, P. Jankowski, J. Jóźwiak, L. Kłosiewicz-Latoszek, I. Kowalska, M. Małecki, A. Prejbisz, M. Rakowski, J. Rysz, B. Solnica, D. Sitkiewicz, G. Sygitowicz, G. Sypniewska, T. Tomasik, A. Windak, D. Zozulińska-Ziółkiewicz, B. Cybulska, PoLA/CFPiP/PCS/PSLD/PSD/PSH guidelines on diagnosis and

therapy of lipid disorders in Poland 2021, Arch. Med. Sci. 17 (6) (2021) 1447–1547.
[3] M. Mazidi, D.P. Mikhailidis, N. Sattar, P.P. Toth, S. Judd, M.J. Blaha, A. V. Hernandez, P.E. Penson, M. Banach, International Lipid Expert Panel (ILEP) & Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. Association of types of dietary fats and all-cause and cause-specific mortality: A prospective cohort study and meta-analysis of prospective studies with 1,164,029 participants, Clin. Nutr. 39 (12) (2020) 3677–3686.
[4] A.S. Chopra, R. Lordan, O.K. Horbańczuk, A.G. Atanasov, I. Chopra, J. O. Horbańczuk, A. Jóźwik, L. Huang, V. Pirgozliev, M. Banach, M. Battino, N. Arkells, The current use and evolving landscape of nutraceuticals, Pharmacol. Res. 175 (2022), 106001.
[5] B.A. Ference, H.N. Ginsberg, I. Graham, K.K. Ray, C.J. Packard, E. Bruckert, R. A. Hegele, R.M. Krauss, F.J. Raal, H. Schunkert, G.F. Watts, J. Boren, S. Fazio, J. D. Horton, L. Masana, S.J. Nicholls, B.G. Nordestgaard, B. van de Sluis, M. R. Taskinen, L. Tokgozoglu, U. Landmesser, U. Laufs, O. Wiklund, J.K. Stock, M. J. Chapman, A.L. Catapano, 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. 38 (32) (2017) 2459–2472.
[6] R. Collins, C. Reith, J. Emberson, J. Armitage, C. Baigent, L. Blackwell, R. Blumenthal, J. Danesh, G.D. Smith, D. DeMets, S. Evans, M. Law, S. MacMahon, S. Martin, B. Neal, N. Poulter, D. Preiss, P. Ridker, I. Roberts, A. Rodgers, P. Sandercock, K. Schulz, P. Sever, J. Simes, L. Smeeth, N. Wald, S. Yusuf, R. Peto, Interpretation of the evidence for the efficacy and safety of statin therapy, Lancet 388 (10059) (2016) 2532–2561.
[7] M. Banach, P.E. Penson, Lipid-lowering therapies: better together, Atherosclerosis 320 (2021) 86–88.
[8] M. Banach, P.E. Penson, Statins and LDL-C in secondary prevention-so much progress, So Far to Go, JAMA Netw. Open 3 (11) (2020), e2025675.
[9] M. Banach, P.E. Penson, M. Vrablik, M. Bunc, K. Dyrbus, J. Fedacko, D. Gaita, M. Gierlotka, Z. Jarai, S.L. Magda, E. Margetic, R. Margoczy, A. Durak-Nalbantic, P. Ostadal, D. Pella, M. Trbusic, C.A. Udroiu, C. Vlachopoulos, D. Vulic, Z. Fras, D. Dudek, Z. Reiner, Central ACSE, South European Countries P. Optimal use of lipid-lowering therapy after acute coronary syndromes: a position paper endorsed by the International Lipid Expert Panel (ILEP), Pharm. Res 166 (2021), 105499.
[10] B. Cybulska, L. Klosiewicz-Latoszek, P.E. Penson, S.M. Nabavi, C.J. Lavie, M. Banach, International Lipid Expert P. How much should LDL cholesterol be lowered in secondary prevention? Clinical efficacy and safety in the era of PCSK9 inhibitors, Prog. Cardiovasc Dis. 67 (2021) 65–74.
[11] M. Banach, A.M. Patti, R.V. Giglio, A.F.G. Cicero, A.G. Atanasov, G. Bajraktari, E. Bruckert, O. Descamps, D.M. Djuric, M. Ezhov, Z. Fras, S. von Haehling, N. Katsiki, M. Langlois, G. Latkovskis, G.B.J. Mancini, D.P. Mikhailidis, O. Mitchenko, P.M. Moriarty, P. Muntner, D. Nikolic, D.B. Panagiotakos, G. Paragh, B. Paulweber, D. Pella, C. Pitsavos, Z. Reiner, G.M.C. Rosano, R.S. Rosenson, J. Rysz, A. Sahebkar, M.C. Serban, D. Vinereanu, M. Vrablik, G.F. Watts, N. D. Wong, M. Rizzo, International lipid expert P. The role of nutraceuticals in statin intolerant patients, J. Am. Coll. Cardiol. 72 (1) (2018) 96–118.
[12] A.F.G. Cicero, A. Colletti, G. Bajraktari, O. Descamps, D.M. Djuric, M. Ezhov, Z. Fras, N. Katsiki, M. Langlois, G. Latkovskis, D.B. Panagiotakos, G. Paragh, D. P. Mikhailidis, O. Mitchenko, B. Paulweber, D. Pella, C. Pitsavos, Z. Reiner, K. K. Ray, M. Rizzo, A. Sahebkar, M.C. Serban, L.S. Sperling, P.P. Toth, D. Vinereanu, M. Vrablik, N.D. Wong, M. Banach, Lipid-lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel, Nutr. Rev. 75 (9) (2017) 731–767.
[13] P.E. Penson, M. Banach, The role of nutraceuticals in the optimization of lipid-lowering therapy in high-risk patients with dyslipidaemia, Curr. Atheroscler. Rep. 22 (11) (2020) 67.
[14] P.E. Penson, M. Banach, Nutraceuticals for the control of dyslipidaemias in clinical practice, Nutrients 13 (9) (2021) 2957.
[15] M. Ruscica, P.E. Penson, N. Ferri, C.R. Sirtori, M. Pirro, G.B.J. Mancini, N. Sattar, P. P. Toth, A. Sahebkar, C.J. Lavie, N.D. Wong, M. Banach, International Lipid Expert P, International Lipid Expert Panel E. Impact of nutraceuticals on markers of systemic inflammation: Potential relevance to cardiovascular diseases - a position paper from the International Lipid Expert Panel (ILEP), Prog. Cardiovasc Dis. 67 (2021) 40–52.
[16] B. Sosnowska, P. Penson, M. Banach, The role of nutraceuticals in the prevention of cardiovascular disease, Cardiovasc Diagn. Ther. 7 (Suppl 1) (2017) S21–S31.
[17] A.F.G. Cicero, A. Colletti, G. Bajraktari, O. Descamps, D.M. Djuric, M. Ezhov, Z. Fras, N. Katsiki, M. Langlois, G. Latkovskis, D.B. Panagiotakos, G. Paragh, D. P. Mikhailidis, O. Mitchenko, B. Paulweber, D. Pella, C. Pitsavos, Z. Reiner, K. K. Ray, M. Rizzo, A. Sahebkar, M.C. Serban, L.S. Sperling, P.P. Toth, D. Vinereanu, M. Vrablik, N.D. Wong, M. Banach, Lipid lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel, Arch. Med Sci. 13 (5) (2017) 965–1005.
[18] Y. Li, L. Jiang, Z. Jia, W. Xin, S. Yang, Q. Yang, L. Wang, A meta-analysis of red yeast rice: an effective and relatively safe alternative approach for dyslipidemia, PLoS One 9 (6) (2014), e98611.
[19] Z. Lu, W. Kou, B. Du, Y. Wu, S. Zhao, O.A. Brusco, J.M. Morgan, D.M. Capuzzi, 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. 101 (12) (2008) 1689–1693.
[20] A.F.G. Cicero, F. Fogacci, A. Zambon, Red yeast rice for hypercholesterolemia: JACC focus seminar, J. Am. Coll. Cardiol. 77 (5) (2021) 620–628.
[21] R. Yuan, Y. Yuan, L. Wang, Q. Xin, Y. Wang, W. Shi, Y. Miao, S.X. Leng, K. Chen, W. Cong, B.C. Red, Yeast rice preparations reduce mortality, major cardiovascular adverse events, and risk factors for metabolic syndrome: a systematic review and meta-analysis, Front Pharm. 13 (2022), 744928.
[22] G. Xu, M. Lin, X. Dai, J. Hu, Comparing the effectiveness of Chinese patent medicines containing red yeast rice on hyperlipidaemia: A network meta-analysis of randomized controlled trials. Endocrinol. Diabetes Metab. 5 (1) (2022), e00314.
[23] G.G. De Backer, Food supplements with red yeast rice: more regulations are needed, Eur. J. Prev. Cardiol. 24 (13) (2017) 1429–1430.
[24] M. Banach, N. Katsiki, G. Latkovskis, M. Rizzo, D. Pella, P.E. Penson, Z. Reiner, A.F. G. Cicero, Postmarketing nutrivigilance safety profile: a line of dietary food supplements containing red yeast rice for dyslipidemia, Arch. Med Sci. 17 (4) (2021) 856–863.
[25] F.L.J. Visseren, F. Mach, Y.M. Smulders, D. Carballo, K.C. Koskinas, M. Back, A. Benetos, A. Biffi, J.M. Boavida, D. Capodanno, B. Cosyns, C. Crawford, C. H. Davos, I. Desormais, E. Di Angelantonio, O.H. Franco, S. Halvorsen, F.D. R. Hobbs, M. Hollander, E.A. Jankowska, M. Michal, S. Sacco, N. Sattar, L. Tokgozoglu, S. Tonstad, K.P. Tsioufis, I. van Dis, I.C. van Gelder, C. Wanner, B. Williams, Societies ESCNC, Group ESCSD. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice, Eur. Heart J. 42 (34) (2021) 3227–3337.
[26] J. Morze, T. Osadnik, K. Osadnik, M. Lejawa, G. Jakubiak, N. Pawlas, M. Gasior, L. Schwingschackl, M. Banach, A network meta-analysis on the comparative efficacy of nutraceuticals on lipid profile, Circulation 140 (2019), A13360.
[27] F. Fogacci, M. Banach, D.P. Mikhailidis, E. Bruckert, P.P. Toth, G.F. Watts, Ž. Reiner, J. Mancini, M. Rizzo, O. Mitchenko, D. Pella, Z. Fras, A. Sahebkar, M. Vrablik, A.F.G. Cicero, Lipid and blood pressure meta-analysis collaboration (LBPMC) group; international lipid expert panel (ILEP). Safety of red yeast rice supplementation: a systematic review and meta-analysis of randomized controlled trials, Pharm. Res 143 (2019) 1–16.
[28] EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), M. Younes, P. Aggett, F. Aguilar, R. Crebelli, B. Dusemund, M. Filipič, M.J. Frutos, P. Galtier, D. Gott, U. Gundert-Remy, G.G. Kuhnle, C. Lambré, J.C. Leblanc, I. T. Lillegaard, P. Moldeus, A. Mortensen, A. Oskarsson, I. Stankovic, I. Waalkens-Berendsen, R.A. Woutersen, R.J. Andrade, C. Fortes, P. Mosesso, P. Restani, F. Pizzo, C. Smeraldi, M. Wright, Scientific opinion on the safety of monacolins in red yeast rice, EFSA J. 16 (8) (2018), e05368.
[29] D.K. Arnett, R.S. Blumenthal, M.A. Albert, A.B. Buroker, Z.D. Goldberger, E. J. Hahn, C.D. Himmelfarb, A. Khera, D. Lloyd-Jones, J.W. McEvoy, E.D. Michos, M. D. Miedema, D. Munoz, S.C. Smith Jr., S.S. Virani, K.A. Williams Sr., J. Yeboah, B Ziaeian, ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the american college of cardiology/american heart association task force on clinical practice guidelines, Circulation 140 (11) (2019) e596–e646.
[30] L. Childress, A. Gay, A. Zargar, M.K. Ito, Review of red yeast rice content and current Food and Drug Administration oversight, J. Clin. Lipido 7 (2) (2013) 117–122.
[31] A. Poli, C.M. Barbagallo, A.F.G. Cicero, A. Corsini, E. Manzato, B. Trimarco, F. Bernini, F. Visioli, A. Bianchi, G. Canzone, C. Crescini, S. de Kreutzenberg, N. Ferrara, M. Gambacciani, A. Ghiselli, C. Lubrano, G. Marelli, W. Marrocco, V. Montemurro, D. Parretti, R. Pedretti, F. Perticone, R. Stella, F. Marangoni, Nutraceuticals and functional foods for the control of plasma cholesterol levels. An intersociety position paper, Pharm. Res 134 (2018) 51–60.
[32] M. Banach, E. Bruckert, O.S. Descamps, L. Ellegård, M. Ezhov, B. Föger, Z. Fras, P. T. Kovanen, G. Latkovskis, W. März, D.B. Panagiotakos, G. Paragh, D. Pella, A. Pirillo, A. Poli, Ž. Reiner, G. Silbernagel, M. Viigimaa, M. Vrablík, A.L. Catapano, The role of red yeast rice (RYR) supplementation in plasma cholesterol control: A review and expert opinion, Atheroscler. Suppl. 39 (2019) e1–e8.
[33] P.E. Penson, M. Banach, Natural compounds as anti-atherogenic agents: Clinical evidence for improved cardiovascular outcomes, Atherosclerosis 316 (2021) 58–65.
[34] P.E. Penson, M. Pirro, M. Banach, LDL-C: lower is better for longer-even at low risk, BMC Med 18 (1) (2020) 320.
[35] I. Bytyci, P.E. Penson, D.P. Mikhailidis, N.D. Wong, A.V. Hernandez, A. Sahebkar, P.D. Thompson, M. Mazidi, J. Rysz, D. Pella, Z. Reiner, P.P. Toth, M. Banach, Prevalence of statin intolerance: a meta-analysis, Eur. Heart J. (2022), https://doi.org/10.1093/eurheartj/ehac015.
[36] P.E. Penson, E. Bruckert, D. Marais, Ž. Reiner, M. Pirro, A. Sahebkar, G. Bajraktari, E. Mirrakhimov, M. Rizzo, D.P. Mikhailidis, A. Sachinidis, D. Gaita, G. Latkovskis, M. Mazidi, P.P. Toth, D. Pella, F. Alnouri, A. Postadzhiyan, H.I. Yeh, G.B. J. Mancini, S. Haehling, M. Banach, J. Acosta, M. Al-Khnifsawi, F. Alnouri, F. Amar, A.G. Atanasov, G. Bajraktari, M. Banach, S. Bhaskar, I. Bytyçi, B. Bjelakovic, E. Bruckert, A. Cafferata, R. Ceska, A.F.G. Cicero, X. Collet, M. Daccord, O. Descamps, D. Djuric, R. Durst, M.V. Ezhov, Z. Fras, D. Gaita, A. V. Hernandez, S.R. Jones, J. Jozwiak, N. Kakauridze, A. Kallel, N. Katsiki, A. Khera, K. Kostner, R. Kubilius, G. Latkovskis, G.B.J. Mancini, A.D. Marais, S.S. Martin, J. A. Martinez, M. Mazidi, D.P. Mikhailidis, E. Mirrakhimov, A.R. Miserez, O. Mitchenko, N.P. Mitkovskaya, P.M. Moriarty, S.M. Nabavi, D. Nair, D. B. Panagiotakos, G. Paragh, D. Pella, P.E. Penson, Z. Petrulioniene, M. Pirro, A. Postadzhiyan, R. Puri, A. Reda, Ž. Reiner, D. Radenkovic, M. Rakowski, J. Riadh, D. Richter, M. Rizzo, M. Ruscica, A. Sahebkar, N. Sattar, M.C. Serban, A.M. A. Shehab, A.B. Shek, C.R. Sirtori, C. Stefanutti, T. Tomasik, P.P. Toth, M. Viigimaa, P. Valdivielso, D. Vinereanu, B. Vohnout, S. Haehling, M. Vrablik, N. D. Wong, H.I. Yeh, J. Zhisheng, A. Zirlik, Step-by-step diagnosis and management of the nocebo/drucebo effect in statin-associated muscle symptoms patients: a position paper from the International Lipid Expert Panel (ILEP), J. Cachex-.-., Sarcopenia Muscle (2022), https://doi.org/10.1002/jcsm.12960.
[37] K. Awad, D.P. Mikhailidis, P.P. Toth, S.R. Jones, P. Moriarty, G.Y.H. Lip, P. Muntner, A.L. Catapano, M.J. Pencina, R.S. Rosenson, J. Rysz, M. Banach, Lipid,

blood pressure meta-analysis collaboration G. Efficacy and safety of alternate-day versus daily dosing of statins: a systematic review and meta-analysis, Cardiovasc Drugs Ther. 31 (4) (2017) 419–431.
[38] P. Penson, P. Toth, D. Mikhailidis, M. Ezhov, Z. Fras, O. Mitchenko, D. Pella, A. Sahebkar, J. Rysz, Z. Reiner, J. Jozwiak, M. Mazidi, M. Banach, Step by step diagnosis and management of statin intolerance: position paper from an international lipid expert panel, Eur. Heart J. 40 (Supplement_1) (2019) P705.
[39] M. Banach, P.E. Penson, Drucebo effect - the challenge we should all definitely face!, Arch. Med Sci. 17 (2) (2021) 542–543.
[40] P.E. Penson, M. Banach, Nocebo/drucebo effect in statin-intolerant patients: an attempt at recommendations, Eur. Heart J. 42 (47) (2021) 4787–4788.
[41] P.E. Penson, G.B.J. Mancini, P.P. Toth, S.S. Martin, G.F. Watts, A. Sahebkar, D. P. Mikhailidis, M. Banach, 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. Cachex-.-. Sarcopenia Muscle 9 (6) (2018) 1023–1033.
[42] K. Dyrbus, M. Gasior, P.E. Penson, M. Banach, Extreme cardiovascular risk-do we need a new risk category? Eur. Heart J. (2022) https://doi.org/10.1093/eurheartj/ehab771.
[43] B. Franczyk, A. Gluba-Brzozka, L. Jurkiewicz, P. Penson, M. Banach, J. Rysz, Embracing the polypill as a cardiovascular therapeutic: is this the best strategy? Expert Opin. Pharm. 19 (17) (2018) 1857–1865.