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Red Yeast Rice for Hypercholesterolemia

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ABSTRACT

The extracts of red yeast rice (RYR) are currently the most effective cholesterol-lowering nutraceuticals. This activity is mainly due to monacolin K, a weak reversible inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, whose daily consumption causes a reduction in low-density lipoprotein (LDL)-cholesterol plasma levels up to 15% to 25% within 6 to 8 weeks. The decrease in LDL-cholesterol is accompanied by a proportional decrease in total and non–high-density lipoprotein cholesterol, plasma apolipoprotein B, and high-sensitivity C-reactive protein. Some trials suggest that RYR use is associated with improvement in endothelial function and arterial stiffness, whereas a long-term study supports its role in the prevention of cardiovascular events. Despite the statin-like mechanism of action, the risk related to 3 to 10 mg monacolin K taken per day is minimal (mild myalgia in previously severely statin-intolerant subjects). RYR could represent a therapeutic tool to support lifestyle improvement in managing mild to moderate hypercholesterolemia in low-risk patients, including those who cannot be treated with statins or other LDL-cholesterol–lowering therapies. (J Am Coll Cardiol 2021;77:620–8) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

POTENTIAL ROLE OF NUTRACEUTICALS IN THE MANAGEMENT OF HYPERCHOLESTEROLEMIA

Hypercholesterolemia is a highly prevalent, well-known dose- and time-dependent cardiovascular disease (CVD) risk factor: the risk is inversely related to the low-density lipoprotein cholesterol (LDL-C) plasma level and directly associated to the time the subject is exposed to elevated LDL-C (1). Considering the very high prevalence of subjects with suboptimal LDL-C level in the general population (approximately 50%) (2), and the relatively small impact of lifestyle improvement on LDL-C levels (from 5% to 10%) (3), great attention has been recently given to single dietary components or natural compounds able to further improve lipid pattern in the context of correct dietary and physical activity habits (4). Very strict diet (i.e., purely plant based) and aggressive lifestyle changes have been associated with an LDL-C reduction up to 20% (5), but medium- to long-term adherence to such intensive lifestyle modification is generally poor, particularly in the primary prevention setting and challenging to implement in the medium to long term in our daily clinical practice (6).

The first formal suggestion for the use of dietary supplements and nutraceuticals to improve plasma lipid levels came from the third report of the National Cholesterol Educational Program (7). These guidelines suggested to add plant sterols, soy proteins, soluble fibers, and polyunsaturated fatty acids to a healthy diet. However, polyunsaturated fatty acids have mainly a triglyceride (TG)-lowering effect (8), whereas the lipid-lowering efficacy of soy proteins seems to be

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HIGHLIGHTS

- Red yeast rice extract is used as cholesterol-lowering nutraceutical.
- Its main bioactive compound (monacolin K) is a weak reversible inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase.
- Relatively large meta-analyses of randomized trials support the efficacy and safety of red yeast rice in people with hypercholesterolemia.

less relevant than previously suggested (9). Recent evidence continues to support the lipid-lowering effect of plant sterols and stanols and soluble fibers, which mainly act by inhibiting the dietary and biliary cholesterol absorption at the bowel level (10). On the other side, it is well known that liver cholesterol synthesis is the main determinant of LDL-C plasma level in most subjects. The European Cardiology Society and European Atherosclerosis Society guidelines, since 2011, suggest the use of red yeast rice (RYR) extract, an inhibitor of the endogenous cholesterol synthesis, in the management of mild hypercholesterolemia (11). Recently, the International Lipid Expert Panel also strengthened this recommendation (12). However, some concerns have also been recently raised on the RYR safety in frail patients (13).

In this narrative review, we highlight the available clinical evidence on the RYR efficacy and safety emphasizing some practical considerations and the potential limitations, which might be considered before supporting the widespread use of RYR. Furthermore, this review does not focus on well-recognized, guidelines-supported statin- and non-statin-based pharmacological approaches (i.e., ezetimibe, PCSK9 inhibitors), which represent the mainstay therapy for patients at high and very high cardiovascular (CV) risk for whom there are unequivocally no indications for the clinical use of RYR.

RED YEAST RICE: BIOACTIVE COMPOUNDS, PHARMACODYNAMIC AND PHARMACOKINETIC

RYR is a nutraceutical obtained by the fermentation of rice (*Oryza sativa*) as result of a yeast (in general *Monascus purpureus*); the typical red coloration is due to the presence of pigments that are by-products of the fermentative metabolism process (14).

RYR contains sugars (25% to 73%, mainly starch), proteins (14% to 31%), water (2% to 7%), fatty acids (1% to 5%), pigments, sterols, and isoflavones (11). During the fermentation process, the yeast enriches the rice of polyketides with clinically detectable cholesterol-lowering action, the monacolins. Usually, the monacolin concentration in RYR dietary supplements is up to 1.9% (12). Depending on the conditions of the yeast fermentation and the strain used, several types of monacolins have been identified to date (i.e., compactin, monacolins M, L, J, X) including the subtype monacolin K, which is structurally identical to lovastatin, and consequently used as a marker of product purification. The main cholesterol-lowering mechanism of action of RYR is due to the ability of monacolins to reversibly inhibit the 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, a key enzyme in the cholesterol synthesis pathway (**Figure 1**), the same inhibited in a stronger way by statins.

Despite the same structure, monacolin K and lovastatin pharmacological profiles look different. Lovastatin is a pro-drug, an inactive gamma-lactone in its native form, that is hydrolyzed in vivo to the β-hydroxy-acid open ring form, which is the most bioavailable and active. In RYR, the monacolin K lactone to acid ratio strongly varies. In particular, the acid form ranges from 5% to 100% of the total of monacolin K, greatly influencing the bioavailability of the molecule. The lactone ring opening can occur following a metabolism in alkaline conditions or enzymatically by small intestine and liver cytochrome P450 (CYP) 3A family (15). Moreover, recent evidence shows that gut microbiota does not convert monacolin K into the β-hydroxy acid form, but catabolizes it, so that gut microbiota might hamper the lipid-lowering effects of both lovastatin and monacolin K by degrading their active metabolite (16).

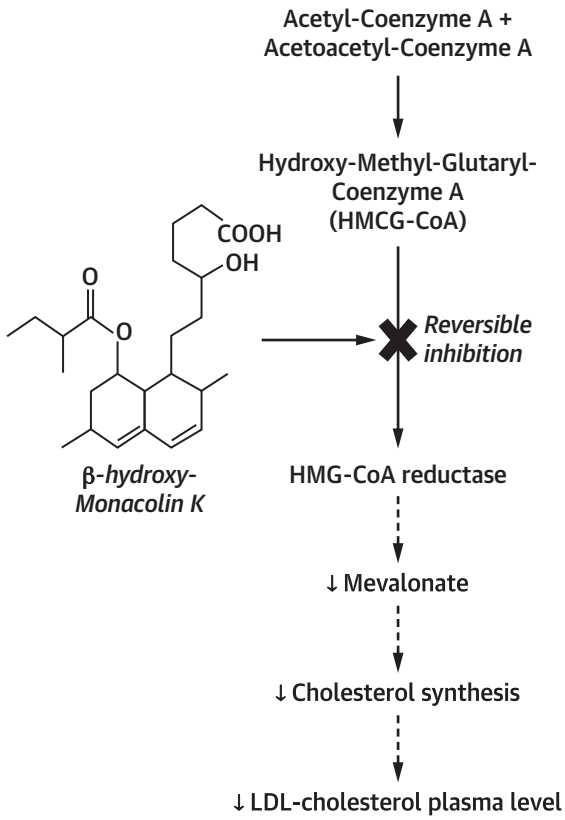
CLINICAL EVIDENCE OF RYR LIPID-LOWERING ACTIVITY

The lipid-lowering efficacy of RYR has been confirmed by some meta-analyses of randomized clinical trials (RCTs), the most recent one including 20 trials and 6,663 subjects, and showing that, after 2 to 24 months of treatment, RYR reduced LDL-C on average of 1.02 mmol/l (95% confidence interval: −1.20 to −0.83) (39.4 mg/dl) compared with placebo, which was comparable to the reduction achieved with low-intensity/low-dosed statins (pravastatin 40 mg, simvastatin 10 mg, lovastatin 20 mg). A small increase in high-density lipoprotein cholesterol (HDL-C) as well as a negligible decrease in TG

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
CV = cardiovascular
CVD = cardiovascular disease
CYP = cytochrome P450
EFSA = European Food Safety Agency
FMD = flow-mediated dilation
HDL-C = high-density lipoprotein cholesterol
HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A
hsCRP = high-sensitivity C-reactive protein
LDL-C = low-density lipoprotein cholesterol
OR = odds ratio
RYR = red yeast rice
TG = triglyceride

FIGURE 1 Main Cholesterol-Lowering Mechanism of Action of Monacolin K



Monacolins reversibly inhibit the 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase.

compared with placebo were also observed. The doses of RYR used were different, varying from 1,200 to 4,800 mg/day and containing from 4.8 to 24 mg of monacolin K (17). In some clinical trials, RYR significantly reduces the plasma levels of apolipoprotein B, while not having any significant effect on plasma lipoprotein(a) (12). Similar data have been confirmed in hypercholesterolemic children (18).

The association of RYR with other bioactive compounds with different mechanisms of action can be functional to an increased cholesterol-lowering effect: so, RYR, inhibiting HMG-CoA reductase, has often been added to substances reducing lipid intestinal absorption (soluble fibers, glucomannan, plant sterols, probiotics) or enhancing the hepatic uptake of cholesterol and inducing LDL-C excretion by bile metabolism (berberine, soy proteins, artichoke extracts) (19).

The most studied association of lipid-lowering nutraceuticals is the one combining RYR (3 mg monacolin K) and berberine (500 mg). A meta-analysis of 14 RCTs including data from 3,159 subjects has shown that the RYR-berberine association is able to significantly improve the plasma level of plasma LDL-C by −0.61 mmol/l (−23.6 mg/dl, corresponding to a percentage reduction of 14.7%) ($p < 0.001$), HDL-C by 0.07 mmol/l (2.7 mg/dl) ($p < 0.001$), TG by −0.16 mmol/l (−14.2 mg/dl) ($p < 0.001$), and glucose by −0.14 mmol/l (−2.52 mg/dl) ($p = 0.010$). These improvements appeared to be maintained in the long-term observation (20). The RYR-berberine association has also been tested in association with ezetimibe in statin-intolerant patients, reaching LDL-C reduction of approximately 35% and TG reduction of approximately 25% (21), as compared with baseline, which is similar to what has been reported for moderate-intensity statins from the European Society of Cardiology/European Atherosclerosis Society 2019 guidelines (11).

Of some interest is also the combination of RYR with plant sterols or artichoke extracts. In a double-blind, placebo-controlled, RCT evaluating the effect of phytosterols 800 mg, RYR (monacolin K 5 mg) and their association in 90 hypercholesterolemic subjects, the group treated with the nutraceutical association experienced an LDL-C reduction by 27% and apoB decrease by 19% (both, $p < 0.001$) (22), in line with what was reported in previous smaller trials (23,24).

The association of RYR (200 mg, containing monacolin K 10 mg) and artichoke extract (500 mg) has also been recently evaluated in a double-bind, placebo-controlled, crossover clinical trial involving 30 adults in primary prevention of CVD with suboptimal LDL-C levels. The enrolled subjects were treated for 6 weeks with the tested nutraceutical compound or placebo, and, then, assigned to the second sequence of the study after 2 weeks of washout. The active treatment led to a significant improvement in LDL-C (−18.2%) and non-HDL-C versus placebo, whereas no changes were observed in other investigated parameters (25), confirming the results of some other previous trials (26,27).

CLINICAL EVIDENCE OF RYR'S EFFECT ON BIOMARKERS OF CARDIOVASCULAR RISK AND HARD OUTCOMES

As RYR act on LDL-C synthesis in a statin-like manner, we should expect that RYR dietary supplements are also able to improve laboratory and instrumental biomarkers of cardiovascular risk.

In a clinical trial involving 50 patients with coronary heart disease, treated with 1,200 mg/day of RYR or placebo for a period of 6 weeks, lipid parameters,

TABLE 1 Positive Effects of RYR in Humans

Parameter	Modification	Notes
Total, LDL and non-HDL-cholesterol	-15% to -25%	Confirmed in different ethnicities and meta-analyses of randomized clinical trials
Apolipoprotein B	Mild to moderate reduction: −10% to −15%	Confirmed in different trials
Triglycerides	Mild reduction -5% to −10%	Confirmed in meta-analyses of randomized clinical trials
HDL-C	Mild increase +5% to +10%	Confirmed in meta-analyses of randomized clinical trials
hsCRP, MMP-2, MMP-9	Mild decrease	Reported in some trials
Flow-mediated dilation	Mild increase	Reported in some trials
Pulse wave velocity	Mild decrease	Reported when RYR associated to other nutraceuticals only
Cardiovascular disease prevention	Moderate reduction	Limited to one large study carried out on Chinese people in secondary prevention for coronary artery disease

Modified by Sahebkar et al. (10).
HDL-C = high-density liporptein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MMP = matrix metalloprotein; RYR = red yeast rice.

levels of high-sensitivity C-reactive protein (hsCRP), and flow-mediated dilation (FMD) were monitored following a high-fat meal (800 calories, with 50 g of fat, 28 g of protein, and 60 g of carbohydrates, at 0 and 4 h). The group treated with RYR at the 6-week follow-up experienced a significant reduction in total cholesterol, LDL-C, TG, and hsCRP serum level and an improvement in postprandial and pre-prandial FMD ($p < 0.001$), whereas there were no significant changes in serum lipids and FMD in the placebo group (28). A similar impact of RYR on endothelial function has also been observed in other clinical trials (29,30).

Furthermore, RYR has been proven to improve arterial stiffness, both in patients affected by mild hypercholesterolemia (30), and patients affected by antiretroviral-related dyslipidemia (31) (**Table 1**).

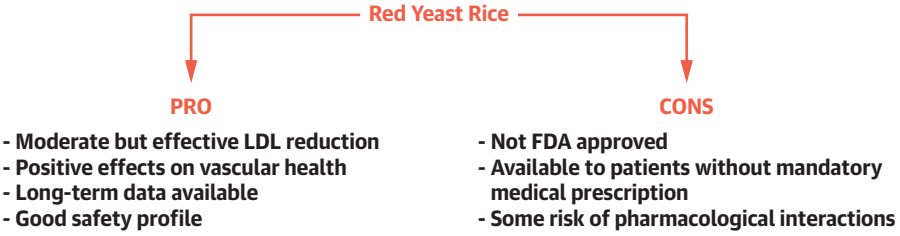
These data are of some interest, considering the strong relationship existing between small changes in endothelial function (32) or arterial stiffness (33) and cardiovascular events.

Clinical trials on hard CV outcomes come mainly from Chinese studies in high CV risk populations, which might represent a potential limitation to a widespread clinical implementation of these results due to specific lifestyle, environmental, and health care settings and highlight the need to confirm these observations in larger, prospective, randomized trials involving populations from different geographic areas. The large CCSPS (China Coronary Secondary Prevention Study), involving 65 medical centers and led by the Chinese Academy of Medical Sciences, was conducted in Chinese patients who experienced a previous myocardial infarction to determine the effects of a partially purified extract of RYR, on lipoprotein and CV endpoints (34). A total of 4,870 patients (age range: 18 to 70 years, 82% men) with average LDL-C levels at baseline (LDL-C 129 mg/dl) were randomly assigned either to placebo or to RYR, equivalent to 6 mg/d of monacolin, for an average of 4.5 years. LDL-C on RYR decreased by 20% over the study period and the primary end point of major coronary events (nonfatal myocardial infarction and death from coronary heart disease) was reduced by 4.7% absolute risk reduction (45% relative risk reduction [RRR]) from 10.4% in the placebo group to 5.7% in the RYR-treated group. Treatment with RYR also significantly decreased RR of CV and total mortality by 30% and 33%, respectively, and the need for coronary revascularization by one-third (**Central Illustration**). Adverse events were not significantly different between the groups. These results as well as the good safety profile were confirmed in a subanalysis of the same study focusing on RYR supplementation and CVD risk in elderly patients (35).

These results appear to confirm and support those reported with statin monotherapy in similar older trials carried out on secondary preventive patients with the first-generation statins: in the CARE (Cholesterol and Recurrent Events) a 42 mg/dl in LDL-C reduction was associated with a significant decrease (−24%) of RRR in coronary events (36), in the LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease), a 35 mg/dl of LDL-C reduction was associated with a significant RRR decrease of coronary events (−23%), coronary death (−24%), and total mortality (−22%) (37), whereas in the Scandinavian Simvastatin Survival Study (4S), a 66 mg/dl of LDL-C reduction was associated with a significant RRR decrease of coronary events (-34%), coronary death (-42%), and total mortality (-30%) (38) (**Central Illustration**). The apparent larger magnitude of clinical benefits of RYR than observed in early statin trials may be accounted for by differences in background therapy (wider use of antiplatelets, antihypertensives, and so forth, in statin

CENTRAL ILLUSTRATION **Effects of Long-Term Treatment With Red Yeast Rice on Hard Outcomes and in Older Secondary Prevention Trials Carried Out With First-Generation Statins: Implication for Use in Clinical Practice**

	Treatment	Patients Involved	Mean Follow-Up Duration	Endpoint	Main Effect (RRR)
Chinese Coronary Secondary Prevention Study (CCSPS)	Red Yeast Rice vs. Placebo	4,870	4.5 years	Nonfatal myocardial infarction and death from coronary heart disease (Primary)	−45%
Cholesterol and Recurrent Events trial (CARE)	Pravastatin 40 mg vs. Placebo	4,159	5 years	Nonfatal myocardial infarction and death from coronary heart disease (Primary)	−24%
Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)	Pravastatin 40 mg vs. Placebo	9,014	6.1 years	Nonfatal myocardial infarction and death from coronary heart disease (Secondary)	−24%
Scandinavian Simvastatin Survival Study (4S)	Simvastatin 20/40 mg vs. Placebo	4,444	5.4 years	Nonfatal myocardial infarction and death from coronary heart disease (Secondary)	−42%



Cicero, A.F.G. et al. J Am Coll Cardiol. 2021;77(5):620–8.

Long-term treatment of Asian patients with red yeast rice (RYR) was associated with an average 20% low-density lipoprotein cholesterol (LDL-C) reduction and a significant reduction in the risk of fatal and nonfatal cardiovascular events in patients already affected by coronary artery disease. These results were comparable to those found in the main older statin secondary prevention trials. Based on the available data, RYR seems to be an acceptable support to lifestyle change in the management of moderately hypercholesterolemic subjects with low added cardiovascular risk. RRR = relative risk reduction.

trials) and by fact that RYRs rarely contain only 1 monacolin (thus, more monacolins could contribute to the final clinical benefits). Moreover, it is relevant, in interpreting the results of these studies with RYRs to focus on the population of patients recruited: these trials have been carried out exclusively in Chinese subjects, who have different statin pharmacodynamics and pharmacokinetics than Western populations, suggesting a greater lipid-lowering effect in Asian individuals at similar daily dose of statin therapy (39).

These data were further confirmed in a large cohort observational study comparing 2,581 surgical patients using RYR pre-operatively with 25,810 age- and sex-matched patients not on RYR, where those consuming it pre-operatively experienced lower risks of stroke (odds ratio [OR]: 0.66; 95% CI: 0.47 to 0.92) and 30-day in-hospital mortality (OR: 0.37; 95% CI: 0.15 to 0.92) (40).

RYR SAFETY IN GENERAL POPULATION AND STATIN-INTOLERANT SUBJECTS

Overall, RYR supplements are usually safe and highly tolerated. However, RYR supplements are not regulated by the U.S. Food and Drug Administration and a wide variability in the amount of monacolin K in available preparations of RYR has been reported. Moreover, recently, concerns regarding the safety of RYRs have been raised after the publication of some case reports claiming toxicity (41). RYR safety mainly depends on the quality of the product assumed, the frailty of the patient assuming the product, and the risk of pharmacological interactions.

During rice fermentation by *M. purpureus*, a potentially dangerous mycotoxin could be a by-product of the process: citrinin (42). In preclinical models, the chronic ingestion of citrinin is nephrotoxic, leading to tubular epithelium hyperplasia,

adenomas, and cancers (a dose of 50 mg/kg body weight is associated with cancer in 100% of the animals tested). Moreover, always in preclinical models, citrinin induces reproductive toxicity, malformations, and embryo toxicity (43,44). For these reasons, although no citrinin-related side effect has yet been registered in humans, the European Food Safety Agency (EFSA) has limited the highest amount of citrinin to 0.2 μg/kg body weight per day, to maintain a good safety profile and no nephrotoxic effects (45). However, in the market, RYR supplements were detected with levels of citrinin exceeding 114 μg per capsule, largely above the safety level (46). Thus, it is strongly recommended to consider only products certified to be citrinin-free.

Monacolin K is extensively metabolized by CYP 3A4, thus CYP 3A4 inhibitors or inducers may cause changes in monacolin K plasma concentrations (47). For this reason, the concomitant use of CYP 3A4 inhibitors such as grapefruit juice (48) and some drugs (cyclosporine, verapamil, azole antifungals, macrolides, nefazodone, HIV protease inhibitors) may increase the risk of myotoxicity (49) and, in exceptional cases, of rhabdomyolysis (50), mainly when used at doses corresponding to 10 mg/day of monacolin K or higher.

According to a large meta-analysis of 53 RCTs comprising 112 treatment arms, which included 8,535 subjects with 4,437 in the RYR arm and 4,303 in the control arm, monacolin K administration is not associated with increased risk of statin-associated muscle symptoms (OR: 0.94; 95% CI: 0.53 to 1.65) for daily doses of monacolin K included between 3 and 10 mg (51). Furthermore, a reduced risk of serious adverse events (OR: 0.54; 95% CI: 0.46 to 0.64) compared with the control group was demonstrated, mainly driven by the reduction in the risk of cardiovascular events observed in the largest study included in the meta-analysis (51).

Despite the metabolism and the mechanism of action of monacolin K being the same of lovastatin, for reasons not yet fully elucidated, RYR seems to be well tolerated by previously statin-intolerant subjects, especially when monacolin K daily doses between 3 mg and 10 mg are used (52). This was demonstrated in relatively large patient cohorts (53,54). In a head-to-head comparison, RYR was tolerated as well as pravastatin and achieved a comparable reduction of LDL-C in a small sample of those previously intolerant to statins other than pravastatin (55). In statin-intolerant subjects, adding RYR to the background therapy with ezetimibe increased the number reaching the desired LDL-C goal without increasing the adverse event rate (56,57).

RYR EXTRACTS FOR HYPERCHOLESTEROLEMIA: AN OPPORTUNITY OR A RISK (USELESS ILLUSION)?

The U.S. Food and Drug Administration issued consumer warnings in 2007 and in 2013 against the use of RYR products due to the lack of significant evidence about their efficacy, safety, and lack of standardization of preparation methods (58). Concomitantly, EFSA has expressed a scientific opinion supporting the health claims about the relationship between administration of RYR and the control of plasma LDL-C levels, suggesting potential benefit associated with a dose of RYR that contains 3 to 10 mg of monacolin K (59). On the other side, the same EFSA recently did not exclude the possibility of risks related to the same monacolin K dosages (37).

Based on the mechanism of action and the available evidence, RYR is undoubtedly an effective lipid-lowering nutraceutical (12). Some short-term heterogeneous trials also show that is has direct vascular protective effect (12), whereas a large clinical trial suggested that it could also reduce CVD events in patients in secondary prevention (34).

Recent evidence focused on the clinical relevance of lifetime exposure to LDL-C levels as a key parameter to evaluate the individual risk of CVD events (60). The concept that "the lower the LDL-C, the better" is a strong, evidence-based fact; however, based on the evidence published in the past 5 years, the updated version of it suggests "the longer the lower LDL-C is maintained, the better." In fact, small differences in LDL-C, that is, 25 to 30 mg/dl (0.6 to 0.8 mmol/l), maintained over a long period (12 to 15 years), would likely result in a CVD risk reduction comparable with a 5-year moderate-high intensity statin approach. This approach would be relevant from a clinical standpoint specifically in a low CVD risk population (61).

Nutraceuticals, namely RYR, can be envisioned as support to a healthy lifestyle to achieve, in a large number of patients at low-intermediate CV risk, a remarkable CV event reduction when started earlier in life and maintained over the years.

A concern could be the cost of the high-quality, highly purified product that, in certain countries, could be remarkably higher than a low-dose, generic statin. On the other sides, it seems that patients willing to pay for a natural alternative to statins are more compliant to therapy than those on conventional treatment (62).

Regarding RYR safety, beyond the encouraging results of the previously cited large meta-analysis of

RCTs (51), citrinin-free RYR containing low doses of monacolin K (3 mg) was shown to be well tolerated in frail subjects.

Moreover, low-dose monacolin K (3 mg/d) has been tested in frail subjects at high risk of a drug-induced adverse event, such as children, elderly individuals, subjects with moderate chronic kidney disease, patients on hormone-therapy following breast cancer, second-generation antipsychotics (18), and those treated with antiretroviral drugs (31). It is important to point out that in all these studies, the RYR option was chosen and prescribed by general physicians and specialists that evaluated patient-by-patient the eventual safety risk (63).

The consumer should be advised to assume certified products without shifting among different products because the marketed supplements could have a wide marked variability in the content of total monacolins (Delta >300% per capsule), monacolin K (lovastatin) (>100% per capsule), and monacolin KA (>200% per capsule), with possible consequences in terms of tolerability and safety (64).

In summary, the administration of citrinin-free certified RYR containing low doses of monacolin K (from 3 to 10 mg per tablet) could be considered an effective and relatively safe lipid-lowering nutraceutical in healthy subjects with mild hypercholesterolemia. They could improve the efficacy of other lipid-lowering nutraceuticals as well as of other nonstatin drugs, when statins are not tolerated or when an evident nocebo effect is diagnosed. The available evidence supporting a widespread use of RYR is still limited and RYR supplements should never replace statins, or the other LDL-C lowering pharmacological approaches as mainstay therapeutic strategy to effectively lower CVD risk specifically in patients at high and very high CV risk as advised by the current guidelines. Finally, statin-like adverse events need to be considered in frail patients assuming RYR extracts with high content of monacolin K associated with drugs interacting with RYR.

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