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JACC STATE-OF-THE-ART REVIEW

The Role of Nutraceuticals in Statin Intolerant Patients

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ABSTRACT

Statins are the most common drugs administered for patients with cardiovascular disease. However, due to statin-associated muscle symptoms, adherence to statin therapy is challenging in clinical practice. Certain nutraceuticals, such as red yeast rice, bergamot, berberine, artichoke, soluble fiber, and plant sterols and stanols alone or in combination with each other, as well as with ezetimibe, might be considered as an alternative or add-on therapy to statins, although there is still insufficient evidence available with respect to long-term safety and effectiveness on cardiovascular disease prevention and treatment. These nutraceuticals could exert significant lipid-lowering activity and might present multiple non–lipid-lowering actions, including improvement of endothelial dysfunction and arterial stiffness, as well as anti-inflammatory and antioxidative properties. The aim of this expert opinion paper is to provide the first attempt at recommendation on the management of statin intolerance through the use of nutraceuticals with particular attention on those with effective low-density lipoprotein cholesterol reduction. (J Am Coll Cardiol 2018;72:96–118)

Statins are recommended for dyslipidemic patients (1,2) given their documented high effectiveness in reducing primary and secondary cardiovascular (CV) endpoints (3–5). It has been shown that they play an essential role in lowering low-density lipoprotein cholesterol (LDL-C) levels. They also have significant non-lipid-lowering properties, including anti-inflammatory, antithrombotic, antioxidant or antiapoptotic activities (3,6).

Many scientific societies have recently paid attention to the muscular adverse effects of statins (7–10). The European Atherosclerosis Society (EAS) has

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introduced the term *statin-associated muscle symptoms* (SAMS), avoiding the term "statin intolerance" (7). The definition of statin intolerance has evolved over the years. In 2016, the Canadian Consensus Working Group Update defined statin intolerance as "a clinical syndrome, not caused by drug interactions or risk factors for untreated intolerance and characterized by significant symptoms and/or biomarker abnormalities that prevent the long-term use and adherence to statins documented by challenge/dechallenge/re-challenge, where appropriate, using at least 2 statins, including atorvastatin and rosuvastatin, and that leads to failure of maintenance of therapeutic goals, as defined by national guidelines" (8). The inclusion of references to national guidelines and objectives in a definition of statin intolerance has the intention to ensure that the practical effort is justified for patients, colleagues, regulatory authorities, and taxpayers (8,9). Apart from SAMS, the exclusion of other undesirable effects may underestimate the number of patients with statin intolerance (10). In clinical practice, statin intolerance limits the effective treatment of patients at risk of atherosclerotic cardiovascular disease (CVD), and represents the main cause of statin nonadherence and discontinuation (11,12). It is, however, important to emphasize that there are only 3 statin-associated adverse effects with the confirmed causality: myalgia/myopathy, temporary elevation of alanine aminotransferase, and new-onset diabetes. Moreover, for most (even 95%) of the patients with SAMS, it is still possible to use statins using a step-by-step approach, as complete statin intolerance affects only 3% to 5% patients (10–12).

In the case of SAMS, it may be advisable to change the dose (and add nonstatin drugs), change the statin preparation, or try alternate-day statin therapy, or if SAMS are associated with all statins even at the lowest dose, then nonstatin drugs (ezetimibe, fibrates, proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors, and niacin if available) and certain nutraceuticals might be considered as alternatives for lipid lowering (13–17).

Innovative nutritional strategies to reduce the main CV risk factors have been developed, including either dietary changes or consumption of specifically targeted functional foods and dietary supplements for the treatment of dyslipidemia (18). Nutraceuticals can help achieve lipid therapeutic goals and reduce CV residual risk; however, data on the latter are still limited (19). Some nutraceuticals have been shown to improve early markers of vascular health, such as endothelial function and pulse wave velocity (PWV); others have been shown to positively modulate lipid metabolism, inhibit hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, and liver cholesterol synthesis, positively

ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular disease

HDL-C = high-density lipoprotein cholesterol

HMG-CoA = hydroxymethylglutaryl coenzyme A

ILEP = International Lipid Expert Panel

LDL-C = low-density lipoprotein cholesterol

PWV = pulse wave velocity

SAMS = statin-associated muscle symptoms

TC = total cholesterol

TG = triglycerides

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influencing subclinical atherosclerosis, endothelial dysfunction, and small dense low-density lipoprotein (18,20). However, clinical evidence that supports the use of nutraceuticals that improve lipid levels is largely variable, and for many of them is still very limited. The data on their use in patients with SAMS/statin intolerance are even less, and for most of them only an expert opinion recommendation might be given based only on their confirmed LDL-C-lowering effectiveness and safety data. Nowadays, there is a great need to determine a recommendation for the possible role of nutraceuticals in patients with statin-associated adverse effects. However, it is simultaneously critical to emphasize that nutraceuticals, both in patients with good adherence to statin therapy as well as with statin intolerance, cannot replace pharmacological therapy, but might help achieve treatment targets.

The purpose of this International Lipid Expert Panel (ILEP) Position Paper is to provide recommendations for nutraceutical therapies for patients with statin intolerance and to complement the recent ILEP papers on the lipid-lowering properties of nutraceuticals (16) and on statin intolerance (11) as well as the EAS statement on SAMS (21), where pathophysiology, diagnosis, and management were extensively discussed (**Central Illustration**).

OPENING STATEMENT

Nutraceuticals described in the published data are numerous and show different levels of effectiveness and evidence of their lipid-lowering effect. The detailed search strategy used for the preparation of this Position Paper is presented in the Online Appendix.

The objective of this consensus is to present the available data on the possible use of nutraceuticals in patients with SAMS. We also consider the nutraceuticals with the best evidence for LDL lowering and clinical efficacy that might be considered for these patients.

In the present Position Paper for each nutraceutical alone, in combination with other nutraceuticals, or in association with lipid-lowering drug therapy, we have briefly described the main mechanism of action, effective dosages, clinical evidence of effects on lipid profile, possible extra lipid-lowering properties (e.g., blood pressure, PWV, flow-mediated dilation [FMD], high-sensitivity C-reactive protein, and metabolic and inflammatory profile), and efficacy and safety profile (if such data were available). The detailed previously mentioned information has been presented in the recent ILEP Position Paper on lipid-lowering nutraceuticals in clinical practice (19).

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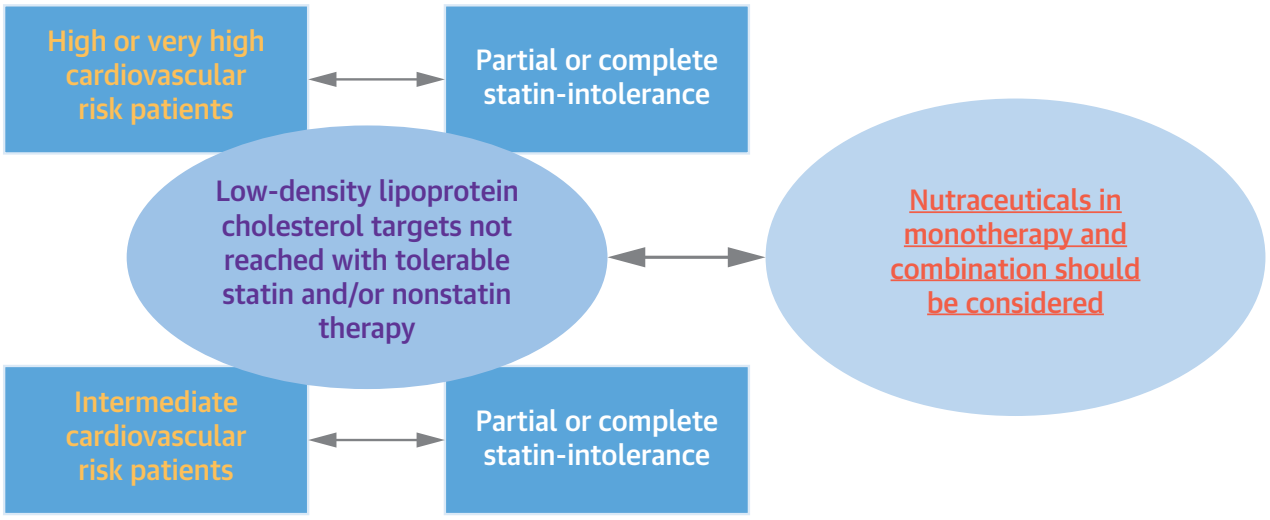
CENTRAL ILLUSTRATION **Role of Nutraceuticals in Statin-Intolerant Patients**



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Main recommendations of the International Lipid Expert Panel (ILEP) on the administration of nutraceuticals in statin-associated muscle symptom patients.

The level of evidence and the strength of recommendation of particular lipid-lowering treatment options have been weighed and graded according to pre-defined scales, as outlined in **Tables 1 and 2**. The experts of the writing and reviewing panels completed Declaration of Interest forms where real or potential sources of conflicts of interest were listed and, if relevant, were included in the footnote at the beginning of this paper.

Physicians and medical professionals of other specialties treating patients with lipid disorders are encouraged to consider the Position Paper in the process of evaluating the clinical status of their patients and to determine and implement medical strategies with nutraceuticals in patients with statin intolerance. However, the Position Paper does not override in any way the individual responsibility of physicians to make appropriate and accurate decisions taking into account the condition of a given patient and in consultation with that patient, and, where necessary, with the patient's 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/use*. The authors of the Position Paper are aware that the use of recommendations depends on several judgment calls that take into account values and preferences of patients.

TABLE 1 **Level of Evidence**

Level of Evidence	Definition
Level A	Data derived from multiple randomized clinical trials or their meta-analysis.
Level B	Data derived from a single randomized clinical trial or large nonrandomized studies.
Level C	Consensus or opinion of experts and/or small studies, retrospectives studies, registries.

TABLE 2 **Classes of Recommendation**

Classes of Recommendation	Definition	Suggested Wording to Use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective.	Is recommended/is indicated.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.	Should be considered.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective and, in some cases, may be harmful.	Is not recommended (no efficacy on lipid profile).

TABLE 3 Nutraceuticals That Might Be Used to Treat Statin Intolerant Patients and Their Influence on LDL-C Levels (Class and Level Recommendations Based On the International Lipid Expert Panel [19])

Agent	Class	Level of Evidence	Mechanism of Action	Patients (Trials)	Dose
Artichoke	IIa	B	Interaction of luteolin with the HMG-CoA reductase enzyme and the pathways of regulation in the liver of SREBPs and ACAT (26–28).	143 hypercholesterolemic patients	1.800 mg/day
				60 hypercholesterolemic patients	2.700 mg/day
				702 dyslipidemic patients (9)	500–2,700 mg/day
Berberine	I	A	Inhibitor of PCSK9 through the ubiquitination and degradation of HNF-1 alpha; acts directly on the expression of LDLR causing up-regulation of the receptors through a post-transcriptional mechanism that stabilizes their mRNA (activation of ERK- and JNK-dependent pathways) (32,33); ↓ intestinal absorption of cholesterol, ↑ fecal excretion and promoting the hepatic cholesterol turnover (34).	130 acute coronary syndrome patients	300 mg/day
				229 hyperlipidemia patients (6)	
Bergamot	IIa	B	HMGF inhibits HMG-CoA reductase and ACAT, ↓ formation of cholesterol esters and limiting the transport of cholesterol in the blood. Naringin inhibits the oxidation of LDL-C, initiates AMPK, and has shown scavenging activity; ↑ the fecal excretion of cholesterol, ↓ the intestinal absorption, and ↑ turnover and excretion of bile acids (37,38).	107 MetS patients	1.300 mg/day
Fibers	IIa	A	Prolonged gastric emptying time; ↑ of satiety; inhibition of hepatic cholesterol synthesis; ↑ fecal excretion of cholesterol and bile salts (40).	916 hypercholesterolemic patients (17)	5 ≥ dose ≤5 g/day
				1,117 mild and moderate hypercholesterolemia patients (21)	3.0–20.4 g/day
				26 mild to moderate hypercholesterolemia patients	3.4 g/day
				531 patients with at least 1 of components of the metabolic syndrome (14)	100–200 g/day
Garlic	IIa	A	Inhibition of HMG-CoA reductase, squalene-monooxygenase and acetyl-CoA synthetase enzymes (19); thiol group reacts with non-acetylated-CoA directly, reducing acetyl-CoA available for endogenous synthesis of cholesterol (45,47).	2,298 hypercholesterolemic patients (39)	5–6 g/day
				970 hypertensive and hyperlipidemic patients (20)	
Green tea	IIa	A	Inhibition of the expression of inducible nitric oxide synthase (50); activation of AMPK stimulating lipogenesis and inhibition of HMG-CoA reductase (51,52).	1,536 dyslipidemic patients (20)	170–1,200 mg/day
				40 patients with CKD	5 g/day
				1,164 diabetic subjects with CHD	≥20 g/day
Lupin	IIa	A	Downregulation of the expression of the hepatic transcription factor of SREBP-1; regulation of SREBP-2; ↓ of cholesterol synthesis; ↑ of apoB receptor activity or ↑ of the fecal excretion of bile salts (56–59).	33 hypercholesterolemic patients	25 g/day
				72 hypercholesterolemic patients	25 g/day
				60 moderately hypercholesterolemic patients	25 g/day
Plant sterols and stanols	IIa	A	Secretion of apoB by enterocytes and hepatocytes; modulation of the cholesterol synthesis reduction and inflammatory cascade (63,64); ↓ intestinal absorption of exogenous cholesterol, competing with it in the formation of solubilized micelles (65,66).	55 hypercholesterolemic patients	2.31 mg/day
				263 patients (8)	1.0-3.0 g/day
				2,084 hypercholesterolemic subjects (41)	1.6 g/day
				60 hypercholesterolemic patients	1.6 g/day
				150 mildly hypercholesterolemic patients	2.0 g/day

↑ = increase; ↓ = decrease; ACAT = acetyl-CoA C-acetyltransferase; ALT = alanine transaminase; AMPK = adenosine-monophosphate-kinase; apo B = apolipoprotein B; AST = aspartate transaminase; BP = blood pressure; CHD = coronary heart disease; CKD = chronic kidney disease; CV = cardiovascular; DHA = docosahexaenoic acid; eCVD = estimated cardiovascular disease; EPA = eicosapentaenoic acid; ERK = extracellular signal regulated kinase; FBG = fasting blood glucose; FMD = flow mediated dilation; HDL = high-density lipoprotein; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme-A; HMGF = human milk growth factor; HNF-1α = hepatocyte nuclear factor 1 alpha; hsCRP = high-sensitivity C-reactive protein; ICAM-1 = intercellular adhesion molecule; IL-6 = interleukin-6; JNK = c-Jun N-terminal kinase; LDL = low-density lipoprotein; MCP-1 = monocyte chemotactic protein 1; MetS = metabolic syndrome; MMP-9 = matrix metalloproteinase-9; PCSK9 = proprotein convertase subtilisin/kexin type 9; PWV = pulse wave velocity; SBP = systolic blood pressure, SREBP-1 = sterol regulatory element binding protein; TC = total cholesterol; TG = triglycerides; VCAM-1 = vascular cell adhesion molecule.

TABLE 3 Continued

Duration	LDL-C Levels	Effects on Other CV Parameters	(Ref. #)	Safety
6 weeks	−22.9% ($p = 0.0001$)	↓ TC 18.5% ($p < 0.001$) ↓ AST ↓ ALT	(29)	Good tolerability and safety in the short-medium term; hepatoprotective effect. Studies on vascular outcomes such as arterial stiffness and endothelial function are needed.
2 months	−11.5% ($p = 0.039$)	↓ TC ($p = 0.002$) ↓ TG ($p = 0.015$)	(30)	
3-12 weeks	−14.9 mg/dl (−0.39 mmol/l) ($p = 0.011$)	↓ TC −17.6 mg/dl (−0.46 mmol/l) ($p < 0.001$) ↓ TG −9.2 mg/dl (−0.11 mmol/l) ($p < 0.001$)	(31)	
1 month	−24% ($p < 0.001$)	↓ IL−6, MCP-1 ($p = 0.05$) ↓ hsCRP, MMPs, ICAM-1, VCAM-1 ($p = 0.01$)	(35)	Side effects are mild to moderate, mostly gastrointestinal. Not adverse effects on liver and kidney function. Direct vascular effects not demonstrated.
56–120 days	−25.1 mg/dl (−0.65 mmol/l) ($p < 0.00001$)	↓ TC −25.5 mg/dl (−0.66 mmol/l) ($p < 0.00001$); ↓ TG −34.5 mg/dl (−0.39 mmol/l) ($p < 0.03$); ↑ HDL-C 4.6 mg/dl (0.12 mmol/l) ($p = 0.03$)	(36)	
120 days	−61 mg/dl (−1.6 mmol/l) ($p < 0.05$)	Large LDL from 424 ± 87 to 653 ± 95 nmol/l ($p < 0.05$); Small LDL from 986 ± 105 to 612 ± 98 nmol/l ($p < 0.05$); Large HDL from 5 ± 3 to 15 ± 4 nmol/l ($p < 0.05$); Small HDL from 18 ± 5 to 14 ± 4 nmol/l ($p < 0.05$)	(39)	Good safety profile, with no side effects detected. Direct vascular effects not demonstrated.
8 ≥ time ≤8 weeks	−8.1 mg/dl (−0.21 mmol/l) ($p < 0.00001$)	↓ TC −10.1 mg/dl (−0.26 mmol/l) ($p < 0.00001$)	(41)	Well tolerated therapy in long-term follow-up. No adverse effects were reported. Reduction of CV risk.
14–182 days	−10.7 mg/dl (0.278 mmol/l) ($p = 0.04$)	↓ TC −14.5 mg/dl (−0.38 mmol/l)	(42)	
8 weeks	−20.2%	↓ LDL-C/HDL-C ratio 14.8%	(43)	
3-16 weeks	−15.99 mg/dl (−0.41 mmol/l) ($p = 0.0286$)	Beneficial effect on TC, TG, body weight, and FBG	(44)	
2 months	−9 mg/dl (−0.23 mmol/l)	↓ TC and TG	(47)	Direct vascular effects not demonstrated. Side effects are usually minimal (mostly gastrointestinal) and the extracts are well tolerated.
2 weeks	−10% ($p < 0.001$)	↓ BP ($p < 0.001$) ↓ Platelet aggregation	(48) (49)	
3-24 weeks	−7.35 mg/dl (−0.19 mmol/l) ($p < 0.0004$)	↓ BP −1.94 mm Hg ($p = 0.0002$) ↓ TC −5.03 mg/dl (−0.13 mmol/l) ($p < 0.0001$)	(53)	The consumption is well tolerated; however, in some cases a rash, transient elevation of BP, and mild gastrointestinal disorders may occur. Moreover, high doses of green tea can cause a deficiency of iron and folate due to its capacity to bind and reduce their intestinal absorption. Direct vascular effects demonstrated.
1 month		↑ FMD ($p = 0.002$)	(54)	
1 yr		↓ PWV	(55)	
4 weeks	−12.0% ($p < 0.008$)	↓ LDL-C/HDL-C ratio ($p = 0.003$) ↑ HDL ($p < 0.036$)	(60)	A good safety profile, causing no severe side effects, and those that occurred were mostly gastrointestinal. Direct vascular effects demonstrated.
28 days	−4% ($p = 0.044$)	↓ TC −4% ↓ TG −9%	(61)	
4 weeks	−12% ($p = 0.02$)	↓ TC −9% ($p = 0.02$) ↓ hsCRP ($p = 0.02$) ↓ SBP ($p = 0.01$)	(62)	
8 weeks	−13.7% ($p < 0.01$)	↓ TC −10.6% ($p < 0.001$)	(67)	High safety profile in the middle-term; however, data for treatment longer than 2 years are still not available. Direct vascular effects not demonstrated.
4-6 weeks	−12 mg/dl (−0.31 mmol/l) ($p < 0.000$)	UNK	(68)	
28 days	−12.8 mg/dl (− 0.33 mmol/l) ($p < 0.05$)	↓ TC −12.8 mg/dl (− 0.33 mmol/l) ($p < 0.001$)	(65)	
6 weeks	−18.8 mg/dl (−0.49 mmol/l) ($p = 0.01$)	↓ plasma isoprostanes ($p = 0.018$)	(69)	
1 month	−16% ($p < 0.002$)	↓ TC −14% ($p < 0.002$) ↓ hsCRP (−17%) and eCVD risk (26%–30%)	(70)	

Continued on the next page

TABLE 3 Continued

Agent	Class	Level of Evidence	Mechanism of Action	Patients (Trials)	Dose
Polyunsaturated omega-3 fatty acid	I	A	Reduction of synthesis of hepatic VLDL, reduction of available substrate for the synthesis of new TG, reduction of the activity of TG-synthesizing enzymes (diacylglycerol acyltransferase or phosphatidic acid phosphohydrolase), the increase of β-oxidation of fatty acids, the reduction of the endogenous synthesis of fatty acids, and the increase of synthesis of phospholipids (71).	16,511 hypercholesterolemia patients (47) 2,270 normolipidemic and borderline patients (1,379) 36 healthy volunteers CHD patients 25 moderately hypertriglyceridemia subjects 662 healthy individuals and dyslipidemic individuals (7)	3.25 g (1.9 g/day EPA/ 1.35 g/day DHA) ≥4 g/day of n-3 PUFA 1–5 g/day of EPA and/or DHA 4.9 g/day 1 g/day EPA/DHA 1,000 mg/twice a day omega 3 ethyl ester PUFAs dosages ranged from 500 mg/day to 4 g/day
Red yeast rice	I	A	Reversible inhibitory action on HMG-CoA reductase (78,79).	6,663 hypercholesterolemic patients (20) 50 CHD patients	1.200–4.800 mg/day 1,200 mg/day of xuezhikang, an extract of Cholestin
Spirulina	IIa	A	Phycocyanobilin can activate atheroprotective heme oxygenase-1 (HMOX-1); phycocyanin ↓ TC and TG levels in serum, ↑ hepatic glycogen level and maintains glucokinase (GK) expression in the liver (82).	522 overweight, diabetic, dyslipidemic patients with ischemic heart disease (7)	1–10 g/day
Soy proteins	IIa	A	↑ apoB receptor activity, ↓ the synthesis of cholesterol and the secretion of hepatic lipoprotein, ↑ clearance of cholesterol from the blood (58).	2,670 overweight, diabetic, dyslipidemic and MetS patients 1,281 dyslipidemic and ischemic patients 14 patients with moderate CV risk	35 mg/day 25–40 g/day and 33–120 mg/day 80 mg

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NUTRACEUTICALS AS LIPID-LOWERING AGENTS

EFFICACY OF SINGLE NUTRACEUTICALS. The use of nutraceuticals as lipid-lowering agents (22,23) has several advantages. First, nutraceuticals have natural origins and are mainly extracted from natural products that have been used as human foods for thousands of years. They are mostly safe and very well tolerated, and their use is supported by the findings from randomized control trials (RCTs), meta-analyses, and some well-designed perspective control studies. Second, the lipid-lowering effect of most nutraceuticals occurs through multiple mechanisms (natural inhibitors of intestinal cholesterol absorption, inhibitors of hepatic cholesterol synthesis, and enhancers of the excretion of LDL-C [19]). The possibility of acting simultaneously on multiple stages of lipid-induced vascular damage may result in the improvement of endothelial dysfunction and arterial stiffness, as well as anti-inflammatory and anti-oxidative properties (24). These properties make nutraceuticals potential valuable candidates for improving the lipid-lowering effects when used in combination with diet, drugs, or other nutraceuticals (23) in the management of dyslipidemia (18). Thus, nutraceuticals with the potential to modify the lipid profile and cardiometabolic properties have the potential to reduce the burden of CVD (23,25). This section provides an up-to-date summary of the findings on the lipid-lowering and cardiometabolic effects of the most important nutraceuticals and recommendations on their use as LDL-lowering agents based on recent ILEP recommendations (26–85) (**Table 3**).

NUTRACEUTICALS COMBINATION EFFICACY. Combinations of nutraceuticals with different lipid-lowering activities and mechanisms of action (19), particularly when associated with an appropriate lifestyle, might have essential synergistic effects (86–107) (**Table 4**), acting on the absorption of lipids from the intestine and/or increasing their excretion (soluble fibers, glucomannan, plant sterols, bergamot, and lupin), enhancing the hepatic uptake of LDL particles (berberine and soybean proteins), inducing

TABLE 3 Continued

Duration	LDL-C Levels	Effects on Other CV Parameters	(Ref. #)	Safety
24 weeks	−2.32 mg/dl (−0.06 mmol/l)	↓ TG −14% ($p < 0.001$)	(72)	No serious side effects have been reported; most of them have been defined as mild gastrointestinal. Direct vascular effects demonstrated.
At least 2 weeks	Variable −2.3, −7.5, −7, −17%, in some studies no effect on lipid profile	↓ TG 9%–26%	(73)	
12 weeks	Not rated	↓ TG 4%–51%	(74)	
		↓ TG ($p = 0.039$)	(75)	
4 weeks	−0.19 mg/dl (0.002 mmol/l) ($p < 0.462$)	↑ FMD ↓ PWV ↓ inflammation	(76)	
2 weeks	−15.52 mg/dl (−0.4 mmol/l) ($p = 0.018$)	↓ TG ($p < 0.05$) ↓ hsCRP ($p < 0.05$) ↓ TG −14.03 mg/dl (−0.16 mmol/l) ($p < 0.001$)	(77)	
1 month	−90.3 mg/dl (−1.02 mmol/l) ($p < 0.0001$)		(80)	The chronic administration of monacolins could be responsible for mild to moderately severe side effects, it is usually well tolerated. The incidence of kidney injury, liver injury, and muscle symptoms was found to be at an acceptable rate. Direct vascular effects demonstrated.
6 weeks	−36.3 mg/dl (−0.94 mmol/l) ($p < 0.001$)	↓ TG ($p < 0.001$) ↓ hsCRP ($p < 0.001$) ↑ FMD ($p < 0.001$)	(81)	
12 weeks to 12 months	−41.32 mg/dl (−1.07 mmol/l) ($p < 0.001$)	↓ TC −46.76 mg/dl (−1.2 mmol/l) ($p < 0.001$) ↓ TG −44.76 mg/dl (−0.53 mmol/l) ($p < 0.001$) ↑ HDL-C 606 mg/dl (15.7 mmol/l) ($p = 0.001$)	(82)	One of the most healing and prophylactic ingredients of nutrition in the 21st century due to its nutrient profile, therapeutic effects and lack of toxicity. According to the available data, it seems to be very well tolerated. Direct vascular effects not demonstrated.
4 weeks to 1 yr	−4.83 mg/dl (−0.13 mmol/l) ($p < 0.0001$)	↓ TC −5.33 mg/dl (−0.14 mmol/l) ($p < 0.0001$)	(83)	The chronic use of a high quantity of soy products containing isoflavones could interfere with thyroid function and fertility. Furthermore, soybean and its derivatives contain high amounts of phytic acid that reduces the absorption of minerals such as calcium, magnesium, copper, iron, and zinc. Direct vascular effects demonstrated.
4–52 weeks		↑ FMD +1.15%	(84)	
6–24 h		↑ PWD ($p < 0.01$)	(85)	

cholesterol excretion (berberine, soy proteins, and chlorogenic acid), inhibiting HMG-CoA reductase enzyme and limiting the hepatic synthesis of cholesterol (monacolins, policosanols, artichoke, allicin, soybean proteins, and bergamot), and reducing the oxidation of LDL and increasing thermogenesis and lipid metabolism (chlorogenic acid) (108). **Table 4** presents the most important studies available on such combinations, their efficacy and safety, as well as ILEP recommendations on their lipid-lowering properties.

NUTRACEUTICALS AND LIPID-LOWERING DRUGS. Nutraceuticals, either alone or in combination, when administered with statins seem to confer additional benefit on plasma lipid profiles (**Table 5**), allowing the statin doses to be reduced (in case of statin intolerance) without diminishing the results in terms of total cholesterol (TC) and LDL-C reduction (109–121) and significantly limiting adverse effects (122). Thus, the recommended goals may be achieved in a safe and tolerable way for most patients (123). Available studies as well as the efficacy and safety of such combinations have been summarized in **Table 5**.

CLINICAL STUDIES ON NUTRACEUTICALS AND STATIN INTOLERANCE

The use of high-intensity statins increases the risk of adverse effects and, therefore, worsens adherence (11,124). Even with good statin therapy adherence, the LDL-C-targeted levels might not be achieved for 30% to 70% of patients (depending on the risk), even in combination with ezetimibe for high-risk and very-high-risk patients (125). In this case, for patients not on target, nutraceuticals might be useful. We would like to strongly emphasize that only highly purified and standardized nutraceuticals should be considered, and they cannot replace statin therapy, but rather serve to complement the LDL-C–lowering effect. This may also apply to patients with statin intolerance taking nonstatin therapy (ezetimibe and/or PCSK9 inhibitors) with/without a statin. It must be stressed that there are still no long-term outcome studies confirming that nutraceuticals prevent CVD morbidity or mortality.

In this section, we focus on nutraceuticals that have already been studied in patients with SAMS. However,

TABLE 4 Combination of Nutraceuticals and Their Influence on LDL-C Levels and Cardiovascular Risk (Class and Level Recommendations Based on the International Lipid Expert Panel [19])

Nutraceutical Combination	Class	Level of Evidence	Patients (Clinical Trial)	Dose/Day	Duration
Red yeast rice and policosanols	I	A	111 moderate hypercholesterolemic patients	340 mg containing 5 mg monacolin K and 10 mg octacosanols	2 months
			240 primary-moderate hypercholesterolemic patients	200 mg containing 3 mg monacolin K and 10 mg aliphatic alcohols	4 months 8 months
			2,408 (411 centers)	200 mg containing 3 mg monacolin K and 10 mg policosanols	16 weeks
			40 children HeFH	200 mg containing 3 mg monacolin K and 10 mg policosanols	8 weeks
Red yeast rice and berberine	IIb	B	40 dyslipidemic patients		
Red yeast rice, policosanols and berberine	I	A	3,159 dyslipidemic and hyperglycemic patients (14)	3 mg monacolin K, 10 mg policosanols, 500 mg berberine	Long term-observation
			100 normal borderline cholesterol patients	200 mg red yeast rice extract (equivalent to 3 mg monacolins), 10 mg policosanol, 500 mg berberine, 0.5 mg astaxanthin, 0.2 mg folic acid, and 2 mg coenzyme Q10 2	3 months
			50 hypercholesterolemic patients	500 mg berberine, 200 mg red yeast rice and 10 mg policosanols	6 weeks
Red yeast rice, policosanols and silymarin	IIb	B	134 low-risk dyslipidemic patients	334 mg containing monacolin 10 mg, 30 mg policosanol and 150 mg silymarin	3 months
			80 moderately hypercholesterolemic patients	334 mg containing monacolin 10 mg, 30 mg policosanol and 150 mg silymarin	8 weeks
Red yeast rice and plant sterols	IIa	B	18 hypercholesterolemic patients	1,200 mg (titration in monacolin K not reported), 1,250 mg phytosterols, 1,250 mg	6 weeks
			90 hypercholesterolemic patients	800 mg phytosterols and red yeast rice (monacolin K 5 mg)	8 weeks
Red yeast rice and artichoke	IIa	B	100 hypercholesterolemic volunteers	Natural cholesterol-lowering supplement containing red yeast rice, policosanols, and artichoke leaf extracts	16 weeks
Red yeast, artichoke and berberine	IIa	B	30 adults with suboptimal LDL-C level	200 mg, containing 10 mg monacolin K, 500 mg artichoke extract, and 50 mg banaba extract	6 weeks
Red yeast rice, policosanols and artichoke	IIa	B	39 moderate hypercholesterolemic patients	166.67 mg red yeast rice (0.4% monacolin K), 3.70 mg sugar cane extract (90% policosanols - 60% octacosanol), 200 mg artichoke leaf dry extract (5-6% chlorogenic acid), 10 mg garlic dry extract (0.8% allicin, 1.8% allicin), 6.67 mg pine bark extract (90% oligomeric proanthocyanidins), 12.86 mg vitamins E, 1.60 mg B2, 2.92 mg B3 (inositol hexanicotinate), 199 mg dicalcium phosphate, 87.36 mg microcrystalline cellulose, 63.22 mg calcium citrate, 34 mg tricalcium phosphate, and 22 mg magnesium stearate	16 weeks
Red yeast rice and antioxidant	IIa	B	25 mildly hypercholesterolemic patients	10 mg of monacolin K and 30 mg CoQ10	4 weeks
			40 moderately hypercholesterolemic	10 mg of monacolin K and 30 mg CoQ10	6 months
			25 moderately hypercholesterolemic	10 mg monacolins with a pool of antioxidants (100 mg of green tea dry extract, 20 mg of CoQ10, 2 mg of astaxanthin, 20 mg of resveratrol, and 50 mg of quercetin)	4 weeks

The action mechanisms of single nutraceuticals cited in this table are deepened in Table 3.
Abbreviations as in Table 3.

it needs to be emphasized that for most of the nutraceuticals presented in the following section, only single studies in SAMS patients have been published, with the exception of red yeast rice (RYR), which has 3 available studies and another 5 for RYR in combination with other nutraceuticals. Thus, the level of evidence is based on the available data and previous recommendations based on LDL-C lowering (19).

TABLE 4 Continued

LDL-C Levels	Effects on CV Parameters	(Ref. #)	Safety
−20% ($p < 0.05$)	↓ TC, LDL-C and TG, both in men and women ($p > 0.05$)	(86)	No serious safety concerns. No adverse effects were detected when liver and muscular enzymes (AST, ALT, and CK) were determined. Direct vascular effects not demonstrated.
−29% ($p < 0.001$)	↓ TC −58 mg/dl (−1.50 mmol/l) −22% ($p < 0.001$) ↓ TG −9 mg/dl (−0.10 mmol/l)−30% ($p < 0.001$) ↓ non−HDL-C −26% ($p < 0.001$)	(87)	
−38% ($p < 0.001$)	↓ TC −59 mg/dl (−1.53 mmol/l) −29.4% ($p < 0.001$) ↓ TG −12 mg/dl (−0.14 mmol/l) −33% ($p < 0.001$) ↓ non−HDL-C −37% ($p < 0.001$)		
16.8%-18.7% ($p < 0.001$)	↓ AST ($p < 0.001$) ↓ ALT ($p < 0.001$)	(88)	
−25.1% ($p < 0.001$)	↓ TC −36.3 mg/dl (−0.94 mmol/l) ($p < 0.001$) ↓ ApoB −0.22 mmol/l ($p < 0.001$)	(89)	
	Improved endothelial function and PWV	(90)	No serious safety concerns have been raised.
−23.85 mg/dl (−0.62 mmol/l), ($p < 0.001$)	↓ TC −26.15 mg/dl (−0.68 mmol/l) ($p < 0.001$) ↓ TG −13.83 (−0.17 mmol/l) ($p < 0.001$) ↓ HDL 2.25 mg/dl (0.06 mmol/l) ($p < 0.001$)	(91)	No serious safety concerns have been raised. Direct vascular effects demonstrated.
−23% ($p < 0.001$)	↓ hsCRP ($p = 0.04$), endothelial microparticle ($p = 0.001$)	(92)	
−41.8 mg/dl (−1.06 mmol/l) ($p < 0.001$)	↓ FMD 3 ± 4% ($p < 0.05$)	(93)	
$p = 0.041$	↓ TC ($p = 0.039$) ↓ sICAM-1 ($p = 0.042$), VCAM-1 ($p = 0.043$), soluble E- selectin ($p = 0.042$), MMP-2 ($p = 0.031$) and MMP-9 ($p = 0.038$), hsCRP ($p = 0.038$), and TNF-alpha ($p = 0.043$)	(94)	Necessary to evaluate the safety issues for this combination. Direct vascular effects demonstrated.
−23.3%	↓ hsCRP −2.4% ↑ endothelial function +17% ↓ PWV −3.3%	(95)	
−33%, −53 mg/dl (−1.37 mmol/l), $p < 0.05$	↓ TC ($p < 0.05$)	(96)	No muscle pains and abnormal liver function tests.
−27.0% ($p < 0.001$)	↓ ApoB −19% ($p < 0.001$)	(97)	Direct vascular effects not demonstrated.
−14.3 ($p < 0.001$)	↓ TC ($p < 0.001$), apoB100 and apoB100/apoA-I ratio ($p < 0.05$)	(98)	No serious safety concerns. Direct vascular effects demonstrated.
−18.2 ($p < 0.001$)	↓ TC −13.6% ($p < 0.001$) ↓ non-HDL −15% ($p < 0.001$) ↓ ALT −10% ($p < 0.024$) ↓ AST −30.9% ($p < 0.011$) ↓ hsCRP −18.2% ($p < 0.019$)	(99)	No serious safety concerns.
−21.4% ($p < 0.001$)	↓ TC −14.1% ($p < 0.001$) ↓ TG −12.2% ($p < 0.05$)	(100)	No serious safety concerns.
−21.99% ($p < 0.05$)	↓ TC −12,45% ($p < 0.05$) ↓ non-HDL-C −14.67% ($p < 0.05$) ↓ MMP-2 −28.5% ($p < 0.05$) ↓ MMP-9 −27.19% ($p < 0.05$)	(101)	No serious safety concerns. Direct vascular effects demonstrated.
(−26.3%; $p < 0.05$)	Endothelial reactive +6%, ↓ PWV −4% (both $p < 0.05$)	(102)	
−22.36% ($p < 0.001$)	↓ TC −18.35 mg/dl (−0.47 mmol/l) ($p < 0.001$), ↓ ApoB −11.8 mg/dl ($p = 0.038$), ↓ hsCRP −0.05 ($p < 0.001$), ↑ endothelial function +11.6% ($p = 0.022$)	(103)	

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RED YEAST RICE. RYR has been used as an alternative to statin therapy in treating patients with mild to moderate hypercholesterolemia, particularly in those considered to be statin intolerant, and clinical studies suggest that RYR is well tolerated, safe, and effective for CVD primary prevention (126-128). In the studies with xuezhikang (XZK)—a purified extract of RYR—the authors showed that 1,200 and 2,400 mg/day of XZK

TABLE 4 Continued

Nutraceutical Combination	Class	Level of Evidence	Patients (Clinical Trial)	Dose/Day	Duration
Berberine and chlorogenic *acid and policosanols*	IIb	B	40 mixed hyperlipidemic patients	500 mg berberine, 67 mg of chlorogenic acid and 143 mg tocotrienols	8 weeks
Berberine and silymarin	IIb	B	102 dyslipidemic patients	500 mg berberine, 105 mg silymarin	3 months
Soy protein and plant sterol	IIa	B	24 dyslipidemic and MetS patients	Phytochemical-enhanced diet with a combination of soy protein and plant sterols in a powdered beverage form of a medical food and a nutraceutical tablet containing a 5:1 ratio of rho iso-alpha acids and acacia proanthocyanidins, each taken twice daily.	12 weeks
			25 hyperlipidemic subjects	16.2 g soy proteins, 1.2 g plant sterols, and 8.3 g viscous fibers	4 weeks

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for 4 to 12 weeks in subjects with dyslipidemia but no coronary heart disease resulted in significant ($p < 0.001$) and clinically meaningful decreases in non-high-density lipoprotein cholesterol (HDL-C) (~24% reduction) and LDL-C (~27% reduction) compared with placebo (129), and significantly decreased CV and total mortality by 30% and 33% in patients with previous myocardial infarction who were randomly assigned either to placebo or to XZK daily (300 mg containing monacolin K at a dose of 2.5 to 3.2 mg/capsule) for an average of 4.5 years (130).

Becker et al. (126) showed that the use of RYR significantly reduced LDL-C and TC levels compared with placebo without increasing the incidence of myalgia in 62 dyslipidemic patients who could not tolerate statin therapy (126). In the RYR group (1,800 mg twice daily), LDL-C decreased by 1.11 mmol/l (43 mg/dl) from baseline at week 12 and by 0.90 mmol/l (35 mg/dl) at week 24. In the placebo group, LDL-C decreased by 0.28 mmol/l (11 mg/dl) at week 12 and by 0.39 mmol/l (15 mg/dl) at week 24. LDL-C level was significantly lower in the RYR group than in the placebo group at both weeks 12 ($p < 0.001$) and 24 ($p = 0.011$). Significant treatment effects were also observed for TC level at weeks 12 ($p < 0.001$) and 24 ($p = 0.016$) (126). RYR (1,200 to 4,800 mg/day) with a known content of the active substance monacolin K (4.8 and 24 mg) was tested against placebo or an active control group in 20 selected RCTs (80). After 4 weeks, RYR reduced LDL-C by 1.02 mmol/l (39 mg/dl; $p < 0.0001$) compared with placebo, and the effect of RYR on LDL was not different from statin therapy (0.03 mmol/l [1.2 mg/dl]; $p = 0.89$) in statin-intolerant patients (80). For all previously mentioned studies, there were no safety concerns (80,126-130). However, it needs to be emphasized that monacolin K is chemically identical to lovastatin, and therefore, some adverse effects typical for statins might appear, despite the fact that available studies in SAMS patients have not confirmed this. There is also a potential safety concern if citrinin is present; variation in the monacolin K content within a given product seems also to be important, therefore only the highly purified, standardized and certified product with good quality control should be used (**Table 6**).

PHYTOSTEROLS. Phytosterols have been used for cholesterol intestinal absorption and hepatic synthesis, leading to a better cholesterol homeostasis in humans. Clinical trials and meta-analyses have not shown any major safety concerns (131), nor is there any evidence of direct vascular effects after their persistent use (19). However, long-term safety is yet to be established. Phytosterol administration should be avoided in patients with phytosterolemia (sitosterolemia). This rare autosomal recessive sterol storage disease is caused by mutations in either the adenosine triphosphate (ATP)-binding cassette transporter genes *ABCG5* or *ABCG8*, leading to impaired elimination of plant sterols and stanols. A similar contraindication refers to patients who are heterozygous for variants of *ABCG5* and *ABCG8* and other genes (132). The increased accumulation of plant sterols and stanols in the blood and tissues leads to moderate to high plasma cholesterol levels, and increased risk of premature atherosclerosis (133).

Becker et al. (134) determined the lipid-lowering effects of phytosterol tablets (900 mg twice daily) and lifestyle change in addition to RYR therapy (RYR 1,800 mg twice daily) in patients with a history of statin refusal or statin-associated myalgias (187 participants; mean LDL-C 154 mg/dl [4 mmol/l]) for 12, 24, and 52 weeks (134). The addition of phytosterol tablets to RYR did not result in further significant

TABLE 4 Continued

LDL-C Levels	Effects on CV Parameters	Reference	Safety
−24% ($p < 0.001$)	↓ TC −19.5 mg/dl (−0.50 mmol/l) ($p < 0.001$) ↓ TG −21.4 mg/dl (−0.24 mmol/l) ($p < 0.001$) ↓ non-HDL-C −19.7 mg/dl (−0.51 mmol/l) ($p < 0.001$) ↓ HOMA index −0.3 ($p < 0.001$)	(104)	No serious safety concerns. Direct vascular effects not demonstrated.
−32.2% ($p < 0.05$)	↓ TC −23.2%	(105)	Safety biochemical measurements included transaminases (AST and ALT), g-GT, and CPK.
−26.5 mg/dl (−0.69 mmol/l) ($p < 0.01$) ↓ total LDL particle number	↓ TC −22.3 mg/dl (−0.58 mmol/l) ($p = 0.01$) ↓ TG −23.3 mg/dl (−0.26 mmol/l) ($p = 0.02$) ↓ non-HDL-C −27.4 mg/dl (−0.71 mmol/l) ($p = 0.01$) ↓ apoB, apoB/apoA-1 ratio −29.3 ($p < 0.01$)	(106)	No serious safety concerns.
−35% ($p < 0.001$)	No difference was seen in BP, HDL-C, and TG	(107)	

lowering of LDL-C levels at weeks 12, 24, or 52 compared with placebo. All participants with the lifestyle changes had significant decreases in LDL-C (−51 mg/dl [−1.3 mmol/l] vs. −42 mg/dl [−1.1 mmol/l]; $p = 0.006$) and TC ($p = 0.003$), and an increase in HDL-C for 1 year when compared with baseline ($p < 0.001$) (134). Based on the current European Society of Cardiology (ESC)/EAS (2016) lipid guidelines (7), phytosterols have well-documented LDL-C lowering (Level of Recommendation: A) and the absence of adverse signals, and therefore may be considered, among others, as an adjunct to pharmacological therapy in high-risk and very-high-risk patients who fail to achieve LDL-C goals on statins or are statin intolerant. However, due to very limited data, further studies are necessary to confirm the real effects of phytosterols on lipid profile in SAMS patients as well as at which doses statin intolerant patients might benefit the most from phytosterols therapy (**Table 7**).

BERGAMOT (CITRUS BERGAMIA). Bergamot has a good efficacy and safety profile in dyslipidemic and other cardiometabolic patients without any adverse effects detected. Bergamot may potentially reduce overall CV risk, but effects on CV outcomes have not been demonstrated (19).

A study by Mollace et al. (135) involved 237 patients divided into 4 groups: A ($n = 104$), subjects with hypercholesterolemia (LDL-C >3.36 mmol/l [130 mg/dl]) treated with bergamot (500 mg/day for 30 days); B ($n = 42$), patients with hyperlipidemia (hypercholesterolemia and hypertriglyceridemia) treated with bergamot (1,000 mg/day for 30 days); C ($n = 59$), patients with metabolic syndrome treated with placebo; and D ($n = 32$), hyperlipidemic patients who stopped treatment with simvastatin because of adverse effects (muscle cramps and increased serum levels of creatine kinase), treated with bergamot (1,500 mg/day for 30 days) after a 60-day wash-out period (135). The results showed dose-dependent lipid-lowering action of bergamot (groups A and B LDL-C: −24.1% and −30.6%, TG: −28.2% and −37.9%, and HDL-C: +22.3% and +40.1%, respectively; $p < 0.001$ for all) compared with baseline. Group C (placebo) did not show significant reductions in serum cholesterol, and group D of patients with statin intolerance showed a significant reduction of LDL-C and TG (−25.0% and −27.6%, respectively; $p < 0.001$ for all), without any side effects (135) (**Table 8**).

SOY PRODUCTS. Some safety concerns have been reported for this product (19). The chronic use of a high quantity of soy products containing isoflavones might interfere with thyroid function and fertility (19). Soybeans and their derivatives contain high amounts of phytic acid that reduces the absorption of some minerals (calcium, magnesium, copper, iron, and zinc) (19). Direct vascular effects, mainly on FMD, have been demonstrated (19).

Substitution of soybean proteins in the diet has been used for the reduction of plasma cholesterol levels in hypercholesterolemic subjects (19). A soya drink, within a crossover design versus a cow's milk preparation of similar composition, was administered to 21 hypercholesterolemic patients (mean baseline plasma cholesterol 8.74 mmol/l [338 mg/dl]) with a history of resistance or intolerance of statin treatment for 4 weeks, with a 4-week interval between treatments (136). The soya supplementation reduced plasma TC levels by 6.5% before cow's milk supplementation and by 7.4% after cow's milk supplementation. Changes in total and LDL-C levels after soya versus cow's milk treatment were −6.1% and −7.0% after 2 weeks and −6.2% and −7.8% after 4 weeks, respectively (both $p < 0.05$) (136) (**Table 9**).

TABLE 5 Efficacy of Nutraceuticals in Combination With Lipid-Lowering Therapy

Nutraceuticals With Lipid-Lowering Drug	Patients (Clinical Trials)	Dose/Day	Duration
Statins and polyunsaturated fatty acids	642 hypertriglyceridemic patients with high cardiovascular risk (214 per arm)	OO 4 g/day with the same dose of statin OM3-FFA 2 g/day (plus 2 g/day OO 2) with the same dose of statin OM3-FFA 4 g/day with the same dose of statin	6 weeks
	171 patients with mixed dyslipidemia and high TG level	OM3-FFA 4 g and simvastatin 20 mg daily Simvastatin 20 mg in monotherapy daily	6 weeks
	18,645 hypercholesterolemic patients	EPA 1,800 mg daily with pravastatin 20 mg or simvastatin 10 mg	5 years
	11,324 patients after a recent myocardial infarction	Statin only (pravastatin 20 mg or simvastatin 10 mg) n-3 PUFA 1 g/day vitamin E 300 mg n-3 PUFA 1 g/day and vitamin E 300 mg **All patients did preventive therapy: aspirin, β-blockers, and inhibitors of angiotensin-converting enzyme (statins were not supported by definitive data on efficacy when the trial was started).*	3.5 years
Statins and soluble fiber	36 healthy volunteers	Psyllium 10 g/day Lovastatin 20 mg/day Lovastatin 20 mg plus psyllium 10 g daily	4 weeks
	68 hypercholesterolemic patients	Simvastatin 20 mg/day Simvastatin 10 mg/day Simvastatin 10 mg plus psyllium 15 g daily	8 weeks
	116 hypercholesterolemic patients	Fiber 25 g plus rosuvastatin 40 mg daily Rosuvastatin 40 mg/day Simvastatin 40 mg plus ezetimibe 10 mg plus fiber 25 g daily Simvastatin 40 mg plus ezetimibe 10 mg daily	12 weeks
Statins/ezetimibe and plant sterols	86 hypercholesterolemic subjects	Atorvastatin 40 mg plus phytosterols 2 g/day Ezetimibe 10 mg plus phytosterols 2 g/day Atorvastatin 40 mg plus Ezetimibe 10 mg plus phytosterols 2 g/day	12 weeks
	11 hypercholesterolemic coronary patients	Simvastatin 20 mg Simvastatin 20 mg plus dietary plant stanol ester margarine (2.25 g of stanols/day) Simvastatin 20 mg plus dietary plant stanol ester margarine (2.25 g of stanols/day) plus cholestyramine 8 g/day	3 months 3 months plus 8 weeks 3 months plus 8 weeks plus other 8 weeks
Statins and tocotrienols	28 hypercholesterolemic subjects	TRF (25 mg) of rice bran alone and in combination with lovastatin 10 mg/day	5 months
Statins and bergamot	77 patients with mixed hyperlipidemia	Rosuvastatin 10 mg plus Bergamot 1,000 mg/day	30 days
Statins and garlic	258 hyperlipidemic subjects	Simvastatin 10 mg plus placebo Simvastatin 10 mg plus black seed 500 mg and garlic 250 mg	8 weeks
Statins and vitamin D	56 hypercholesterolemic patients	Vitamin D 2,000 IU plus statin/day Statin plus placebo/day	6 months

BMI = body mass index; LOX-1 = receptor for oxidized low-density lipoprotein; OM3-FFA = omega-3 free fatty acids; OO = olive oil; oxLDL = oxidized low-density lipoprotein; n3 PUFA = polyunsaturated omega-3 fatty acids; PKB = protein kinase B; TRF = tocotrienol-rich fraction; other abbreviations as in Table 3.

TABLE 5 Continued

LDL-C Levels	Effects on CV Parameters	(Ref. #)	Safety
+1.1% (p = 0.025) +4.6% (p = 0.025) +1.3% (not significant)	↓ TG levels −5.9% (p < 0.001) ↓ non−HDL −0.9% (p < 0.05) ↓ TG levels −20.6% (p < 0.001) ↓ non−HDL −3.9% (p < 0.05) ↓ TG levels −14.6% (p < 0.001) ↓ non-HDL −6.9% (p < 0.05) ↑ Aπ AI (p < 0.05) ↓ apoB (p < 0.05)	(109)	OM3-FFA was well tolerated without adverse reactions. Limited data, further studies are necessary.
−28% (p < 0.001) −27% (p < 0.001)	↓ TG −41% (p = 0.0007) ↓ TC ↓ apoB ↓ apoE ↓ TG levels −13.9% (p = 0.0007) ↓ TC ↓ apoB ↓ apoE	(110)	
−25% −19%	↓ TG −9% (p < 0.011) −19% in major coronary events (p = 0.011) ↓ TG −4% (p < 0.011)	(111)	
No clinically important change in LDL-C in any of the treatment groups at the first visit. The difference in blood lipids, however, was more modest than any other value during the study (data not shown).	−10% in risk for the combined primary endpoint of death, nonfatal myocardial infarction, and nonfatal stroke (p = 0·048) −20% in risk for fatal events (p = 0.008)	(112)	
−3.6% (p = 0.004) −24.8% (p = 0.02) −30.9% (p = 0.02)	↓ TG −10.9% (p = 0.03) ↓ TG −32.9% (p = 0.03) ↓ TG −26.2% (p = 0.03)	(113)	No safety concerns. Limited data, further studies are necessary.
−63 mg/dl (−1.63 mmol/l) (p = 0.03) −55 mg/dl (−1.42 mmol/l) (p = 0.03) −63 mg/dl (−1.63 mmol/l) (p = 0.03)	↓ TG -8 mg/dl (−0.09 mmol/l) (p < 0.01) ↓ TC −61 mg/dl (−1.58 mmol/l) (p < 0.01) ↓ apoB −43 mg/dl (p < 0.01) ↓ TG −23 mg/dl (−0.26 mmol/l) (p < 0.01) ↓ TC −57 mg/dl (−1.47 mmol/l) (p < 0.03) ↓ apoB −47 mg/dl (p < 0.03) ↓ TG −17 mg/dl (−0.19 mmol/l) (p < 0.01) ↓ TC −66 mg/dl (−1.71 mmol/l) (p < 0.03)	(114)	
−70 mg/dl (−1.81 mmol/l) (p < 0.001) −64 mg/dl (−1.66 mmol/l) (p < 0.001) −80 mg/dl (−2.07 mmol/l) (p < 0.001) −72 mg/dl (−1.86 mmol/l) (p < 0.001)	↓ apoB −50 mg/dl (p < 0.03) ↓ body weight (p < 0.04) ↓ BMI (p < 0.002) ↓ blood glucose (p < 0.047) ↓ body weight (p < 0.04) ↓ BMI (p < 0.002) ↓ blood glucose (p < 0.047)	(115)	
−6.5% (p < 0.05) Insignificantly reduced −4.0% (p < 0.036)	↓ TC −7.5% (p < 0.05)	(116)	No safety concerns. Limited data, further studies are necessary.
−39% (p < 0.001) −52% (p < 0.05) −67% (p < 0.001)	↓ TC −5.0% (p < 0.04) ↑ HDL-C 15% (p < 0.01)	(117)	
−25% (p < 0.001)	↓ TC −25.0% (p < 0.001) ↑ HDL-C 53% (p < 0.002)	(118)	No study concerns. Limited data, further studies are necessary.
−53%	↓ TG −36.0% ↑ HDL-C 37% ↓ malondialdehyde, oxLDL receptor LOX-1 and phosphoPKB	(119)	No study concerns. Limited data, further studies are necessary.
−11.6% (p < 0.01) −29.4% (p = 0.01)	↓ TG −6.9% (p < 0.01) ↑ HDL-C +10.4% (p = 0.02) ↓ non−HDL-C −10.8% (p < 0.01) ↓ TG −20.1% (p = 0.01) ↑ HDL-C +21.4% (p = 0.01) ↓ non−HDL-C −27.4% (p = 0.01)	(120)	No study concerns. Limited data, further studies are necessary.
	↓ TC −28.5 mg/dl (−0.74 mmol/l) (p < 0.001) ↓ TG −37.1 mg/dl (−0.48 mmol/l) (p < 0.001) ↓ TC −22.1% (p < 0.001) ↓ TG −28.2% (p = 0.01)	(121)	No study concerns. Limited data, further studies are necessary.

TABLE 6 Red Yeast Rice

Class	Level	Active Daily Doses	Expected Effects on LDL-C	Safety Issues
I	A	1,200–4,800 mg (3–10 mg* of monacolin K)	−15% to −25%	Due to content of monacolin K some adverse effects typical for statins might appear

*Maximum recommended doses as dietary supplement recommended by the European Food Safety Authority (EFSA) (128).

LDL-C = low-density lipoprotein cholesterol.

POLYUNSATURATED OMEGA-3 FATTY ACIDS. In certain clinical situations, such as in patients who are unable to tolerate statin therapy and who also have persistent severe elevations in triglycerides (TGs), omega-3 acids might represent an important natural alternative choice (19). Based on available studies, some adverse effects have been reported, but the results are conflicting (19). It was shown that among patients with a recent episode of sustained ventricular arrhythmia and an implantable cardiac defibrillator, fish oil supplementation might be proarrhythmic (137). There are also some opposite data on the possible effect of polyunsaturated omega-3 fatty acids (PUFA) on sudden cardiac death (138,139).

Direct vascular effects (FMD, PWV) have been demonstrated, as well as their role in reduction of CV outcomes (19). However, due to conflicting results on the role of PUFA in reduction of CV outcomes (140,141), some dyslipidemia guidelines do not recommend using PUFA to reduce CVD events (142), in contrast to other guidelines (2,7). These recommendations do not mean that PUFA should not be used as an adjunct to nonstatin lipid-lowering agents and/or other nutraceuticals to improve the lipid profile in patients with statin intolerance (19).

The first data on icosapent ethyl (IPE) in patients with statin intolerance suggested that it was potentially effective in this group of patients (143). Reddy et al. (143) evaluated the lipid effects of IPE 4 g/day (high-purity prescription omega-3 eicosapentaenoic acid) in 2 patients with coronary artery disease (CAD) with statin intolerance who were self-treating with fish oil dietary supplements (follow-up 3 to 27 months). After initiating IPE, improvements were noted in both patients in TC (−12%; −21%), LDL-C (−3%; −24%), TG (−34%; −16%), non-HDL-C (−12%; −22%), the omega-3 index (+42%; +8%), and eicosapentaenoic acid levels (+275%; +138%). IPE was well tolerated, with no adverse events reported (143).

Taking into account that PUFA mainly works on TG levels with a relatively small effect on LDL-C, they should be mainly considered for statin-intolerant patients with obesity, diabetes (insulin resistance), or metabolic syndrome in whom elevated LDL-C is accompanied by high levels of TGs (atherogenic dyslipidemia). These patients might be at higher risk of statin intolerance, among others, due to liver steatosis, steatohepatitis, and concomitant therapy (9). Finally, we recommend using PUFA from sources of confirmed quality (e.g., pure algal-based long-chain n-3 fatty acids), because of their lack of mercury, dioxins, and other contaminants—requiring distillation techniques to remove potential toxins—as well as saturated fats, which might be present in some fish oils (**Table 10**).

TABLE 7 Phytosterols

Class	Level	Active Daily Doses	Expected Effects on LDL-C	Safety Issues
IIa	C	Phytosterols 800–2,400 mg	−7% to −10%	Should be avoided in patients with phytosterolemia and those who are heterozygous for variants of *ABCG5* and *ABCG8* and other genes.

LDL-C = low-density lipoprotein cholesterol.

OTHER NUTRACEUTICALS WITHOUT STUDIES IN STATIN-INTOLERANT PATIENTS. There are also some nutraceuticals with a good safety profile, high efficacy on LDL-C as well as on other lipid parameters, and beneficial effects on a vascular level; however, so far, they have not been investigated in patients with SAMS (**Table 3**).

Taking this into account, based on expert opinion, it seems that artichoke (10% to 23% LDL-C reduction), berberine (15% to 20% LDL-C reduction), and spirulina (5% to 15% LDL-C reduction), may be considered in statin-intolerant patients with a Class IIb, Level of Evidence: C.

NUTRACEUTICALS IN COMBINATION. In 252 selected clinical report forms, Cicero et al. (123) evaluated the tolerability and efficacy of RYR (3 mg of standardized in monacolin K) plus berberine (500 mg), and berberine alone (500 mg), phytosterols (900 mg) plus psyllium (3.5 g) to improve hypercholesterolemia control in patients who had statin-related myalgia, previous failed treatment with at least 2 low-dose statins (LDS), and well-tolerated treatment with ezetimibe. The treatment with standard lipid-lowering diet plus ezetimibe alone was associated with a mean LDL-C reduction of 17 ± 2%. The additive LDL-C-lowering effects with the various tested treatments were −19 ± 4% with RYR + berberine, −17 ± 4% with berberine twice daily, and −10 ± 3% with phytosterols + psyllium twice daily, without significant differences between the

investigated subgroups ($p > 0.05$). Overall, all tested protocols were very well tolerated (123).

In a single-blind, single-center, randomized, prospective, and parallel group trial, the authors compared the efficacy and tolerability of a combination (Armolipid Plus, Meda Health Sales Ireland, Dunboyne, Ireland) of RYR (200 mg, corresponding to 3 mg of monacolin K), policosanol (10 mg), berberine (500 mg), folic acid (0.2 mg), coenzyme Q10 (2 mg), and astaxanthin (0.5 mg) with ezetimibe for 3 months in 100 statin-intolerant patients (ezetimibe n = 50, nutraceutical n = 50) with percutaneous coronary intervention (PCI) who did not achieve their therapeutic target for 12 months (144). After 3 months, compared with 0 patients in the ezetimibe group, 14 patients (28%) in the nutraceutical group achieved their therapeutic target. After 3 months, patients continued the assigned therapy only if the therapeutic goal (LDL-C <100 mg/dl [2.6 mmol/l]) was reached. In case of LDL-C >100 mg/dl (2.6 mmol/l), conversely, the other therapy was added to the assigned one (i.e., nutraceuticals for patients on ezetimibe and vice versa), and the combination of the 2 therapies was continued until the end of the study. At 1-year follow-up, 58 patients (72.5%) of the combined therapy group (n = 86) and 14 (100%) of the nutraceutical group reached the therapeutic goal (144). In both groups, LDL-C (95 ± 3 mg/dl [2.46 ± 0.08 mmol/l] vs. 95 ± 10 mg/dl [2.46 ± 0.26 mmol/l]), TC (163 ± 7 mg/dl [4.22 ± 0.18 mmol/l] vs. 164 ± 13 mg/dl [4.24 ± 0.34 mmol/l]), and TG (140 ± 21 mg/dl [1.58 ± 0.24 mmol/l] vs. 140 ± 21 mg/dl [1.58 ± 0.24 mmol/l]) values progressively and significantly decreased from baseline throughout treatment ($p < 0.001$ for all), whereas HDL-C (40 ± 7 mg/dl [1.03 ± 0.18 mmol/l] vs. 41 ± 8 mg/dl [1.06 ± 0.21 mmol/l]) values progressively and significantly increased in both groups ($p < 0.001$) (144).

In the ADHERENCE (Low-dose Statins and Nutraceuticals in High-intensity Statin-intolerant Patients) trial, efficacy and tolerability of LDS was compared with LDS therapy and a combination of nutraceuticals—Armolipid Plus—in a group of patients with CAD who had undergone PCI in the preceding 12 months (n = 100), were high-dose statin intolerant, and did not achieve ≥50% reduction in LDL-C with LDS treatment (145). After 3 months, patients in the LDS + Armolipid Plus (n = 50) group had a substantial reduction in LDL-C (−26.8%; $p < 0.0001$) and TC (−17.5; $p < 0.0001$), and 70% of patients in this group reached the treatment target (LDL-C <70 mg/dl), whereas patients in the LDS group did not (145). In case of intolerance to statins, Armolipid Plus offers an effective alternative that is devoid of the safety risks associated with synthetic pharmacological therapy (145,146). Armolipid Plus induces reductions in TC (11% to 21%; $p = 0.001$) and LDL-C (15% to 31%; $p = 0.001$) levels, which is equivalent to changes associated with LDS. In patients, with mild to moderate hyperlipidemia who are intolerant to statins and who do not achieve their therapeutic target with ezetimibe, Armolipid Plus can promote a further at least 10% reduction in TC and LDL-C. Moreover, Armolipid Plus offers the additional benefit of improving vascular stiffness, which is an independent predictor of CV events (146).

In a recent study, Pisciotta et al. (147) evaluated 228 subjects with primary hypercholesterolemia who had a history of statin intolerance or refusing statin treatment and who underwent lipid-lowering therapy with a nutraceutical pill (containing berberine 500 mg, policosanol 10 mg, and RYR 200 mg) and ezetimibe (as alternative treatments) in monotherapy or in combination (147). In hypercholesterolemic subjects, the nutraceutical pill compared with ezetimibe resulted in more effective reduction of LDL-C (−31.7 vs. −25.4%; $p < 0.001$) and was better tolerated; LDL-C levels below 3.36 mmol/l (≤130 mg/dl) were observed in 28.9% of subjects treated with the nutraceutical pill and 11.8% of those treated with ezetimibe ($p < 0.007$) (147). Combined treatment with these drugs was as effective as statins in moderate doses (LDL-C −37%, TC −23%) (147).

In another study, Di Pierro et al. (148) administered Berberis aristata (588 mg, containing berberine 500 mg) and Silybum marianum (105 mg) extracts (Berberol, PharmExtracta, Pontenure, Italy) twice daily to 45 patients diagnosed with type 2 diabetes with hypercholesterolemia and statin intolerance (some of them had reduced the statin dose "until the disappearance of symptoms"; others had opted for

TABLE 8 Bergamot (Citrus Bergamia)

Class	Level	Active Daily Doses	Expected Effects on LDL-C	Safety Issues
IIb	B	500–1,500 mg	−15% to −25%	No safety concerns

LDL-C = low-density lipoprotein cholesterol.

TABLE 9 Soy Products

Class	Level	Active Daily Doses	Expected Effects on LDL-C	Safety Issues
IIb	B	25–100 g	−6% to −10%	Possible interfering with thyroid function and fertility; ↓ absorption of calcium, magnesium, copper, iron, and zinc

LDL-C = low-density lipoprotein cholesterol.

TABLE 10 Polyunsaturated Omega-3 Fatty Acids

Class	Level	Active Daily Doses	Expected Effects on LDL-C	Safety Issues
IIa	B	1-4 g	−3% to −7%	Fish oil supplementation might be proarrhythmic especially in patients at the risk of arrhythmias.

LDL-C = low-density lipoprotein cholesterol.

treatment with ezetimibe; and others were not undergoing any treatment). The intake of berberine/silymarin with statins led to an improvement of lipid parameters (LDL-C −15% and −28%, respectively, after 6 and 12 months; $p < 0.01$) and also when added to ezetimibe (LDL-C −20% and −33%, respectively, after 6 and 12 months; $p < 0.01$). In the control group, in which only berberine/silymarin was administered, there was also a significant reduction of LDL-C (−17% [$p < 0.01$] and −26% [$p < 0.05$], respectively, after 6 and 12 months) (148).

Taking into account the recent evidence, it seems that the only recommendation that can be made is for the combination of nutraceuticals with Armolipid Plus. However, there is an expectation to have more data on other combinations, as it seems that polypills might be a much more effective option for patients with statin intolerance than nutraceuticals in monotherapy (**Table 11**).

WHICH NUTRACEUTICALS CAN BE USEFUL IN STATIN INTOLERANCE, AND FOR WHICH PATIENTS?

Statin therapy can reduce plasma cholesterol (3,5) and high-sensitivity C-reactive protein levels, and this is directly associated with a significant improvement in CV risk (1,2,6,149,150). Hence, it is believed that attenuation of inflammation by cholesterol lowering may have a positive influence on vascular injury (151) and CV prognosis (152).

There is an increasing interest in the efficacy of nutraceuticals for dyslipidemia management (15,19,60-69,153-156) in patients with statin intolerance, and they might or should be considered, especially in case of lack of any other possibilities to achieve the LDL-C goal of the therapy. It is, however, important to emphasize once again that nutraceuticals can complement lipid-lowering therapy with statin and nonstatin agents, but they cannot replace them.

TABLE 11 Nutraceuticals in Combination: Armolipid Plus

Class	Level	Active Daily Doses	Expected Effects on LDL-C	Safety Issues
I	A	RYR 200 mg (equivalent to Monacolin K 3 mg), Policosanol 10 mg, berberine 500 mg folic acid (0.2 mg), astaxanthin (0.5 mg), and coenzyme Q10 (2 mg)	−15% to −30%	No safety concerns

LDL-C = low-density lipoprotein cholesterol.

With this background, nutraceuticals can be very useful in case of statin intolerance if they improve the control of low-grade systemic inflammation (157) and lipid abnormalities (LDL-C reduction usually <10% to 20%). In fact, LDL-C reductions with lifestyle improvements are most often in the range of 5% to 15%, an amount that, if maintained over a long period, may result in meaningful CVD risk reduction (158-160). There are nutraceuticals or combinations of nutraceuticals that go beyond this target of LDL-C reduction (RYR 15% to 25% [19,126,128]; plant sterols and stanols 8% to 12% [19,161]; soluble fiber 5% to 15% [19,41-43,65,162-164]; bergamot 15% to 25% [19]; berberine 15% to 20% [19]; artichoke 5% to 15% [19,29,36]; RYR and policosanols 15% to 21% [19,91]; RYR, policosanols, and berberine 20% to 25%; RYR and plant sterols 25% to 30% [96,97]; RYR and artichoke 14% to 21% [19,100]; RYR, policosanol, and silymarin 14% to 23% [19,95,98]; RYR and antioxidants 20% to 26% [19]; RYR, policosanol, and silymarin 14% to 23% [19]; and berberine combined with bioactive lipid-lowering agents other than RYR 16% to 24% [19]), and in addition, lipid-lowering effects exert essential atheroprotective properties (23,165-167). Based on the different mechanisms of action (inhibition of cholesterol synthesis primarily through action on the enzyme HMG-CoA reductase [policosanol, polyphenols, garlic, and above all, RYR], increase in LDL receptor activity [berberine], and reduction of intestinal cholesterol absorption [garlic, plant sterols, and probiotics]), some nutraceuticals are then able to enhance (126,127,135-137,145-147) or potentially replace the action of statins (63-66,50-52,58,168,169). For example, the current ESC/EAS lipid guidelines state that the use of purified RYR products can be considered in people with hypercholesterolemia who are not qualified for statin treatment after considering the overall CV risk (7). Berberine, curcumin, polydatin, PUFA-enriched fish oil, docosahexaenoic acid-enriched canola oil, and marine n-3 PUFAs have been identified to lower PCSK9 levels, an important regulator of lipid metabolism and an efficient target for plasma LDL-C reduction (170). Curcumin has analgesic, antioxidant (171), and anti-inflammatory properties possibly relevant to the treatment of SAMS by preventing and reducing muscular fatigue, blocking the inflammatory pathway of the nuclear factor, attenuating muscular atrophy, and improving

TABLE 12 Which Nutraceuticals Can be Useful in Statin Intolerance, and for Which Patients

Recommendations	Class	Level	(Ref. #)
In high-risk or very-high-risk patients with complete statin intolerance who have not reached LDL-C targets with nonstatin therapy, nutraceuticals in monotherapy and combination should be considered.	IIa	B	(123,144,148)
In high-risk or very-high-risk patients with partial statin intolerance who have not reached LDL-C targets with tolerable statin therapy and/or nonstatin therapy, nutraceuticals in monotherapy and combination should be considered.	IIa	B	(123,143,145,148)
In individuals with statin intolerance and high cholesterol levels (and other risk factors) with intermediate CV risk who have not reached LDL-C targets, nutraceuticals in monotherapy and combination should be considered.	IIa	A	(80,123,126,134–136,146,147)

Abbreviations as in Table 3.

regeneration of muscle fibers after injuries (172). Since curcumin also has lipid-modifying properties, it may serve as additive to therapy in SAMS patients, enabling effective LDL-C reduction with decreased statin dose (173). Curcumin may also modulate the production of HDL and biomarkers of HDL functionality, including apolipoprotein AI (↑), cholesteryl ester transfer protein (↓), lecithin cholesterol acyl transferase (↑), paraoxonase-1 (↓), myeloperoxidase (↓), and lipoprotein-associated phospholipase A2 (↓) (174–177). However, well-designed studies in patients with SAMS are still necessary to confirm the efficacy of curcumin (174–177).

Besides the nutraceuticals with LDL-lowering properties, it is worth mentioning those, such as β-hydroxy β-methylbutyric acid, β-alanine, and carnosine, that are known to improve muscle mass, muscle function, hypertrophy, lean body mass, aerobic performance and exercise capacity, and muscle protein synthesis, as well as to decrease muscle damage and muscle protein breakdown and fatigue (178,179). All of these effects, along with the respective mechanistic bases (e.g., effect on muscle fibers and mitochondrial biogenesis), might be relevant for SAMS patients, especially in the combination with nutraceuticals with potent LDL-lowering action (178,179).

An important issue is that nutraceuticals administered in statin-intolerant patients should not have any adverse effects. It has been shown that the safety profile of RYR is similar to that of LDS or even less (175). The incidence of developing muscular symptoms was lower in RYR groups (0% to 23.8%) compared with control groups (0% to 36%). There were no cases of rhabdomyolysis or myopathy with creatine kinase levels >10 times the upper limit of normal (80). The EAS consensus paper on SAMS recommends an approach with a plant sterol diet, soy proteins, viscous fibers, and nuts alone or in combination with a statin in patients with SAMS (21). The current ESC/EAS lipid guidelines state that, based on the reduction of LDL-C and the absence of adverse events, the use of plant sterols/stanols can be considered: 1) in subjects with high cholesterol levels with low to intermediate CV risk who do not qualify for pharmacological treatment; 2) in combination with pharmacotherapy in high-risk or very-high-risk patients who have been statin-intolerant or who have not reached LDL-C targets with statin therapy; and 3) in adults and children (age >6 years) with familial hypercholesterolemia (7).

In patients with statin intolerance, nutraceuticals in monotherapy and in combination therapy with other nutraceuticals or nonstatin therapy might be considered in: 1) high-risk or very-high-risk patients with complete statin intolerance (who cannot tolerate any dose of statins) and who have not reached LDL-C targets with nonstatin therapy; 2) high-risk or very-high-risk patients with partial statin intolerance (who can tolerate a dose of statin that is less than required based on the CV risk) and who have not reached LDL-C targets with tolerable statin therapy and/or nonstatin therapy; and 3) individuals with high cholesterol levels (and other risk factors) with intermediate CV risk with statin intolerance and who have not reached LDL-C targets (**Table 12**).

CONCLUSIONS

Statin discontinuation due to exaggerated toxicity-related concerns is a significant problem worldwide and appears to be growing. Statin discontinuation as a consequence of statin intolerance is associated with a significantly increased risk of CV morbidity and mortality (13). Nutraceuticals can be natural alternatives and support to pharmacological therapies in statin-intolerant patients, because they might significantly reduce LDL-C; exert other non-lipid-lowering properties, including reduction of other parameters of lipid profile, glucose, blood pressure,

inflammation, and oxidative stress; and improve FMD and PWV. Equally important, despite still insufficient data, is that therapy with nutraceuticals seems to be very safe and well tolerated. However, further studies in individuals who are intolerant to statins (with a suitable number of patients and longer follow-up), are still necessary to confirm the effectiveness and safety of nutraceuticals, to prove that they maintain their efficacy in the long-term (years) with a specific dosage, as well as to answer the question of whether this therapy might have a positive effect on CV outcomes.

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APPENDIX For the detailed search strategy used for the preparation of this Position Paper, please see the online version of this paper.