Documento Internazionale sulla gestione nutraceutica della statino-intolleranza

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STATE-OF-THE-ART REVIEW

The Role of Nutraceuticals in Statin Intolerant Patients

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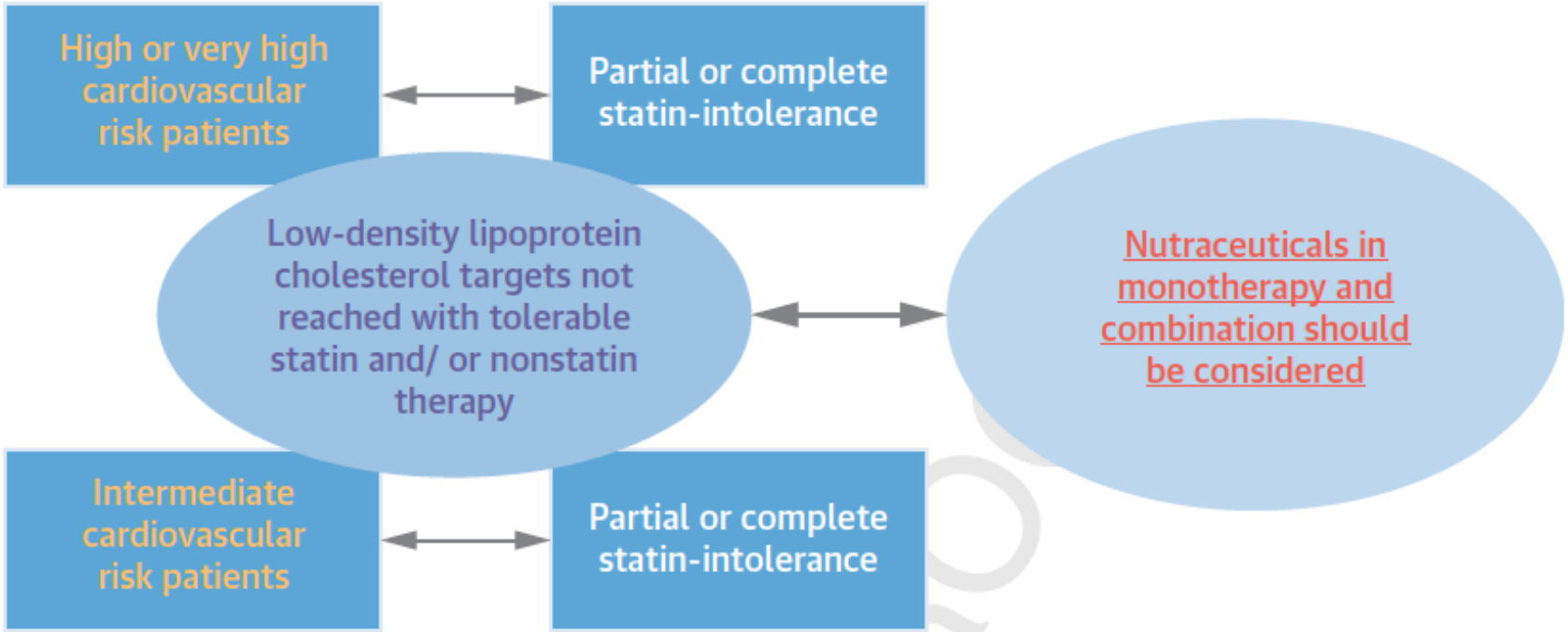
PROOF

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;■:■–■) © 2018 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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



Banach, M. et al. J Am Coll Cardiol. 2018;■(■):■-■.

Main recommendations of the International Lipid Expert Panel (ILEP) on the administration of nutraceuticals in statin-associated muscle symptom 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	Duration	LDL-C Levels	Effects on Other CV Parameters	Reference	Safety
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 60 hypercholesterolemic patients 702 dyslipidemic patients (9)	1.800 mg/day 2.700 mg/day 500-2,700 mg/day	6 weeks 2 months 3-12 weeks	−22.9% ($p = 0.0001$) −11.5% ($p = 0.039$) −14.9 mg/dl (−0.39 mmol/l) ($p = 0.011$)	↓ TC 18.5% ($p < 0.001$) ↓ AST ↓ ALT ↓ TC ($p = 0.002$) ↓ TG ($p = 0.015$) ↓ TC −17.6 mg/dl (−0.46 mmol/l) ($p < 0.001$) ↓ TG −9.2 mg/dl (−0.11 mmol/l) ($p < 0.001$)	(29) (30) (31)	Good tolerability and safety in the short-medium term; hepatoprotective effect. Studies on vascular outcomes such as arterial stiffness and endothelial function are needed.
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 229 hyperlipidemia patients (6)	300 mg/die	1 month 56-120 days	−24% ($p < 0.001$) −25.1 mg/dl (−0.65 mmol/l) ($p < 0.00001$)	↓ IL-6, MCP-1 ($p = 0.05$) ↓ hsCRP, MMPs, ICAM-1, VCAM-1 ($p = 0.01$) ↓ 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) ($p = 0.03$)	(35) (36)	Side effects are mild to moderate, mostly gastrointestinal. Not adverse effects on liver and kidney function. Direct vascular effects not demonstrated.
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/die	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.
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) 1,117 mild and moderate hypercholesterolemia patients (21) 26 mild to moderate hypercholesterolemia patients 531 patients with on at least 1 of components of the metabolic syndrome (14)	5 ≥ dose ≤5 g/die 3.0-20.4 g/day 3.4 g/day 100-200 g/day	8 ≥ time ≤8 weeks 14-182 days 8 weeks 3-16 weeks	−8.1 mg/dl (−0.21 mmol/l) ($p < 0.00001$) −10.7 mg/dl (0.278 mmol/l) ($p = 0.04$) −20.2% −15.99 mg/dl (−0.41 mmol/l) ($p = 0.0286$)	↓ TC −10.1 mg/dl (−0.26 mmol/l) ($p < 0.00001$) ↓ TC −14.5 mg/dl (−0.38 mmol/l) ↓ LDL-C/HDL-C ratio 14.8% beneficial effect on TC, TG, body weight, and FBG	(41) (42) (43) (44)	Well tolerated therapy in long-term follow-up. No adverse effects were reported. Reduction of CV risk.
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) 970 hypertensive and hyperlipidemic patients (20)	5-6 g/day	2 months 2 weeks	−9 mg/dl (−0.23 mmol/l) −10% ($p < 0.001$)	↓ TC and TG; ↓ BP ($p < 0.001$); ↓ Platelet aggregation	(47) (48) (49)	Direct vascular effects not demonstrated. Side effects are usually minimal (mostly gastrointestinal) and the extracts are well tolerated.
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) 40 patients with CKD 1,164 diabetic subjects with CHD	170-1,200 mg/day 5 g/day ≥20 g/day	3-24 weeks 1 month 1 year	−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) ($p < 0.001$) ↑ FMD ($p = 0.002$) ↓ PWV	(53) (54) (55)	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.
Lupin	IIa	A	Down-regulation 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 72 hypercholesterolemic patients 60 moderately hypercholesterolemic patients	25 g/day 25 g/day 25 g/day	4 weeks 28 days 4 weeks	−12.0% ($p < 0.008$) −4% ($p = 0.044$) −12% ($p = 0.02$)	↓ LDL-C/HDL-C ratio ($p = 0.003$) ↑ HDL ($p < 0.036$) ↓ TC −4% ↓ TG −9% ↓ TC −9% ($p = 0.02$) ↓ hsCRP ($p = 0.02$) ↓ SBP ($p = 0.01$)	(60) (61) (62)	A good safety profile, causing no severe side effects, and those that occurred were mostly gastrointestinal. Direct vascular effects demonstrated.
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 263 patients (8) 2,084 hypercholesterolemic subjects (41) 60 hypercholesterolemic patients 150 mildly hypercholesterolemic patients	2.31 mg/day 1.0-3.0 g/day 1.6 g/day 1.6 g/day 2.0 g/day	8 weeks 4-6 weeks 28 days 6 weeks 1 month	−13.7% ($p < 0.01$) −12 mg/dl (−0.31 mmol/l) ($p < 0.000$) −12.8 mg/dl (− 0.33 mmol/l) ($p < 0.05$) −18.8 mg/dl (−0.49 mmol/l) ($p = 0.01$) −16% ($p < 0.002$)	↓ TC −10.6% ($p < 0.001$) UNK ↓ TC −12.8 mg/dl (− 0.33 mmol/l) ($p < 0.001$) ↓ plasma isoprostanes ($p = 0.018$) ↓ TC −14% ($p < 0.002$) ↓ hsCRP (−17%) and aCVD risk (26%–30%)	(67) (68) (65) (69) (70)	High safety profile in the middle-term; however, data for treatment longer than two years are still not available. Direct vascular effects not demonstrated.

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.

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.

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.

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.

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

Recommendations	Class	Level	Reference
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.

Grazie !