JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 72, NO. 1, 2018
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PUBLISHED BY ELSEVIER

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)
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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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ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.04.040

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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