

Management of Statin Intolerance in 2018: Still More Questions Than Answers

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Abstract Statin therapy is generally well tolerated and very effective in the prevention and treatment of cardiovascular disease, regardless of cholesterol levels; however, it can be associated with various adverse events (myalgia, myopathy, rhabdomyolysis, and diabetes mellitus, among others). Patients frequently discontinue statin therapy without medical advice because of perceived side effects and consequently increase their risk for cardiovascular events. In patients with statin intolerance, it may be advisable to change the dose, switch to a different statin, or try an alternate-day regimen. If intolerance is associated with all statins—even at the lowest dose—non-statin drugs and certain nutraceuticals can be considered. This review focuses on the definition of statin intolerance and on the development of clinical and therapeutic strategies for its management, including emerging alternative therapies.

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Key Points

Statins are the gold standard for managing dyslipidemia in patients with elevated cardiovascular risk. Discontinuation of statin therapy is associated with an increase in cardiovascular events.

An important issue in the management of patients with statin intolerance/statin-associated muscle symptoms is the need to avoid statin discontinuation. Options include step-by-step reduction of the statin dose (dechallenge), switching to a different statin, or using intermittent dosages (alternate-day therapy).

New non-statin agents, as well as alternative therapy with nutraceuticals with or without a non-statin drug, may help to improve therapy adherence and reduce the risk for patients with true statin intolerance. Further studies in patients intolerant to statins are necessary to confirm the effectiveness and safety of nutraceuticals. In addition, these agents will have to be tested in long-term randomized controlled trials to more definitively assess their efficacy for reducing cardiovascular risk.

1 Introduction

Statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) effectively reduce the burden of atherogenic lipoprotein in serum [1]. Statins are a mainstay globally in cardiovascular (CV) pharmacotherapy [2], not

only in patients with dyslipidemia [3] but also in patients with coronary artery disease (CAD), acute coronary syndromes (ACS), diabetes mellitus (DM), stroke, hypertension, and chronic kidney disease (CKD) (with or without coexistent dyslipidemia) [4]. The decrease in CV mortality incidence worldwide has been attributed to the lowering of cholesterol to prevent CAD and total CV disease (CVD) [5]. A 21% decrease in CVD mortality and morbidity (stroke and fatal coronary events) can be achieved by lowering low-density lipoprotein cholesterol (LDL-C) by 1.0 mmol/l (38.7 mg/dl) [6]. The beneficial role of statins in primary and secondary prevention [7–9] is among the most intensively studied issues in modern medicine. The Cholesterol Treatment Trialists (CTT) collaboration demonstrated a 12% reduction in all-cause mortality per mmol/l reduction in LDL-C and corresponding significant reductions in myocardial infarction (MI) or coronary death (23%), the need for coronary revascularization (24%), and in fatal or non-fatal stroke (17%) after 5 years of statin therapy [10].

Statin are generally safe and well tolerated, but not all patients are able to use a statin. Statin intolerance is most frequently attributed to muscle-related adverse events [11–14]. Statin discontinuation rates remain high, even among patients with coronary heart disease (CHD) (over 50% after 1 year) [15, 16]. Unfortunately, statin non-adherence correlates highly with risk for acute CV events, increasing the risk for recurrent MI and CHD [17, 18]. This narrative review discusses the definition, diagnosis, and management of statin intolerance as well as novel treatment approaches that might be considered.

2 Methods

2.1 Search Strategy

We searched electronic databases (MEDLINE [1990–30 April 2017], Embase, and SCOPUS [1993–30 April 2017], DARE [1993–30 April 2017]) and Web of Science Core Collection (up to 30 April 2017), and abstracts from national and international meetings. Where necessary, the relevant authors were contacted to obtain further data. The main search terms were <statins intolerance> OR <statin-associated side effects> OR <statin-related side effects> OR <statin-induced side effects> OR <statin-associated/related symptoms> OR <statin associated muscle symptoms> OR SAMS OR <statin-associated/related myalgia> OR <statin associated/related myopathy> AND <new-onset diabetes> OR NOD AND <management> OR <alternative therapy> OR <alternate-day therapy> OR <nutraceuticals> OR <non-statin drugs> AND <cardiovascular disease> OR CVD OR <CV event> OR

<CV risk>. We used the wild-card term “*” to increase the sensitivity of the search strategy.

The main inclusion criterion was data from studies, trials, and meta-analyses on the association between statin intolerance and CVD and on statin intolerance and use of alternative therapies. Two authors (AMP and RVG) examined every article separately, also investigating reviews, case studies, and experimental studies. Any doubt or issues were resolved by discussion with a third party (MB).

2.2 Epidemiology and Definition of Statin Intolerance

Although statins are the mainstay of lipid-lowering treatment, as many as 20% of individuals with a clinical indication for statin therapy are unable to take a daily statin because of some degree of intolerance [19], and 40–75% of patients discontinue their statin therapy within 1–2 years after initiation [18].

The definition of statin intolerance (Table 1) is a question of great interest and debate [20]. Intolerance (partial or complete) should be defined as an inability to tolerate a suitable dose of a statin required for a given patient’s CV risk (e.g., intolerance of atorvastatin 40–80 mg or rosuvastatin 20–40 mg by a patient with ACS). Intolerance can become clinically apparent with a variety of clinical adverse effects that significantly impair organ function and/or quality of life after intake of any statin at any dose (complete intolerance) with or without associated laboratory abnormality (increase in creatine kinase [CK]), or can manifest with temporal associations between symptoms and the onset of therapy or increased dose (partial intolerance) (usually within 3–6 months). Discontinuation or dose reduction of the drug (statin dechallenge) or replacement with another statin can result in remission of symptoms and confirms a diagnosis of statin intolerance [20]. According to Mancini et al. [21], about 70–80% of statin-treated patients are tolerant to treatment, and 20–30% are suspected to be statin intolerant. These authors also note that a certain diagnosis of statin intolerance is found in about 5–6% of patients [21]. According to an evaluation by Banach and colleagues [14, 18], a step-by-step approach (very careful physical examination of the patient, assessing patient history and risk for drug interactions, and exclusion of all possible risk factors and conditions that might increase the risk of statin intolerance, including the so-called “nocebo effect”—psychologically conditioned symptoms as a result of expectations due to achieved knowledge of drug-related side effects) yields a diagnosis of complete statin intolerance in only 2–3% of patients.

Table 1 Definitions of statin intolerance

Society	Definition of statin intolerance	Year	References
National Lipid Association (NLA)	“Inability to tolerate at least two statins: one statin at the lowest starting daily dose and another statin at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal laboratory determinations, which are temporally related to statin treatment and reversible upon statin discontinuation”	2014	[22]
International Lipid Expert Panel (ILEP)	“Inability to tolerate at least two statins: one statin at the lowest starting daily dose and another statin at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal laboratory determinations, which are temporally related to statin treatment and reversible upon statin discontinuation. The resolution of symptoms or changes in biomarkers or even significant improvement with dose reduction or withdrawal of treatment; symptoms or changes in biomarkers are not attributable to predispositions (drug–drug interactions and recognized conditions), increasing the risk of statin intolerance”	2014	[23]
European Atherosclerosis Society (EAS)	“The assessment of statin-associated muscle symptoms (SAMS) includes the nature of muscle symptoms, increased creatine kinase levels and their temporal association with initiation of therapy with statin, and statin therapy suspension and rechallenge”	2015	[24]
Canadian Consensus Working Group	“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/rechallenge, where appropriate, using at least two statins, including atorvastatin and rosuvastatin, and that leads to failure of maintenance of therapeutic goals, as defined by national guidelines”	2016	[25]

The definition of statin intolerance has evolved over the years. In late 2014, the National Lipid Association (NLA) defined this syndrome as an inability to tolerate at least two statins—one statin at the lowest starting daily dose and another statin at any daily dose—due to either objectionable symptoms (real or perceived) or abnormal laboratory determinations that are temporally related to statin treatment and reversible upon statin discontinuation [22]. In addition to this, the International Lipid Expert Panel (ILEP) definition included the resolution of symptoms or changes in biomarkers or even significant improvement with dose reduction or withdrawal of treatment; symptoms or changes in biomarkers are not attributable to predispositions (drug–drug interactions and recognized conditions), increasing the risk of statin intolerance [23]. The European Atherosclerosis Society (EAS) consensus paper suggested a more clinically oriented definition and recommended that the assessment of statin-associated muscle symptoms (SAMS) include the nature of muscle symptoms, increased CK levels and their temporal association with initiation of statin therapy, and statin therapy suspension and rechallenge [24]. 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/rechallenge, where appropriate, using at least two statins, including atorvastatin and rosuvastatin, and that leads to failure of maintenance of

therapeutic goals, as defined by national guidelines” [25]. This is the most complete and a very pragmatic definition of complete statin intolerance. The explicit inclusion of references to national guidelines and objectives in a definition of statin intolerance has the intent to ensure that the practical effort is justified for patients, colleagues, regulatory authorities, and taxpayers [25, 26].

2.3 Symptoms and Biomarkers of Statin Intolerance

2.3.1 Symptoms of Statin Intolerance

The patient’s subjective assessment of the perceived risks and disadvantages compared with the benefits of therapy is important for an effective approach to statin intolerance. Most cases of statin intolerance are related to patient complaints; suspension of therapy due to laboratory abnormalities is much less common. Statin intolerance is not simply the occurrence of symptoms in general, but rather the symptoms that are perceived as unacceptable [27]. Identifying true cases of statin intolerance is, therefore, of great practical importance in order to avoid unnecessary suspension of statin therapy by patients who would otherwise benefit from them [27]. However, assessing the probability that negative symptoms are causally related to statins is often difficult. Symptoms (more than 75%) are more likely to be attributable to statins if they appear within the first 3 months of statin therapy and if they improve after suspension and reoccur after reintroduction [28, 36]. Statins have specific adverse effects

(myalgias 3–5%; myopathy 0.1–0.2%; new-onset diabetes [NOD] 9–27%, and hepatotoxicity, usually <1%) [27] demonstrable or not from abnormal blood markers, including muscle (e.g., CK) or liver function studies (hepatic transaminases—mainly alanine aminotransferase [ALT]) [27]. For the latter, it is worth emphasizing that in fact there is no confirmed link between statin therapy and liver damage, and most of the current guidelines and consensus papers recommend measuring transaminases only before statin therapy initiation and during treatment if symptoms develop [14].

The main adverse reactions due to statins include myalgia, myotoxicity, and NOD [28, 29]. The risk of developing NOD depends on the presence of prediabetes (insulin resistance, carbohydrate metabolism disorders), the number of metabolic syndrome components (overweight, elevated blood pressure, high triglycerides, low high-density lipoprotein cholesterol [HDL-C], and hyperglycemia), and the duration and intensity of statin therapy. As the number of metabolic syndrome components increases, so does the risk for NOD in statin-treated patients [30]. In general, one must treat approximately 1000 patients annually to see one new case of NOD on low-dose statin therapy, or 500 patients per year to see one new case on moderate- to high-dose statin therapy [31]. However, taking into account the available data, it is clear that the benefits associated with statin therapy outweigh the risk of NOD (for patients at high and very high CV risk, the number needed to treat [NNT] vs. the number needed to harm [NNH] is >3–5 times higher) [32–35].

In the JUPITER primary prevention trial, the CV and mortality benefits of statin therapy exceeded the diabetes hazard, including among those at higher risk for developing diabetes. During a follow-up period of up to 5 years, a total of 86 vascular events or deaths were avoided, with no NOD diagnosed in patients with no major diabetes risk factors (CV events –39%, $p = 0.0001$; no increase of diabetes, $p = 0.99$), and 93 vascular events or deaths were avoided for every 54 NOD cases diagnosed in patients with one or more factors for diabetes development (CV events –39%, $p = 0.0001$; increase in diabetes 28%, $p = 0.01$). Moreover, statin therapy was associated with a time to NOD of only 5.4 weeks compared with placebo [36]. To reduce the risk of NOD while receiving statin therapy, patients should be advised to exercise, reduce caloric intake, lose weight, and stop smoking, all interventions that should be undertaken in any case.

Statin therapy should be continued in patients with NOD. In such cases, patient management includes a hypoglycemic diet, loss of excessive body weight, and prescription of antidiabetic drugs, if appropriate [34]. The approach to lipid lowering in overweight or obese primary prevention patients is to introduce statins after careful

estimation of CV risk and treatment of adverse event risks when nonpharmacological therapy is not effective [35].

SAMS, including myalgia—ranging from mild to severe in intensity—muscle stiffness and tenderness, cramps, and loss of muscle strength [23, 37], are by far the most common adverse effects and one of the most important reasons for discontinuing statin therapy. The prevalence of SAMS is around 3–5% in randomized controlled trials including patients with dyslipidemia [38] and up to 20% in observational studies [39, 40], although the EAS consensus paper reported a SAMS prevalence as high as 29% [24]. PRIMO (Prediction of Muscular Risk in Observational conditions), a survey conducted in general medicine clinics in France, showed that 10.5% of patients receiving statins reported muscle symptoms, though the prevalence varied with individual statins (fluvastatin had the lowest rate of SAMS, whereas simvastatin had the highest) [41]. The USAGE (Understanding Statin Use in America and Gaps in Education) study investigated current and former statin users via an internet-based survey and showed that SAMS occurred in 60% of current and 25% of former users and that SAMS were the primary reason for treatment discontinuation [42]. Finally, data from the STOMP (Effect of Statins on Skeletal Muscle Function and Performance) study, a randomized, double-blind, placebo-controlled trial, indicated that myalgia occurred in 9.4% of patients receiving atorvastatin but also in 4.6% of subjects receiving placebo, for an overall incidence of statin-attributable SAMS of ~5% [43].

The NLA Task Force on Statin Safety (updated in 2014) [44] classified the clinical presentation of SAMS as four distinct entities: (1) myalgia, (2) myopathy, (3) myositis, and (4) myonecrosis (including rhabdomyolysis). Myalgia is defined as muscle pain or flu-like symptoms (heaviness, tenderness, stiffness, aches or cramps) with normal CK levels [44]. It is very important to know which muscle aches are typically associated with SAMS. Based on the proposal by the NLA, the SAMS Clinical Index (SAMS-CI) score, recently updated by Rosenson et al. [45], provides the greatest score (3 points) for the typical large muscle symmetric (e.g., bilateral) aches, 2 points for bilateral aches of the smaller distal or proximal musculature, and 1 point for asymmetric, non-uniform symptoms [44]. In the STOMP study [43], subjects who reported myalgia while taking statins reported predominantly leg symptoms (hip flexor, quadriceps, hamstring, and/or calf aches; quadriceps or calf cramps; and/or quadriceps, hamstring, and/or calf fatigue), whereas those receiving placebo reported more diverse symptoms such as whole-body fatigue and groin pain [43, 44]. The SAMS-CI score might be a very useful tool with which to confirm statin-related myalgia and to exclude the nocebo effect.

Myopathy with muscle weakness (not attributed to pain) can occur with normal or elevated CK [29]. Factors predisposing to the development of myopathy include age >75 years, female sex, renal and hepatic dysfunction, hypothyroidism, alcohol abuse, excessive physical exertion, genetic susceptibility, perioperative period, and concurrent use of drugs inhibiting the metabolism of statins, such as clarithromycin, erythromycin, azole antifungals, diltiazem, verapamil, amiodarone, fibrates (particularly gemfibrozil), cyclosporin, clopidogrel, sulfonamides, and red yeast rice [23, 34, 37]. It has been also observed that low levels of vitamin D and coenzyme Q10 (CoQ10) might increase the risk of statin intolerance; however, available data do not yet enable recommendations on their supplementation to prevent SAMS [46, 47]. Myopathy is a general term encompassing all forms of muscle disease, including toxic disorders as well as acquired and heritable metabolic disorders. The term does not necessarily connote symptoms or any degree of CK elevation. Muscle biopsy also suggests some myopathic statin-induced abnormalities that may be present in the context of normal CK levels [43].

Myositis with muscle inflammation is associated with other symptoms (e.g., tenderness to palpation), CK elevation, and leukocyte infiltration into muscle tissue. Myonecrosis is always associated with muscle injury and elevation of serum CK [29]. The most serious, and fortunately very rare, form of myonecrosis is rhabdomyolysis (1.6 per 100,000 patient-years), in which muscle breakdown is responsible for a massive release of CK and myoglobin, with resulting myoglobinuria and acute renal failure [29]. However, rhabdomyolysis currently occurs principally in cases of genetic predisposition as well as drug–drug interactions [48]. According to the EAS consensus paper on SAMS, it is important to remember the cut-off point value of 4, above which muscle symptoms seem to be more attributable to statin therapy [24].

2.3.2 Biomarkers of Statin Intolerance

New biomarkers for statin-induced myopathy are emerging. Unfortunately, most cannot be commonly used because of complexities in methodology and costs, and their sensitivity and specificity still need to be defined [11]. The most widely used serum marker is the serum CK level [49], but its exclusive use as a diagnostic marker is inadequate and non-specific because high serum levels are not always associated with myopathy [50]. CK levels can be elevated by exercise in a dose-independent manner [29] and by drug interactions, genetic variants, CoQ10 deficiency, and vitamin D deficiency [51].

Routine liver function analyses are no longer recommended in the management of statin therapy because the

diagnostic yield is low and not cost effective [11]. Statin-associated liver abnormalities (aminotransferase levels) are rare, mild, dose-related, and not related to reduction in LDL-C. Thus, drug- and dose-specific effects are more important determinants of liver and muscle toxicity than magnitude of LDL-C lowering [52, 53]. They are also usually temporary, and it is possible to return to baseline levels after 2–4 weeks [52, 53]. Persistent elevation of ALT more than three times the upper limit of normal (ULN) were observed in $\leq 1\%$ of patients treated with statins. These are dose related, with rates of $<0.5\%$ for moderate-dose rosuvastatin and at all doses, and slightly higher rates (about 1%) with atorvastatin or simvastatin 80 mg [52]. ALT elevations often improve even when statin therapy is continued. The incidence of liver failure is the same among statin-treated patients as in the general population not treated with statins [54]. Finally, it is worth remembering that the use of statins prevents about 33% of major CVD events when compared with placebo, and statins may cause serious liver disease in 1/1,000,000 (NNH is 1 million). Between 10 and 30% of patients do not receive statins because of fear of hepatotoxicity [14, 23].

Other early markers also might predict and diagnose statin intolerance [11]. One such biomarker being considered, at least in in vitro experiments, is lactate dehydrogenase, but its clinical utility in cases of statin-induced myopathy has not been validated [56]. A study that treated rats with drugs that are highly toxic to myocytes (carbamate acetylcholinesterase inhibitor; isoproterenol, a synthetic catecholamine), but not with statins, identified fatty acid binding protein 3 (FABP3) and myosin light chain 1 (MLC1) as biomarkers of skeletal muscle toxicity based on the specific tissue distribution of these proteins [55, 56]. Burch et al. [57] evaluated skeletal muscle troponin I (sTnI), myosin light chain 3 (MYL3 [S3]), CK isoform M (CKM), and FABP3 compared with CK in the monitoring of drug-induced skeletal muscle injury. sTnI, MYL3, CKM, and FABP3 all outperformed CK and/or added value for the diagnosis of drug-induced novel skeletal muscle injury (i.e., myocyte degeneration/necrosis) [57]. In addition, when used in conjunction with CK, sTnI, MYL3, CKM, and FABP3 individually and collectively improved diagnostic sensitivity and specificity, as well as diagnostic certainty, for novel skeletal muscle injury and responded in a sensitive manner to low levels of novel skeletal muscle injury degeneration/necrosis in rats. CKM showed the strongest correlation ($r = 0.47$, $p < 0.0001$), followed by FABP3 ($r = 0.52$, $p < 0.0001$), MYL3 ($r = 0.48$, $p < 0.0001$), sTnI ($r = 0.47$, $p < 0.0001$), aspartate transaminase (AST; $r = 0.46$, $p < 0.0001$), and CK ($r = 0.32$, $p < 0.0001$) [57]. These findings support the suggestion that sTnI, MYL3, CKM, and FABP3 are suitable for voluntary use, in conjunction with CK, in

regulatory safety studies in rats to monitor drug-induced skeletal muscle injury and for the potential translational use of these exploratory biomarkers in early clinical trials to ensure patient safety [57]. Dobkin [58] suggested the functional evaluation of hip-flexor and abductor performance (because it occurred independently of CK levels). Wu et al. [59] proposed the evaluation of the kinetics of recovery exercise phosphocreatine by means of phosphorus magnetic resonance spectroscopy (^{31}P -MRS). In this study, patients were treated for 4 weeks with statin therapy and were shown to have a prolonged metabolic recovery time in the calf despite no change in serum CK levels [59]. Unfortunately, several drawbacks are associated with these muscle-specific markers: rapid clearance, dependence of renal dysfunction, heterogeneous response depending on the type of myotoxicants in general, and the difficulty and high costs of measurements [11, 60].

Laaksonen et al. [61] proposed lipidomic evaluation of plasma muscle gene profiles, which helped to identify several sensitive biomarkers of metabolic alterations induced in skeletal muscle by high-dose statin regimens (increased expression of arachidonic acid 5-lipoxygenase activating protein, phospholipase C, numerous species of phosphatidylethanolamine, selective pools of long-chain triglycerides, and phosphocholine ether). However, such complex genomic and combined lipidomic analyses are very difficult to perform and, above all, to interpret routinely in clinical practice. Two microRNAs (miRNAs; 133a/b and 499-5p) were evaluated as potential biomarkers of tissue damage because of their long half-lives in serum. The serum levels of miR-133a/b were reported as sensitive and specific markers of cardiac and skeletal muscle toxicity [62]; miR-499-5p might serve as a biomarker for statin-enhanced muscle injury during exercise because it was increased in the plasma of runners after a marathon and increased when muscle contraction was combined with exposure to statins [63]. Further studies are still necessary to confirm the specificity and sensitivity of innovative biomarkers in statin-treated patients.

2.3.3 Statin Intolerance Management

Probably the most important issue in the management of patients with statin intolerance/SAMS is the need to continue statin therapy. It is especially critical for patients with high and very high CV risk, as therapy discontinuation for 4–6 weeks might cause atheroma plaque instability [64] and increases the risk of CV events [17]. A further aspect to consider is inflammation. Sposito et al. [65] assessed the existence of a rebound inflammatory effect after statin withdrawal in the acute phase of MI. At baseline, statin users presented with a lower C-reactive protein (CRP) than patients not receiving a statin before the MI. By the fifth

day post-MI, median CRP was significantly higher in the group from whom statins had been withdrawn.

Complete statin intolerance, which requires statin discontinuation, affects <5% of patients with statin intolerance symptoms [23, 25]. Numerous approaches to maintaining statin persistence have been published [24, 25, 29, 34]. Therefore, we would especially like to focus on combination therapy for patients not able to tolerate suitable statin doses. Briefly, we can always consider step-by-step reduction of the dose (dechallenge) and intermittent dosages (alternate-day therapy). We know this does not significantly influence the magnitude of LDL-C reduction for rosuvastatin and atorvastatin [66]. The lipophilicity and hydrophilicity of statins seems to be important, and changing from a hydrophilic to a lipophilic statin may be of some benefit in the SAMS setting [23, 24]. We have also observed that both statin groups had the same effects concerning efficacy and safety in patients with ACS [67]. Hydrophilic statins (rosuvastatin and pravastatin) seem to cause fewer statin intolerance symptoms, and this is especially important for elderly patients [23] (Table 2).

2.4 Alternative Drug Treatment

The use of lipid-lowering therapy in clinical practice has become progressively more challenging because exaggerated patient concerns over side effects and potential toxicity can lead to poor adherence to statin therapy or discontinuation [15, 22] despite the highly established benefits of LDL-C reduction [68, 69]. The use of ezetimibe monotherapy is still limited (due to US FDA recommendations in the USA as well as restricted reimbursement in Europe, leading to use in <5–10% of the patients who require it according to guideline recommendations) [13], and use of the monoclonal antibodies directed against proprotein convertase subtilisin kexin type 9 (PCSK9) tends to be severely restricted by managed care formularies. Statin monotherapy or statin combination therapy with other currently available drugs do not all have the same capacity to induce appropriate reductions in LDL-C in patients at high CV risk [70]. Therefore, there is a clinical need for new therapies, alone or in combination with current drugs (Table 2), to lower LDL-C.

Bempedoic acid (ETC-1002) has a unique mechanism of action (adenosine triphosphate-citrate lyase inhibition) [71, 72]. The efficacy of combination therapy with statins and bempedoic acid has been evaluated in a randomized controlled trial (NCT02072161) [73]. A total of 134 patients who had been treated with one of a series of statin regimens (atorvastatin 10 or 20 mg; simvastatin 5, 10, or 20 mg; rosuvastatin 5 or 10 mg; or pravastatin 10, 20, or 40 mg) for at least 3 months before the trial began were randomized to bempedoic acid 120 or 180 mg or placebo

Table 2 Therapeutic possibilities for the treatment of statin-intolerant patients and their influence on low-density lipoprotein cholesterol levels

Agent	Subjects	Dose	Duration	LDL-C levels	References
BA with low-dose statins	134 hypercholesterolemic pts	120 mg/day	12 weeks	$-17.3 \pm 4.0\%$ ($p < 0.01$)	[73]
		180 mg/day		$-24.3 \pm 4.2\%$ ($p < 0.001$)	
		PL		$-4.2 \pm 4.2\%$	
BA	56 hypercholesterolemic pts	240 mg/day vs. PL	8 weeks (increase by 60 mg q2w)	-28.7% ($p < 0.001$)	[74]
BA with or without EZE	177 hypercholesterolemic pts	120 mg/day	12 weeks	-27.5 ± 1.3 mg/dl ($p = 0.0008$)	[75]
		180 mg/day		-30.1 ± 1.3 mg/dl ($p < 0.0001$)	
		EZE 10 mg/day		-21.2 ± 1.3 mg/dl ($p < 0.0001$)	
		120 mg + EZE 10 mg/day		-43.1 ± 2.6 mg/dl ($p < 0.0001$)	
		180 mg + EZE 10 mg/day		-47.7 ± 2.8 mg/dl ($p < 0.0001$)	
BA	12,600 statin-intolerant pts expected	180 mg/day	6 years	Ongoing	[76]
ATO	60 hypercholesterolemic pts	10 mg/day	6 weeks	100 ± 25 mg/dl ($p = 0.3$)	[129]
		20 mg/alternate day		68 ± 28 mg/dl ($p < 1.0$)	
		20 mg/day		96 ± 41 mg/dl ($p < 1.0$)	
ROS	45 hypercholesterolemic pts	20 mg/alternate day	6 weeks	-40.9% ($p < 0.0001$)	[130]
		10 mg/day		-78.5% ($p < 0.0001$)	
ATO	61 hypercholesterolemic pts	20 mg/alternate day	3 months	-95 ± 31 mg/dl ($p < 0.05$)	[131]
		20 mg/day		-94 ± 28 mg/dl ($p < 0.05$)	
ROS	37 dyslipidemic pts	10 mg/alternate day	6 weeks	-57 ± 1.2 mg/dl ($p < 0.01$)	[132]
		10 mg/day		-60 ± 1.0 mg/dl ($p < 0.01$)	
PRA	104 dyslipidemic pts	Half-dose alternate days vs. daily	4 months	113 ± 21 mg/dl ($p < 0.04$) 104 ± 24 mg/dl ($p < 0.04$)	[133]
ATO	54 hypercholesterolemic pts	10 mg/day	6 weeks	No statistically significant differences between the three groups regarding total or a percentage	[134]
		10 mg/alternate day			
		20 mg/alternate day			
ATO	40 hypercholesterolemic pts	20 mg/alternate day	12 weeks	No statistically significant differences between the two groups	[135]
		20 mg/day			
ATO	60 pts with CAD	10 mg/alternate day	6 weeks	105 ± 26 mg/dl ($p < 0.008$)	[136]
		10 mg/day		88 ± 21 mg/dl ($p < 0.008$)	

Table 2 continued

Agent	Subjects	Dose	Duration	LDL-C levels	References
FLU	23 hypercholesterolemic pts	40 mg/alternate day	6 weeks	144 ± 21 mg/dl (<i>p</i> < 0.05)	[137]
		20 mg/day		138 ± 19 mg/dl (<i>p</i> < 0.05)	
ROS	80 pts with primary hypercholesterolemia	10 mg/alternate day	8 weeks	105.07 ± 26.30 mg/dl (<i>p</i> < 0.001)	[138]
		10 mg/day		94.10 ± 40.16 mg/dl (<i>p</i> < 0.001)	
ATO	100 dyslipidemic pts	10 mg/alternate day	3 months	73.6 ± 14.71 mg/dl (<i>p</i> < 0.0001)	[139]
		10 mg/day		93.79 ± 17.48 mg/dl (<i>p</i> < 0.0001)	
ATO	141 pts with dyslipidemia or CAD	Alternate day vs. daily	12 weeks	Alternate-day dosing of ATO was inferior to daily dosing in maintaining the NCEP-ATP III goal	[140]
EZE	432 pts with primary hypercholesterolemia	5 mg/day	12 weeks	- 15.7% (<i>p</i> < 0.01)	[141]
		10 mg/day		- 18.5% (<i>p</i> < 0.01)	
EZE + statins	769 pts with primary hypercholesterolemia	Statin + EZE 10 mg/day	8 weeks	- 25.1% (<i>p</i> < 0.001)	[142]
		Statin + PL		- 3.7% (<i>p</i> < 0.001)	
EZE + SIM	720 pts with FH	SIM + EZE 10 mg/day	24 months	141.3 ± 52.6 mg/dl (<i>p</i> < 0.01)	[143]
EZE + SIM	1128 pts with hypercholesterolemia and metabolic syndrome	EZE/SIM 10/20 mg/day	6 weeks	- 49.6% (<i>p</i> < 0.001)	[144]
		EZE/SIM 10/40 mg/day		- 53.9% (<i>p</i> < 0.001)	
EZE + ROS	239 pts with high risk of CHD	EZE/ROS 10/40 mg/day	6 weeks	- 70% (<i>p</i> < 0.001)	[145]
		ROS 40 mg		- 56% (<i>p</i> < 0.001)	
PCSK9 inhibitor EVO with moderate- and high- intensity statins	1117 primary hypercholesterolemia and mixed dyslipidemia pts	140 mg vs. PL	10 weeks	66–75% (<i>p</i> < 0.001)	[83]
		420 mg vs. PL	12 weeks	63–65% (<i>p</i> < 0.001)	
PCSK9 inhibitor EVO with statin or EZE	1359 dyslipidemic pts	70 mg q2w + statin or EZE	12 weeks	- 40.20% (<i>p</i> < 0.001)	[86]
		105 mg q2w + statin or EZE		- 52.86% (<i>p</i> < 0.001)	
		140 mg q2w + statin or EZE		- 59.26% (<i>p</i> < 0.001)	
		280 mg q4w + statin or EZE		- 42.55% (<i>p</i> < 0.001)	
		350 mg q4w + statin or EZE		- 47.00% (<i>p</i> < 0.001)	
		420 mg q4w or EZE		- 52.66% (<i>p</i> < 0.001)	
PCSK9 inhibitor EVO with statin	511 pts with uncontrolled LDL-C and history of intolerance to two or more statins	420 mg/month	24 weeks	- 102.9 mg/dl (<i>p</i> < 0.001)	[88]
PCSK9 inhibitor ALI with EZE	361 pts at moderate to high CV risk with statin intolerance	ALI 75 mg q2w	24 weeks	- 102.9 mg/dl (<i>p</i> < 0.001)	[96]
		EZE 10 mg		- 31.2 mg/dl (<i>p</i> < 0.001)	
Inclisiran with statin	501 pts at high CVD risk with elevated LDL-C	Single dose of 200–500 mg/day or double dose of 100–300 mg/day	180 days	27.9–41.9% after a single dose 35.5–52.6% after two doses (for both <i>p</i> < 0.001)	[98]

Table 2 continued

Agent	Subjects	Dose	Duration	LDL-C levels	References
Red yeast rice DS	83 pts in dietary treatment	2.4 g/day red yeast rice	12 weeks	From 4.47 ± 0.70 to 3.49 ± 0.70 ($p < 0.05$)	[99]
Plant extracts (red yeast rice, sugar cane-derived policosanols, and artichoke leaf extracts)	39 pts with moderate hypercholesterolemia	Red yeast rice 166.67 mg (0.4% monacolin K), sugar cane extract 3.70 mg (90% policosanols–octacosanol 60%), artichoke leaf dry extract 200 mg (5–6% chlorogenic acid) daily	16 weeks	– 14.1% ($p < 0.001$)	[102]
Natural nutraceuticals (red yeast, policosanols, and berberine)	933 dyslipidemic pts	1 tablet/day associated with diet	16 weeks	– 23.5% ($p < 0.001$)	[103]
Nutraceutical combination (red yeast rice extract, berberine, policosanols, astaxanthin, CoQ10, folic acid)	30 pts with moderate CV risk	Berberine 500 mg, policosanols 10 mg, folic acid 0.2 mg, CoQ10 2.0 mg, astaxanthin 0.5 mg daily	8 weeks	– 21.1% ($p < 0.001$)	[104]
Acid ethyl ester (AMR101)	702 statin-treated pts	4 or 2 g/day	12 weeks	– 6.2% ($p = 0.0067$)	[112]
Chokeberry flavonoid extract	44 pts after MI	85 mg tid of chokeberry flavonoid extract (<i>Aronia melanocarpa</i> E.)	6 weeks	Ox-LDL levels – 29% ($p < 0.000$)	[114]
Spirulina	312 pts	1–10 g/day	2–12 months	– 41.32 mg/dl ($p < 0.001$)	[116]
BER vs. EZE	228 pts with primary hypercholesterolemia	Berberine 500 mg, policosanols 10 mg, red yeast rice 200 mg EZE 10 mg/day	6 months	– 31.7% ($p < 0.001$) – 25.4% ($p < 0.001$)	[146]

AEs adverse events, *ALI* alirocumab, *ATO* atorvastatin, *BA* bempedoic acid, *BER* berberine, *CAD* coronary artery disease, *CHD* coronary heart disease, *CoQ10* coenzyme Q10, *CV* cardiovascular, *CVD* cardiovascular disease, *DS* dietary supplement, *EVO* evolocumab, *EZE* ezetimibe, *FH* familial hypercholesterolemia, *FLU* fluvastatin, *LDL-C* low-density lipoprotein cholesterol, *MI* myocardial infarction, *NCEP-ATP III* National Cholesterol Education Program Adult Treatment Panel III, *ND* not defined, *Ox-LDL* oxidized low-density lipoprotein, *PCSK9* proprotein convertase subtilisin/kexin type 9, *PL* placebo, *PRA* pravastatin, *pts* patients, *qxw* every *x* weeks, *ROS* rosuvastatin, *SIM* simvastatin, *tid* three times daily

[73]. LDL-C was reduced significantly with bempedoic acid 120 or 180 mg daily, respectively, compared with placebo: $-17.3 \pm 4.0\%$ ($p < 0.01$) and $-24.3 \pm 4.2\%$ ($p < 0.001$) [73]. Thompson et al. [74] conducted a multicenter, double-blind, 8-week trial in a group of patients intolerant to at least one statin and reported that ETC-1002 was effective at reducing LDL-C (by almost 29%) and was well tolerated in patients with SAMS. A recent phase IIb trial in which patients with and without statin intolerance received daily treatment with ETC-1002 120 or 180 mg alone or with ezetimibe confirmed these results. These treatments reduced LDL-C more than did ezetimibe alone and had a similar tolerability profile [75]. It is worth mentioning that a new phase III trial (NCT02993406) investigating whether treatment with bempedoic acid versus placebo decreases the risk of CV events in 12,600 statin-intolerant patients has commenced [76] (Table 2).

PCSK9 monoclonal antibodies constitute a breakthrough for statin-intolerant patients or those in whom LDL-C is

not adequately managed with statins [77–79]. Evolocumab and alirocumab have recently received marketing authorization in the EU and the USA [79]. The approved indications for evolocumab are (1) adults with primary hypercholesterolemia (heterozygous familial hypercholesterolemia [HeFH] and non-familial), unable to achieve LDL-C goals with the maximum tolerated dose of a statin or alone or in combination with other lipid-lowering therapies in patients who are intolerant to statins, or for whom a statin is contraindicated; (2) adults and adolescents aged ≥ 12 years with homozygous familial hypercholesterolemia (HoFH) in combination with other lipid-lowering therapies [80]. Alirocumab is approved for adults with primary hypercholesterolemia (HeFH and non-familial) or mixed dyslipidemia, in patients unable to achieve their LDL-C goals with maximum tolerated dose of a statin or, alone or in combination with other lipid-lowering therapies, in patients who are intolerant to statins or for whom a statin is contraindicated [81].

Evolocumab and alirocumab have been studied in numerous phase II and phase III clinical trials involving high-risk patients, including those with statin intolerance and those with familial hypercholesterolemia (FH) [82–88]. Evolocumab reduces LDL-C by approximately 60–65%, influences all other lipid profile parameters, and has favorable effects on lipoprotein(a) [89–92]. Evolocumab is also very well tolerated as monotherapy, added to statins, or added to statins plus ezetimibe [82], without major adverse effects such as myalgia, CK elevations, NOD [93], or neurocognitive disorders [94]. In a pooled analysis of four phase III studies, the effectiveness and safety of evolocumab was comparable in patients with or without type 2 DM (T2DM) and did not differ between T2DM subgroups [82]. Toth et al. [87] reported a comprehensive safety assessment of evolocumab in 6026 patients in 12 phase II and III parent trials with a median exposure of 2.8 months, and in 4465 of those patients who continued with a median follow-up of 11.1 months in two open-label extension (OLE) trials, demonstrating a favorable benefit–risk profile for evolocumab. Overall adverse event (AE) rates were similar between evolocumab and control groups in the parent trials (51.1 vs. 49.6%) and in year 1 of the OLE trials (70.0 vs. 66.0%), as were those for serious AEs (SAEs). Elevations of serum transaminases, bilirubin, and CK were infrequent and similar between groups [87]. Muscle-related AEs were similar between evolocumab and control groups. Neurocognitive AEs were infrequent and balanced during the double-blind parent studies (five events [0.1%] in the evolocumab groups vs. six events [0.3%] in the control groups). No neutralizing anti-evolocumab antibodies were detected [87]. The GAUSS-3 (Goal Achievement after using an anti-PCSK9 antibody Intolerant statins subject-3) trial was a statin intolerance study that included 511 adult patients with a history of intolerance to two or more statins [88]. Patients were treated with non-statin therapies (evolocumab vs. ezetimibe). After 2 years, LDL-C levels were significantly more reduced (by 36.1%) in the evolocumab group than in the ezetimibe group ($p < 0.001$). Muscle symptoms were reported in 28.8% of ezetimibe-treated patients and 20.7% of evolocumab-treated patients ($p = 0.17$) [88]. The recently published FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial provided strong evidence on CV endpoints and additional long-term safety (mean 26 months) in 27,564 patients with established CVD (MI, ischemic stroke, or symptomatic peripheral artery disease). Patients were randomized to receive either subcutaneous evolocumab 140 mg every 2 weeks, subcutaneous evolocumab 420 mg every month, or matching placebo injections [95]. All patients were receiving background statin therapy (almost 70% receiving high-intensity statin

therapy). The addition of evolocumab to statin therapy (with or without ezetimibe) significantly reduced the primary endpoint (composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) and key secondary endpoints (composite of CV death, MI, or stroke) of the trial by 15% (hazard ratio [HR] 0.85; 95% confidence interval [CI] 0.79–0.92; $p < 0.001$) and 20% (HR 0.80; 95% CI 0.73–0.88; $p < 0.001$), respectively [95].

The available evidence for alirocumab suggests that this treatment is also (similarly) effective in reducing LDL-C and is well tolerated. The results of the ODYSSEY ALTERNATIVE trial in patients with statin intolerance demonstrated good tolerability and efficacy [96]. The ODYSSEY phase III program includes more than 23,000 patients and 14 studies with alirocumab alone or in combination with other lipid-lowering agents, and as monotherapy in patients with primary HeFH, non-FH, or statin intolerance [97]. The ODYSSEY OUTCOMES study is not yet completed (it will likely be presented at the American College of Cardiology meeting in March 2018) and is assessing the CV benefit of alirocumab in 18,600 patients (at higher risk than in the FOURIER trial), over approximately 5 years of follow-up (the mean follow-up will be at least 3 years). A subgroup analysis of 2341 patients with and without T2DM in ODYSSEY LONG-TERM showed that alirocumab effects were also consistent, regardless of the clinical history of patients with T2DM at baseline [97] (Table 2).

Another approach to PCSK9 inhibition is in development. The ORION-1 (Trial to Evaluate the Effect of ALN-PCSSC Treatment on LDL-C) trial found that inclisiran, a chemically synthesized small interfering RNA designed to target PCSK9 messenger RNA, lowered PCSK9 and LDL-C levels among patients at high CV risk who had elevated LDL-C levels [98]. In this trial, over the course of 180 days, 501 patients received a single dose of inclisiran 200, 300, or 500 mg or two doses (at days 1 and 90) of inclisiran 100, 200, or 300 mg [98]. At day 180, inclisiran significantly reduced ($p < 0.001$ vs. placebo) LDL-C levels from 27.9 to 41.9% after a single dose and 35.5 to 52.6% after two doses. Two doses of inclisiran 300 mg produced the greatest reduction in LDL cholesterol levels at day 180 (48% of patients had LDL-C < 50 mg/dl [< 1.3 mmol/l]) [98]. At day 240, PCSK9 and LDL-C levels remained significantly lower than at baseline with all inclisiran regimens. Inclisiran may emerge as an important therapeutic option for statin-intolerant patients, as lipid-lowering occurs with few serious AEs or symptoms of immune system activation [98] (Table 2). An advantage of this drug is that it can be administered every 6 months.

This class of new drugs will be used in the long term, generally for the rest of the treated patients' lives. Despite

claims that millions of patients with dyslipidemia could benefit from these PCSK9 inhibitors, these treatments will actually meet the health needs of a small population of patients (at very high CV risk who benefit the most) because of the high costs in all countries in which they are marketed.

2.5 Alternative Nutraceutical Therapy

It is known that lipid-lowering therapy might not be enough to completely attenuate the risk of CVD, residual risk still exists, and that alternative therapy with nutraceuticals may help improve therapy adherence and reduce the risk of patients with statin intolerance [37]. Natural products can be used in combination with a non-statin (as well as with small doses of synthetic or natural statins) in subjects with statin intolerance.

Monacolins such as policosanols and bergamot inhibit HMG-CoA reductase, and red yeast rice extract (*Monascus purpureus*) contains a variety of monacolins [99]. A 2005 study in 111 Caucasian individuals demonstrated that a brand dietary supplement comprising *M. purpureus* titrated extract and octacosanols, which contain a low dose of niacin, resulted in LDL-C lowering by 20% ($p < 0.001$) and a reduction of triglyceride plasma level by 16% ($p < 0.01$) in patients with moderate hypercholesterolemia with no clinically relevant changes in muscle and liver toxicity markers [100]. LDL-C lowering was similar to that obtained with pravastatin [100]. Red yeast rice used in combination with plant sterols mimicked the effect of statins and ezetimibe by significantly lowering LDL-C by 33% and total cholesterol by 19% in only 6 weeks of nutraceutical therapy [101]. Red yeast rice extract contains nine varieties of bioactive constituents (monacolins) with the same formulation as lovastatin. Furthermore, co-administration of leaf extracts and red yeast rice significantly reduced LDL-C (21.4%; $p < 0.001$) and total cholesterol (14.1%; $p < 0.001$) after 16 weeks [102]. The combination of berberine with red yeast rice significantly improved different lipid parameters (i.e., lowered total cholesterol, LDL-C, and triglyceride levels [$p < 0.001$ for all] and increased HDL-C concentration [$p < 0.001$]) after 16 weeks of treatment [103]. Comparable results were observed in another clinical trial [104]. This study showed results similar to those with pravastatin in subjects with moderate dyslipidemia and metabolic syndrome: the same combination induced an increase of 4.8% in HDL-C and a lowering of 21.1% in total cholesterol and 21.1% in LDL-C [104]. In the setting of statin intolerance, Armolipid Plus[®], a formulation that contains natural substances (red yeast rice, policosanols, and berberine combined with folic acid, astaxanthin, and coQ10) with putative complementary lipid-lowering properties, offers an effective alternative

devoid of the safety risks associated with synthetic pharmacological therapy because it has a combination of low doses of its active ingredients—low enough not to be associated with untoward effects but high enough to exert therapeutic effects in combination with other complementary substances [105]. Armolipid Plus[®] can reduce total cholesterol (11–21%) and LDL-C (15–31%) levels, which is equivalent to changes associated with low-dose statins. In patients with mild to moderate hyperlipidemia intolerant to statins who do not achieve LDL-C targets with ezetimibe, Armolipid Plus[®] can promote a further 10% reduction in total cholesterol and LDL-C. Moreover, Armolipid Plus[®] offers additional benefits in terms of improvements in vascular stiffness, which is an independent predictor of CV events [105].

The mechanism of action of policosanols, a mix of eight long-chain aliphatic alcohols derived from the fermentation of sugar cane, rice, wheatgerm, or sunflower seeds is not yet clear [106]. Data on the lipid-lowering effects of policosanols are contradictory. The down-regulation of cell HMG-CoA reductase by this formulation has been proposed [107]. Its lipid-lowering activity might be comparable to that of statins, and it may be even more effective at increasing HDL-C and lowering side effects [108]; however, the data on their actual effectiveness are still contradictory [106, 109–111]. Further research is needed to determine with certainty whether policosanols have beneficial lipid-lowering effects and whether they might have beneficial effects for patients who are intolerant to statins.

The efficacy of icosapent ethyl (IPE; Vascepa[®] [formerly AMR101]; Amarin Pharma Inc., Bedminster, NJ, USA) in improving lipid parameters was demonstrated in a 12-week randomized, placebo-controlled trial (ANCHOR) that enrolled statin-treated patients at high CV risk with well-controlled LDL-C levels and persistently high triglyceride levels (≥ 200 and < 500 mg/dl) [112]. Compared with placebo, IPE 4 and 2 g daily reduced median triglyceride levels from baseline by 21.5% ($p < 0.0001$) and 10.1% ($p = 0.0005$), respectively, without increasing LDL-C levels. The 4-g daily dose decreased LDL-C levels by 6.2% ($p = 0.007$) and significantly reduced other lipid parameters compared with a light liquid paraffin placebo, including apolipoprotein B (9.3%; $p < 0.0001$), very low-density lipoprotein cholesterol (VLDL-C) (24.4%; $p < 0.0001$), lipoprotein-associated phospholipase A2 (19.0%; $p < 0.0001$), and high-sensitivity CRP (hsCRP) (22.0%; $p = 0.0005$) [112]. One study of IPE in statin-intolerant patients suggested it might be potentially effective in this group of patients [113].

In a double-blind study, Naruszewicz et al. [114] used chokeberry extract in 44 patients (11 women and 33 men, mean age 66 years) who survived an MI and received statin therapy for at least 6 months (80% dose of simvastatin

40 mg daily) [114]. Subjects were randomized to receive either chokeberry flavonoid extract (*Aronia melanocarpa* E.) 85 mg three times daily or placebo for 6 weeks. The study extract comprised the following constituents: anthocyanins (about 25%), polymeric procyanidins (about 50%), and phenolic acids (about 9%) [114]. Compared with placebo, flavonoids significantly reduced serum 8-isoprostans ($p < 0.000$) and oxidized LDL levels ($p < 0.000$) (by 38 and 29%, respectively), as well as hsCRP ($p < 0.007$) and monocyte chemoattractant protein-1 (MCP-1) ($p < 0.001$) levels (by 23 and 29%, respectively). In addition, significant increases in adiponectin ($p < 0.03$) levels and reductions in systolic and diastolic blood pressure, by a mean average of 11 and 7.2 mmHg, respectively, were found [114]. The abovementioned results mean this extract is potentially beneficial for statin-intolerant patients, but further studies in these subjects are necessary to definitively confirm its effectiveness and safety profile.

Spirulina is a filamentous, water blue-green microalga (Cyanobacterium) [115]. The hypolipemic properties of spirulina have not been conclusively studied. One meta-analysis [116] of seven randomized controlled trials showed a significant effect from supplementation with spirulina, with reduced plasma concentrations of total cholesterol (-46.76 mg/dl; $p < 0.001$), LDL-C (-41.32 mg/dl; $p < 0.001$), triglycerides (-44.23 mg/dl; $p < 0.001$), and elevated levels of HDL-C (6.06 mg/dl; $p = 0.001$). The impact of spirulina on plasma concentrations of total cholesterol and triglycerides was independent of administered dose (dose range: 1–10 g/day). Spirulina contains high levels of antioxidants (e.g., beta-carotene), phycocyanin, microelements (K, Na, Ca, Mg, Fe, Zn), vitamins (tocopherols), eight necessary amino acids, polyunsaturated fatty acids (PUFAs)—especially γ -linolenic acid—and phenolic compounds [117]; however, the active components responsible for the hypolipidemic effects of spirulina are not fully understood. This meta-analysis was the first to evaluate the effects of spirulina supplementation on serum lipid parameters based on the results from randomized controlled trials, but further well-designed trials are required to clarify the clinical value of spirulina supplementation as an add-on to conventional and novel lipid-lowering therapies in patients with dyslipidemia.

Curcumin, a natural dietary polyphenol responsible for the yellow color of the Indian spice turmeric (*Curcuma longa* L.), has analgesic, antioxidant [118], and anti-inflammatory properties relevant to the treatment of SAMS as it prevents and reduces muscular fatigue, blocks the inflammatory pathway of the nuclear factor, attenuates muscular atrophy, and improves regeneration of muscle fibers after injuries [119]. Since curcumin also has lipid-modifying properties, it may serve as an additive to therapy

in patients with SAMS, enabling effective reduction of LDL-C and possibly a lower statin dose [120]. Curcumin may modulate the production of HDL and biomarkers of HDL functionality by increasing apolipoprotein AI (apoAI) and lecithin cholesterol acyl transferase (LCAT) and decreasing cholesteryl ester transfer protein (CETP), paraoxonase-1 (PON1), myeloperoxidase (MPO), and lipoprotein-associated phospholipase A2 (Lp-PLA2) [121]. Curcumin is safe to consume, even at dosages of up to 8–12 g daily [122]; however, so far, its low bioavailability and efficacy profile in vivo has limited its clinical application [123]. Further clinical trials with curcumin formulations with improved bioavailability are necessary to examine its effects on lipid metabolism and SAMS treatment.

Several nutraceuticals exert lipid-lowering and atheroprotective properties [124–126]. Berberine, curcumin, polydatin, n-3 PUFA-enriched fish oil, docosahexaenoic acid (DHA)-enriched canola oil, marine n-3 PUFAs, and quercetin-3-O-b-D-glucoside have been identified as able to lower PCSK9 levels, an important regulator of lipid metabolism and an efficient target for plasma LDL-C reduction [127]. In particular, the use of some of these agents is supported by data from human trials in patients with at least one condition related to the metabolic syndrome, HeFH, or dyslipidemia. Administration of a pill containing berberine 500 mg for 6 months reduced LDL-C by 10.5% ($p < 0.0001$) in patients with HeFH, an effect the authors suggested was associated with an indirect berberine-mediated inhibitory effect on PCSK9 [127]. Xuezhikang is a cholestin extract that contains a mixture of lovastatin (dominant compound), plant sterols, and isoflavones. Administration of xuezhikang 1200 mg daily for 8 weeks increased plasma PCSK9 levels by 34% ($p = 0.006$) and decreased LDL-C and total cholesterol by 28 and 22% ($p = 0.001$, $p = 0.002$), respectively [127]. Enrichment of canola oil with DHA was shown to lower circulating PCSK9 and triacylglycerol levels by 6%. Furthermore, circulating PCSK9 levels were found to be significantly and positively associated with LDL-C, triacylglycerol, and apolipoprotein B (apoB) levels, whereas no association was found between PCSK9 and HDL-C levels [127]. Consumption of marine n-3 PUFAs 2200 mg daily for 12 weeks decreased circulating PCSK9 levels by 11.4 and 9.8% in premenopausal and postmenopausal women, respectively. In contrast, plasma LDL-C levels showed no significant changes [127].

Therefore, some nutraceuticals such as berberine and curcumin are suggested as useful adjuncts to statin therapy because of their inhibition of PCSK9 independent of sterol-responsive element-binding protein. Nevertheless, evidence from well-designed randomized controlled trials is required to support the added value of such a combination

in reducing CV events compared with statin monotherapy [127] (Table 2).

3 Conclusions

Statins are generally safe and very efficacious agents for reducing the burden of atherogenic lipoproteins in serum and the risk for acute CV events, including MI, stroke, death, and need for revascularization. The most common statin-related side effect associated with therapy non-adherence and discontinuation is myalgia. Statin discontinuation out of exaggerated toxicity-related concerns is a significant problem worldwide and appears to be growing. Negative press reporting about statin therapy is highly correlated with statin discontinuation and significantly increased risk for CV morbidity and mortality [128]. A step-by-step approach, including careful examination of all other possible factors that may increase the risk of statin intolerance, might help patients continue statin therapy when experiencing statin-associated side effects. Complete statin intolerance is relatively rare (<5%), and for these patients as well as for those who can only tolerate low-to-moderate dose statin therapy and require incremental LDL-C reduction, consideration should be given to the use of ion-exchange resin (if available), ezetimibe, and the PCSK9 inhibitors. Ongoing investigation into whether bempedoic acid and inclisiran with or without statin therapy are well tolerated in the longer term is needed. Interest in the efficacy of nutraceuticals for dyslipidemia management in patients with statin intolerance is increasing. Although the LDL-C reduction potential of these compounds is promising, they have not yet been tested in clinical trials powered for clinical endpoints, and they might be considered, especially when other means with which to achieve the LDL-C goal of the therapy are lacking. However, further studies in patients intolerant to statins are necessary to confirm their effectiveness and safety.

Compliance with Ethical Standards

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