Chapter 23
Statin Intolerance: An Overview for Clinicians

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A. J. Jenkins, P. P. Toth (eds.), *Lipoproteins in Diabetes Mellitus*, Contemporary Diabetes, https://doi.org/10.1007/978-3-031-26681-2_23

Introduction

The most common forms of cardiovascular disease (CVD) are ischemic heart disease (IHD), 49.2%, and ischemic stroke, 17.7%, which are classified as atherosclerotic cardiovascular disease (ASCVD). CVD is the leading cause of death globally, and ASCVD is responsible for 70% of all cardiovascular (CV) deaths [1, 2]. The latest statistics of the European Society of Cardiology (ESC) confirm that among both men and women, the main causes of premature death in 2021 were IHD (17% for both sexes) and stroke (12% for women and 8% for men) [3]. In 2019, 17.9 million people died of CVD, which represents 32% of all global deaths [2]. Such a large global burden of ASCVD is related to the high prevalence of well-recognized, mostly modifiable risk factors for these diseases. Increased level of low-density lipoprotein cholesterol (LDL-C) has been ranked as the third most common cardiovascular risk factor in the world [1]. An increase of LDL-C by every 1 mmol/L is associated with a significant increase in the risk of ASCVD by 16% (HR = 1.16; 95% CI: 1.12–1.21), while among people aged 20–49, this increase is higher, i.e., by 47% (HR = 1.47; 95% CI: 1.32–1.64) [4]. A study by Navar-Boggan et al. showed that the incidence of moderate dyslipidemia in young adults who were not treated with statins increased the risk of coronary artery disease (CAD) by 67% (HR = 1.67; 95% CI: 1.06–2.64) over 15 years of follow-up [5]. The atherogenic effect of LDL-C appears to be dependent on both the level of circulating LDL-C and the duration of the exposure (Fig. 23.1) [6].

Considering such a significant influence of the increased level of LDL-C on the risk of ASCVD, recent Polish guidelines (2021) on the diagnosis and therapy of lipid disorders indicated that LDL-C concentration is a key lipid parameter determining the CV risk and defining the goals of lipid-lowering therapy (class: I; level: A) [10]. Lowering low-density lipoprotein cholesterol (LDL-C) by 38.7 mg/dL (1.0 mmol/L) results in 21% decrease in CVD morbidity and mortality [11]. It is recommended that lipid-lowering therapy (LLT) follows the principle of "the lower, the better," but it is also critically important to achieve the therapeutic goal for LDL-C as soon as possible in accordance with the "the earlier, the better" principle and to maintain it for as long as possible ("the longer, the better") [10, 12, 13]. Currently, it is recommended to use intensive lipid-lowering therapy, and for the selected group of patients at high and extremely high CVD risk—up-front combination therapy [10, 14]. This approach brings greater CV benefits, especially in patients with higher baseline LDL-C levels [10] as confirmed by the results of the meta-analysis of 34 RCTs conducted by Navarese et al. These researchers showed that more intensive LDL-C lowering was associated with greater reductions in all-cause mortality and CVD mortality among patients with LDL-C levels ≥100 mg/dL (all-cause mortality: change in RRs per 40 mg/dL increase in baseline LDL-C, 0.91; 95% CI: 0.86–0.96; CVD mortality: change in RRs per 40 mg/dL increase in baseline LDL-C, 0.86; 95% CI: 0.80–0.94) [15]. Similar results were obtained in a

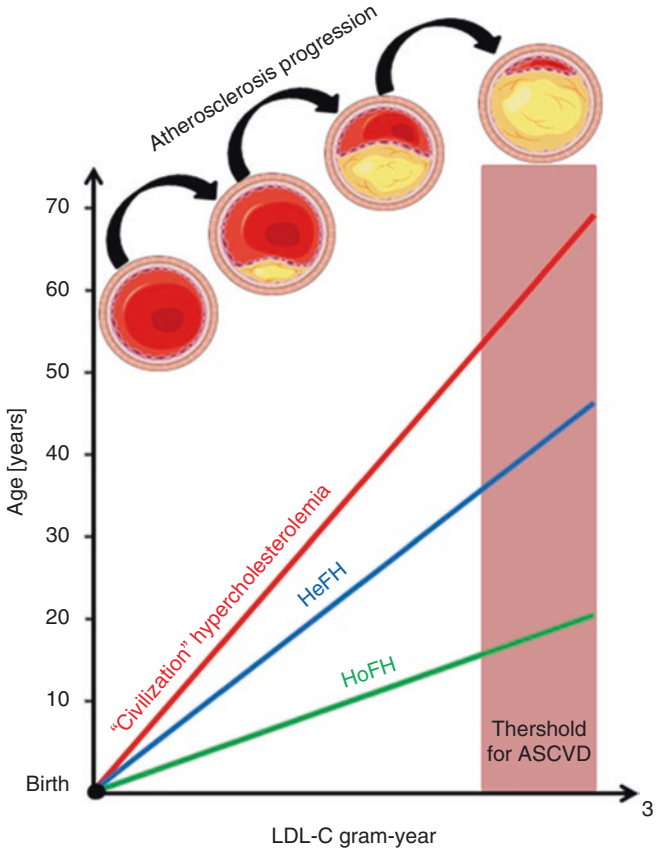


Fig. 23.1 Relationship between LDL-C accumulation over time and risk of ASCVD. *Abbreviations*: *LDL-C* low-density lipoprotein cholesterol, *ASCVD* atherosclerotic cardiovascular disease, *HeFH* heterozygous familial hypercholesterolemia, *HoFH* homozygous familial hypercholesterolemia. (Data taken from Refs. [6–9])

meta-analysis of 46 RCTs by Ma et al., showing that more intensive treatment was associated with a lower risk of all-cause mortality (RR = 0.91; 95% CI: 0.88–0.95), CV mortality (RR = 0.89; 95% CI: 0.86–0.92), MI (RR = 0.79; 95% CI: 0.77–0.81), coronary revascularization (RR = 0.80; 95% CI: 0.76–0.84), and cerebrovascular events (RR = 0.84; 95% CI: 0.80–0.88) compared with the less intensive treatment [16]. Current LDL-C targets are determined by CV risk and may require LDL cholesterol reduction to <1.4 mmol/L (<55 mg/dL) and ≥50% of baseline (primary and secondary prevention in patients of very high CV risk) (class: I, level: C, and class: I, level: A, respectively), and even lower to <1.0 mmol/L in those at extremely high CVD risk [10, 17].

Statins: A Brief Clinical Overview

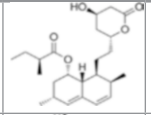
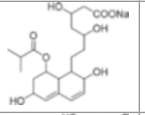
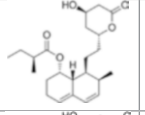
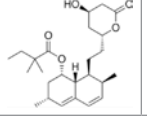
Statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors] (Table 23.1) are the gold standard, first-line agents in the treatment of hypercholesterolemia, and among all lipid-lowering agents, statins have the best documented efficacy in the primary and secondary prevention of CVD in patients with acute coronary syndromes (ACS), dyslipidemia, CAD, hypertension, diabetes mellitus (DM), stroke, and chronic kidney disease (CKD), irrespective of cholesterol levels [10]. As already mentioned, effective treatment should be based on optimal, intensive lipid-lowering therapy. It is recommended that high-intensity statins are prescribed in tolerated doses to achieve the goals set for specific CV risk level (class: I, level: A) [10]. Among the statins, only rosuvastatin at a dose of 20–40 mg and atorvastatin at a dose of 40–80 mg reduce the baseline LDL-C level by 50% [22–24]. As demonstrated by Zhang et al. in a network meta-analysis of 50 RCTs, rosuvastatin had the strongest effect on LDL-C reduction, followed by atorvastatin and pitavastatin [25].

The efficacy of statin use in the primary prevention of CVD has been summarized in a meta-analysis of randomized clinical trials (RCTs) by Yebyo et al., which included 94,283 subjects. Statins have been shown to reduce the risk of nonfatal MI by 38% (RR = 0.62; 95% CI: 0.53–0.72), CVD mortality by 20% (RR = 0.80; 95% CI: 0.71–0.91), all-cause mortality by 11% (RR = 0.89; 95% CI: 0.85–0.93), nonfatal stroke by 17% (RR = 0.83; 95% CI: 0.75–0.92), unstable angina by 25% (RR = 0.75; 95% CI: 0.63–0.91), and composite major CV events by 26% (RR = 0.74; 95% CI: 0.67–0.81) [26]. A meta-analysis of 9 RCTs conducted by Tramacere et al. in patients with stroke or transient ischemic attack (TIA) showed that statin use (with 2.5-year follow-up) reduced the risk of ischemic stroke by 19% (OR = 0.81; 95% CI: 0.70–0.93), ischemic stroke or TIA by 25% (OR = 0.75; 95% CI: 0.64–0.87), and CV events by 25% (OR = 0.75; 95% CI: 0.69–0.83) [27]. Moreover, a meta-analysis of 16 RCTs by Yu et al. showed that intensive statin therapy in patients with ACS reduced the risk of major adverse CV events by 23% (RR = 0.77; 95% CI: 0.68–0.86) [28]. Finally, a meta-analysis of 5 RCTs by de Vries et al. in patients with diabetes and CVD showed that the use of standard-dose statins reduced any major CV or cerebrovascular event by 15% (RR = 0.85; 95% CI: 0.79–0.91). Intensive statin therapy reduced this risk by a further 9% (RR = 0.91; 95% CI: 0.84–0.98) [29].

Importantly, a meta-analysis of 15 RCTs by Koskinas et al. showed that statins reduced the risk of major vascular events by 19% (RR = 0.81; 95% CI: 0.76–0.86) in secondary prevention patients [30]. Summarizing the effectiveness of statins in the primary and secondary prevention of CVD, we should also mention the results of the meta-analysis of 76 RCTs by Mills et al., which showed that treatment with these drugs reduced the risk of all-cause mortality by 10% (RR = 0.90; 95% CI: 0.86–0.94) and CVD mortality by 20% (RR = 0.80; 95% CI: 0.74–0.87) [31].

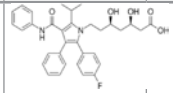
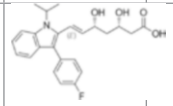
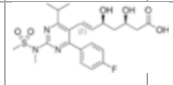
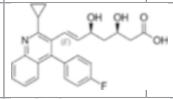
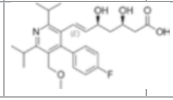
It is critically important to note that statin use is highly effective in both men and women with a similar CV risk. Fulcher et al. in their meta-analysis of 27 RCTs with

Table 23.1 Statins' chemical and pharmacological characteristics

Class of statins		Statin	Chemical structure	Dose range and half-life	Solubility and bioavailability	Metabolism	Clearance	Max. effect on LDL-C (%)
Type 1	Natural	Lovastatin		10–80 mg 2 h	Lipophilic 5%	CYP3A4 OAT1B1 P-gp	Hepatic	80 mg **−41%**
		Pravastatin		20–80 mg 2 h	Hydrophilic 15%	Non-CYP450 OAT1B1 OAT1B3	Hepatic and kidney	80 mg **−41%**
		Mevastatin/compactin (first statin)			Lipophilic	CYP3A4	Hepatic	
	Semisynthetic	Simvastatin		5–40 mg 2 h	Lipophilic 5%	CYP3A4 OAT1B1 P-gp	Hepatic	80 mg **−48%**

(continued)

Table 23.1 (continued)

Class of statins		Statin	Chemical structure	Dose range and half-life	Solubility and bioavailability	Metabolism	Clearance	Max. effect on LDL-C (%)
Type 2	Synthetic	Atorvastatin		10–80 mg 14 h	Lipophilic 15%	CYP3A4 OAT1B1 P-gp	Hepatic	80 mg **−54%**
		Fluvastatin		20–80 mg 3 h	Lipophilic 25%	CYP2C9 OAT1B3	Hepatic	80 mg **−34%**
		Rosuvastatin		5–40 mg 19 h	Hydrophilic 20%	CYP2C9 OAT1B1 OAT1B3	Hepatic and kidney	40 mg **−60%**
		Pitavastatin		1–4 mg 12 h	Lipophilic 50%	CYP2C9 OAT1B1 P-gp	Hepatic	4 mg **−48%**
		Cerivastatin			Lipophilic	Various CYP3A	Hepatic	Withdrawn from the market

Data taken from Refs. [18–21]

Abbreviations: *LDL-C* low-density lipoprotein cholesterol, *CYP* cytochrome P_{450}, *OAT1B1* organic anion transporting polypeptide B1, *OAT1B3* organic anion transporting polypeptide B3, *Pgp* P-glycoprotein

174,000 subjects showed that the proportional reductions per 1.0 mmol/L reduction in LDL-C in major CV events were similar overall for women (RR = 0.84; 99% CI: 0.78–0.91) and men (RR = 0.78; 99% CI: 0.75–0.81). These net benefits translated into reductions in all-cause mortality with statin therapy for both women (RR = 0.91; 99% CI: 0.84–0.99) and men (RR = 0.90; 99% CI: 0.86–0.95) [32].

Thus, statins are very effective drugs in the primary and secondary prevention of CV and are well established in the recommendations for lipid-lowering therapy. Taking into account the demonstrated effectiveness of these drugs, it is not surprising that these drugs are the most commonly used lipid-lowering drugs in the world. In 2018, 172.6 million people worldwide were using lipid-lowering drugs, 145.8 million of whom were taking statins (85.5%). Moreover, the frequency of statin use is increasing every year [33]. In addition to the well-documented lipid-lowering effect of statins (in addition to their many pleiotropic effects), their beneficial properties on the improvement of the prognosis in COVID-19 patients have recently been emphasized [34–37].

Statins: Safety of Use

Taking into account the important role of statins in CVD prevention, an important issue from the clinical point of view is the safety of their use. According to the position paper from an International Lipid Expert Panel (ILEP) (Fig. 23.2), the main potential side effects of statins are statin-associated muscle symptoms (SAMSs), temporary elevation of aminotransferase alanine (ALT), and new-onset diabetes (NOD) [38].

Fig. 23.2 Professor Maciej Banach is the founder and president of the International Lipid Expert Panel (ILEP): www.ilep.eu

The safety of statin therapy in primary prevention was assessed in a meta-analysis of 62 RCTs by Cai et al., which included 120,456 subjects who were followed for an average of 3.9 years. It was shown that statin use was significantly associated with the risk of muscle symptoms (OR = 1.06; 95% CI: 1.01–1.13), liver dysfunction (OR = 1.33; 95% CI: 1.12–1.58), and kidney dysfunction (OR = 1.14; 95% CI: 1.01–1.28). There was no significant association between statin use and risk of developing diabetes and clinically confirmed muscle disorders. Importantly, no dose-response relationship between statins and side effects was found. The authors of the meta-analysis concluded that the risk of adverse events attributable to statins was low and definitely did not outweigh their efficacy in preventing CVD [39]. The abovementioned meta-analysis by Yebyo et al. showed that the use of statins in primary prevention was associated with a borderline significant increase in the risk of myopathy (RR = 1.08; 95% CI: 1.01–1.15), kidney dysfunction (RR = 1.12; 95% CI: 1.00–1.26), and liver dysfunction (RR = 1.16; 95% CI: 1.02–1.31). A network meta-analysis showed that atorvastatin had the best safety profile [26], in contrast to the findings of the PRIMO study, in which hydrophilic statins—pravastatin and rosuvastatin—were found to have the best safety profile [40]. Considering the results of the REAL-CAD study, it may be that pitavastatin has the best safety profile, as the prevalence of SAMS and NOD for this statin was found to be comparable to placebo [41]. Finally, the largest meta-analysis on the prevalence of statin intolerance (SI), with almost 4.2 million patients, clearly showed that there is no difference in the prevalence of statin intolerance between hydrophilic and lipophilic statins [42].

SAMS

The study by Navar et al., covering 7938 patients from 140 primary care, cardiology, and endocrinology practices in the United States, showed that the most frequently reported adverse event in patients using statins was muscle aches/cramps (29%) [43]. On the other hand, as shown by a meta-analysis by Davis and Weller involving 153,000 patients, the use of statins regardless of the dose did not significantly affect the risk of any muscle problems (RR = 1.02; 95% CI: 1.00–1.04) [44]. A meta-analysis of 22 studies by Riaz et al. with a mean follow-up time of 4.1 years (statins = 66024, placebo = 63656) indicated that there was no significant difference in the risk of myopathy between statins and placebo (OR = 1.20; 95% CI: 0.88–1.62) [45]. The safety of statins was also assessed in a meta-analysis of 135 RCTs by Naci et al. involving 246,955 subjects. It was shown that the effect of statins on the risk of myalgia was not significant (OR = 1.07; 95% CI: 0.89–1.29). It was also found that statins did not significantly affect the risk of elevated levels of creatine kinase (CK) (OR = 1.13; 95% CI: 0.85–1.51) [46]. In a study by Herrett et al., involving 200 patients (randomized N-of-1) recruited from 50 general practices in England and Wales, it was shown that muscle symptoms were not significantly different between 2-month periods of treatment with 20 mg of atorvastatin or placebo (MD statin minus placebo: −0.11, 95% CI: −0.36 to 0.14) [47]. Thus, the prevalence of

SAMS among statin users does not appear to be high, as clearly confirmed in the meta-analysis by Bytyci et al. mentioned above [42]. As indicated in the Scientific Statement from the American Heart Association (AHA), the risk of statin-induced serious muscle injury, including rhabdomyolysis, is <0.1%, and the risk of rhabdomyolysis is 1.6 cases per 100,000 patient-years [48].

It seems that some of the SAMSs reported in studies may result from the coexistence of predisposing factors, including comorbidities (see later) [42, 49] or genetic polymorphisms (e.g., solute carrier organic anion transporter, *SLCO1B1*) [50]. Drug interactions with statins (e.g., macrolides, HIV/AIDS drugs, antifungal drugs, warfarin, amiodarone, anticancer drugs) may play an important role in the development of SAMS. The risk of statin toxicity is increased by drug-drug interactions that increase the concentration of statins in the plasma, with up to 50% of statin-mediated adverse events thought to be because of drug-drug interactions [49].

Kidney Dysfunction

It is worth noting that the increased risk of kidney failure reported in some meta-analyses in patients using statins may not be directly related to the action of these drugs. There is no data confirming the causal relationship between statin therapy and acute kidney injury [51]. Rhabdomyolysis is an important risk factor for acute kidney injury. In a study by Yang et al. of 329 patients with rhabdomyolysis, the incidence of acute kidney disease in this group of patients was 61.4% [52]. The incidence of statin-induced rhabdomyolysis was assessed by Safitri et al. in an analysis of 1,129,477 patients. Statin-induced rhabdomyolysis has been shown to occur in 0.009% of patients [53]. As indicated in the Scientific Statement from the AHA, statins do not cause or worsen proteinuria in the long term, do not cause acute kidney injury in individuals without rhabdomyolysis, and do not worsen kidney function [48], and indeed may improve renal functional parameters [54].

The forementioned meta-analysis by Davis and Weller showed that, regardless of the intensity of statin therapy, the risk of developing rhabdomyolysis was not statistically significant (RR = 1.41; 95% CI: 0.80–2.51) [44]. It should be emphasized that the use of statins may have a positive effect on kidney function. A meta-analysis of 33 RCTs by Zhao et al. of 37,391 patients with chronic kidney disease (CKD) showed that statins improved kidney function by significantly reduced urinary albumin (WMD: −2.04; 95% CI: −3.53 to −0.56) and protein (WMD: −0.58; 95% CI: −0.95 to −0.21) excretions and increased creatinine clearance (WMD: 0.86; 95% CI: 0.32–1.41) [55]. This beneficial effect of statins is due, inter alia, to the antioxidant and anti-inflammatory properties of these drugs [56]. Moreover, in a meta-analysis of 9 RCTs by Lv et al., including 3426 patients with diabetic nephropathy, it was shown that after statin treatment, estimated glomerular filtration rate (eGFR) in the experimental group was higher than in the control group (MD = 5.80; 95% CI: 2.21–9.40), and serum creatinine was lower than in the control group (MD = −0.46; 95% CI: −0.69 to −0.24) [57]. These findings may be associated

with significantly improved outcomes, especially in patients who do not require dialysis. Barylski et al. showed that statin therapy in subjects with non-dialysis-dependent CKD resulted in a marked reduction in death from all causes (RR: 0.66; 95% CI: 0.55–0.79; $P < 0.0001$), cardiac causes (0.69; 95% CI: 0.55–0.68), cardiovascular events (0.55; 95% CI: 0.4–0.75), and stroke (RR: 0.66; 95% CI: 0.5–0.88) [58].

Thus, the impact of statin use on the kidney disfunction seems doubtful and is probably due to other comorbid factors. Moreover, the results of clinical studies show that statins may significantly improve kidney function.

Liver Dysfunction

The increased risk of liver dysfunction with statins reported in some studies is also controversial and overestimated. Here, it is critically important to always pay attention to the definition of liver dysfunction and to remember that statin-related elevation of ALT is temporary in almost all cases, and that after 4–6 weeks, all patients may be treated again with statins.

Naci et al. showed that statin users were at higher risk of elevated ALT and AST levels (OR = 1.51; 95% CI: 1.24–1.84) [46]. In a meta-analysis of 16 studies conducted by Liang et al., which included 74,078 individuals, a marginally statistically significant correlation was found between statin use and risk of hepatic injury (OR = 1.18; 95% CI: 1.01–1.39). It was found that only intensive statin therapy was associated with an increased risk of liver injury (OR = 3.62; 95% CI: 1.52–8.58). A safety sub-analysis of specific types of statins showed that only fluvastatin, which is now *de facto* not used in clinical practice, significantly increased the risk of liver injury (OR = 3.50; 95% CI: 1.07–11.53). Importantly, it was found that long-term statin therapy was not associated with the risk of liver injury (OR = 1.15; 95% CI: 0.98–1.36) [59]. Another meta-analysis of 5 studies by Masson et al., including 2548 patients with abnormal liver tests at baseline, found that more intensive statin-based LLTs were associated with a similar occurrence of serious alteration of liver tests (OR = 0.90; 95% CI: 0.21–3.99) compared to less intensive treatment or placebo [60]. As indicated in the Scientific Statement from the AHA, risk of serious hepatotoxicity during statin therapy is ≈0.001%, which means that the number needed to harm (NNH) is 1:1,000,000 (with NNT = 30 for the reduction of CVD events) [48].

It should be emphasized that the use of statins in patients with hepatic dysfunction may be beneficial. In a meta-analysis conducted by Vahedian-Azimi et al., including 195,602 patients with chronic viral hepatitis, it was shown that statin use significantly reduced the risk of death by 39% in a 3-year follow-up. Moreover, the risk of hepatocellular carcinoma (HCC), fibrosis, and cirrhosis in those on statins decreased by 53% (OR = 0.47; 95% CI: 0.28–0.81), 45% (OR = 0.55; 95% CI: 0.34–0.87), and 41% (OR = 0.59; 95% CI: 0.55–0.62), respectively. Although alanine transaminase (ALT) and aspartate transaminase (AST) were reduced slightly

following statin therapy, this reduction was not statistically significant [61]. Similar results were obtained in patients with chronic liver disease (CLD). A meta-analysis by Kim et al., including 121,058 patients with CLD, showed that statin use did not significantly reduce the risk of liver fibrosis progression and cirrhosis. Moreover, in patients with cirrhosis, statin use was associated with 46% lower risk of hepatic decompensation (RR = 0.54; 95% CI: 0.46–0.62) and 46% lower mortality (RR = 0.54; 95% CI: 0.47–0.61) [62]. A meta-analysis of 14 studies by Fatima et al., involving 1,247,503 subjects, showed that statins may significantly reduce the risk of developing nonalcoholic fatty liver disease (NAFLD) (OR = 0.69; 95% CI: 0.57–0.84). Furthermore, statins were found to significantly reduce ALT levels (WMD: −27.28; 95% CI: −43.06 to −11.51), AST levels (WMD: −10.99; 95% CI: −18.17 to −3.81), and GGT levels (WMD: −23.40; 95% CI: −31.82 to −14.98) in patients presenting with NAFLD at baseline. Statin therapy was also found to significantly reduce steatosis grade ($P = 0.01$), NAFLD activity score ($P < 0.00001$), necro-inflammatory stage ($P < 0.00001$), and fibrosis ($P = 0.04$) [63]. Similar results were obtained by Pastori et al. in a meta-analysis of 22 studies covering 2345 NAFLD patients. In all interventional studies, except one, patients had raised ALT, AST, and GGT at baseline. It was found that ALT, AST, and gamma-glutamyl transferase (GGT) were reduced after statin treatment with a percentage mean difference of −35.41% (95% CI: −44.78 to −26.04), −31.78% (95% CI: −41.45 to −22.11), and −25.57% (95% CI: −35.18 to −15.97), respectively [64]. A recently published study by Wang et al., including 601,733 cancer patients and 2,406,932 patients in control, showed that those patients who used statins had a significantly lower risk of liver cancer (OR = 0.43; 95% CI: 0.40–0.47) [65].

Thus, clinically significant liver damage from statins is a very rare side effect of these drugs, for which causality has not been confirmed besides transient elevation of ALT, and fluvastatin (which is no longer recommended). Statins are safe in patients with liver dysfunction and may improve liver function and prognosis in these patients. Therefore, there is a clear recommendation for statin therapy in all patients with chronic liver diseases, and the only contraindication is acute liver disease.

NOD

As Scientific Statement from the AHA statin therapy modestly increases the risk of developing NOD, HR is ≈1.1 for moderate-dose and 1.2 for intensive statin therapy for 5 years. The risk is largely confined to patients with multiple preexisting risk factors for diabetes mellitus. The absolute risk of statin-induced NOD in major trials is ≈0.2% per year. The size of any effect in routine clinical practice will depend on the baseline risk for developing NOD in the patient population [48].

A meta-analysis of 5 statin trials with 32,752 participants conducted by Preiss et al. showed that odds ratios were 1.12 (95% CI: 1.04–1.22) for NOD among participants receiving intensive therapy compared with moderate-dose therapy. As

compared with moderate-dose statin therapy, the NNH per year for intensive-dose statin therapy was 498 for NOD while the number needed to treat (NNT) per year for intensive-dose statin therapy was 155 for CV events (over 3× higher benefit) [66]. A similar relationship was demonstrated in the meta-analysis of 29 RCTs by Thakker et al. It was found that statin use was statistically borderline significantly associated with the risk of NOD (OR = 1.12; 95% CI: 1.05–1.21) [67]. Naci et al. showed that statin users were at low risk—only 9% of the increase of NOD (OR = 1.09; 95% CI: 1.02–1.16) [46]. Finally, in the meta-analysis of 17 RCTs by Navarese et al., no significant effect of statin use (vs. placebo and comparison of different statins at different doses) on the risk of NOD was found [68]. In turn, Kamran et al. in a meta-analysis of patients with CVD and kidney disease showed that statin use is significantly but still relatively weakly associated with the risk of NOD (OR = 1.61; 95% CI: 1.55–1.68). The authors indicate that the observed results may be overestimated since statin users are people who often have concomitant risk factors for diabetes [69]. It is also worth noting the results of the meta-analysis by Danaei et al., including 285,864 subjects, which showed that the risk of statin-induced NOD was significantly influenced by other risk factors. Hazard ratio NOD in crude analysis was 1.45 (95% CI: 1.39–1.50), while only 1.14 (95% CI: 1.10–1.19) after multiadjustment [70].

Thus, the results of many clinical studies indicate that the use of statins may be associated with the risk of NOD, but the effect is small and probably related to the morbidity of people using these drugs. The profit and loss balance (NNT vs. NNH) indicate that the low risk of NOD should not be a reason for not using statins.

Efficacy and Safety of Statin Use Among Older People

A meta-analysis of 8 studies by Savarese et al. including 24,674 elderly subjects without established CVD showed that statins significantly reduced the risk of MI by 39.4% (RR = 0.606; 95% CI: 0.434–0.847) and the risk of stroke by 23.8% (RR = 0.762; 95% CI: 0.626–0.926) compared with placebo [71]. A meta-analysis of 8 studies by Teng et al. also demonstrated the efficacy and safety of statins among elderly people in primary prevention. It was shown that statins significantly reduced the risk of composite major adverse CV events (RR = 0.82; 95% CI: 0.74–0.92), nonfatal MI (RR = 0.75; 95% CI: 0.59–0.94), and total MI (RR = 0.74; 95% CI: 0.61–0.90) [72]. In a meta-analysis of 35 RCTs by Kostis et al., it was shown that statins reduced the risk of death from any cause (P = 0.03) among subjects >75 years of age in primary prevention [73]. Moreover, the meta-analysis of 23 studies by Ponce et al. involving 60,194 elderly patients assessed the effectiveness of statins in both primary and secondary prevention. It was shown that statins in primary prevention reduced the risk of CAD (RR = 0.79; 95% CI: 0.68–0.91) and MI (RR = 0.45; 95% CI: 0.31–0.66). In secondary prevention, it was found that statins reduced all-cause mortality (RR = 0.80; 95% CI: 0.73–0.89), CV mortality (RR = 0.68; 95% CI: 0.58–0.79), CAD (RR = 0.68; 95% CI: 0.61–0.77), MI (RR = 0.68; 95% CI:

0.59–0.79), and revascularization (RR = 0.68; 95% CI: 0.61–0.77) [74]. A meta-analysis of 28 RCTs by Armitage et al. showed that statin therapy or a more intensive statin regimen produced an 18% (RR = 0.82; 95% CI: 0.77–0.81; 0.70–0.95) proportional reduction in major CV events per 1.0 mmol/L reduction in LDL-C in patients >75 years of age. This relationship was significant only in patients with preexisting CVD [75]. In a meta-analysis of 10 observational studies by Awad et al. involving 815,667 elderly people in primary prevention, statin use was shown to reduce the risk of stroke (HR = 0.85; 95% CI: 0.76–0.94), all-cause death (HR = 0.86; 95% CI: 0.79–0.93), and death from causes of CV (HR = 0.80; 95% CI: 0.78–0.81), and the significant effect was maintained also in those >75 and even 85 years of age [76]. In summary, we have no doubt on the benefits of statin therapy in older adults, including those >75 years of age in primary and secondary prevention, however with stronger EBM for those with established CVD.

The meta-analyses cited above found no significant association between statin use and risk of new cancer onset, myalgia, elevation of liver transaminases, NOD, and serious adverse events [71, 72, 74, 76]. A meta-analysis of 11 RCTs by Zhou et al. of 18,192 older adults found no significant association between statin use and risk of SAMS, or other serious adverse events [77]. As demonstrated by Ott et al. in a meta-analysis of 25 RCTs including 46,836 subjects, statins did not significantly affect the risk of cognitive impairment [78]. Indeed, in a meta-analysis of 25 studies, Chu et al. obtained different results, showing that statins were significantly associated with a reduced risk of all-cause dementia (RR = 0.849; 95% CI: 0.787–0.916) [79].

Thus, the results of clinical studies show that statin use in the elderly is of significant benefit to CV prognosis and is very well tolerated. However, it needs to be strongly emphasized that taking into account that the metabolism of both cholesterol and drugs changes with age, owing to changes in pharmacokinetics and pharmacodynamics, statin doses should be increased gradually in elderly patients, as age itself is a significant risk factor of statin intolerance.

Efficacy and Safety of Statin Use Among Children

Statins are also effective in treating children and adolescents with familial hypercholesterolemia (FH). As indicated by the recommendations from the National Lipid Association (NLA) Expert Panel on Treatments for Pediatric Familial Hypercholesterolemia, statins are preferred for initial pharmacologic treatment in children after initiation of diet and physical activity management. Moreover, they indicate that clinical studies with medium-term follow-up suggest safety and efficacy of statins in children [80]. In a study by Luirink et al. involving 184 children with FH and 77 unaffected siblings who were followed for 20 years, the effectiveness of statin use was assessed. The mean progression of carotid intima-media thickness (CIMT) over the entire follow-up period was 0.0056 mm per year in patients with FH and 0.0057 mm per year in siblings. The incidence of CV events

and of death from CV causes at 39 years of age was lower among the patients with FH than among their affected parents (1% vs. 26% and 0% vs. 7%, respectively) [81]. A literature review by Peterson et al. found lower rates of ASCVD-related events and death in individuals with FH who were treated with statins from childhood, compared to those who initiated statins in adulthood [82]. A study by Kavey et al. involving 289 children treated with statins for severe LDL-C elevation demonstrated that after 2.7 years of follow-up, there was a significant reduction in LDL-C ($P < 0.001$) and non-HDL-C ($P < 0.001$). Therapy was not associated with a significant increase in the risk of elevated ALT ($P = 0.45$/year), AST ($P = 0.73$/year), CK ($P = 0.09$), and glucose levels ($P = 0.87$/year). Potentially, statin-related symptoms were recorded for 7% of patients (muscle pain, fatigue, rash, abdominal pain, and "yellow eyes") [83]. A meta-analysis of 10 RCTs by Anagnostis et al. of 1191 children and adolescents with FH summarized the efficacy and safety of statins. Compared with placebo, statins led to a mean relative reduction in total cholesterol, low-density LDL-C, triglyceride, and apolipoprotein B (apo-B) concentrations by −25.5% (95% CI: −30.4% to −20.5%), −33.8% (95% CI: −40.1% to −27.4%), −8.4% (95% CI: −14.8% to −2.03%), and −28.8% (95% CI: −33.9% to −23.6%), respectively. HDL-C was increased by 3.1% (95% CI: 1.1–5.2%). Statins were well tolerated, with no significant differences in ALT/AST and CK levels or other adverse effects compared with placebo. Statins exerted no effect on growth or sexual development [84]. In our analyses, we clearly showed that children with FH presented subclinical atherosclerosis manifested as decreased arterial wall elasticity. We also confirmed that the efficacy of LLT is very low, however with a very good safety profile [85, 86].

Thus, the use of statins is recommended in sick children with FH and is highly effective in the prevention of CVD and is safe and well tolerated. All the abovementioned aspects have been extensively discussed in the recent Position Paper of the Mighty Medic and ILEP on the risk assessment and clinical management of children and adolescents with heterozygous FH [87].

Safety of Statin Use Among Pregnant Women

As indicated by PoLA/CFPiP/PCS/PSLD/PSD/PSH guidelines on diagnosis and therapy of lipid disorders in Poland 2021: (1) statins are not recommended due to the risk of teratogenicity, despite the lack of evidence unequivocally confirming such a relationship; (2) there are more and more reports on the lack of risk of using statins and their benefits, especially for pregnant women with an underlying disease that threatens the life of the mother and the fetus (diagnosed cardiovascular disease and homozygous FH) [10]. The need to reconsider the views on the safety of statin use during pregnancy is confirmed by the results of recent meta-analyses.

A meta-analysis of 9 studies by Vahedian-Azimi et al. found no significant association between statin therapy and stillbirth (OR = 1.30; 95% CI: 0.56–3.02). While

statin exposure was significantly associated with increased rates of spontaneous abortion (OR = 1.36; 95% CI: 1.10–1.68), it was nonsignificantly associated with increased rates of induced abortion (OR = 2.08; 95% CI: 0.81–5.36) and elective abortion (OR = 1.37; 95% CI: 0.68–2.76). A nonsignificant numerically reduced rate of preterm delivery was observed in statin users (OR = 0.47; 95% CI: 0.06–3.70) [88]. In a systematic review of 136 pregnant women and 35 placental samples from hypertensive and normotensive women, Vahedian-Azimi et al. showed that statins might be beneficial for preventing or treating preeclampsia [89]. Moreover, another meta-analysis by Vahedian-Azimi et al. of 6 studies (1,267,240 participants) showed that statin use in pregnancy does not increase the risk of birth defects (OR = 1.48; 95% CI: 0.90–2.42), including cardiac anomalies (OR = 2.53; 95% CI: 0.81–7.93) and other congenital anomalies (OR = 1.19; 95% CI: 0.70–2.03) [90].

In conclusion, the use of statins during pregnancy is not currently recommended, but the results of recent studies may change this view in the near future, especially in line with complete lack of new lipid-lowering drugs (including the most innovative ones) for this more and more challengeable group of patients with many concomitant diseases, who may have high CVD risk.

Statin Intolerance: Definition and Real Global Prevalence

Taking into account the above critical discussion on the safety of statins, it seems that true (=confirmed, primary) intolerance to these drugs is not (contrary to popular belief) a common phenomenon. Statin intolerance should be defined as the inability to receive statin therapy adequate (with respect to the product or the dose) to manage the existing cardiovascular risk [91]. In other words, statin intolerance is not only the lack of statin treatment due to clinical or biochemical symptoms, but also the phenomenon of underdosage or the use of a statin too weak in relation to the cardiovascular risk [91]. There are several formal definitions of statin intolerance (Table 23.2).

The largest meta-analysis in the world by Bytyçi et al., published in the European Heart Journal in 2022, summarizes the prevalence of global statin intolerance and factors that increase the risk of developing this disorder. The meta-analysis covered 176 clinical studies (112 RCTs and 64 cohort studies) with 4,143,517 patients. It has been shown that the **overall prevalence of statin intolerance worldwide is 9.1% (8.1–10%)**. It means, in other words, that statin intolerance is overdiagnosed, and that 91% of patients on statin can be treated effectively without any safety concerns. Moreover, the prevalence was even smaller when defined using the National Lipid Association (NLA), the ILEP, and the European Atherosclerosis Society (EAS) criteria [7.0% (6.0–8.0%), 6.7% (5.0–8.0%), 5.9% (4.0–7.0%), respectively]. The prevalence of statin intolerance in RCTs was significantly lower compared with cohort studies [4.9% (4.0–6.0%) vs. 17% (14–19%)]. In primary prevention, statin intolerance was slightly less frequent than in secondary prevention [8.2% (6–10%)

Table 23.2 Approved definitions of statin intolerance

Society, year [Ref #]	Definition of statin intolerance
National Lipid Association (NLA), 2014 [92]	"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"
European Atherosclerosis Society (EAS), 2015 [93]	"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"
International Lipid Expert Panel (ILEP) Unified Definition, 2015 [38]	1. The inability to tolerate at least two different statins—one statin at the lowest starting average daily dose and the other statin at any dose 2. Intolerance associated with confirmed, intolerable statin-related adverse effect(s) or significant biomarker abnormalities 3. Symptom or biomarker change resolution or significant improvement upon dose decrease or discontinuation 4. Symptoms or biomarker changes not attributable to established predispositions such as drug-drug interactions and recognized conditions increasing the risk of statin intolerance
Canadian Consensus Working Group, 2016 [94]	"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"
Luso-Latin American Consortium, 2017 [95]	"(I) Pharmacologic (Ia) inability to tolerate at least two statins at any dose, OR (Ib) inability to tolerate doses higher than 5 mg of rosuvastatin; 10 mg atorvastatin; 20 mg of simvastatin; 20 mg of pravastatin; 20 mg of lovastatin; 40 mg of fluvastatin; or 2 mg of pitavastatin, AND (Ic) symptoms or CK changes NOT attributable to established drug-drug interactions and recognized conditions increasing the risk of statin intolerance; (II) symptomatic (IIa) intolerable muscle symptoms (muscle pain, weakness, or cramps, even with normal or mildly changed CK) OR (IIb) severe myopathy (SAMS 4); (III) etiologic (IIIa) plausible time relationship (0–12 weeks) with the introduction of statin, dose increase or introduction of a drug competing for the same metabolic pathway, AND/OR (IIIb) resolution or improvement of symptoms after discontinuation of statin (usually in 2–4 weeks), AND (IIIc) with worsening in less than 4 weeks after the new exposure (rechallenge)"

Data taken from Refs. [92–95]

vs. 9.1% (6–11%)]. It is also worth mentioning that statin lipid solubility (Table 23.1) did not affect the prevalence of statin intolerance [4.0% (2.0–5.0%) vs. 5.0% (4.0–6.0%)]. This meta-analysis identified and for the first time confirmed (it was hitherto mainly an expert opinion) a number of factors and conditions that influenced the risk of statin intolerance (Fig. 23.3) [42].

So, based on this analysis of >4 million patients, the prevalence of statin intolerance is low when diagnosed according to international definitions, and the authors

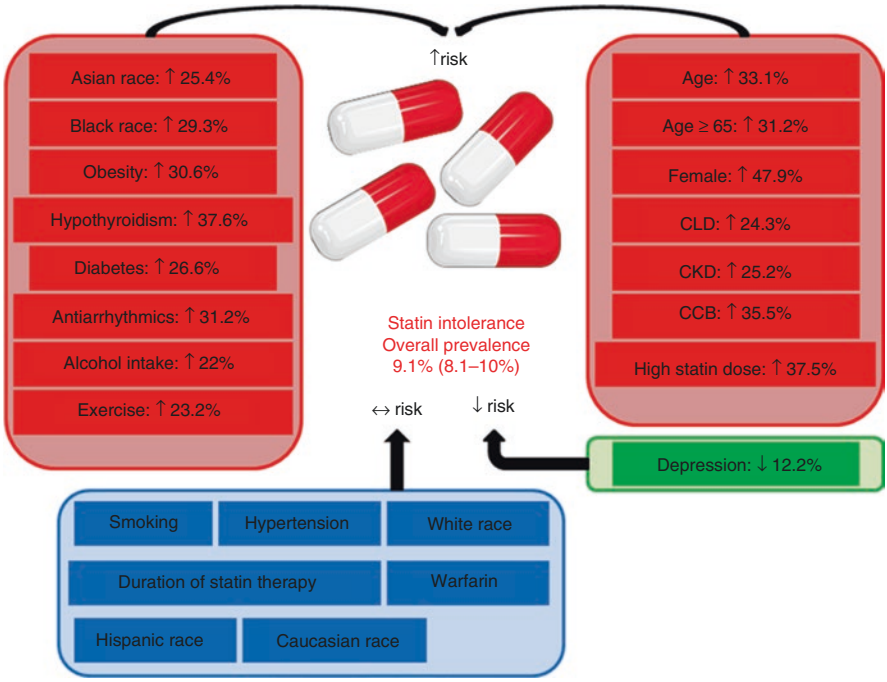


Fig. 23.3 Factors that influence the risk of statin intolerance. *Abbreviations*: *CLD* chronic liver disease, *CKD* chronic kidney disease, *CCB* calcium channel blockers. (Data taken from Ref. [42])

strongly recommend diagnosing SI based on these definitions, as this may represent an effective way to exclude nocebo/drucebo effect. These results support the concept that the prevalence of complete statin intolerance is overestimated and highlight the need for a careful step-by-step assessment of patients with potential symptoms related to statin intolerance.

Nonadherence/Discontinuation of Statin Therapy: Prevalence, Causes, and Consequences

Although true statin intolerance is not a common finding, patients either will find themselves unwilling to use these drugs or may stop treatment with these drugs. Statin discontinuation and nonadherence are the main reasons for the low effectiveness of lipid-lowering treatment. It is worth noting that only one in three patients in Europe achieves therapeutic goal; only 18% of patients in Europe, and only 13% in Central and Eastern European countries, achieve the therapeutic goal among very-high-risk patients (<55 mg/dL/<1.4 mmol/L); in patients with extreme risk, less than 10% achieve their therapeutic goal (<40 mg/dL/<1 mmol/L) [96, 97].

Prevalence

The prevalence of statin discontinuation is changeable. A literature review by Hope et al. found that the proportion of patients classed as "adherent" to statin ranged from 17.8% to 79.2% [98]. In a study by Bradley et al., including 5693 patients who had indications for the use of statins, it was found that 464 (30.7%) had discontinued therapy. Fear of side effects and perceived side effects were the most common reasons cited for declining or discontinuing a statin [99]. Huber et al., in a RCT of 486 patients after ACS, obtained different results. It was shown that after 3.9 years of follow-up, 10.5% of them were nonadherent to statin treatment (this is clearly related to the type of study—RCT—and the extent of patients' monitoring and management) [100]. Similar results were obtained in a study by Giral et al. involving 120,173 elderly people, which demonstrated that 14.3% of participants discontinued statin use during the 2.4-year follow-up [101]. However, the authors did not evaluate what percentage of patients were administered statins irregularly or at ineffective doses. Moreover, a study by Sigglekow et al., involving 289,666 new statin users, compared the level of adherence in patients with primary and secondary prevention. It was found that primary prevention patients discontinued statin use more frequently (29.8% vs. 19.7%) [102]. In the study by Vinogradov et al., covering 431,023 patients with primary prevention (137-week follow-up) and 139,314 patients with secondary prevention (181-week follow-up), it was shown that 47% and 41%, respectively, discontinued statin use [103]. Rezende Macedo do Nascimento et al. in a study involving 73,716 adult patients followed for approx. 7 years showed that the percentage of nonadherence patients was lower in the secondary prevention group (48.0% vs. 65.4%) with the lowest percentage of nonadherence among patients undergoing intensive statin therapy for both primary (55.9%) and secondary (36.3%) prevention [104]. A study by Booth et al., including 158,795 patients with MI who were followed for 182 days, showed that 15.4% of patients discontinued statin therapy after this period. Moreover, it was found that moderate- and high- vs. low-intensity statins were associated with a lower risk for statin discontinuation (moderate intensity: relative risk RR = 0.93; 95% CI: 0.89–0.96; high intensity: RR = 0.95; 95% CI: 0.91–0.99). It is worth mentioning that statin persistence after reinitiation (rechallenge) was also low (only 45.8% had high persistence) [105]. However, the relationship between the intensity of statin therapy and the level of adherence is inconsistent. A study by Rodriguez et al., including 347,104 adults with ASCVD, showed that patients taking moderate-intensity statin therapy were more adherent than patients taking high-intensity statin therapy (OR = 1.18; 95% CI: 1.16–1.20) [106]. In a study by Colantonio et al., involving 29,932 patients aged 66–75 years, it was shown that 6 months and 2 years after MI, 17.3% and 19.1% had low adherence, and 12.4% and 18.8% discontinued their statin, respectively [107]. A meta-analysis of 22 cohort studies by Mann et al. found that age had a reverse U-shaped association with adherence; the oldest (≥70 years) and youngest (<50 years) subjects had lower adherence than the middle-aged (50–69 years) subjects. A history of CVD predicted better adherence to statins (odds of nonadherence 0.68;

95% CI 0.66–0.78) [108]. A meta-analysis of 82 studies by Ofori-Asenso et al., including three million older (≥65 years) statin users from 40 countries around the world, assessed adherence and persistence in therapy with these drugs. It was shown that after a 1-year follow-up, 59.7% (primary prevention 47.9%; secondary prevention 62.3%) of users were adherent. Among new statin users, 48.2% were nonadherent and 23.9% discontinued within the first year [109]. A meta-analysis of 67 studies conducted by Lemstra et al. showed that the level of adherence to statin medications depended on the type of study (what is obviously not a surprise). Among observational studies, 49.0% of patients were adherent to statin medications at 1 year of follow-up, and among RCTs 90.3%. Importantly, this meta-analysis found that the factors increasing the level of nonadherence included primary prevention, new statin users, copayment, lower income status, fewer than two lipid tests performed, and not having hypertension [110]. A review of the literature by Ingersgaard et al. attempted to summarize the factors contributing to nonadherence among patients using statins. These factors include female sex, older and younger age, non-white race, low socioeconomic position, high copayments, being a new statin user, comorbidities, side effects, regimen complexity, type and intensity of statin dose, smoking, alcohol consumption, imperceptible benefits, and medical distrust [111].

Causes

It is worth noting that the cause of the lack of adherence is not always caused by the side effects of statins, as indicated by the results of clinical studies, but on the other hand SI seems to be one of the most common reasons of statin nonadherence. The previously cited meta-analysis by Teng et al. did not show a significant relationship between the side effects of statins and the risk of treatment discontinuation in the group of older patients (RR = 1.10; 95% CI: 0.85–1.42) [72]. Similar findings were reported in the previously cited meta-analysis by Zhou et al. (RR = 1.05; 95% CI: 0.83–1.33) [77]. The risk of statin therapy discontinuation due to side effects was also not significant in the pediatric group, as reported by Kavey et al. [83]. In a meta-analysis by Anagnostis et al., it was found that the percentage of individuals discontinuing statin therapy in the pediatric group was very low and amounted to 0–1.9% [84]. The abovementioned meta-analysis by Riaz et al. showed no significant difference in the risk of discontinuation of statin use between placebo and drugs (13.9% vs. 13.3%; OR = 0.99; 95% CI: 0.93–1.06). The sub-analysis including 14 RCTs also showed no significant difference (OR = 0.99; 95% CI: 0.9–1.1). Moreover, the analysis by specific statin types also showed no difference in the risk of treatment discontinuation compared to placebo [45].

Based on the available data, the most important reason for statin nonadherence is a lack of suitable patient education. A study by Wouters et al., involving 229 patients, showed that 40–70% doubted the necessity of or lacked knowledge about the efficacy of statins, 27–35% of the patients were worried about joint and muscle side effects, and 23% had encountered practical problems regarding information about

statins, taking of tablets, or problems with the package, or the blister [112]. Good communication with patients, appropriate education on the disease, and explanation of the necessity of statin therapy and its efficacy and safety are also the best solution to exclude the nocebo/drucebo effect [113]. Experiencing more practical problems was also associated with increased unintentional nonadherence (OR = 1.54; 95% CI: 1.13–2.10), whereas worrying about side effects was associated with increased intentional nonadherence (OR = 1.90; 95% CI: 1.17–3.08) [112]. The important role of the lack of sufficient information by the physician on the safety of statin use in the development of nonadherence was also raised by Tarn et al. The researchers stated that 27.2% of 173 patients were afraid of side effects and therefore did not comply with medical recommendations [114].

It is therefore very important to educate patients on the benefits of statin use based on the principles of evidence-based medicine (EBM). This point was extensively discussed in the recent ILEP recommendations on nocebo/drucebo effect management—the first recommendations of their kind in the world [115]. The public is very susceptible to all kinds of information and misinformation on television, in newspapers, or on social media. For example, a study by Matthews et al. showed that media coverage in the United Kingdom meant that patients already taking statins were more likely to stop taking them for both primary and secondary prevention after the period of high media coverage (OR = 1.11, 95% CI: 1.05–1.18, and OR = 1.12, 95% CI: 1.04–1.21, respectively). The elderly, and those who had used statins for a long time, had the highest risk of withdrawing from statin therapy [116]. A literature review by Nelson et al. indicated that the media has a key role in informing discussion on the public agenda but also on how issues are framed. Most studies evaluating news coverage suggest that the content on statins is predominantly negative and focused on potential harm (which receives 8–10 times more coverage than benefits of therapy). Studies utilizing quasi-experimental and interrupted time series design have shown that periods of negative news stories on statins in multiple countries are associated with (1) less statin commencement in eligible patients, (2) high rates of discontinuation, and (3) poor long-term adherence [117]. As noted in their study by Golder et al., the topic of statins is widespread in various types of social media, where users of these drugs exchange views and advice [118]. As indicated by Jones et al., statin-related websites vary widely in the quality of consumer-facing information they present. Moreover, individuals engaging in a search of statin-related information are not likely to treat pertinent information equally, differentially weighting the information that informs their medical decisions [119]. A very important role in creating a negative attitude towards statins is played by fake news spread, among others, by “antistatin movements.” A study by Scherer et al. showed that a person who is susceptible to online misinformation about one health topic may be susceptible to many types of health misinformation. Individuals who were more susceptible to health misinformation had less education and health literacy, less healthcare trust, and more positive attitudes towards alternative medicine [120]. It should also be emphasized that the cause of fake news may

be misinterpretations of the results of clinical studies or direct extrapolation of the results of experimental studies to humans (it is important to emphasize that only 1% of drugs tested on animals/cell cultures are appropriate for clinical use in humans) [121].

Thus, the lack of sufficient knowledge and the spread of fake news about the safety of statins play an important role in nonadherence of these drugs. Table 23.3 summarizes the factors associated with statin nonadherence.

Table 23.3 Factors associated with statin nonadherence

Patient-related factors 	Voluntary • Lack of understanding of current disease condition • Difficulty accepting disease severity • Previous negative experience to therapy • Skeptical on recommended treatment efficacy • Poor trust in the healthcare provider • Cultural and ethnic beliefs • Susceptibility to false information about statins on the internet and on TV Involuntary • Low level of health literacy or education • Increased susceptibility to medication adverse effects • Other comorbidities or concomitant conditions such as "psychological problems or cognitive impairments" • Unstable family background • Difficulty affording therapy
Physician-related factors 	• Complex medication regimen • Poor awareness about patient adherence • Insufficient explanation to patients about their medical condition and medications (benefits, side effects, time needed for medication to work, etc.) • Multiple physicians providing varying and possibly conflicting details to the patients • Specialty of prescriber • Poor understanding between patient and physician
Healthcare system-related factors 	• The economics of healthcare systems restricts the time spent between the physician and the patient. This results in insufficient time to: – Provide proper patient education (about their medical condition or medication) – Assess patient medication-taking behavior – Address patients' concerns – Offer encouragements and tips to improve adherence • Cost of medication • Insufficient clinical monitoring

Data taken from Ref. [122]

Complications

The consequences of noncompliance and discontinuation of statin use are critically important in everyday clinical practice. Rodriguez et al. showed that in comparison with the patients most adherent to statin therapy, those less adherent to medical recommendations were characterized by an 8–30% increase in the risk of death [106]. Giral et al. found that statin discontinuation led to a significant increase in the risk of any CV event (HR = 1.33; 95% CI: 1.18–1.50), coronary event (HR = 1.46; 95% CI: 1.21–1.75), and cerebrovascular event (HR = 1.26; 95% CI: 1.05–1.51) [101]. The consequences of statin discontinuation on the risk of major CV event (MACE: MI, ischemic stroke or TIA, coronary revascularization, and death due to MI or ischemic stroke) were also assessed by Thompson et al. in a study involving 67,418 older long-term statin users, including 27,463 in the primary prevention and 39,955 in the secondary prevention. It was shown that patients who discontinued statin therapy were characterized by a 32% and 28% higher risk of MACE during the 6-year follow-up, respectively [123]. In turn, a study by Rea et al. of 29,047 older patients exposed to polypharmacy showed that patients who discontinued statin use had a higher risk of hospital admissions for heart failure (HR = 1.24; 95% CI: 1.07–1.43), any CV outcome (HR = 1.14; 95% CI: 1.03–1.26), deaths from any cause (HR = 1.15; 95% CI: 1.02–1.30), and emergency admissions for any cause (HR = 1.12; 95% CI: 1.05–1.19) [124]. In a study by Rannanheimo et al., covering 97,575 new statin users aged 45–75 years, followed for 3 years, it was shown that those with better adherence had a significantly better prognosis (25% lower risk of any CV event or death) than those with low adherence. Patients with good adherence had also a lower incidence of ACS (HR = 0.56; 95% CI: 0.49–0.65) and acute cerebrovascular events (HR = 0.67; 95% CI: 0.60–0.76) [125]. Serban et al. investigated 105,329 Medicare beneficiaries who began a moderate- or high-intensity statin dosage after hospitalization for MI between 2007 and 2013. Statin intolerance was defined as down-titrating statins and initiating ezetimibe therapy, switching from statins to ezetimibe monotherapy, having ICD diagnostic codes for rhabdomyolysis or an antihyperlipidemic adverse event, followed by statin down-titration or discontinuation, or switching between ≥3 types of statins within 1 year after initiation. High adherence to statin therapy over the year following hospital discharge was defined as the proportion of days covered ≥80% [126]. Overall, 1741 patients (1.65%) had statin intolerance, and 55,567 patients (52.8%) had high statin adherence. The multivariate-adjusted hazard ratios (HR) comparing beneficiaries with statin intolerance versus those with high statin adherence were 1.50 (95% CI 1.30–1.73) for recurrent MI, 1.51 (1.34–1.70) for CHD events, and 0.96 (0.87–1.06) for all-cause mortality [126]. Finally, a meta-analysis by Martin-Ruiz et al. found that patients with the best adherence to statin had a significant reduction in risk: IHD by 18%, CVD by 47%, cerebrovascular disease by 26%, and death by 49% compared to patients with worst adherence to these drugs [127].

Thus, statin discontinuation or insufficient adherence to medical recommendations significantly worsens the prognosis of patients. In conclusion, it should be stated that the degree of compliance with medical recommendations regarding statin

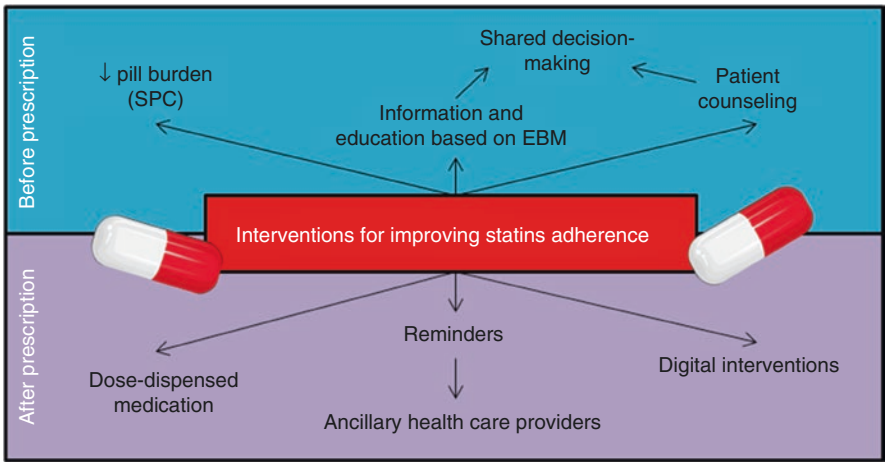


Fig. 23.4 Interventions for improving statin adherence. *Abbreviations*: *SPC* single pill combination, *EBM* evidence-based medicine. (Data taken from Ref. [122])

therapy is insufficient. A significant percentage of patients discontinue statin therapy. In most cases, the discontinuation of statin therapy seems not to result from the occurrence of side effects, but from insufficient knowledge and prejudice against these drugs. Insufficient adherence to medical recommendations and discontinuation of statin therapy significantly increase the risk of CV and worsen the prognosis of patients, and this is now considered as an important risk factor of CVD events. Figure 23.4 shows ways to improve adherence to statin use.

It is also worth mentioning that a very effective method of improving compliance with recommendations is the use of preparations based on a single pill combination (polypills, fixed combination, SPC) [128]. Patients with CVD often take several tablets (e.g., lipid-lowering drug, antihypertensive drug) or require several lipid-lowering drugs, and the combination of active substances in one SPC may significantly improve adherence. In a study by Rea et al., involving 256,012 patients, the effect of statin and ezetimibe in single tablets and as SPC on adherence was assessed. It was shown that the use of SPCs was associated with an 87% (95% CI: 75–99%) greater likelihood of high adherence and a 79% lower risk of poor adherence to treatment [129]. In the RCT by Lafeber et al., which included 78 patients with CVD, the effectiveness of the use of aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and hydrochlorothiazide 12.5 mg in the form of SPC or individual drugs was assessed. The authors showed that therapy with a SPC was associated with an increased adherence and that the SPC was highly preferred by patients [130]. It is also worth mentioning the meta-analysis of 44 studies by Parati et al., which showed that SPC therapy leads to improved adherence and persistence compared with free-equivalent combination therapy and may lead to better blood pressure control in patients with hypertension [131].

Thus, to effectively increase adherence and persistence, SPC-based therapy should always be considered (class: IIa, level: C), which is also reflected in the clinical recommendations [10].

Statin Intolerance: Diagnosis and Therapeutic Management

Management of patients with statin intolerance should consider the ILEP 2015 and 2022 recommendations [38, 115]. The management of statin intolerance has also been discussed in detail in the Polish guidelines 2021 on diagnosis and management of lipid disorders [10]. Additionally, in the management of statin intolerance, the ILEP position in the field of statin therapy in athletes and patients performing regular intense exercise can be used [132].

As shown earlier, genuine statin intolerance is not a common occurrence. Complete statin intolerance occurs in only a small minority of treated patients (estimated prevalence of only **3%**) [115]. Many perceived adverse effects are misattributed (e.g., physical musculoskeletal injury and inflammatory myopathies), and subjective symptoms occur as a result of the fact that patients expect them to do so when taking medicines (the nocebo/drucebo effect)—which may account for 50–70% of all patients with muscle weakness/pain [115]. The drucebo effect (a combination of DRUg and plaCEBO or noCEBO) relates to beneficial or adverse effects of a drug, which result from expectation and are not pharmacologically caused by the drug. The concept of the drucebo effect was first designed and introduced by Professor Maciej Banach and the ILEP [113]. Penson et al., based on a literature review, showed that the contribution of the drucebo effect to statin-associated muscle pain ranged between 38% and 78% [133].

When discussing the phenomenon of statin intolerance, attention should be paid to several key elements. When intolerance occurs, symptoms appear in 90% of cases within the first 6 months after initiation of statin therapy or dose increase, and in 75% within the first 12 weeks of this therapy [134]. Symptoms of intolerance are unlikely to occur 1 year after treatment initiation or dose increase, unless a new factor increasing this risk appears (disease exacerbation or initiation of a new medication which interacts with statins) [134]. The most common reasons of statin intolerance are SAMS [135]. In statin-intolerant patients, the appropriate management (so-called step-by-step approach, i.e., thorough history taking and gradual exclusion of reasons for intolerance, prompt initiation of appropriate management) may contribute to the fact that more than 95% of those patients may still receive statins [136]. Currently, in the management of patients with statin intolerance, the dominant rule of thumb for statins is to try to keep even the smallest statin dose that is tolerated and/or used even every 2–3 days (data indicate this as a possibility for atorvastatin and rosuvastatin [137]), and in the case of complete intolerance to statins, ezetimibe should be started immediately [12] and for high-risk patients other available non-statin therapies (bempedoic acid, PCSK9 inhibitors, inclisiran, as well as nutraceuticals or their combinations with proven lipid-lowering effect) should be considered [138]. Among the nutraceuticals that can be used in patients with statin intolerance, it is worth remembering that curcumin has been recognized to have lipid-lowering properties [10, 139, 140].

A detailed management algorithm for patients with suspected statin intolerance is presented in Fig. 23.5 [10]. The diagnostic process should take into account a number of factors that increase the risk of statin intolerance (Fig. 23.3) [42].

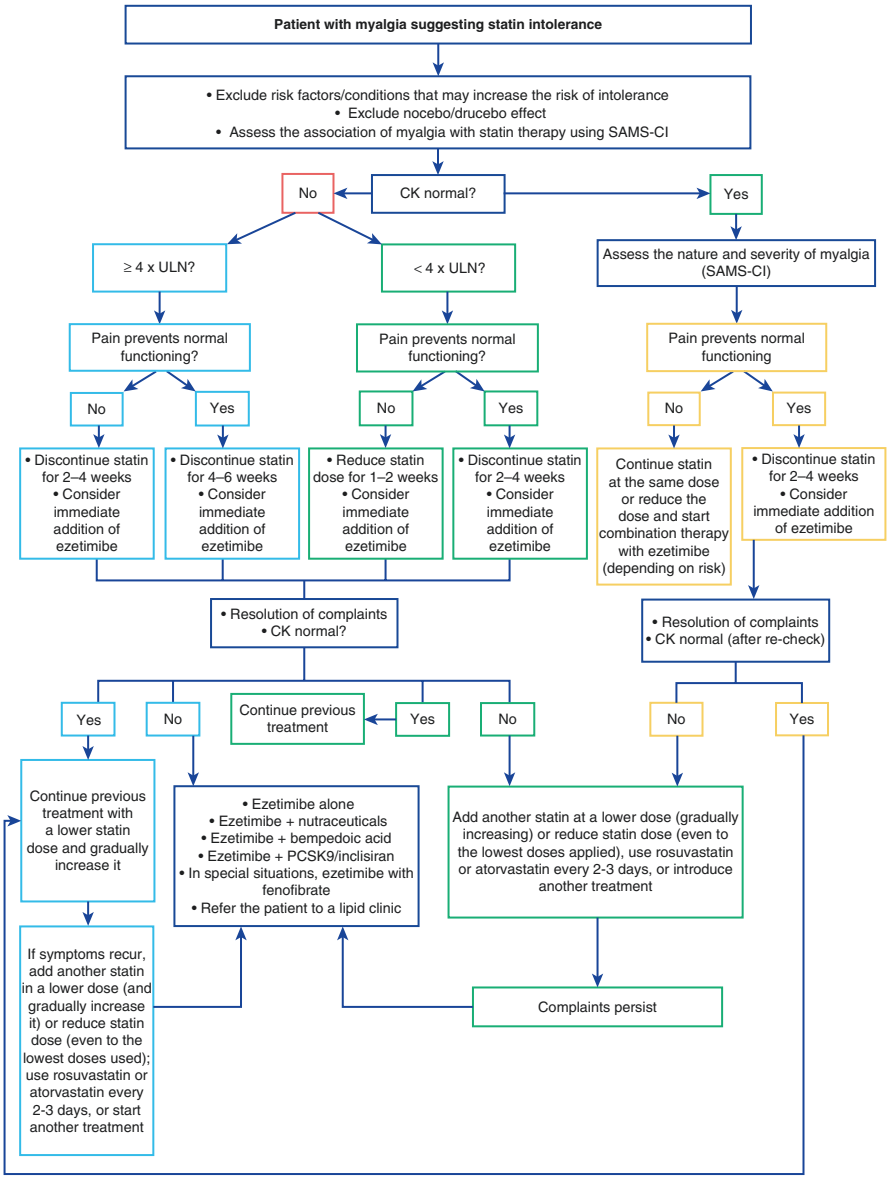


Fig. 23.5 Polish Lipid Association (PoLA) 2021 detailed recommendations for the management of patients with statin intolerance. *Abbreviations*: *SAMS-CI* Statin-Associated Muscle Symptom Clinical Index, *CK* creatine kinase, *ULN* upper limits of normal. (Reproduced with permission from Ref. [10])

It is also worth mentioning that pitavastatin, due to its bioavailability of 50% and metabolism practically without the participation of CYP450 (Table 23.1), is associated with the lowest risk of intolerance. In a study by Jeong et al., including 502 patients with high risk of developing diabetes, observed for 3 years, it was shown

that the incidence of NOD was similar between the pitavastatin 1 and 4 mg groups (4.2% vs. 2.8%, $P = 0.36$) [141]. In a study by Liu et al., including 8337 nondiabetic patients taking moderate-intensity statins (2 mg/day pitavastatin, 10 mg/day atorvastatin, and 10 mg/day rosuvastatin), it was shown that during 4 years of follow-up, pitavastatin group had a higher probability of being NODM free than the atorvastatin and rosuvastatin groups [142]. Pitavastatin also has the lowest potential risk of myalgia (estimated at about 2% for 4 mg), which is similar to placebo based on the available studies [10].

SAMS: Management Tips

One of the most difficult challenges is not only the proper management, but most of all the correct diagnosis, which will make it more probable that our patient is statin intolerant. In this context, the authors recommend the use of the SAMS scale-Clinical Index (Table 23.4), which makes it possible to give credence to the pain you are experiencing muscle has been associated with the use of statins [143]. This also, in a relatively easy way, helps to exclude the drucebo effect.

Table 23.4 Modified statin-associated muscle symptom-clinical index (SAMS-CI)

SAMS-CI	Score
1. Location and pattern of muscle symptoms *(if more than one category applies, record the highest number)*	
Symmetric, hip flexors, or thighs	3
Symmetric, calves	2
Symmetrical, proximal upper extremity[a]	2
Asymmetric, intermittent, or not specific to any area	1
2. Timing of muscle symptom onset in relation to starting statin regimen	
<4 weeks	3
4–12 weeks	2
>12 weeks	1
3. *Dechallenge*—timing of muscle symptom improvement after withdrawal of statin	
<2 weeks	2
2–4 weeks	1
No improvement after 4 weeks	0
4. *Rechallenge*—timing of recurrence of similar muscle symptoms in relation to starting second regimen	
<4 weeks	3
4–12 weeks	1
>12 weeks or similar symptoms did not reoccur	0
Interpretation *(likelihood that the patient's muscle symptoms are due to statin use)*	**Probable 9–11 Possible 7–8 Unlikely 2–6**

Adapted from Refs. [10, 143]

[a] The coracobrachialis muscle, the biceps brachii muscle, the brachialis muscle

The ILEP recommendations for the management of SAMS are summarized in Tables 23.5, 23.6, 23.7, 23.8, 23.9, and 23.10.

In the differential diagnosis of elevated CK levels, a number of other causes should be considered (Table 23.9) [115].

Table 23.5 ILEP recommendations on the management with patients **with intolerable SAMS and CK <4 ULN**

Recommendations	Class	Level
If intolerable muscle pain occurs, discontinue statin therapy for 2-4 weeks until symptoms have resolved.	IIb	C
Immediately start ezetimibe in high-risk and very high-risk patients.	IIb	C
Rechallenge with statin therapy is recommended.	I	C
SLAP algorithm is recommended to maximize long-term adherence to lipid-lowering therapy.	I	C

Reproduced with permission from Ref. [115]
Abbreviations: *SAMS* statin-associated muscle symptom, *CK* creatine kinase, *ULN* upper limits of normal

Table 23.6 SLAP approach to managing partial statin intolerance

	Step	Brief description	Rationale
S	Switch statin	Rechallenge patient with a different statin Consider using a drug with alternative partitioning chemistry (hydrophilic vs. lipophilic) or metabolic pathway to the drug which caused intolerance	Some adverse effects may be drug rather than class specific Patient may be unwilling to be rechallenged with a drug they associate with adverse effects
L	Lower dose	Reduce daily dose of statin	Adverse effects are dose dependent Adequate LDL-C reduction may be possible with a lower dose
A	Alternate-day dosing	Consider alternate-day dosing	Adverse effects are dose dependent Adequate LDL-C reduction may be possible with alternate-day dosing
P	Polypharmacy	Add another lipid-lowering drug with proven efficacy on hard outcomes	If adequate LDL-C reduction cannot be achieved with monotherapy, polypharmacy is appropriate

Reproduced with permission from Ref. [115]
Abbreviations: *LDL-C* low-density lipoprotein cholesterol

Table 23.7 ILEP recommendations on the management **with SAMS with CK >4 ULN**

Recommendations	Class	Level
Where serious muscle damage is suspected, or CK >10 ULN, statin therapy should be stopped immediately and (multi)specialist advice sought.	I	B
After symptoms release, treatment should follow the guidance for individuals with complete statin intolerance (*Figure 5*)	IIa	C

Reproduced with permission from Ref. [115]
Abbreviations: *CK* creatine kinase, *ULN* upper limits of normal, *SAMS* statin-associated muscle symptom

Table 23.8 ILEP recommendations on the management **with patients without SAMS and CK >4 ULN**

Recommendations	Class	Level
In patients with CK ≥4x ULN without SAMS, statin therapy should be stopped for at least 4 weeks, after which biomarkers should be re-investigated.	IIa	C
Statin rechallenge at a lower dose or combination therapy with ezetimibe may be considered after CK normalization.	IIb	C
SLAP algorithm is recommended to maximize long-term adherence to lipid-lowering therapy.	I	C

Reproduced with permission from Ref. [115]
Abbreviations: *CK* creatine kinase, *ULN* upper limits of normal, *SAMS* statin-associated muscle symptom

NOD: Management Tips

As detailed above, NOD is not a common side effect of statins. The ILEP recommendations for NOD are summarized in Table 23.11 [115].

When planning lipid-lowering therapy with statins in patients with a higher risk of NOD, it is worth remembering about pitavastatin, which has a lower diabetogenic effect compared to other statins [10].

ALT Elevated Level: Management Tips

As discussed in detail above, statin hepatotoxicity is not a common side effect of statins. ILEP recommendations for elevated ALT levels in patients treated with statins are presented in Table 23.12.

The lipid-lowering properties of nutraceuticals that may be helpful in the management of statin-intolerant patients are shown in Table 23.13 [115].

Table 23.9 The most common causes of CK elevation

Chronic diseases	Medications	Toxins	Metabolic disturbances	Muscle trauma/disorders	Others
Endocrine disorders Hyperthyroidism Hypothyroidism Hypoparathyroidism Acromegaly Cushing's syndrome Connective tissue disorders Rheumatological diseases Cardiac disease (heart failure, valvular, tachycardia, myocarditis, acute coronary syndrome) Acute kidney disease Viral illnesses Celiac disease	Statins Fibrates Antiretrovirals Beta-blockers Clozapine Angiotensin receptor-blocking agents Hydroxychloroquine Isotretinoin Colchicine Steroids	Ethanol Cocaine Heroin Amphetamine	Hyponatremia Hypokalemia Hypophosphatemia	Muscle dystrophies Metabolic and mitochondrial disorders of muscle Inflammatory myopathies Others Familial elevated CK Sarcoid myopathy Motor neuron diseases Charcot-Marie-Tooth disease Other congenital diseases Intramuscular injections Needle electromyography Seizures	Ethnicity (black Americans may have elevated baseline CK levels) Intensive exercise Surgery Malignancy Macro-CK Severe chills Predisposition to malignant hyperthermia Idiopathic hyperCKaemia

Reproduced with permission from Ref. [115]

Table 23.10 Summary of the ILEP recommendations on the management with SAMS

Recommendations	Class	Level
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered.	I	C
In patients with the family history of statin intolerance, and those being on the SI risk, starting with the combination therapy of lower dose of statin and ezetimibe (with the doses suitable for the given CVD risk) might be considered.	IIb	C
In patients with complete statin intolerance, ezetimibe may be considered immediately after statin discontinuation.	IIa	C
In secondary prevention, patients with acute coronary syndrome (ACS) and with complete statin intolerance, combination therapy with ezetimibe and PCSK9 inhibitors may be considered immediately after statin discontinuation.	IIb	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe should be considered.	IIa	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), bempedoic acid or fixed combination of bempedoic acid with ezetimibe may be considered.	IIb	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), inclisiran added to ezetimibe may also be considered.	IIb	C

Reproduced with permission from Ref. [115]
Abbreviations: *SI* statin intolerance, *CVD* cardiovascular disease, *PCSK9* proprotein convertase subtilisin kexin type 9 inhibitors

Table 23.11 ILEP recommendations on the management with new-onset diabetes (NOD)

Recommendations	Class	Level
If NOD occurs, it is recommended to continue statin therapy at the indicated dose.	I	B
In patients at risk of developing NOD, moderate-intensity statin therapy and/or combination therapy, depending on the risk, may be considered.	IIb	C
All individuals on a statin who have major risk factors for NOD, particularly impaired fasting glucose, should be informed about the risk and monitored for hyperglycemia.	IIa	A

Reproduced with permission from Ref. [115]

Table 23.12 ILEP recommendations on the management with elevated level of ALT

Recommendations	Class	Level
If ALT rises to <3× ULN, statin therapy should be continued, and re-checking liver enzymes may be considered after 4 weeks, especially with ALT >2x ULN.	IIa	C
If ALT rises to >3× ULN statin therapy at a lower dose (step-by-step dechallenge) may be considered. Ezetimibe may be started immediately, taking into account the patient's baseline risk and lipid profile.	IIb	C
Re-challenge of statin therapy with original dose may be considered after 2-4 weeks.	IIb	C
SLAP algorithm is recommended to maximize long-term adherence to lipid-lowering therapy	I	C

Reproduced with permission from Ref. [115]
Abbreviations: *ALT* alanine aminotransferase, *ULN* upper limits of normal

Table 23.13 Summary of the ILEP recommendations on the application of nutraceuticals in statin-intolerant patients

Nutraceuticals	Active Daily Doses	Expected Effects on LDL–C	Safety Issues	Recommendations	
				Class	Level
Red Yeast Rice	Up to 1,200 mg (*up to 3 mg of monacolin K*)*	–15% to –25%	Due to content of monacolin K some adverse effects typical for statins might appear	I	A
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	IIa	B
Bergamot	500–1,500 mg	–15% to–25%	No safety concerns	IIb	B
Soy Products	25–100 g	–6% to –10%	Possible interfering with thyroid function and fertility; ↓absorption of calcium, magnesium, copper, iron, and zinc	IIb	B
Polyunsaturated Omega–3 Fatty Acids**	2–4 g	–3% to –7%	Fish oil supplementation might be proarrhythmic (the risk of atrial fibrillation) especially in patients at the risk of arrhythmias	IIa	B
Berberine	500–1,500 mg	–15% to –25%	No safety concerns	IIa	C
Artichoke	1,800 mg/day	–15 to –23 %	Good tolerability in short-medium term	IIa	B

Reproduced with permission from Ref. [115]
Abbreviations: *LDL-C* low-density lipoprotein cholesterol
[a] Maximum recommended doses as dietary supplement recommended by the draft (2021) recommendations by the European Food Safety Authority (EFSA)
[b] Attention should be paid to increased risk of atrial fibrillation

Conclusions

Lipid disorders are the most important risk factor for ASCVD (the leading cause of premature death in the world), because they are both common and poorly managed. Effective LLT is the basis of the primary and secondary prevention of CVD. Statins are the gold standard in lipid-lowering therapy. These drugs are highly effective and, most importantly, prolong life. Statins are usually very well tolerated; however, in common with all medicines, statins may cause adverse events in some patients. The most common side effects of statins, for which the causality has been confirmed, are SAMS, NOD, and elevated ALT. Genuine statin intolerance is uncommon—globally, it affects 9.1% of treated patients. A number of risk factors can increase the risk of developing statin intolerance. Widespread negative attitudes towards statins and the drucebo effect negatively affect adherence. A significant percentage of patients discontinue statin use or exhibit a nonadherence attitude. It has been clearly shown that nonadherence and discontinuation of statin therapy significantly increase the risk of CV. Therefore, proper diagnosis and management of statin-intolerant patients are extremely important. In statin-intolerant patients, the appropriate management (so-called step-by-step approach, i.e., thorough history taking and gradual exclusion of reasons for intolerance, prompt initiation of appropriate management) may contribute to the fact that more than 95–97% of those patients may still receive statins. In the management of patients with statin intolerance, the recommendations of the ILEP should be applied.

The authors of this chapter wish to highlight that due to the constant progress of knowledge in the field of lipid-lowering treatment and statin intolerance issue [144], there is a continual and permanent need for updated information in this area.

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