

## Review Article

# High Intensity Lipid Lowering Drugs Further Than Statins

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Lipid-lowering therapies are crucial in reducing the risk of Atherosclerotic Cardiovascular Disease (ASCVD), and statins are the primary drugs used for this purpose. However, statins come with some side effects such as muscle symptoms, liver dysfunction, renal insufficiency, eye conditions, and an increased risk of Type 2 diabetes mellitus. The risk of developing Type 2 diabetes mellitus is dependent on the dose and duration of statin use. Long-term use of statins ( $\geq 5$  years) has been associated with a significant increase in the risk of diabetes. In this review, we will discuss several new therapies for lipid-lowering, including Ezetimibe, Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors, Bempedoic acid, Lomitapide, Pemafibrate, and angiopoietin-like 3 inhibitor Evinacumab. In addition to drugs, there are several plant-based agents and dietary strategies such as plant sterols, soluble and dietary fiber, nuts, red yeast rice, and a plant-based diet that have shown promise in reducing cholesterol levels. Furthermore, supplementation with Bergamot has also shown benefits in managing cardiometabolic risk in dyslipidemic subjects. These natural compounds and dietary approaches offer a complementary and natural way to manage cholesterol levels. It's important to note that while these agents can contribute to lowering cholesterol levels, they are not meant to replace prescribed medications for individuals with high cholesterol.

**Keywords:** Dyslipidemia; Non-statin; PCSK9 inhibitors

**Abbreviation:** ACL: Adenosine triphosphate-Citrate Lyase; AMPK: Monophosphate-Activated Protein Kinase; ANGPTL3: Angiopoietin-Like 3; ApoB: Apolipoprotein B; ASCVD: Atherosclerotic Cardiovascular Disease; CV: Cardiovascular; DASH: Dietary Approaches to Stop Hypertension; EAS: The European Atherosclerosis Society; eGFR: Estimated Glomerular Filtration Rate; ELIPSE HoFH: Evinacumab Lipid Studies in Patients with Homozygous Familial Hypercholesterolemia; EMA: European Medicines Agency; ESC: European Society of Cardiology; FDA: Food and Drug Administration; GalNAc: N-acetylgalactosamine; HDL-C: High-Density Lipoprotein Cholesterol; HeFH: Heterozygous Familial Hypercholesterolemia; HMG-CoA: 3-Hydroxy-3-Methylglutaryl-Coenzyme A; HoFH: Homozygous Familial Hypercholesterolemia; hsCRP: High-Sensitivity C-Reactive Protein; IDL: Intermediate-Density Lipoproteins; I-ROSETTE: Ildong ROSuvastatin & ezETimibe for hypercholesterolemia; LDL: Low Density Lipoprotein; LDL-C: Low Density Lipoprotein Cholesterol; LDLR: Low density lipoprotein receptor; MED: Mediterranean; MTP: microsomal triglyceride transfer protein; NPC1L1: Niemann-Pick C1-Like 1 protein; OBS: observational setting; PCSK9: Proprotein Convertase Subtilisin/kexin Type 9; PPAR $\alpha$ : Peroxisome Proliferator-Activated Receptor Alpha; RCT: Randomized Controlled Trials; RISC: RNA-Induced Silencing Complex; siRNA: Small Interfering RNA; TG: Triglycerides; TRL: TG-Rich Lipoproteins; VLDL: Very Low Density Lipoprotein

## Introduction

A metabolic disorder known as dyslipidemia causes blood Triglycerides (TG) and cholesterol levels to increase in the bloodstream. It is characterized by elevated Low-Density Lipoprotein Cholesterol (LDL-C), also known as hypercholesterolemia, and combined with low levels of high-density lipoprotein cholesterol (HDL-C) and raised Triglycerides (TG), mainly in the form of TG-Rich Lipoproteins (TRL) like chylomicrons and Very-Low-Density Lipoprotein (VLDL). Cardiovascular diseases, including peripheral vascular disease, coronary heart disease, and cerebrovascular disease (stroke), are prevalent non-communicable diseases worldwide and are responsible for 31% of all deaths [1]. Elevated LDL-C is a significant risk factor for these diseases [2]. Also, the obesity epidemic and sedentary lifestyle that have exacerbated other lipid-related diseases, require aggressive lipid suppression medication and clinical follow-up to prevent plaque buildup and cardiovascular events. First-line treatment for hypercholesterolemia is using 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitors, such as statins, for primary and secondary prevention. In the middle of the 1970s, statins were first developed as cholesterol-lowering medications. After being used for over four decades, statins are now among the drugs that are mostly prescribed all over the world, particularly for cardiovascular diseases. Statins decrease cholesterol synthesis in the liver by increasing LDLR expression. This leads to increased LDL uptake and decreased plasma levels of other ApoB-containing lipoproteins [3]. While statins are effective in lowering cholesterol and preventing cardiovascular events, they come with a risk of side effects, including muscle symptoms, liver dysfunction, renal insufficiency, eye conditions, and an increased risk of Type 2 diabetes mellitus [4]. The risk of new-onset Type 2 diabetes mellitus is time-varying and dose-dependent, with long-term statin use ( $\geq 5$  years) related with a statistically significant raise in the risk of diabetes. The diabetogenic effect was not statistically significant for pitavastatin, but atorvastatin and rosuvastatin showed the largest risks [5]. Statins have been associated with an increased risk of self-reported muscle symptoms, such as pain and weakness, which can affect patient compliance and quality of life [6]. Additionally, Patients with severely impaired liver function are also at risk due to the importance of hepatic excretion of all statins. Blinded placebo-controlled trials have not confirmed the existence of chronic myalgias or other pain disorders. A significant and reproducible rise in liver enzymes (alanine and aspartate aminotransferases) is observed in 1 to 3% of patients but actual liver damage may not occur [7]. Recent developments in lipid-lowering treatments have introduced promising options for managing dyslipidemia and reducing the risk of cardiovascular disease. These therapies beyond statins encompass a wide range of options, each with its unique mechanism of action and potential benefits. Evidence-based medications like angiopoietin-like 3 inhibitors, ATP-citrate lyase inhibitors, PCSK9 modulators, and microsomal triglyceride transfer protein inhibitors can effectively lower down lipids as mentioned in Table no. 1. This evidence-based review focuses on the clinical and benefit-risk evaluation of these non-statin drugs and also some plant-based compound for lowering lipids.

## Ezetimibe

Ezetimibe is a newer agent approved for the treatment of hyperlipidemia. Its mode of action has been found to be complementary to that of statins. Ezetimibe is a medication that helps to lower cholesterol by blocking a protein called Niemann-Pick

C1-Like 1 (NPC1L1), which in turn prevents the absorption of dietary cholesterol. A meta-analysis of eight Randomized Controlled Trials (RCTs) showed that taking ezetimibe alone (10 mg/day) for 12 weeks can reduce LDL-C levels by an average of 18.58%. The study also found significant reductions in total cholesterol (13.49%) and triglycerides (8.6%) compared to those who received a placebo [8].

Additionally, ezetimibe is a safe and effective drug that lowers LDL-C, particularly in high-risk individuals, such as those with post-acute coronary syndrome [9]. Moreover, it is also proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, which prevents the degradation of LDL receptors in hepatocytes [10]. Furthermore, combining ezetimibe with rosuvastatin has been studied extensively to assess its efficacy and safety in treating patients with primary hypercholesterolemia. The combination therapy has been found to significantly lower LDL-C levels compared to rosuvastatin alone. The I-ROSETTE study investigated the effect of adding ezetimibe to rosuvastatin in 396 participants. The adjusted mean LDL-C level after 8 weeks of treatment increased by 57.0% from baseline in the ezetimibe/rosuvastatin group, which was superior to the total rosuvastatin groups [11]. Additionally, the combination therapy resulted in achieving the target LDL-C levels in 90.7% of participants, which was significantly higher than the 72.9% in the rosuvastatin monotherapy group [12].

## Bempedoic Acid

Bempedoic acid, also known as Nexletol, inhibits ATP-Citrate Lyase (ACL) which is an enzyme involved in the pathway for de novo cholesterol synthesis [13]. Bempedoic acid also activates Adenosine Monophosphate-Activated Protein Kinase (AMPK), which in turn downregulates glucose-6-phosphatase and phosphoenolpyruvate carboxykinase. This mechanism may lower LDL-C in the liver, with upregulation of hepatic LDLR, thus increasing LDL-C clearance from the blood and also downregulates pro-inflammatory pathways [14,15]. It is noteworthy that Bempedoic acid is metabolized only in the liver and not in muscle, which could be advantageous for patients with statin intolerance. A Phase II trial, which included statin-intolerant patients and utilized PCSK9 inhibition, demonstrated a significant reduction in LDL-C levels of up to 24% with favorable tolerability [16,17]. In randomized controlled trials conducted on patients with ASCVD disease and/or heterozygous familial hypercholesterolemia who were already on the maximum possible dose of lipid-lowering therapy, the treatment of bempedoic acid was found to be effective. Compared to the placebo, it reduced the levels of LDL-C by 18%, non-HDL-C by 13.3%, apoB by 11.9%, and hsCRP by 21.5%. This study was called CLEARHarmony and it was conducted on a large number of patients [18].

When added to ezetimibe with or without additional lipid-lowering medication (CLEARSerenity), bempedoic acid 180 mg once daily decreased LDL-C by 23.6% and hsCRP by 25.4% in patients with a history of statin intolerance in requiring additional LDL-Clearing [19]. A convincing case for their combination emerged as it was found that ezetimibe and bempedoic acid decrease LDL-C through various pathways. A combination of fixed doses of bempedoic acid and ezetimibe was found to significantly reduce LDL-C levels by 38% when compared with a placebo in a Phase 3 double-blind trial, with a highly favorable safety profile [20]. In contrast to the impact of statins on blood sugar levels, bempedoic acid was associated with a lower risk of new-onset diabetes and hyperglycemia when compared to a placebo [21]. The finding might have to do with bempedoic acid's effect on glucose metabolism.

doic acid's stimulation of AMPK, which lowers gluconeogenesis. Moreover, fatty acid production is inhibited by AMPK activation, statins do not have a similar effect [13].

### Strategies Targeted towards Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9)

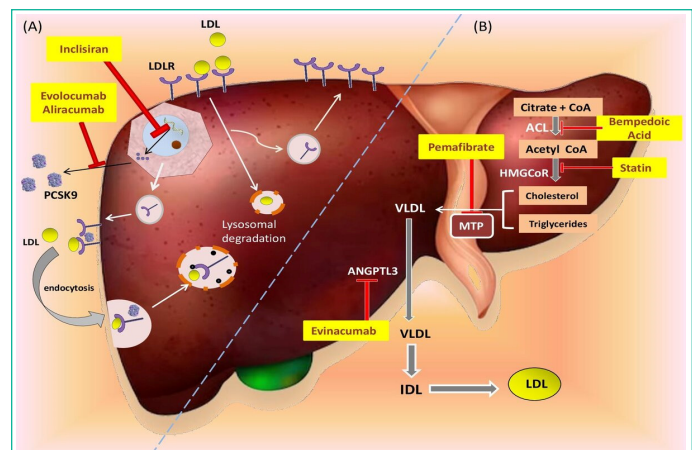
The discovery of proprotein convertase subtilisin/kexin9 (PCSK9) and the development of its inhibitors have opened up a new and exciting era in lipid management for many patients with residual cardiovascular risk, despite intensive statin therapy [22]. The PCSK9 protein acts as a chaperone to transport the LDL receptor to the lysosome. Lowering the levels of PCSK9 promotes the recycling of LDL receptors to the cell surface, which in turn helps in clearing LDL from the bloodstream as shown in Figure 1A. The discovery that lifelong low levels of LDL-C and reduced cardiovascular risk are associated with loss of function mutations in PCSK9, has led to the development of targeted therapies that inhibit PCSK9 [23]. PCSK9 inhibitors are a new class of drugs used to treat hypercholesterolemia in patients with intolerance or inadequate response to statins. They are also used for secondary prevention or in cases of familial hypercholesterolemia. The first strategy for lowering PCSK9 was based on monoclonal antibodies (mAbs) targeting the protein. Alirocumab and evolocumab are two of the medications that have undergone clinical trial examination and are presently available for purchase. They are both fully humanized mAbs that bind specifically to human PCSK9. Monoclonal antibodies against PCSK9 neutralize it outside cells, while gene expression strategies act inside cells (Figure 1B). Strategies to suppress PCSK9 are being developed, such as inhibiting function or interfering with expression. PCSK9-specific gene silencing by siRNA with the agent inclisiran has seen rapid translation to clinical use.

#### Evolocumab

Evolocumab is a monoclonal Immunoglobulin G2 (IgG2). It can be administered subcutaneously in doses of 140 mg or 420 mg. Administering this medication resulted in median peak blood concentrations within 3-5 days. The medication reduced plasma LDL-C levels by 53% to 75%. It can be used as a monotherapy or in conjunction with statin therapy. It can also be administered to patients with statin intolerance or patients with heterozygous familial hypercholesterolemia. Maximum suppression of circulating unbound PCSK9 occurred by four hours [24]. Evolocumab decreased plasma LDL-C levels by 31% in patients with homozygous familial hypercholesterolemia (HoFH) with dysfunctional LDLRs [4]. Additional PCSK9-Related Cardiovascular Outcomes Research the FOURIER study, which included patients with ASCVD and LDL-C levels  $\geq 70$  mg/dL or non-HDL-C levels  $\geq 100$  mg/dL on statin therapy, showed that evolocumab decreased the risk of cardiovascular disease by 15% Hazard Ratio [HR], 0.85; 95% Confidence Interval [CI], 0.79 to 0.92 [25].

#### Alirocumab

IgG1 monoclonal antibody is known as alirocumab. The recommended initial dose is 75 mg subcutaneously once every two weeks or 300 mg monthly once every four weeks. The dosage may be changed to 150 mg administered every two weeks if the LDL-C response is inadequate [26]. When given as a monotherapy, in combination with statin therapy, or to individuals who have developed a statin intolerance, alirocumab decreased plasma LDL-C levels by 45% to 53%. Alirocumab lowered plasma LDL-C levels by 39%–58% in patients with HeFH and by 11.9%–



**Figure 1:** Targets and mechanisms of action of non-statin therapies for lipid lowering. **A)** The regulation of LDL particle clearance involves the binding of secreted Proprotein convertase subtilisin/kexin type 9 (PCSK9) to LDLR on the liver surface, leading to the degradation of LDL-LDLR-PCSK9 complex. This process reduces the cell surface LDLR. However, the presence of PCSK9 inhibitors such as monoclonal antibodies evolocumab and alirocumab, as well as siRNA agent inclisiran, can increase the uptake of LDL cholesterol by the LDLR and recycle more LDLRs at the cell surface. **B)** New cholesterol-lowering treatments are being developed that focus on different aspects of lipid metabolism. Statins target the enzyme hydroxymethylglutaryl coenzyme A reductase (HMGCoR). The latest medicines aim at various facets of lipid metabolism, as shown in figure.

34.3% in individuals with HoFH, depending on the patient's genotype. In the ODYSSEY OUTCOMES trial, which evaluated the effects of alirocumab on cardiovascular outcomes after acute coronary syndrome, patients with an acute coronary syndrome, plasma LDL-C  $\geq 70$  mg/dL, non-HDL-C  $\geq 100$  mg/dL, or apolipoprotein B (apo B)  $\geq 80$  mg/dL who had been on statin therapy observed a 15% reduction in cardiovascular risk (HR, 0.85; 95% CI, 0.78 to 0.93) [27].

#### Inclisiran

Inclisiran is a synthetic small interfering RNA (siRNA) that targets PCSK9. It is conjugated to triantennary N-acetylgalactosamine carbohydrates (GalNAc), which directs siRNA to the liver [28]. It functions within hepatocytes by attaching itself to the RNA-Induced Silencing Complex (RISC) and preventing PCSK9 mRNA translation. This lowers PCSK9 synthesis and its release into the extracellular environment. The Inclisiran treatment for low-density lipoprotein cholesterol (LDL-C) in patients with heterozygous familial hypercholesterolemia (HeFH) showed significant reductions in plasma LDL-C levels. In the ORION-9 trial, patients with HeFH and plasma LDL-C  $\geq 100$  mg/dL were treated with a 300-mg dose of inclisiran sodium. In the ORION-10 trial, patients with ASCVD reduced their LDL-C levels by 52.3%. The ORION-11 trial showed a 49.9% reduction in LDL-C levels. The ongoing phase-3 trial will further clarify the cardiovascular benefits of inclisiran [29]. Inclisiran was recently approved by the FDA (December 22, 2021) and the EMA (December 9, 2020) for the treatment of residual hypercholesterolemia in patients based on the existing clinical evidence with heart failure or cardiovascular disease, failed to achieve the desired LDL goal with maximally tolerated statin treatment [30,31]. These novel strategies may have advantages over antibody treatments, such as increased durability, more convenient dose schedules, and potentially lower costs if they are proven to decrease CV events in outcomes trials.

**Table 1:** Comparative pharmacological aspects of non-statin drugs [28,52,53].

Features	Ezetimibe**	Bempedoic acid*	Evolocumab*	Alirocumab*	Inclisiran*	Lomitapidea*	Pemafibrate***	Evinacumab*
Class	Small molecule	Small molecule	Fully human mAb	Fully human mAb	siRNA	Small molecule	Small molecule	Fully Human mAb
Marketing approval	2002(FDA) 2003 (EMA)	2020 (FDA, EMA)	2015 (FDA,EMA)	2015 (FDA,EMA)	2020 (EMA)	2013 (EMA) 2012(FDA)	Not approved by FDA & EMA	2021 (FDA,EMA)
Target	NPC1L1	ACL	PCSK9	PCSK9	PCSK9	MTP	PPAR $\alpha$	ANGPTL3
Dosage	10 mg/ day	180mg/ day	Subcutaneous injection (140 mg every 2 weeks or 420 mg once monthly)	Subcutaneous injection (75-150 mg once every 2weeks or 300 mg once every 4 weeks)	Subcutaneous injection (284 mg every 3-6 months)	5mg/day (starting dose) With titration to max 60mg/day	0.1-0.4 mg twice / day	Intravenous infusion over 60 minutes (15mg/kg every 4 weeks)
LDL-C reduction from baseline	15-20%	15-23.5%	57-72%	47-61%	40-51%	45% (RCT)-60%(OBS)	7-10% LDL-C and 45% triglycerides	47%
Cardio vascular benefit	Yes	Yes	Yes	Yes	Not determined	Yes	Yes	Not determined

### Lomitapidea

Lomitapidea is an FDA approved medication used to reduce cholesterol in patients with HoFH when used with other lipid-lowering drugs and a low-fat diet. The endoplasmic reticulum lumen contains Microsomal Triglyceride transfer Protein (MTP), which is immediately bound by lipitapide and inhibited. Suppressing MTP prevents the hepatocytes and enterocytes from forming lipoproteins containing apo-B, which lowers the production of VLDL and chylomicrons and, as a result, lowers plasma levels of LDL-C [32]. With dosages ranging from 5 to 60 mg per day, lomitapide was given in addition to statins. After 26 weeks, the mean LDL-C decrease was 50%, and after 78 weeks of treatment, it was 38% for the patients. The most prevalent adverse effects were hepatic steatosis (liver fat content raised from 1.0% at baseline to 8.6%), gastrointestinal problems (27 out of 29 participants were reduced with a low-fat diet), and raised alanine transaminase levels in 4 people (which resolved upon dose reduction) [33].

### Pemafibrate

Pemafibrate, marketed as Parmodia, is the first selective peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ) modulator. It shows more than 2,500 times stronger PPAR $\alpha$  activation compared with fenofibric acid, the active form of fenofibrate [34]. Pemafibrate and fenofibrate significantly decreased plasma TG levels by 46% and 39%, respectively, in a phase 3 comparative trial comprising Japanese patients whose plasma TG levels ranged from 150 to 500 mg/dL. In comparison to fenofibrate, pemafibrate has shown less adverse effects over the years. According to clinical trials, it decreases plasma triglyceride levels in patients from Europe by 54.4% and in Japanese patients by 50% [35]. Ten thousand patients with type 2 diabetes mellitus and plasma TG levels of 200 to 500 mg/dL while receiving statin therapy participated in a phase 3 cardiovascular trial that observed Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides [36]. Notably, Pemafibrate has demonstrated to improve liver function test values and is less likely to increase serum creatinine or decrease the Estimated Glomerular Filtration Rate (eGFR) in comparison to other available fibrates. Moreover, very few drug-drug interactions were noticed even when used simultaneously with statins [34]. Additionally, the use of pemafibrate was linked to an increased occurrence of adverse renal events and venous thromboembolism, which is consistent with findings from other trials. and suggest that among statin-treated patients, fibrates, including pemafibrate,

cannot be recommended for cardiovascular risk reduction [36]. Pemafibrate has also been found to have dose-dependent beneficial effects on liver enzymes and to increase splanchnic glucose uptake. However, it does not seem to improve glucose metabolism. It is important to consider the potential benefits and risks of pemafibrate, especially in the context of individual patient characteristics and medical history [37].

### Evinacumab

Evinacumab, available under the trade name Evkeeza, is a monoclonal antibody that inhibits circulating Angiotensin-like 3 (ANGPTL3). It is an effective and safe treatment for homozygous and heterozygous Familial Hypercholesterolemia, resistant hypercholesterolemia, hypertriglyceridemia and homozygous familial hypercholesterolemia (HoFH) [38]. Evinacumab binds to ANGPTL3, allowing lipoprotein lipase (LPL) and endothelial lipase (EL) to enhance the clearance of Very Low-Density Lipoprotein (VLDL) remnants via remnant receptors in the liver, resulting in the decrease of LDL cholesterol levels [39]. In the ELIPSE HoFH trial, patients diagnosed with Homozygous Familial Hypercholesterolemia and having a plasma LDL-C level of 70 mg/dL or more while undergoing statin therapy, were administered evinacumab intravenously every four weeks at a dosage of 15 mg/kg body weight. As a result, they experienced a significant decrease of 49% in their plasma LDL-C levels and 50% reduction in plasma TG levels. Evinacumab reduced plasma LDL-C levels by 43.4% in patients with LDLR null-null variants, compared to a 16.2% increase in the placebo group. Adverse events were similar, including liver fat increase. In a phase 2 trial, it reduced plasma LDL-C levels by over 50% [40].

### The Specific Components Found in Plants Play a Crucial Role in Controlling Lipid Levels

There is substantial evidence to suggest that specific foods, food groups, and overall dietary practices can improve dyslipidemia and reduce the risk of cardiovascular disease. The Mediterranean (MED) diet and Dietary Approaches to Stop Hypertension (DASH) diet, Nordic diet and Portfolio diet, and other plant-based dietary patterns have been shown to protect against cardiovascular disease risk and related risk factors, such as LDL-C. These foods, including fruits, legumes, nuts, whole grains, seeds and vegetables, are rich in unsaturated fatty acids, plant proteins, dietary fiber, phytonutrients, and vitamins [41]. They are low in saturated fats and energy density compared to animal sources. The beneficial effects of these plant-based

foods have different mechanisms that influence cardiovascular disease development, such as dyslipidemia. Replacing saturated fats with unsaturated fatty acids, particularly vegetable oil PUFA, has been shown to lower LDL-C and lower the risk of cardiovascular disease. Dietary fiber, particularly viscous Soluble Fibers like beta-glucan, reduces cholesterol absorption and re-absorption, and produces short-chain fatty acids in the colon, which may affect hepatic cholesterol synthesis [42].

Various studies have investigated the effect of bergamot, a nutraceutical derived from *Citrus bergamia*, on human lipid parameters. The data from these studies revealed that 75% of them showed a significant decrease in LDL-C, triglycerides, and total cholesterol. The reduction in LDL-C ranged from 12.3% to 31.3%, in triglycerides from 7.6% to 40.8%, and in total cholesterol from 11.5% to 39.5%. Additionally, eight trials reported an increase in HDL-C after the intervention of bergamot. These studies suggest that bergamot has a dose-dependent effect and can potentially work synergistically when combined with statins [43].

The revised ESC/EAS guidelines for the management of dyslipidemias included for the first time a recommendation for plant sterols as part of lifestyle changes to reduce serum cholesterol levels by inhibiting intestinal cholesterol absorption [44]. These plant sterols are part of plant foods, mainly in unrefined vegetable oils, grains, nuts, and olive oil. A typical Western diet contains equal amounts (approximately 400 mg) of both plant sterols and cholesterol each day. It was found that Phytosterol-enriched low-fat milk and margarine results in a 10–15% LDL-C reduction [45], whereas fortified cereals reduce LDL-C by 5.4% [46]. To date, different food products enriched with phytosterols are available: milk, soy, and yogurt products; soy and fruit drinks; cereal; sausage, etc. However, not all plant-based dietary patterns are equally effective in lowering cardiovascular disease risk. Shifting to a more plant-based dietary pattern will not only improve cardiovascular health but also be more environmentally sustainable.

Also, small amount of statin like compound monacolin K, is found in nutritional supplement obtained from red yeast rice. In several randomized trials, it was demonstrated that there was a reduction of approximately 15% in LDL levels [47]. On March 24th, 2024, The Economics Times News agency Kyodo reported that the consumption of red yeast rice supplements (beni-koji) manufactured by Kobayashi Pharmaceutical Co. has been linked to two deaths and over a hundred hospital admissions. One of the deaths resulted from kidney illness caused by long-term use of beni-koji supplements. It is important to exercise caution when using this unregulated substance with a diverse product composition, as it was found to be nephrotoxic [48]. It's important to note that while these agents can contribute to lowering cholesterol levels, they are not meant to replace prescribed medications for individuals with high cholesterol. It is suggested to consult with a healthcare professional before making any significant changes to your diet or starting any new supplements or natural remedies.

## Conclusions

In conclusion, lipid-lowering therapies play a crucial role in reducing the risk of Atherosclerotic Cardiovascular Disease (ASCVD). While statins are the primary drugs used for this purpose, they come with certain side effects and an increased risk of Type 2 diabetes mellitus, particularly with long-term use. This emphasizes the importance of exploring alternative therapies

that can effectively lower cholesterol levels while minimizing adverse effects.

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