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Modern trends in hypolipidemic therapy

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Despite treatment with statins, patients with excessive levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides have a relatively high risk of developing complications from cardiovascular diseases (CVDs).

For the past ten years, research of various hypolipidemic medications has been in constant development. Hypolipidemic medication is applied for treatment of patients with statin intolerance or inability to reach the recommended LDL-C level.

Inclisiran is a small interfering ribonucleic acid, targeted at the proprotein convertase subtilisin/kexin type 9 (PCSK9), exerts effects similar to monoclonal antibodies against PCSK9. Bempedoic acid, an ATP-citrate lyase enzyme inhibitor, is nowadays considered a promising option of statin-intolerant patients' treatment. Pemafibrate, an agonist of the peroxisome proliferator-activated receptor alpha, had demonstrated an exceptional risk/benefit ratio during the phase 2 of the clinical trials, nevertheless, the phase 3 was terminated due to ineffectiveness shown by the late interim analysis. High doses of icosapent ethyl, the ethylic ester of eicosapentaenoic acid, has a beneficial effect on the cardiovascular system.

For the time being, there still are not enough data on the use of novel medications for the primary prevention of CVDs. For faster integration into clinical practice, safety and effectiveness of these methods, as well as cost-efficiency, have to be demonstrated by the randomized study of cardiovascular outcomes.

Keywords: Monoclonal antibodies to proprotein convertase subtilisin/kexin 9, inclisiran, bempedoic acid, pemafibrate, eicosapentaenoic acid, docosahexaenoic acid.

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Introduction

Cardiovascular diseases (CVDs) are a leading cause of mortality not only in Russia, but worldwide as well [1]. In 2022 alone, CVDs caused 831 557 deaths in the Russian Federation. The mortality from neoplasia was almost 3 times lower. Most deaths were associated with complications of coronary heart disease (CHD) (54.2% of all deaths) and cerebrovascular disease (29.2% of all deaths). These diseases are commonly caused by atherosclerosis, which is strongly associated with dyslipidemia[1].

The goal of hypolipidemic therapy is to reduce the risk of developing atherosclerotic CVDs, most commonly caused by elevated levels of low-density lipoprotein cholesterol (LDL-C). Statins are the first-line drugs for treating hypercholesterolemia. For patients at high risk of CVD, with familial hypercholesterolemia (FH), or with type 2 diabetes mellitus (T2DM), it is recommended to achieve a target LDL-C level of < 1.8 mmol/L and reduce it by ≥50% from the baseline [2]. Nevertheless, the persisting risk of CVDs demonstrates an ongoing clinical need for the development and implementation of medications that effectively lower the blood levels of atherogenic particles [3].

Sufficient data on the efficacy of novel lipid-lowering drugs and their potential for clinical application have been accumulated in the literature. This review includes an analysis of new hypolipidemic drugs that affect blood levels of LDL and triglycerides (TG).

Methods

All material for this review was compiled from peer-reviewed articles published over the past 10 years on platforms such as PubMed, eLIBRARY.RU, cyberleninka.ru and other research databases. This time frame was selected as it encompasses the publication of key clinical studies on the subject. Search terms included "hypolipidemic therapy," "PCSK9 inhibitors," "inclisiran," and "bempedoic acid."
Studies or articles that did not meet quality standards were excluded.

Results

LDL-C-lowering drugs

A number of clinical and genetic studies have demonstrated that LDL particles cause CVDs, and that reducing CVD risk is dependent on lowering blood LDL-C levels [4].

Inhibition of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) with monoclonal antibodies

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a liver enzyme that binds to LDL-C receptors on hepatocyte membranes and reduces their expression. As a result of its action, the level of LDL-C in the plasma increases.

Evolocumab and alirocumab are monoclonal antibodies that inhibit this enzyme. These antibodies reduce the concentration of PCSK9 in the blood plasma, leading to increased expression of LDL-C receptors and, consequently, a decrease in blood LDL-C levels. PCSK9 inhibitors also reduce TG and lipoprotein(a) levels while simultaneously increasing apolipoprotein A-I (apoA-I) levels [5].

Evolocumab is indicated for patients with heterozygous and homozygous FH. It can be used as monotherapy or in combination for patients already on statin therapy who are not achieving their target LDL-C levels. This drug is also recommended for patients with statin intolerance [6, 7]. In patients with homozygous familial hypercholesterolemia, evolocumab reduced plasma LDL-C levels by 31% [8]. The cardiovascular outcomes study FOURIER (Further cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk) confirmed the feasibility of using evolocumab for hyperlipidemia. This study followed 27,564 patients with a plasma LDL-C level ≥ 1.8 mmol/L or non-high-density lipoprotein cholesterol (non-HDL-C) ≥2.6 mmol/L, who had atherosclerotic changes in various vascular beds and were concurrently receiving treatment with statins and ezetimibe. According to the results of this study, adding evolocumab to therapy reduced LDL-C levels by 59% from 2.4 mmol/L to 0.78 mmol/L, and the risk of CVD was reduced by 15% (hazard ratio (HR) = 0.85; 95% confidence interval (CI): 0.79-0.92, p <0.001) [9, 10].

[1] Federal State Statistics Service (Rosstat) «Demographic Yearbook of Russia 2023» https://rosstat.gov.ru/folder/210/document/13207

In the prospective, randomized, double-blind, placebo-controlled EVOPACS study, serum LDL-C levels were measured in 308 patients hospitalized with acute coronary syndrome (ACS) and elevated LDL-C levels, who had been on statin therapy for at least 4 weeks prior to hospitalization (LDL-C ⩾1.8 mmol/L with high-intensity statin therapy; ⩾2.3 mmol/L with low- or moderate-intensity statin therapy; or ⩾3.2 mmol/L in patients taking statins inconsistently). Patients were randomized 1:1 to receive either evolocumab 420 mg subcutaneously or placebo in the hospital and for an additional 4 weeks after discharge (totaling 8 weeks), in addition to atorvastatin 40 mg therapy. The mean LDL-C level decreased from 3.61 to 0.79 mmol/L at week 8 in the evolocumab group and from 3.42 to 2.06 mmol/L in the placebo group; the difference in the mean percentage change from baseline was ~40.7% (95% CI: 45.2 to 36.2%; p < 0.001). An LDL-C level of <1.8 mmol/L was achieved at week 8 in 95.7% of patients in the evolocumab group compared to 37.6% in the placebo group, confirming the feasibility of using evolocumab [11].

The benefits of PCSK9 inhibitor drugs are also demonstrated by the results of the multicenter, double-blind, placebo-controlled, randomized clinical trial GLAGOV [10]. The study included 968 patients aged 18 years and older with specific clinical indications identified during coronary angiography. Specifically, they had at least one epicardial coronary stenosis obstructing 20% or more of the vessel lumen. Furthermore, these patients had a target vessel that could be visualized and whose obstruction did not exceed 50%. At the start of the study, patients were on stable-dose statin therapy for at least 4 weeks and had an LDL-C level of ⩾2.1 mmol/L or between 1.6 and 2.1 mmol/L with one major or three minor risk factors for CVD. Major risk factors included: non-coronary atherosclerotic vascular disease, myocardial infarction (MI), or hospitalization for unstable angina within the previous 2 years, as well as type 2 diabetes. Minor risk factors included: smoking, hypertension, low high-density lipoprotein cholesterol (HDL-C) levels, family history of early coronary heart disease, high-sensitivity C-reactive protein (hs-CRP) level ⩾0.2 mmol/L, or age ⩾50 years for men and ⩾55 years for women. The study patients were randomized to receive monthly subcutaneous injections of either evolocumab 420 mg (484 patients) or placebo (484 patients) for 76 weeks, in addition to statins. The primary efficacy measure was the change in percent atheroma volume (PAV) from baseline to week 78, measured by serial intravascular ultrasound (IVUS). Secondary efficacy measures were the change in total atheroma volume (TAV) and the percentage of patients with plaque regression.

The safety and tolerability of evolocumab were also assessed. Among the 968 patients treated, lower LDL-C levels were achieved in the evolocumab group: 2.41 mmol/L in the placebo group versus 0.95 mmol/L in the evolocumab group, with a between-group difference of –1.46 mmol/L (95% CI: –1.55 to –1.38 mmol/L; p < 0.001). The primary efficacy parameter, PAV, increased by 0.05% with placebo and decreased by 0.95% with evolocumab — a difference of –1.0% (95% CI: –1.8% to -0.64%; p < 0.001). The secondary efficacy parameter, TAV, decreased by 0.9 mm^3 with placebo and by 5.8 mm^3 with evolocumab, a difference of –4.9 mm^3 (95% CI: –7.3 to –2.5 mm^3; p < 0.001). Evolocumab induced plaque regression in a greater percentage of patients than placebo: 64.3% vs. 47.3%, a difference of 17.0% (95% CI: 10.4 to 23.6%); for PAV: 61.5% vs. 48.9%, a difference of 12.5% (95% CI: 5.9 to 19.2%; p < 0.001); for TAV, p < 0.001. Thus, it can be concluded that the combination of evolocumab and statins promotes the regression of atherosclerotic plaques in patients with coronary heart disease, as confirmed by IVUS data [12].

The efficacy and safety of another drug in this class, alirocumab, in patients with high cardiovascular risk and uncontrolled hypercholesterolemia despite maximally tolerated statin doses, were established in the multicenter, double-blind, randomized, placebo-controlled study ODYSSEY COMBO II. This study included 720 patients with confirmed CVD and elevated LDL-C ⩾1.8 mmol/L, or without confirmed CVD history but with high cardiovascular risk and LDL-C ⩾ 2.6 mmol/L, despite maximum statin doses (rosuvastatin 20/40 mg, atorvastatin 40/80 mg, or simvastatin 80 mg) used for more than 1 year. Patients were randomized into 2 groups. The first group received alirocumab 75 mg subcutaneously every 2 weeks (plus oral placebo tablets). The second group received oral ezetimibe 10 mg daily (plus subcutaneous placebo injections) on top of statin therapy. At week 24, the mean reduction in LDL-C from baseline was 50.6 ± 1.4% for alirocumab versus 20.7 ± 1.9% for ezetimibe (difference 29.8 ± 2.3%; p<0.0001); 77.0% of patients receiving alirocumab and 45.6% of patients receiv-

ing ezetimibe achieved LDL-C levels <1.8 mmol/L (p<0.0001). The mean achieved LDL-C level at week 24 was 1.3 ± 0.04 mmol/L for alirocumab and 2.1 ± 0.05 mmol/L for ezetimibe and was maintained until week 52. Alirocumab was generally well-tolerated, with no signs of an excess of treatment-emergent adverse events observed [13].

The efficacy of long-term (78 weeks) treatment with alirocumab was demonstrated in two multicenter, randomized, double-blind, placebo-controlled studies, ODYSSEY FH I (486 patients) and FH II (249 patients), in patients with heterozygous familial hypercholesterolemia (HeFH) and inadequate LDL-C control despite maximally tolerated statin therapy (rosuvastatin 20–40 mg, atorvastatin 40–80 mg, or simvastatin 80 mg) with or without other lipid-lowering drugs for at least 4 weeks prior to the study (6 weeks for fenofibrate; other fibrates such as clofibrate, gemfibrozil, bezafibrate, ciprofibrate, except fenofibrate, were not permitted). Patients with HeFH without a history of cardiovascular events, as well as patients who had experienced MI or ischemic stroke, were included in the study if their LDL-C level did not reach the target value, according to current guidelines, for primary (≥2.6 mmol/L) or secondary (≥1.8 mmol/L) prevention respectively. Study patients were randomized in a 2:1 ratio to receive alirocumab 75 mg every 2 weeks or placebo. The alirocumab dose was blindly increased to 150 mg at week 12 if the patient's LDL-C level at week 8 was ≥1.8 mmol/L. Throughout the study, patients continued taking statins and other lipid-lowering medications. The mean LDL-C level decreased from a baseline of 3.7 mmol/L to 1.8 mmol/L after treatment (–57.9% compared to placebo) at week 24 in patients randomized to the alirocumab group in the ODYSSEY FH I study, and from 3.5 mmol/L to 1.8 mmol/L (–51.4% compared to placebo) in the ODYSSEY FH II study (p < 0.0001). This reduction was maintained until week 78. An LDL-C level of <1.8 mmol/L (regardless of cardiovascular risk) was achieved at week 24 by 59.8% and 68.2% of patients receiving alirocumab in the ODYSSEY FH I and FH II studies, respectively [14].

The multicenter, randomized, double-blind, placebo-controlled study ODYSSEY OUTCOMES demonstrated an improvement in cardiovascular outcomes after ACS in 18,924 patients receiving high-intensity statin therapy with the addition of 75 mg alirocumab. At baseline, the mean LDL-C level in the study patients was 2.38 ± 0.80 mmol/L. In the alirocumab group, the mean LDL-C level at 4 months, 12 months, and 48 months after randomization was 1.0 mmol/L, 1.2 mmol/L, and 1.7 mmol/L respectively; in the placebo group, the mean LDL-C level at 4 months, 12 months, and 48 months after randomization was 2.4 mmol/L, 2.5 mmol/L, and 2.7 mmol/L respectively. In an analysis conducted in the alirocumab group (which excluded values measured after alirocumab discontinuation and after blinded substitution of alirocumab with placebo), the mean LDL-C level at 4 months, 12 months, and 48 months was 0.98 mmol/L, 1.1 mmol/L, and 1.4 mmol/L respectively; these levels were on average 62.7%, 61.0%, and 54.7% lower than the corresponding levels in the placebo group. The primary composite endpoint (PCE) included: death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. The median follow-up duration was 2.8 years. A PCE event occurred in 903 patients (9.5%) in the alirocumab group and 1052 patients (11.1%) in the placebo group (HR = 0.85; 95% CI: 0.78–0.93; p < 0.001). A total of 334 patients (3.5%) died in the alirocumab group and 392 patients (4.1%) in the placebo group (HR = 0.85; 95% CI: 0.73–0.98). Thus, it can be concluded that alirocumab is capable of not only reducing LDL-C levels but also reducing the risk of cardiovascular complications and death in patients after ACS [15].

The effect of alirocumab on coronary artery atherosclerosis in patients who underwent percutaneous coronary intervention (PCI) for acute MI was studied in the recently conducted multicenter, double-blind, placebo-controlled, randomized clinical trial PACMAN-AMI. In this study, 300 patients who underwent PCI for acute MI (participant enrollment: from May 9, 2017, to October 7, 2020; final follow-up: October 13, 2021) were randomized to receive 150 mg of alirocumab (148 patients) subcutaneously every two weeks or placebo (152 patients). Treatment began less than 24 hours after urgent PCI and was administered for 52 weeks in addition to high-intensity statin therapy (rosuvastatin 20 mg). At 52 weeks, the mean change in PAV was –2.13% with alirocumab versus –0.92% with placebo, a difference of –1.21% (95% CI: –1.78% to –0.65%; p < 0.001). The mean change in minimal fibrous cap thickness was 62.67 μm with alirocumab versus 33.19 μm with placebo, a difference of 29.65 μm (95% CI: 11.75–47.55; p =

0.001) [16]. Thus, in patients with acute MI, the addition of alirocumab to high-intensity statin therapy, compared with placebo, led to significantly greater regression of coronary plaque at 52 weeks.

Considering current clinical guidelines, PCSK9 inhibitors should be prescribed to patients receiving therapy with statins and ezetimibe at maximally tolerated doses, who have a high risk of CVD and a plasma LDL-C level ⩾1.8 mmol/L [2].

With subcutaneous administration of alirocumab at doses of 75 and 150 mg and evolocumab at a dose of 140 mg every 2 weeks to patients with atherosclerotic CVD on background statin therapy, a 60% reduction in LDL-C level and a 15% reduction in the risk of CVD complications were observed [2].

PCSK9 inhibition via RNA interference

Inclisiran is a small interfering RNA that inhibits the synthesis of the PCSK9 protein in hepatocytes. The effect of this drug lasts longer than that of other lipid-lowering agents [17].

In the ORION-9 study evaluating the effect of inclisiran treatment on LDL-C levels in HeFH, which included 482 patients with HeFH and a baseline plasma LDL-C level ⩾2.6 mmol/L on statin therapy, inclisiran sodium at a dose of 300 mg (equivalent to 284 mg of inclisiran free acid) was administered on days 1, 90, 270, and 450. The mean baseline LDL-C level was 4.0 ± 1.4 mmol/L. On day 510, inclisiran reduced plasma LDL-C levels by 47.9%. The mean absolute change in LDL-C level from baseline on day 510 was a reduction of 1.5 mmol/L (95% CI: –1.7 to –1.4 mmol/L) in the inclisiran group and an increase of 0.3 mmol/L (95% CI: 0.1 to 0.4 mmol/L) in the placebo group, with a between-group difference of 1.8 mmol/L (95% CI: –2.0 to –1.6 mmol/L; p < 0.001). A higher frequency of injection site reactions was noted in the inclisiran group compared to the placebo group (17.0% vs. 1.7%). Most adverse events were assessed as mild, with no serious complications identified [18].

In the ORION-10 study, which involved a total of 1561 patients with atherosclerotic CVD such as coronary heart disease, peripheral artery atherosclerosis, etc., a dose of 284 mg of inclisiran (as the free acid) was administered on days 1, 90, 270, and 450. The mean baseline LDL-C level was 2.71 ± 0.99 mmol/L. On day 510, inclisiran reduced plasma LDL-C levels by 52.3% (95% CI: 48.8 to 55.7%). The absolute change in LDL-C level on day 510 was –0.05 mmol/L in the placebo group and –1.45 mmol/L in the inclisiran group, with a between-group difference of –1.40 mmol/L (95% CI: –1.48 to –1.32 mmol/L; p < 0.001). The percentage change on day 510 was 13.5% with placebo and –69.8% with inclisiran, representing a between-group difference of -83.3% (95% CI: –89.3% to –77.3%; p < 0.001) [19].

Russian clinical guidelines approve inclisiran for subcutaneous administration at 284 mg, with a regimen of three doses in the first year and two doses annually thereafter [2].

Bempedoic Acid

ATP-citrate lyase (ACLY) catalyzes the ATP-dependent conversion of citrate and coenzyme A (CoA) into oxaloacetate and acetyl-CoA. Acetyl-CoA, a precursor of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA), is crucial for cholesterol biosynthesis. Thus, inhibition of ACLY leads to reduced levels of acetyl-CoA and cholesterol synthesis [20].

Bempedoic acid (BA) is a prodrug that acts as a selective ACLY antagonist after activation by acyl-CoA synthetase-1. Since this enzyme is primarily expressed in the liver, BA has minimal impact on other body tissues, particularly skeletal muscle. Unlike statins, patients treated with BA exhibited a lower incidence of myopathy, rhabdomyolysis, or other muscle-related adverse effects [20]. Among the most common side effects are increased plasma uric acid levels and the development of gout [21].

In addition to lowering LDL-C levels, BA also affects the level of high-sensitivity C-reactive protein (hs-CRP) [22].

The CLEAR Harmony and CLEAR Wisdom studies investigated the effect of BA therapy on cholesterol levels, involving 2230 and 779 patients, respectively, with atherosclerotic CVD and familial hypercholesterolemia and a plasma LDL-C level ⩾1.8 mmol/L despite maximally tolerated statin therapy, with BA added to their regimen. Plasma LDL-C levels decreased by approximately 18%. In the CLEAR Harmony study, the baseline LDL-C was ⩾1.8 mmol/L, while in CLEAR Wisdom, the mean baseline LDL-C was 3.1 ± 0.98 mmol/L. In CLEAR Harmony, at 12 weeks of BA therapy, the mean LDL-C level decreased by 0.5 mmol/L. Treatment with BA led to a significantly greater reduction in LDL-C levels compared to

the placebo group, both at week 12 ($p < 0.001$) and week 24 ($p < 0.001$). In the CLEAR Wisdom study, at week 12, BA reduced LDL-C significantly more than placebo (–15.1% vs. +2.4%, respectively; $p < 0.001$). The mean LDL-C level at week 12 was 2.5 mmol/L in the BA group compared to 3.9 mmol/L in the placebo group [20, 23].

While the aforementioned studies assessed the efficacy of BA as an add-on lipid-lowering therapy in patients on maximum statin therapy, the CLEAR Serenity study included 345 patients with hypercholesterolemia and a history of intolerance to at least two statins (one statin at the lowest available dose). Patients were randomized 2:1 to receive oral BA 180 mg or placebo once a day for 24 weeks. At baseline, the mean LDL-C level was 4.08 ± 1.03 mmol/L, non-HDL-C was 4.99 ± 1.16 mmol/L, mean total cholesterol was 6.32 ± 1.2 mmol/L, apolipoprotein B (apoB) was 3.66 ± 0.81 mmol/L, and the median hs-CRP was 0.03 μmol/L (Q1-Q3: 0.01-0.05 μmol/L). BA treatment significantly reduced LDL-C from baseline to week 12 (placebo-corrected difference, –21.4% [95% CI: –25.1% to –17.7%]; $p < 0.001$). Significant reductions in BA group compared to placebo were also observed for non-HDL-C (–17.9%), total cholesterol (–14.8%), apoB (–15.0%), and hs-CRP (–24.3%); ($p < 0.001$ for all comparisons). BA was well-tolerated and safe. The most common muscle-related adverse event was myalgia, observed in 4.7% and 7.2% of patients receiving BA and placebo, respectively. This study expanded the evidence for the long-term use of BA in patients with statin intolerance [24].

BA affects blood levels of urea nitrogen, uric acid, and creatinine, increasing their levels. The drug also led to a decrease in hemoglobin levels. The incidence of gout was higher in the BA group compared to the placebo group (1.6 per 100 person-years vs. 0.5 per 100 person-years). The incidence of new-onset diabetes/hyperglycemia was lower in the BA group compared to the placebo group (4.7 per 100 vs. 6.4 per 100) [21].

The use of BA for the primary prevention of CVD was evaluated in the double-blind, randomized, placebo-controlled cardiovascular outcomes trial CLEAR Outcomes, involving 13,970 patients at high CVD risk, with statin intolerance, and an LDL-C level ≥2.59 mmol/L, who received BA (180 mg/day). Among the 13,970 patients included, 4,206 (30%) met the criteria for primary CVD prevention; of these, 2,100 were randomized to the BA treatment group and 2,106 to the placebo group. The mean LDL-C level was 3.69 mmol/L, mean HDL-C was 1.32 mmol/L, median TG was 4.19 mmol/L, and median hs-CRP was 0.06 mmol/L. Compared to placebo, BA reduced LDL-C by 21.3% after 6 months of treatment and reduced hs-CRP by 21.5% after 12 months of treatment. In the subgroup of high-risk CVD patients, the use of BA for primary CVD prevention was associated with a reduced incidence of major cardiovascular events. Specifically, BA reduced the risk of major adverse cardiovascular events by 13% (HR = 0.87; 95% CI 0.79–0.96; $p = 0.004$) [25, 26].

Thus, BA has become a long-awaited pharmacological alternative for lowering LDL-C levels both in patients not achieving target LDL-C levels on maximally tolerated statin therapy and in patients with statin intolerance. BA can be prescribed as monotherapy or as an add-on to treatment with maximally tolerated doses of statins and ezetimibe in patients who have not reached their target LDL-C level.

Agents for reducing triglyceride levels

Epidemiological and clinical studies clearly demonstrate a correlation between CVD risk and plasma TG levels. However, TGs play a secondary role in the formation of atherosclerotic plaques and are not directly involved in their development, as they can be broken down by most cells in the body. Consequently, TGs are not a direct cause of atherosclerosis. Nevertheless, recent attention has focused on the causal relationship between TGs, triglyceride-rich lipoproteins (TRLs), and their remnants in the risk of developing atherosclerosis. Genetic, epidemiological, and clinical studies suggest a causal link between TRLs and their remnants and an increased risk of atherosclerosis, and this dyslipidemia may be an independent risk factor for adverse cardiovascular events. Specifically, in patients with obesity, metabolic syndrome, diabetes, and chronic kidney disease, abnormal levels of TRLs and their remnants significantly increase the risk of developing atherosclerosis and CVD. The accumulation of excessively synthesized TRLs in the plasma, impaired function of enzymes involved in TRL lipolysis, and disrupted hepatic clearance of cholesterol-rich TRL remnants can lead to the deposition of TRLs and their remnants in the arteries, promoting the formation of foam cells and arterial wall inflammation. Thus, understanding the pathogenesis of

TRL-induced atherosclerosis and implementing targeted treatment may slow the progression of atherosclerosis, thereby reducing the morbidity and mortality from CVD, particularly coronary heart disease resulting from coronary artery atherosclerosis [27].

According to American clinical guidelines, omega-3 fatty acids or fibrates are prescribed to patients with hypertriglyceridemia for the prevention of pancreatitis [28]. European clinical guidelines recommend prescribing omega-3 polyunsaturated fatty acids in combination with statins for patients with elevated blood TG levels between 1.5 and 5.6 mmol/L [29].

Pemafibrate

Fibrates are TG-lowering drugs that act as agonists of the peroxisome proliferator-activated receptor alpha (PPARα). These receptors are located on the membranes of hepatocytes, platelets, macrophages, as well as muscle, heart, kidney, and adipose tissue cells. Upon activation, PPARα receptors stimulate or suppress genes responsible for metabolic processes in the body. A meta-analysis demonstrated that fibrates reduce the risk of CVD in a subgroup of patients with high baseline plasma TG levels [30].

Drugs in this class include: pemafibrate, bezafibrate, gemfibrozil, and fenofibrate.

Pemafibrate is the first selective PPARα receptor agonist. Its activity exceeds that of fenofibrate, or more precisely its active form (fenofibric acid), by more than 2500 times. Pemafibrate demonstrates 2500 times greater affinity than fenofibric acid (the active metabolite of fenofibrate) for human PPAR-α, with over 5000 times greater affinity for PPAR-α than for PPAR-γ or -δ, thus requiring much lower doses and consequently limiting adverse effects [31].

The efficacy and safety of add-on therapy with pemafibrate for treating residual hypertriglyceridemia despite statin treatment were evaluated in a multicenter, randomized, double-blind, placebo-controlled, parallel-group, comparative clinical study on Japanese patients. The study included 751 patients with dyslipidemia who were taking pitavastatin. They were randomized into four groups of 188 patients each, assigned to receive either placebo or pemafibrate at doses of 0.1, 0.2, or 0.4 mg/day. These patients had residual dyslipidemia with mean fasting TG levels between 3.9 mmol/L and 4.3 mmol/L despite pitavastatin treatment, while the mean LDL-C level ranged from 3.0 mmol/L to 3.2 mmol/L. Treatment continued for 12 weeks. Results from this first study showed that TG levels decreased significantly by approximately 50% from baseline to week 12 in all combination therapy groups, whereas no significant changes were observed in the pitavastatin monotherapy group. A dose-dependent reduction in TG levels was confirmed, and the decrease in TG levels from baseline to week 12 was statistically significant ($p<0.001$) in all pemafibrate combination therapy groups compared to the pitavastatin monotherapy group [32].

The incidence of adverse events and adverse drug reactions in the pemafibrate combination therapy groups was comparable to that in the statin monotherapy groups, without any significant findings in the study [32].

The efficacy and safety of pemafibrate were also convincingly demonstrated among patients in a European randomized, double-blind, placebo-controlled Phase II study. The study included 408 patients who had been taking a stable dose of a statin (except pravastatin, lovastatin, or fluvastatin) for at least 12 weeks prior to the study and continued taking the same statin at an unchanged dosage throughout the study. At enrollment, the observed patients had fasting TG levels between 1.97 mmol/L and 5.65 mmol/L, HDL-C concentrations of ⩽1.30 mmol/L for men and ⩽1.43 mmol/L for women, and LDL-C concentrations not exceeding target values by more than 0.259 mmol/L. Patients were randomized to placebo or one of the following pemafibrate dosing regimens: 0.05 mg twice daily, 0.1 mg twice daily, 0.2 mg twice daily, 0.1 mg once daily, 0.2 mg once daily, or 0.4 mg once dailyRandomized patients received two tablets in the morning and two in the evening for 12 weeks. The tablets contained either the investigational drug (at doses of 0.05 mg, 0.1 mg, or 0.2 mg per tablet) or a matching placebo. Study results showed that pemafibrate reduced TG levels at any dosage ($p<0.001$), with the greatest placebo-adjusted reduction from baseline to week 12 observed in the 0.2 mg twice-daily regimen group (54.4%). A significant increase in HDL-C levels, ranging from 7.4% to 12.9%, was also observed at all dosages except 0.1 mg once daily ($p<0.05$). A significant increase in LDL-C levels, ranging from 9.2% to 20.5%, was observed at all dosages except 0.05 mg twice daily ($p<0.05$). Pemafibrate was safe and generally well-tolerated. However, some pa-

tients exhibited a minor increase in serum creatinine and homocysteine concentrations [33].

Omega-3 Fatty Acid formulations

Omega-3 polyunsaturated fatty acids include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which exert their effects indirectly through the activation of peroxisome proliferator-activated receptors (PPAR). By reducing the concentration of very-low-density lipoproteins, they lower triglyceride levels in the blood plasma [34].

Although omega-3 fatty acids are recommended for patients with severe hypertriglyceridemia in addition to statin therapy, the benefits of this approach for both primary and secondary prevention of CVD have not been confirmed by most conducted studies [34, 35].

For example, the multicenter, randomized, double-blind, placebo-controlled REDUCE-IT trial involved 8,179 patients with elevated plasma TG levels (1.69 to 5.63 mmol/L), LDL-C levels (1.06 to 2.59 mmol/L), and a history of atherosclerotic CVD or diabetes, who were receiving stable statin therapy for at least 4 weeks prior to the study. Patients were randomly assigned to groups receiving 2 grams of icosapent ethyl (an ethyl ester of eicosapentaenoic acid — an omega-3 polyunsaturated fatty acid ethyl ester) twice daily (total daily dose of 4 g) or placebo. Patients were followed for a median of 4.9 years. The primary composite endpoint was a combination of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. A key secondary endpoint (KSE) was the composite of cardiovascular death, nonfatal MI, or nonfatal stroke. PCE events occurred in 17.2% of patients in the icosapent ethyl (IE) group compared to 22.0% in the placebo group (HR=0.75; 95% CI: 0.68–0.83; p<0.001); corresponding rates for the KSE were 11.2% and 14.8% (HR=0.74; 95% CI: 0.65–0.83; p<0.001). The incidence of additional ischemic endpoints was significantly lower in the icosapent ethyl group than in the placebo group, including the rate of cardiovascular death — 4.3% vs. 5.2% (HR=0.80; 95% CI: 0.66–0.98; p=0.03). A greater number of patients in the icosapent ethyl group were hospitalized for atrial fibrillation or flutter compared to the placebo group (3.1% vs. 2.1%, p=0.004). Serious bleeding events were observed in 2.7% of patients in the icosapent ethyl group and 2.1% in the placebo group (p=0.06) [36].

The effect of icosapent ethyl on the progression of coronary atherosclerosis in patients with elevated TG levels on statin therapy was studied in the randomized, double-blind, placebo-controlled EVAPORATE trial. This study included 80 patients aged 30 to 85 years with diagnosed coronary atherosclerosis (≥20% stenosis in one coronary artery by invasive coronary angiography or coronary computed tomography angiography (CCTA)), elevated fasting TG (1.52-5.63 mmol/L), and LDL-C levels from ≥1.04 to ≤2.98 mmol/L, who were on stable statin therapy (with or without ezetimibe), and adhering to a diet and exercise regimen for ≥4 weeks prior to the study. All patients followed a low-cholesterol diet and continued their current statin therapy during the study. Patients were randomized 1:1 to receive IE 4 g/day or mineral oil as a placebo to assess the rate of plaque volume progression via CCTA. Patients underwent interim scanning at 9 months and final scanning at 18 months using CCTA. The predefined PCE was the change in plaque volume at 18 months between the IE and placebo groups. The study results showed a significant reduction in the PCE, as IE reduced plaque volume by 17%, while in the placebo group, plaque volume more than doubled (+109%) (p=0.0061). Significant differences in progression rates between the IE and placebo groups were also observed at the end of the study, including volumes of fibrous and fibrofatty plaques, which regressed in the IE group and progressed in the placebo group (p<0.01 for all). However, no statistically significant differences were found in the main lipid parameters (total cholesterol, LDL-C, HDL-C, and TG) from baseline to follow-up with either therapy [37].

However, opposing results were obtained in the randomized, double-blind, placebo-controlled, event-driven STRENGTH trial, which evaluated the long-term outcomes of risk reduction with omega-3 carboxylic acids in patients at high cardiovascular risk with hypertriglyceridemia on statin therapy [38, 39]. This drug is an omega-3 fatty acid formulation that undergoes an additional manufacturing step of hydrolyzing and distilling ethyl esters into omega-3 free fatty acids (omega-3 carboxylic acids) with a 75% concentration of EPA and DHA. Given its free fatty acid formulation, the drug does not require hydrolysis by pancreatic lipase, unlike conventional omega-3 ethyl

esters, to enhance intestinal absorption. This higher bioavailability is supported by its lack of dependence on dietary fat content.

The study included 13,086 patients aged ≥18 years who had been on a stable diet and taking statins for at least 4 weeks prior to the study initiation, with confirmed:

- LDL-C level < 2.59 mmol/L; however, subjects were also eligible for participation if their LDL-C level was ≥ 2.59 mmol/L, provided they were receiving high-intensity or maximally tolerated statin therapy, with or without ezetimibe;
- Atherogenic dyslipidemia, defined as TG levels ≥ 2.03 mmol/L and < 5.650 mmol/L and HDL-C < 1.09 mmol/L for men or < 1.22 mmol/L for women, measured after an overnight fast;
- High risk of future cardiovascular events.

The mean age of the studied patients was 62.5 ± 9.0 years. The cohort included 35% women and 65% men; 70% of all patients also had diabetes. The median LDL-C level was 1.94 mmol/L, the median TG level was 2.71 mmol/L, the median HDL-C level was 0.93 mmol/L, and the median hs-CRP level was 0.05 mmol/L.

Patients who met all inclusion criteria and voluntarily agreed to participate were randomized in a 1:1 ratio to receive either the study drug at 4 g/day or a corresponding placebo (corn oil). The study duration was 5 years.

The PCE was a composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina. KSEs included:

- The composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina in patients with established cardiovascular disease at baseline;
- The composite of cardiovascular death, nonfatal MI, and nonfatal stroke in the entire cohort and in patients with established cardiovascular disease at baseline;
- The composite of cardiac death, nonfatal MI, coronary revascularization, and hospitalization for unstable angina in the entire cohort and in patients with established cardiovascular disease at baseline;
- Cardiovascular death in the entire cohort and in patients with established cardiovascular disease at baseline;
- All-cause mortality in the entire cohort and in patients with established cardiovascular disease at baseline.

Prespecified tertiary efficacy endpoints (TCE) included newly diagnosed atrial fibrillation, thrombotic complications, and newly diagnosed heart failure. Changes in lipid levels, inflammatory markers, and EPA/DHA levels were also prespecified efficacy parameters. A retrospective analysis examined the association between plasma and erythrocyte EPA/DHA concentrations and the incidence of cardiovascular events [38, 39].

The study was terminated prematurely after 1,384 patients experienced a PCE, based on an interim analysis of the study results that indicated a low probability of clinical benefit for Epanova compared to the corn oil placebo. Of the 13,078 treated patients, 12,633 (96.6%) completed the study with confirmed PCE status. The PCE occurred in 785 patients (12.0%) receiving Epanova compared to 795 patients (12.2%) receiving placebo (HR = 0.99; 95% CI: 0.90–1.09; p = 0.84). The Epanova group had a higher incidence (24.7%) of gastrointestinal adverse effects (diarrhea, nausea, dyspepsia, and abdominal discomfort) compared to patients receiving placebo (14.7%) [38, 39].

Among patients at high cardiovascular risk taking statins, the addition of the omega-3 carboxylic acid formulation to usual background therapy did not lead to a significant change in the composite outcome of major adverse cardiovascular events compared to corn oil-based placebo. These results do not support the use of this specific omega-3 fatty acid formulation for reducing the incidence of major cardiovascular events in high-risk patients [38, 39].

Conclusion

Hypolipidemic therapy is primarily conducted to reduce the risk of CVDs. Statins have established themselves as first-line drugs for lowering plasma levels of LDL-C, a well-known risk factor for CVD. However, even with optimal statin therapy, a significant residual cardiovascular risk persists. Consequently, new drugs with mechanisms different from statins that lower LDL-C levels, as well as new targets beyond LDL-C for intervention to reduce the risk of atherosclerosis progression, are undoubtedly necessary.

Modern physicians have at their disposal a wide array of hypolipidemic drug classes with diverse mechanisms of action, the efficacy and safety of

which have been demonstrated in large, randomized, placebo-controlled trials. Consequently, for patients with dyslipidemia and atherosclerotic CVD who fail to achieve their target lipid profile on maximally tolerated statin therapy or in statin-intolerant patients, a broad selection of alternative hypolipidemic agents is now available. It is crucial to emphasize, nonetheless, that statins remain the first-line therapy for initiating lipid-lowering treatment.

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