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ALTERNATIVES TO STATINS IN THE TREATMENT OF HYPERCHOLESTEROLEMIA

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ABSTRACT

Hypercholesterolemia is one of the main modifiable risk factors for cardiovascular disease. Elevated levels of LDL (low-density lipoprotein) cholesterol lead to the development of atherosclerosis and cardiovascular complications. Statins are the mainstay of hypercholesterolemia therapy, but in some patients, therapeutic goals are not achieved or side effects occur. It is necessary to develop alternatives to statins for the treatment of hypercholesterolemia. Drugs that act on other stages of cholesterol synthesis are being sought. Publications covering observational studies, randomized controlled trials (RCTs), and meta-analyses on alternative therapies for hypercholesterolemia to statin treatment were analyzed. The following were described: cholesterol absorption inhibitor (ezetimibe), ATP citrate lyase inhibitor (bempedoic acid), PCSK9 inhibitors (evolocumab, alirocumab) , siRNA against PCSK9 (inclisiran), ANGPTL3 inhibitors (evinacumab), ANGPTL4, ANGPTL8 and ANGPTL3/8 complex inhibitors, fibrates and nutraceuticals (plant sterols, fermented red yeast rice extract (Red Yeast Rice, RYR) , berberine). The impact of these drugs on patients' lipid profiles and cardiovascular risk was discussed. Attention was also drawn to the need for individualization of hypercholesterolemia therapy.
Aim of this study: The objective of this study is to summarize the latest reports on alternative therapies for hypercholesterolemia to statins.
Materials and methods: A literature review was conducted using the professional PubMed database. Searches included combinations of the keywords: “hypercholesterolemia,” “ezetimibe,” “bempedoic acid,” and “PCSK9 inhibitors.”

KEYWORDS

Hypercholesterolemia, Ezetimibe, Bempedoic Acid, PCSK9 Inhibitors

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Introduction

Hypercholesterolemia, and particularly elevated LDL cholesterol (LDL-C) levels, is a major risk factor for cardiovascular disease. Statins are the primary class of lipid-lowering drugs used in both primary and secondary prevention [1].

Statins inhibit the activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), a key enzyme in the cholesterol biosynthesis pathway in the liver, leading to a reduction in its production and an increase in the expression of LDL receptors on hepatocytes [2]. Intensive statin therapy can reduce LDL-C by as much as 50–60%, which is particularly important in patients with high and very high cardiovascular risk [3]. Statins also have pleiotropic effects, such as anti-inflammatory action, improvement of endothelial function, and stabilization of atherosclerotic plaques [4]. Statins have been shown to reduce the risk of cardiovascular events [5].

Some patients are intolerant to statins. The most commonly observed adverse effects include myopathies [2]. In patients with very high cardiovascular risk, statins alone are not always sufficient to achieve LDL-C target values, which necessitates the development of alternative pharmacological strategies [6,7].

Main alternatives and additions to therapy

Ezetimibe — cholesterol absorption inhibitor

Ezetimibe works by selectively binding to the NPC1L1 sterol transporter in the small intestine, which leads to reduced absorption of dietary and bile cholesterol. As a result, less cholesterol reaches the liver and LDL-C uptake from the blood increases. Studies have shown that adding ezetimibe to a statin increases LDL-C reduction by an additional 15–24% compared to statin alone [8]. A retrospective clinical study published in 2025 showed that patients treated with the combination of ezetimibe + rosuvastatin achieved a greater reduction in LDL-C and improvement in lipid profile compared to statin monotherapy [6]. Clinical trials have shown a reduction in the incidence of cardiovascular events, especially when ezetimibe is administered to patients with coronary artery disease [9].

Studies confirm the benefits of combination therapy. Analyses based on the large IMPROVE-IT study confirmed that adding ezetimibe to statins in patients after acute coronary syndrome leads to an additional reduction in LDL-C and improved clinical outcomes, including a lower risk of recurrent cardiovascular events [10]. Ezetimibe is also used in combination with bempedoic acid (discussed later in this review) in patients who are intolerant to statins [9].

Although statins have a greater effect on LDL-C than ezetimibe, this drug as monotherapy also lowers LDL-C levels in patients with hypercholesterolemia, as confirmed by clinical studies [11].

Ezetimibe has a favorable safety profile and is generally well tolerated by patients, with an incidence of adverse events comparable to placebo in randomized controlled trials [12]. Furthermore, adding ezetimibe to statins does not significantly increase the risk of serious adverse events [8].

Bempedoic acid (ATP citrate lyase inhibitor)

Bempedoic acid (also known as ETC-1002) is a prodrug that is activated in the liver by very-long-chain acyl-CoA synthetase-1 (ACSVL1) to the active metabolite bempedoic acid–CoA, which selectively inhibits ATP citrate lyase (ACLY). Inhibition of ACLY reduces the production of cytosolic acetyl-CoA, which in turn limits cholesterol biosynthesis. This results in increased expression of LDL receptors in hepatocytes and accelerated uptake of LDL-C from the bloodstream. ACLY inhibition in muscle tissue is minimal, which explains the lower risk of myopathy compared to statins [13]. In addition, ACLY is associated with other metabolic processes, such as fatty acid synthesis and inflammatory pathways, indicating potential additional effects of bempedoic acid beyond LDL-C reduction [14].

Bempedoic acid administered orally at a dose of 180 mg/day has good bioavailability and is activated mainly in the liver, which limits exposure in muscles. It does not interact significantly with cytochrome P450, but the metabolite bempedoic acid glucuronide may affect organic anion transporters (OAT), which is important in the context of drug interactions. This drug reversibly inhibits the renal transporters OAT 2 and OAT 3, so its use is associated with an increase in plasma creatinine and uric acid concentrations [13].

Clinical trials have shown that bempedoic acid effectively lowers LDL-C levels in patients with hypercholesterolemia. Monotherapy and combination therapy with ezetimibe or statins led to a significant reduction in LDL-C, apolipoprotein B, and high-sensitivity C-reactive protein (hs-CRP) — often with a greater effect in combination with ezetimibe in patients intolerant to statins [15].

In an analysis of a large sample of approximately 14,000 patients in the CLEAR Outcomes study, treatment with bempedoic acid was associated with an approximately 20% reduction in LDL-C and a significant reduction in the risk of first and subsequent cardiovascular events in a high-risk population with statin intolerance [16].

One of the key therapeutic successes is the effect of bempedoic acid on cardiovascular events, which has been confirmed in prospective clinical trials. Prespecified CLR (CLEAR Outcomes) analyses showed that treatment with bempedoic acid reduced the total incidence of MACE-4 (composite event: cardiovascular death, myocardial infarction, stroke, revascularization) and subsequent MACE episodes compared to placebo [16]. Additional analyses indicate that bempedoic acid used in patients with statin intolerance reduced median hsCRP and mean LDL-C by approximately 21% after 6 months [17].

In clinical trials, bempedoic acid has been shown to have a generally good safety profile. The most commonly observed adverse events are hyperuricemia, gout, and mild changes in liver enzymes. No significant increase in the incidence of myopathy was observed compared to placebo [13].

Bempedoic acid represents an important addition to lipid-lowering therapy, especially in patients who are intolerant to statins or who do not achieve LDL-C targets despite maximum statin therapy. Its mechanism of action, limited expression of the active form outside the liver, and promising data on the reduction of

cardiovascular events make it a valuable clinical tool [15]. The inclusion of bempedoic acid in treatment may contribute to better achievement of individual therapeutic goals, especially in high-risk groups and in people with statin intolerance.

PCSK9 inhibitors (monoclonal antibodies: evolocumab, alirocumab)

PCSK9 is a protein produced primarily in the liver that binds to the LDL receptor on the surface of hepatocytes and accelerates its degradation, limiting the recirculation of receptors on the cell surface and reducing the uptake of LDL cholesterol (LDL-C) from the circulation. PCSK9 inhibitors block this protein, increase the number of available LDL receptors, and intensify its clearance from the bloodstream [18].

There are two types of PCSK9 inhibitors: monoclonal antibodies, such as alirocumab and evolocumab, administered subcutaneously every few weeks, and RNA interference (siRNA)- inclisiran, which inhibits PCSK9 synthesis in the liver and acts over a longer period with less frequent administration (approximately every 6 months) [18]. Inclisiran is described in more detail later in the review.

Clinical trials have shown that PCSK9 inhibitors can reduce LDL-C levels by as much as 50–60% in patients with hypercholesterolemia, including those with familial hypercholesterolemia or high cardiovascular risk [18].

Large clinical trials, such as FOURIER and ODYSSEY Outcomes, have shown that the use of PCSK9 inhibitors is associated with a significant reduction in cardiovascular events, as well as a reduction in the incidence of cardiovascular events such as heart attack or stroke [18].

In patients with heterozygous familial hypercholesterolemia (HeFH), PCSK9 inhibitors significantly reduce LDL-C, often achieving therapeutic targets that are difficult to achieve with statins alone or in combination with ezetimibe [19]. PCSK9 inhibitor therapy is recommended in guidelines for patients at high cardiovascular risk who have not achieved sufficient LDL-C reduction despite maximum therapy with statins and other drugs [20].

PCSK9 inhibitors generally have a good safety profile. The most commonly reported adverse reactions are injection site reactions and flu-like symptoms [18].

Clinical trials have shown a reduction in cardiovascular events (including heart attack and stroke) in high-risk patients using PCSK9 inhibitors. These drugs are particularly useful in patients with heterozygous familial hypercholesterolemia or in patients in whom statins and ezetimibe are not sufficiently effective or are not tolerated. The main barriers remain the cost and the need for subcutaneous administration every few weeks [21].

Inclisiran- siRNA against PCSK9

Inclisiran is a synthetic siRNA that binds to mRNA encoding PCSK9 in the liver, leading to its degradation and a reduction in PCSK9 protein levels. The reduction in PCSK9 results in a greater number of LDL receptors on the surface of hepatocytes, which increases LDL uptake from the blood. This mechanism is fundamentally different from that of statins, which inhibit the enzyme HMG-CoA reductase [22]. An advantage of inclisiran is its convenient dosing schedule (initially, after 3 months, then every 6 months), which may improve adherence. Data on the impact on end-point cardiovascular events are still being collected. Although significant reductions in LDL-C have been demonstrated, further studies with longer follow-up are needed [23].

The ORION studies (ORION-9, ORION-10, ORION-11) involving patients with heterozygous familial hypercholesterolemia (HeFH) and high cardiovascular risk showed a significant reduction in LDL-C levels. The study lasted 18 months, with patients receiving four doses of inclisiran at 284 mg (one dose on days 1, 90, 270, and 450). Inclisiran therapy resulted in a 40-55% reduction in LDL-C compared to placebo [24].

Meta-analyses of randomized controlled trials confirm that inclisiran significantly reduces LDL-C (by approximately 46–51%) and other lipid parameters, such as apoB and total cholesterol. These changes are associated with a good safety profile, without a significant increase in serious adverse events [25].

In the ORION-5 study of homozygous familial hypercholesterolemia (HoFH), inclisiran did not show a significant reduction in LDL-C, indicating limited efficacy in this patient group [26].

Meta-analyses have shown that inclisiran is well tolerated and that the incidence of serious adverse events is similar to that of placebo. The most commonly reported side effect was mild reactions at the injection site [27].

Data on the effect of inclisiran on end-point cardiovascular events are still being collected. Although significant reductions in LDL-C have been demonstrated, further studies with longer follow-up periods are necessary [23].

ANGPTL3 inhibitors (evinacumab)

Hypercholesterolemia, particularly in the form of homozygous familial hypercholesterolemia (HoFH), is a significant cardiovascular risk factor and often does not respond adequately to standard LDL-lowering therapies despite treatment with maximum doses of statins, ezetimibe, and PCSK9 inhibitors. New pharmacological strategies are needed, especially those that act independently of the LDL receptor. One target for therapy is ANGPTL3 (angiopoietin-like protein 3), which regulates lipoprotein metabolism by inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL) [28].

ANGPTL3 is a protein secreted mainly by the liver that inhibits LPL and EL activity, contributing to increased triglyceride and LDL-C levels. Natural mutations that inactivate ANGPTL3 are associated with lower lipid levels and a reduced risk of cardiovascular disease, highlighting the therapeutic potential of pharmacological inactivation of this protein [29].

Evinacumab is a fully human IgG4 monoclonal antibody directed against ANGPTL3. It binds to circulating ANGPTL3, neutralizing its inhibitory effect on LPL and EL, which leads to increased triglyceride lipolysis and accelerated removal of apoB-rich lipoproteins, including LDL. The mechanism of action of evinacumab is independent of LDL receptor function, which distinguishes it from other lipid-lowering therapies and enables its efficacy in HoFH [30].

In a phase III study (ELIPSE HoFH), evinacumab administered intravenously at a dose of 15 mg/kg every 4 weeks resulted in an approximately 47% reduction in LDL-C compared to placebo in patients with HoFH despite maximum lipid therapy. This effect was independent of residual LDL receptor activity [31].

Phase II trial data showed that evinacumab significantly reduces LDL-C levels in patients with hypercholesterolemia resistant to standard treatment, with LDL-C reductions of approximately 50% [31]. Studies have shown that inhibition of ANGPTL3 by evinacumab increases the rate of apo-B IDL (intermediate-density lipoprotein) and apo-B LDL breakdown, contributing to a significant reduction in LDL-C [32].

Evinacumab is generally well tolerated. The most commonly reported adverse reactions include nasopharyngitis, flu-like symptoms, dizziness, and injection site reactions. No significant differences in the incidence of adverse reactions were observed between the treatment group and the placebo group [31].

Unlike statins, ezetimibe, or PCSK9 inhibitors, which increase LDL uptake by the LDL receptor, evinacumab acts independently of this mechanism. This makes it particularly useful in patients with minimal or no LDL receptor function [31]. ANGPTL3 inhibitors, such as evinacumab, open up new perspectives in the treatment of severe hypercholesterolemia, including HoFH and mixed hyperlipidemia [33].

Inhibitors of ANGPTL4, ANGPTL8, and the ANGPTL3/8 complex

ANGPTL4 is secreted by adipocytes, hepatocytes, and muscle cells. Its activity inhibits lipoprotein lipase (LPL) by breaking down the active form of the enzyme, which limits the hydrolysis of triglycerides (TG). Observations at the molecular level have shown that loss of ANGPTL4 function leads to a decrease in TG and an increase in HDL (high-density lipoprotein) cholesterol, which is beneficial in the context of atherogenesis and coronary heart disease risk [34].

ANGPTL8 interacts with ANGPTL3 and ANGPTL4 to form complexes that differentiate the effect on LPL activity in different tissues. The ANGPTL3/8 complex has a stronger inhibitory effect on LPL than ANGPTL3 alone, leading to an increase in TG and potentially LDL-C. The antagonism of the interaction between ANGPTL8 and ANGPTL3 therefore promotes LPL activation and improves the lipid profile [35].

The therapeutic mechanism involves blocking the action of ANGPTL4, which increases LPL activity and accelerates the metabolism of TG and cholesterol particles. Preliminary clinical trials of the ANGPTL4-inhibiting antibody MAR001 have shown that its administration results in a significant reduction in TG (52.7% at week 12 of treatment with a dose of 450 mg) and residual cholesterol (RC) (52.5%) with a good safety profile [36].

Animal models have indicated possible adverse metabolic effects (e.g., lymph node inflammation), but analysis of epidemiological data suggests that ANGPTL4 inhibition in humans may be relatively safe [36].

Although direct ANGPTL8 inhibitors are in early-stage research, ANGPTL3/8 complex antagonism is currently being tested in the context of treating mixed dyslipidemia. In a clinical trial, an antibody blocking ANGPTL3/8 (LY3475766) lowered TG, RC, and LDL-C while increasing HDL cholesterol, making it a promising therapeutic tool [37].

ANGPTL4 and ANGPTL8 inhibitors work differently than statins or PCSK9 inhibitors — instead of increasing LDL-C removal via the LDL receptor, they modulate TG and HDL metabolism by affecting

LPL/EL. Their use may therefore complement existing therapies, especially in patients who do not respond to statin treatment and other interventions [36].

Preliminary clinical trial results indicate that pharmacological inhibition of ANGPTL4 and the ANGPTL3/8 complex may be beneficial in patients with hypercholesterolemia, particularly in cases of elevated TG and mixed dyslipidemia. The activity of these inhibitors may not only lead to a reduction in LDL-C, but also to an improvement in the TG and HDL-C profile, which may reduce the risk of atherosclerotic cardiovascular disease (ASCVD) [37].

Further research is needed to assess the long-term impact of ANGPTL4, ANGPTL8 and ANGPTL3/8 complex inhibitors on cardiovascular events, optimal strategies for combining them with conventional therapy, and precise identification of the population that will benefit most from this therapy.

Fibrates

Fibrates activate the PPAR-α receptor (peroxisome proliferator-activated receptor alpha), which leads to increased lipoprotein lipase (LPL) activity, reduced TG synthesis, increased HDL-C concentration through increased production of apolipoproteins A-I and A-II and an effect on the metabolism of very light density lipoprotein (VLDL) and LDL metabolism, including a partial reduction in LDL-C. These mechanisms translate into a clinically significant reduction in blood triglyceride levels (usually by 20-50%) and an increase in HDL cholesterol, although the effect on LDL cholesterol is variable and depends on the patient's lipid profile [38].

An analysis of 63 randomized controlled trials showed that fibrates significantly reduce triglyceride levels compared to placebo. Fenofibrate and bezafibrate showed a significant reduction in TG, and fenofibrate also had a beneficial effect on apolipoprotein B and non-HDL cholesterol (non-HDL-C) [39].

Pemafibrate — a selective PPAR-α modulator (SPPARMα) — exhibits more targeted agonistic activity, with a potentially better efficacy and safety profile compared to classic fibrates. As a result, pemafibrate may induce stronger regulation of PPAR-α target genes with less impact on renal and hepatic parameters [40]. Pemafibrate significantly reduces TG levels and improves other lipid parameters compared to placebo or other fibrates. In a clinical meta-analysis, pemafibrate reduced TG and non-HDL-C and increased HDL-C, while maintaining a favorable safety profile [41].

Although triglyceride reduction is a well-documented effect of fibrates, translating this into clinical benefits, such as reducing the risk of cardiovascular events, is more complex. A meta-analysis showed that fibrate therapy is associated with a reduction in the risk of MACE (major adverse cardiovascular events), but this was more correlated with a reduction in LDL-C than with a decrease in TG. It was shown that each 1 mmol/L reduction in LDL-C after fibrate therapy was associated with a reduction in the risk of MACE, while the change in TG was not significantly associated with this reduction [42].

Studies involving patients with high TG or atherogenic dyslipidemia have observed a greater therapeutic effect in terms of cardiovascular risk, suggesting a possible context dependent on the patient's lipid profile [38].

In studies with pemafibrate (e.g., the PROMINENT study involving the use of pemafibrate in patients with diabetes), TG reduction did not translate into a significant reduction in cardiovascular events, indicating the complexity of the relationship between TG levels and clinical outcomes [38]. Studies show a significant reduction in TG and improvement in HDL-C with good drug tolerance, even in long-term therapy [43]. The most common side effects of fibrates are interactions with other drugs, including statins, which increase the risk of myopathy and worsening liver and kidney parameters. In the case of pemafibrate, few drug interactions have been observed, and there have been fewer cases of increased serum creatinine and decreased estimated glomerular filtration rate (eGFR). Pemafibrate is metabolized in the liver and excreted into bile, while many available fibrates are excreted mainly by the kidneys [40].

When assessing the effect of fibrates on triglyceride levels, both their pharmacological effect on lipid metabolism and its clinical consequences should be taken into account. TG reduction is beneficial in itself, especially in patients with hypertriglyceridemia and an increased risk of acute pancreatitis, but its direct impact on reducing the incidence of cardiovascular events remains unclear and often depends on the simultaneous reduction of other lipid fractions [44]. New generations of fibrates, such as pemafibrate, may offer improved TG reduction efficacy and safety profiles, which may influence future treatment recommendations [45]. Further studies are needed to accurately assess the impact of fibrates on patient clinical outcomes.

Nutraceuticals

Nutraceuticals can be divided into several groups, differing in their mechanisms of action.

Plant sterols compete with cholesterol in the intestines for transporters, limiting cholesterol absorption and reducing LDL-C levels. Clinical studies have shown that combinations of sterols and other nutraceuticals significantly lower LDL-C in patients with hypercholesterolemia [46].

Fermented red yeast rice extract (Red Yeast Rice, RYR) contains monacolins, including monacolin K, an HMG-CoA reductase inhibitor similar in action to statins. Clinical studies have shown that RYR supplementation leads to a statistically significant decrease in LDL-C and total cholesterol within 4–12 weeks [47]. However, caution is needed when using products containing monacolin due to their statin-like effects and the risk of myopathy [48].

Berberine increases the expression of LDL receptors in the liver, improving LDL-C uptake from the blood. In combination with other nutraceuticals, such as policosanol and RYR, it has been shown to effectively lower lipids in randomized clinical trials [49].

Soluble fiber binds bile acids, leading to increased cholesterol excretion. Polyphenols (e.g., bergamot or garlic extracts) have antioxidant properties and may support the lipid profile, although their effects require further research [49].

In an RCT involving 88 patients with mild hypercholesterolemia, supplementation with a combination of plant sterols and RYR led to a significant reduction in LDL-C of approximately 20% compared to placebo [46]. Another short-term study showed that a functional beverage containing RYR, sterols, and berberine significantly improved lipid profiles after 12 weeks [47].

A meta-analysis of RCTs confirmed that the combination of berberine, policosanol, and RYR effectively improves the lipid profile by reducing LDL-C and total cholesterol [50].

Nutraceuticals are particularly considered in patients with moderate hypercholesterolemia, in primary prevention, and in individuals with statin intolerance, as an alternative or supplement to pharmacotherapy. Although most studies indicate good tolerance and safety, it is important to remember the potential variability in the composition of preparations and the need for clinical monitoring [51].

Nutraceuticals represent a promising strategy in the treatment of hypercholesterolemia, particularly as a supplement to conventional therapy. However, differences in the quality of preparations, heterogeneity of studies, and the lack of large, long-term clinical trials limit clear recommendations. Further research is needed to better determine the optimal doses and patient populations that will derive real benefits from this therapy in terms of preventing cardiovascular events.

Conclusions

There are many alternative therapies to statins for treating hypercholesterolemia, the clinical effects of which are still being studied. These therapies are particularly important in patients who cannot tolerate statins or who have very high LDL-C levels.

Ezetimibe is an effective and safe tool in the treatment of hypercholesterolemia. Its use in monotherapy may be useful in patients who are intolerant to statins, while in combination therapy with statins it significantly improves the achievement of target LDL-C concentrations and may contribute to improved health outcomes. Future large-scale studies and long-term clinical observations may further define its role in cardiovascular prevention [6,11].

Bempedoic acid is an effective and safe inhibitor of ATP citrate lyase, which significantly lowers LDL-C and reduces the risk of cardiovascular events in patients with hypercholesterolemia. Due to its mechanism of action and tolerability, it is a valuable therapeutic option in the treatment of dyslipidemia, especially in patients with statin intolerance or those requiring additional LDL-C reduction [13,15].

PCSK9 inhibitors represent a breakthrough in the treatment of hypercholesterolemia in patients who do not achieve therapeutic goals with statin therapy or who cannot tolerate statins. By increasing LDL receptor recycling, PCSK9 inhibitors enable a reduction in LDL-C cholesterol levels and a reduction in cardiovascular events [118,21].

Inclisiran offers a new way to lower LDL-C thanks to its unique siRNA technology and convenient twice-yearly dosing schedule. Study results indicate high efficacy in lowering LDL-C and a good safety profile, making it a valuable addition to therapy in patients with hypercholesterolemia resistant to standard treatment or where adherence issues exist. Further large cardiovascular outcome studies are ongoing and are expected to provide additional information on the reduction of cardiovascular risk [23,24].

Evinacumab, as an ANGPTL3 inhibitor, represents a significant expansion of therapeutic options for patients with severe hypercholesterolemia, particularly HoFH and hypercholesterolemia resistant to standard treatment. Thanks to its unique mechanism of action independent of the LDL receptor, evinacumab can significantly reduce LDL-C levels in patients who do not achieve therapeutic goals with other drugs [29,31].

ANGPTL4 is a protein that regulates the activity of lipoprotein lipase (LPL) and endothelial lipase (EL), inhibiting their activity and affecting the transport of TG (triglycerides) and cholesterol. ANGPTL8 interacts with ANGPTL3 and ANGPTL4 in the formation of complexes that modulate LPL activity, especially after a meal [34]. Genetic studies indicate that loss-of-function variants in the ANGPTL4 and ANGPTL8 genes are associated with lower TG and higher HDL-C, while reducing the risk of cardiovascular disease [52]. ANGPTL4 and ANGPTL8 inhibitors are a promising direction for the treatment of dyslipidemia, complementing classic lipid-lowering drugs. Empirical evidence from genetic, clinical, and molecular studies indicates that their use may improve the lipid profile, particularly in patients resistant to standard therapies [35,36].

Fibrates are effective drugs in reducing triglyceride levels, using the mechanism of PPAR-α activation and lipid metabolism modulation [38]. TG reduction is clinically significant, especially in patients with severe hypertriglyceridemia and in the prevention of complications such as pancreatitis. The translation of TG reduction into a reduction in the risk of cardiovascular events is unclear and often interdependent with other changes in the lipid profile [42]. Modern fibrates, including pemafibrate, show promising results in controlling TG and improving lipid parameters, but further studies are needed to determine their full impact on clinical outcomes [45].

Nutraceuticals offer various mechanisms of action that lower LDL cholesterol levels and improve the lipid profile. The best-documented effects are associated with plant sterols, red yeast rice and berberine. Adding nutraceuticals to therapy may be beneficial in selected patients, but their use should be based on scientific evidence and clinically monitored [50,51].

The choice of treatment for hypercholesterolemia should be personalized: in patients with statin intolerance bempedoic acid + ezetimibe or monoclonal PCSK9 inhibitors/inclisiran may be beneficial, while in patients with HoFH, treatment with evinacumab is recommended. Factors such as cost, availability, administration route, interactions and patient preferences influence the therapeutic decision [53].

In patients who do not achieve target LDL-C levels despite the maximum tolerated dose of statins, combination therapy is recommended. The addition of ezetimibe or PCSK9 inhibitors leads to a further significant reduction in LDL-C and cardiovascular risk [54, 55].

The future of hyperlipidemia therapy includes further development of RNA (siRNA) therapy, genome analysis in the treatment of familial hypercholesterolemia, new metabolic targets (including ANGPTL3, ANGPTL4) and optimization of combination strategies. Further studies involving long-term observations of how new drugs affect cardiovascular risk will be decisive for their widespread use [56].

Disclosure

Author's Contribution

Conceptualization, Methodology, Formal analysis, Resources, Writing- original Draft Preparation, Writing-Review and Editing, Visualization and Supervision: Agnieszka Bajkacz.

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