REVIEW ARTICLE

Treatment of dyslipidemia: PCSK-9 in focus

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Summary

Cardiovascular disease is the leading cause of death worldwide, accounting for one-third of the total global mortality. Dyslipidemia is one of the most common risk factors and plays a cardinal role in the development and progression of atherosclerotic cardiovascular disease. Since statin therapy is often insufficient, or cardiovascular disease continues to develop despite achieving target lipid levels, current attention is focused on new therapeutic options with significantly greater efficacy. The reduction in LDL cholesterol levels with PCSK-9 inhibitors is about 60% when used as monotherapy and as much as 85% when combined with high-intensity statins and/or other lipid-lowering therapies. Alirocumab and evolocumab are two monoclonal antibodies that effectively bind to the LDL receptor, interfering with its degradation. Inclisiran is a small interfering RNA that interferes with the synthesis of PCSK-9 molecules and effectively reduces LDL-C. Indications for PCSK-9 inhibitors usage are increasingly expanding due to the discovery of their pleiotropic effects. Additionally, the focus is on discovering new mechanisms of PCSK-9 inhibition that would open the door to the development of new therapeutic agents. Studies on the efficacy and safety of oral PCSK9 inhibitors are ongoing, along with early-stage clinical trials exploring gene-editing strategies for the treatment of dyslipidemias.

The purpose of this review article is to provide an overview of the current knowledge on the application of PCSK-9 inhibitors.

Keywords: dyslipidemia, LDL cholesterol, PCSK-9

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide, accounting for one-third of all-cause mortality. It is estimated to claim around 17.9 million lives each year (1,2). It was the Framingham heart study of the mid-20th century that first established a causative relationship between lipids and accelerated atherogenesis and atherosclerotic cardiovascular disease (ASCVD) (3). Risk factors for ASCVD include hypertension, diabetes, dyslipidemia, tobacco smoking, lack of physical activity and sedentary lifestyle (4,5). Dyslipidemia is the most prevalent risk factor for CVD, playing a crucial role in the onset and advancement of ASCVD (2-4). Dyslipidemia represents an imbalance of lipid metabolism manifested by elevated values of total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C) and triglycerides (Tg) and/or decreased values of high-density lipoprotein-cholesterol (HDL-C) or a combination of mentioned disorders (5-7). The USA data indicate that more than 30% of adults have elevated TC and LDL-C, while approximately 20% have elevated Tg values (7). According to WHO data, dyslipidemia is the cause of more than 4 million deaths each year worldwide (8).

Dyslipidemia can be classified as a primary (inherited) disorder of gene mutation causing overproduction or defective clearance of lipid fractions or as a secondary disorder because of other medical conditions or medication use (6,9,10). Data from 2019 suggest that increased values of LDL-C are responsible for 44% of coronary artery disease (CAD) mortality and 22% ischemic stroke mortality (10). Inherent dyslipidemias can be heterozygous or homozygous. Individuals with heterozygous familial hypercholesterolemia (FH) in most WHO regions are noted to have a higher prevalence of type 2 diabetes compared to those in Europe. Obesity significantly elevates the risk of diabetes in these individuals, particularly when associated with age and use of FH lowering medications (11). Lifestyle interventions focusing on diet and physical activity have been widely studied for their role in reducing obesity, and have shown promising outcomes not only in the prevention of type 2 diabetes (T2D) but also in lowering the risk of cardiovascular diseases (CVD) (12).

In regards of CVD risk assessment, the SCORE (Systemic Coronary Risk Estimation) calculator is in use, particularly the SCORE-2 for estimating the 10-year CVD risk and SCORE2-OP for estimating CVD risk in older individuals (13). However, despite effective risk assessments and the use of standard therapeutic strategies new cardiovascular (CV) events still occur. Identifying FH patients and other high-risk individuals is a key priority in modern preventive cardiology and clinical lipidology (14). It has become evident that residual CVD risk remains implementation of standard medical treatments and interventions, even after achieving LDL-C target values (15,16). Recently, some of the new studies have suggested that the levels of LDL-C are not the only factors significant for the development of ASCVD, but also the cumulative exposure to elevated cholesterol levels over the years, suggesting the necessity of using drugs as early as possible to lower LDL-C levels and reduce the risk for ASCVD (17). Clinical trial results with newly developed lipid-lowering agents demonstrated a significant decrease in CV events. These agents' mechanism of action includes enhancing LDL receptor (LDLR) expression or reducing cholesterol absorption, leading to a substantial reduction in LDL-C (18). The focus has thus shifted from "high-intensity statin therapy" to "high-intensity LDL-C lowering" incorporating combination therapy at an early stage (19). This is how the concept of "lower is better" was born (20). Guidelines emphasize the need for early detection and increased utilization of combination therapies to mitigate the global burden of familial hypercholesterolemia (21).

GUIDELINES FOR MANAGING DYSLIPIDEMIAS: FOCUS ON LIPID MODIFICATION TO REDUCE CV RISK AND OUTLINE THE ROLE OF PCSK-9 INHIBITORS

The most recent comprehensive guidelines of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) for the treatment of dyslipidemia recommend that, after precise CV risk stratification, stepwise approach should be applied, starting with statins, then adding ezetimibe and finally proprotein-convertase subtilisin/kexin type-9 (PCSK-9) inhibitors **(Table 1)** (22,23). The use of high intensity statins is recommended as the first-line therapy for primary and secondary prevention in patients with hypercholesterolemia. If LDL-C target values are not reached for patients on the maximum tolerated dose of statins, adding ezetimibe is recommended as a second-line treatment for primary and secondary prevention. If the desired targets are not reached with the aforementioned combination therapy (statin+ezetimibe), the addition of a PCSK-9 inhibitor is advised in secondary prevention (evidence class Ia).

Furthermore, the guidelines additionally state that PCSK-9 inhibitors can also be recommended for primary CV prevention in high-risk FH patients (with ASCVD or with other major risk factor) who did not reach LDL-C target levels despite maximum tolerated statin therapy and ezetimibe (evidence class Ic). Also, ezetimibe and/or PCSK-9 inhibitors should be considered in patients with dyslipidemia who have statin intolerance as an addition to ezetimibe (evidence class IIb/C) (22,23). Having in mind that early and effective lowering of LDL-C is necessary for a better reduction of new CV events, a new consensus statement highlights the need to adopt combination lipid-lowering therapy as first-line strategy for very-high risk patients, including combination with PCSK-9 inhibitors (19).

Table1. Recommendation for dyslipidemia treatment (The submitted table is the work of the author and is based on information available in the cited reference European Heart Journal, Vol 41, Issue 1, 2020, 111–188.)

CVrisk cegory	Risk factors	Target levels of plasma LDL-C and therapy approach
Low risk	• SCORE<1%	LDL-C<3.0 mmol/L
Moderate risk	• SCORE 1-5% • Young patients (T1DM <35 years, T2DM<50 years without other RF)	LDL-C<2.6 mmol/L
High risk	• 10-year SCORE risk ≥ 5% and ≤10% • Patients with total-C > 8 mmol/l, LDL>4.9 mmol/l or BP≥180/110 mmHg • Patients with diabetes without complications, if the disease lasts longer than 10 years with other risk factors • Moderate HBI (GFR 30- 59mL/min/1.73m^2) • FH without risk factors	LDL-C<1.8 mmol/L **Moderately intense statin**
Very high risk	• 10-year SCORE risk ≥ 10% • Documented ASKVB - clinical methods or visualization methods • Type 2 diabetes with macro and microvascular complications or with 3 risk factors present • Type 1 diabetes with micro and macrovascular complications, or with 3 risk factors present or if the disease lasts longer than 20 years • Severe HBI (GFR <30mL/min/1.73m^2) • FH with ASKVB or with risk factors	LDL-C<1.4mmol/L or <50% reduction in LDL-C if the goal is not reached Application of high-intensity therapy for LDL reduction **Maximum dose of statin+ezetimibe+ PCSK9 inhibitor**
Extremely high risk	• Patients with ACS who experience a new cardiovascular event within two years (does not have to be of the same nature as the first) and they are already getting maximally tolerable dose of statin	LDL-C< 1.0 mmol/L Application of high intensity LDL-C reduction therapy **Maximum dose of statin+ezetimibe+PCSK9 inhibitor**

Other therapeutic agents for dyslipidemia treatment are also in use. Bempedoic acid has been approved for use in patients who are statin intolerant. The main therapeutic objective in treating dyslipidemias is to reduce LDL-C, however there is now clear evidence that lowering lipoprotein Lp (a) levels also help reduce CVD risk as it is also a standalone risk factor for CVD additionally (23). Pelacarsen and olpasiran are emerging therapeutic options designed at lowering Lp (a). LDL apheresis is a specialized medical treatment, like dialysis, for lowering LDL-C. It is typically intended for patients with severe hypercholesterolemia that are unresponsive to conventional treatment or for individuals with statin intolerance or high Lp (a) cholesterol (24,25). Other innovative small molecules such as evinacumab, lomitapide, mipomersen, volanesorsen and olezarsen target different stages in the metabolism of atherogenic lipoproteins, and show great promise in FH therapy (2,13,20).

PCSK-9 INHIBITORS AS A NEW THERAPEUTIC AGENT FOR LOWERING LDL-C

Discovery of PCSK-9

The Nobel Prize awarded to Goldstein and Brown was a landmark discovery of the role of the LDLR, which opened the door to further research that brought new discoveries including that of PCSK-9. This new knowledge and understanding of LDLR function in clearing LDL-C, explained the mechanism of FH that lay in LDLR gene mutation. Additionally, novel cellular processes such as receptor-mediated endocytosis, receptor recycling and receptor regulation have been described. Later, a major regulatory pathway was discovered whose role is to control the number and function of LDLR. It was then that the PCSK-9 enzyme and its gene on chromosome 1 were identified for the first time (26). The physiological role of PCSK-9 was first recognized through the discovery that functional mutations in the PCSK-9 gene lead to dominant FH. A 2003 study identified a mutation in the PCSK-9 gene in French families with no known mutations in the LDLR or apolipoprotein B (APOB) genes, which was linked to markedly elevated concentrations of LDL-C (27). A gain-of-function (GOF) mutations in the PCSK-9 gene indicated that there was a new factor in cholesterol homeostasis still unknown. The Dallas Heart Study, conducted on a multi-ethnic population including a subset of African Americans found a loss of function mutation (LOF) in the PCSK-9 gene, linked to reduced serum LDL-C and a significantly lower incidence of CVD was observed (28). These findings put a spotlight on PCSK-9 which in short time become a promising treatment target for FH.

Role of PCSK-9 on lipid metabolism

PCSK-9 is an enzyme predominantly synthetized in the liver. Its function is reflected in its binding to the LDLR which is then degraded at the lysosome, resulting in the

reduction of LDL receptor recycling, downregulating receptor activity. The main consequence is the increase of LDL-C concentration in the serum (28-30). When not bound to PCSK-9, LDLR binds to LDL-C and enters the cell, separates from LDL-C in the endosomes and is returned to the plasma membrane, while LDL-C is directed to lysosomes for breakdown (31). PCSK-9 gene variants account for 2–4% of FH. These gene mutations cause grater cholesterol concentration than LDLR or APOB polymorphisms (32). Patients with GOF mutations are predisposed to elevated LDL-C levels and the development of FH accompanied by an increased CV risk with cholesterol levels exceeding 13 mmol/L (33). Individuals with LOF mutations in PCSK-9 exhibit an increased density of liver LDLR accompanied by decreased LDL-C concentrations, resulting in CVD reduction of 50 to 86% (34).

In recent years an idea of blocking PCSK-9 with a monoclonal antibody has first come to light. Inhibition of the PCSK-9 enzyme with monoclonal antibodies increases the availability of LDLR ("upregulation of the LDLR") and enhancing LDL-C clearance. Effectiveness of PCSK-9 inhibitors depend on the presence of LDLR, in that sense these medications are ineffective in patients with homozygous FH (HoFH) (28). To date, two fully human monoclonal antibodies are available: alirocumab and evolocumab. Both antibodies are developed using transgenic mouse platforms and work by preventing the interaction between PCSK-9 and LDLR. Alirocumab and evolocumab can reduce LDL-C levels by 60–70% and are approved for the treatment of patients with FH and established CVD (35). In addition, a novel strategy utilizing RNA interference therapy has been developed to inhibit the cellular production of PCSK-9. Inclisiran, a novel molecule, is a synthetically produced small interfering RNA (siRNA) that targets PCSK-9 **(Figure 1)**. This small interfering RNA attaches within the cell an RNA-induced silencing complex (RISC), which in turn cuts mRNA molecules responsible for encoding PCSK-9. The fragmented mRNA is broken down through a catalytic process to prevent PCSK-9 protein synthesis in the liver. Inclisiran's RNA–induced silencing complex can degrade multiple PCSK-9 mRNAs (36). Within 24 hours of subcutaneous injection, inclisiran becomes undetectable in plasma due to its rapid, specific, and efficient uptake by hepatocyte (31). Recent studies have shown that the molecule resistin-adipokine from adipose tissue lowers the expression of the LDLR at the level of hepatocytes subsequently increasing the expression of PCSK-9 molecule. This fact potentially opens the possibility for new therapeutic options that would aim at the resistin-adipokine inhibition resulting in ASCVD prevention (26).

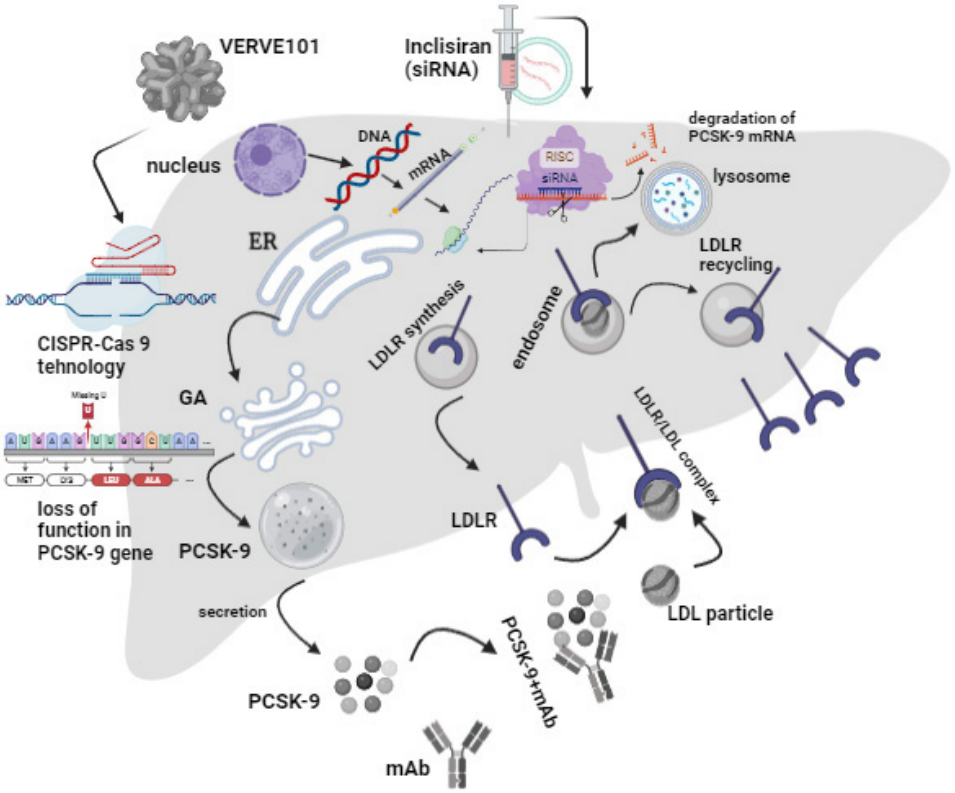

Figure 1. Mode of action of PCSK-9 inhibitors (The submitted figure is the work of the author and is based on information available in the cited references European Heart Journal 2022;43(34):3198-3208)

PCSK-9 - proprotein-convertase subtilisin/kexin type-9; mAb – monoclonal antibody; CISPR – Cas 9 - clustered regularly interspaced short palindromic repeats; LDL - low density lipoprotein; LDLR- low density lipoprotein receptor; RISC - RNA-induced silencing complex; ER – endoplasmatic reticulum; GA – Golgi apparat; mRNA - messenger RNA, DNA - deoxyribonucleic acid.

Additional benefits of PCSK-9 inhibitors

It has been observed that PCSK-9 inhibitors have a strong influence in reducing CV risk besides solely reducing LDL-C, or rather, PCSK-9 inhibitors have other pleiotropic effects that make them extremely superior (26). It is unequivocally confirmed that PCSK-9 inhibitors decrease the concentrations of pro-inflammatory cytokines while promoting the production of anti-inflammatory cytokines (e.g., IL-10). Additionally, their use reduces the expression of TNF alpha and C-C chemokine receptor type 2 (CCR2). As mentioned earlier, PCSK-9 inhibitors reduce oxidative stress by lowering the production of NADPH oxidase and the production of adhesive membrane molecules (ICAM and VCAM) (37,38). In addition, PCSK9 inhibition ultimately contributes to the stabilization of atherosclerotic plaques by reducing the necrotic core of the atheroma, as demonstrated through intracoronary imaging in randomized controlled trials such as PACMAN-AMI, HUYGENS, and GLAGOV (37). The studies have also shown that PCSK-9 inhibitors in some degree have a direct proinflammatory effect on blood vessels, through LDLR related protein 1 (LDL-RP1). All these mechanisms are key pathophysiological factors of the evolution of ASCVD (37-40).

PCSK-9 inhibitors are associated with both antiaggregant and anticoagulant effects through direct and indirect activation of the scavenger receptor CD36 and low-density lipoprotein receptor-1 (LOKS-1) on the hepatocyte membrane. They also exabit an antiplatelet effect by lowering Lp(a) levels, which reduces the stimulation of toll-like receptor 2 (TLR2) on the surface of lipid-peroxide-modified phospholipids, transported specifically by Lp(a) particles. The anticoagulant effect is reflected in the reduction of tissue factor and factor VIII levels (37,41).

There is data that PCSK-9 inhibitors also have an antineoplastic effect by reducing serum levels of LDL-ch and TG. Reduction of PCSK9 activity has a function in inhibiting the progression of colorectal cancer and breast cancer (42). Their effect on TLR and their modulation could have a significant function in regulating the immune response to sepsis and septic shock (43).

PCSK-9 inhibition by monoclonal antibodies: evolocumab and alirocumab

Evolocumab and alirocumab are anti-PCSK9 monoclonal antibodies approved for clinical use, either as monotherapy or in combination with statins and/or ezetimibe. These monoclonal antibodies reduce LDL-C levels around 60% in monotherapy and even 85% together with other hypolipemic therapies. They can be administered every two weeks or once a month. FOURIER and ODYSSEY are randomized, double-blind, placebo-controlled trials that demonstrated that adding evolocumab or alirocumab to standard lipid-lowering therapy in high cardiovascular risk patients significantly reduces the absolute risk of ischemic events and overall mortality (29,30).

The FOURIER study demonstrated that Evolocumab reduces LDL-C levels in plasma by 53% to 75%, based on its use as monotherapy or in conjunction with statins in patients with heterozygous familial hypercholesterolemia (HeFH), while in HoFH with defective LDL-R, that percentage is drastically lower and amounts to about 31% (43). The incidence of cardiovascular death, myocardial infarction (MI), stroke, hospitalization for unstable angina, or coronary revascularization as the primary outcome was significantly lower in a statistical sense compared to the placebo group receiving statin therapy alone (13,30). Perhaps the most significant finding was that the benefit of using PCSK-9 was greater among high-risk subgroups with recent or multiple MI and multivessel coronary artery disease, in that regard PCSK-9 was recommended in guidelines for the treatment of dyslipidemia in secondary prevention (30,44). Dosage of evolocumab is 140 mg/ml every two weeks or 420 mg once a month (44).

The ODYSSEY study demonstrated that Alirocumab lowers LDL-C by 39% to 58% in patients with HeFH and by 11.9% to 34.3% in patients with HoFH (44). The study revealed that patients with recent CVD on high-intensity statin therapy had a significantly reduced risk of recurring cardiovascular events compared to the placebo group (45). Furthermore, it has been demonstrated that the use of Alirocumab has beneficial impacts in reducing oxidative stress, creation of inflammatory cytokines, lowering the function of metalloproteinase 2, osteopontin and osteoprotegerin, which are critical stages in the formation of atherosclerotic plaques (46). The dose of alirocumab is 75 mg once every two weeks with a possible titration up to 150 mg based on the level of LDL-C. Alternative to this dosing regimen is 300 mg once a month (44).

Besides lowering LDL-C, monoclonal antibodies reduce TC, Tg, non-HDL-C, apo B and slight increase in HDL-C. Unlike statin therapy, both available monoclonal antibodies can reduce an Lp(a) for up to 30% (44,45). There is no need to adjust the dose depending on age, gender, body weight, renal or mild to moderate hepatic insufficiency. In patients on previous statin therapy, the dose interval may be shorter because of the increased expression of the PCSK-9 molecule caused by statins. For now, there is no precise data for patients who have severe renal and hepatic insufficiency (47,48).

Two more trials, the EMACS and EVACS trials have directly demonstrated PCSK-9 superiority in combination with a statin in lowering LDL-C after acute coronary syndrome during hospital treatment, however, there is still no precise data on cardiovascular outcomes and serious side effects (49,50). The use of monoclonal antibodies has few side effects. With therapies targeting RNA symptoms of immune activation are always in focus but found to be rear in patients using inlisiran. Some flu-like symptoms were reported. Apart some mild injection-site

reactions, some neurocognitive events were recorded in patients taking monoclonal antibodies including dementia, delirium, cognitive disorders, amnestic and attention disorders, disturbances in thinking and perception, and mental impairment disorders (51). Alirocumab was evaluated in the ODYSSEY long-term trial, and the data indicated that it caused myalgia and injection site reactions, along with mild neurocognitive and ophthalmologic events. It was also observed that a higher proportion of patients had low vitamin E or K levels, although these were not clinically significant. The primary limitation to their broader use is their high cost (29).

PSCK-9 inhibition by siRNA-based therapeutic agents: inclisiran

In recent years, RNA-based therapies have undergone significant development. This therapy involves the management or prevention of diseases using RNA-based molecules. RNA molecules are classified into coding RNAs and non-coding RNAs (ncRNAs). NcRNAs, which do not encode functional proteins, include various types, such as small interfering RNAs (siRNAs). Small interfering RNA molecules exert possibility as treatment options for a variety of diseases, including cancer, viral and bacterial infections (52). They have demonstrated successful inhibitory effects on tumor growth, along with high specificity, low adverse effects, safety, and high efficiency even at very low doses. SiRNAs are resistant to nuclease enzymes degradation in contrast to antisense agents (53). The safety of siRNAs refers to the absence of harmful chemicals in the siRNA synthesis processes (54). Unlike other antisense agents, siRNA exerts its inhibitory effects on gene expressions during the post-translation stages without interfering with DNA or inducing any mutation in its structure (55).

The first treatment based on siRNA, received approval by the Food and Drug Administration (FDA) in 2018. In 2020 Leqvio®, (inclisiran 284 mg/1.5 mL) was put on the map by the European Medicines Agency and by the United States Food and Drug Administration in 2021 for primary hypercholesterolemia or mixed dyslipidemia (52,53). As mentioned above, Inclisiran is a small interfering ribonucleic acid (siRNA) that inhibits the synthesis of PCSK-9 in hepatocytes. It is approved for the treatment of patients with HeFH, familial combined hyperlipidemia and confirmed atherosclerotic CVD (13,30,56). Inclisirans mechanism of action is linked to the activation of the RNA-induced silencing complex (RISC), which cleaves intracellular mRNA, thus blocking translation and preventing the synthesis of PCSK-9. The result of these actions is the reduction in circulating levels of PCSK-9 by up to 70% (37). SiRNA consists of two complementary RNA strands, an antisense (guide) strand, and a sense (passenger) strand. The siRNA enters the hepatocytes with precise and rapid hepatic uptake (53). When the siRNA is loaded into the RNA induced-silencing complex (RISC) in hepatocytes, only the antisense strand becomes activated, as the sense strand is selectively removed by the Argonaut 2 (57). The complex formed by the antisense strand and RISC binds to PCSK9 messenger RNA (mRNA) transcripts, selectively and catalytically cleaving the mRNA. This process inhibits the translation of complementary mRNA transcripts. Every complex exabits an extended half-life, enabling it to degrade multiple mRNA copies, which allows for dosing intervals of several months in patients. It is quickly cleared from the circulation via hepatic uptake and renal excretion, becoming undetectable in the plasma by 48 h post-delivery (53). With PCSK-9 inhibition, there is an "up regulation" of LDLR resulting in the clearance of LDL-C (13,37,44). It is delivered via subcutaneous injection at a dose of 284 mg. Following the initial dose, the second dose is given after three months, with following doses administered every 6 months (44,56). In comparison to PCSK-9 monoclonal antibodies, inclisiran has a more convenient dosing regimen, it is given twice a year, guaranteeing better compliance (13,56). The ORION studies examined the efficacy and safety of the drug in patients receiving highest tolerated doses of statins and other lipid-lowering drugs. Inclisiran has been shown to reduce LDL-C by about 50% compared to the placebo group following a one-year follow-up (13,56,58). Like monoclonal antibodies, inclisiran also promotes lowering of total cholesterol, Tg, non-HDL-C, Lp(a) and as well increasing HDL-C (58). The ORION-4 and VICTORION-2 PREVENT studies are large long-term studies that will assess the incidence of new CVD in patients with confirmed atherosclerotic CVD who were previously on statin therapy, and these studies are still ongoing. The main endpoint of these studies is expected to provide results on the reduction of major cardiovascular advance (MACE) in patients on inclisiran therapy (56,58).

Data from three pivotal Phase III placebo-controlled ORION trials not only assessed the lipid-lowering efficacy of inclisiran, but also evaluated its impact on major adverse cardiovascular events (MACE). Each trial enrolled patients at high risk of CV events who, although receiving the highest tolerated doses of statins, continued to have elevated LDL-C levels. The study population consisted of patients with HeFH (ORION-9), ASCVD (ORION-10, ORION-11), and high-risk, primary prevention patients referred to as ASCVD risk equivalent (ORION-11). Patients in the ORION-11 trial included individuals with no prior history of ASCVD, but who had either type 2 diabetes mellitus or HeFH, or a predicted 10-year CVD risk of >20% based on the Framingham risk score or equivalent (59). The data demonstrated that adding inclisiran to existing lipid-lowering therapies was associated with a 26% reduction of MACE. Favorable trends towards a reduced risk of both fatal and non-fatal MI in comparison to placebo were also observed. Strokes were numerically less present in the inclisiran treatment arm.

The exposure tame in these studies was 18 months, but to fully assess the benefit of lipid-lowering therapy with PCSK-9 inhibitors on CV events, we need greater long-term absolute reduction of LDL-C levels (59).

The ORION-5 trial was a double-blind, placebo-controlled, open-label, multicenter trial, assessing the long-term effects, tolerability, and safety of inclisiran in HoFH patients. Results showed that inclisiran did not significantly reduce LDL-C and was not superior to placebo in patients already on maximal lipid-lowering medications. HoFH patients with higher residual LDLR function may experience greater LDL-c reduction in comparison to patients with lesser residual LDLR function (60). The ORION-13 and -16 trials, designed to evaluate the efficacy and safety of inclisiran in adolescents aged 12 to 17 years with HoFH and HeFH, are currently in progress (61).

It has been speculated that inhibition of hepatic PCSK-9 synthesis may have greater benefits in CVD prevention compared to monoclonal antibodies alone, especially in the light of their well-known pleiotropic effects (37). However, there is not enough evidence to substantiate these findings. We are waiting for future studies to provide the answers.

Regarding the safety profile of inclisiran, pooled data from 7 clinical trials represent the largest data set to date, demonstrating that twice-annually injections are both safe and well tolerated when used in conjunction with statins and/or other oral lipid lowering agents in patients with increased levels of LDL-C, including those with ASCVD, ASCVD risk equivalent, and HeFH (62). The majority of reported adverse events were mild and moderate, including myalgia, cough, mild rash, hyperpigmentation, headache, nasopharyngitis, and dizziness (53). In the ORION 3, with four years of extended exposure, the most frequently occurring adverse events in the inclisaran arm were nasopharyngitis reported in 19% of patients, and injection site reactions in 14% of patients (63). In contrast to monoclonal antibody that resides in blood, siRNA is quickly absorbed by the liver. Repeated exposure to inclisiran leads to sustained reduction of circulating PCSK9 levels, with impacts spanning from 62,2% to 77,8% over 4 years, without any indication of compensatory mechanisms or escape phenomena that would compromise its LDL cholesterol lowering efficacy (63). Possible harmful metabolic effects of inclisiran, as suggested by latest meta-analysis of genetic association studies, indicated to increased probability of developing type 2 diabetes (64).

NOVEL AND FUTURE LIPID-MODULATING THERAPY BASED ON PCSK-9

Oral PCSK-9 inhibitor: MK-0616

MK-0616 is an oral PCSK-9 inhibitor, at present in a phase 3 of randomized, double-blind, placebo-controlled study. The aim of the study is to assess the efficacy and safety of this macrocyclic peptide after 24 weeks in adults with hypercholesterolemia. First results showed that orally administered PCSK-9 inhibitor in a dose of 6 to 30 mg resulted in a decrease of LDL-C up to 60.9% in comparison to placebo following designated follow-up period of 8 weeks in patients with hypercholesterolemia and ASCVD on statin therapy (65). CORALreef Outcomes (TIMI 77) is a randomized, double-blind study whose aim is to evaluate the efficacy of MK-01616 in patients with high CV risk on statin therapy versus a placebo group. Preliminary results of this study will come out on November 2029, and it will aim to answer weather therapy with MK-0161 will prolong the time of onset of new CV event (66).

PCSK-9 vaccines

PCSK-9 vaccines are liposomal immunogenic combination of PCSK9-tetanus peptide with an aluminum adjuvant, which in an animal model showed long-term synthesis of PCSK-9 antibodies and reduction of LDL-C and VLDL-C by 51.7% in BALB/c mice and 19.2% in C57BL/650 mice (67).

Gene therapy

CRISPR/Cas system (clustered regularly interspaced short palindromic repeats) is a technology that changes the function of the PCSK-9 gene making it non-functional (68). VERVE-101 is a mRNA packed in lipid nanoparticles silencing the gene for PCSK-9. This innovative molecule is being evaluated in phase 1b of Heart-1 clinical trial in patients with high-risk HeFH, established ASCVD and uncontrolled LDL-C levels despite patents being on maximum doses of oral therapy. Early-stage research conducted in mice and non-human primates (NHP) have demonstrated that a single intravenous administration of VERVE-101 can effectively inactivate the PCSK-9 gene in the liver (69). The first results of Heart-1 study were presented at the AHA Scientific Sessions in November 2023 and they showed that the NHPs treated with VERVE-101 achieved a marked decrease in LDL-C up to 55% and lower blood PCSK-9 protein up to 84% that remained permanently reduced during more than two years of follow-up. VERVE-101 is believed to be a single-course therapy capable of producing profound LDL-C reduction lasting for decades. The initial clinical trial conducted in volunteers with HeFH and developed ASCVD is ongoing (69).

CONCLUSION

The positive role of PCSK-9 inhibition in dyslipidemia therapy and ASCVD prevention is clearly shown in several randomized clinical studies. The mechanisms of inhibition of the PCSK-9 molecule will probably be further refined in more depth in the future, and time will allow

the development of additional therapeutic possibilities. For now, indications for PCSK-9 use are clear, but they will be expanded in further investigations. Due to the exceptional effectiveness of this group of drugs, it is believed that the results of ongoing studies will answer even more precisely their importance and the possibility of application in patients immediately after a cardiovascular event during hospital treatment, as well as their benefits or potential risks in patients with renal or hepatic insufficiency.

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TERAPIJA DISLIPIDEMIJE: PCSK-9 U FOKUSU

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Sažetak

Kardiovaskularne bolesti su vodeći uzrok morbiditeta u svetu i čine trećinu svih uzroka smrtnosti. Dislipidemija kao najznačajniji faktor rizika ima značajnu ulogu u nastanku i progresiji aterosklerotske kardiovaskularne bolesti. Terapija statinima često ne uspeva da obezbedi ciljne vrednosti LDL holesterola, a i kada se one postignu, kardiovaskularni događaji se i dalje javljaju, što ukazuje na potrebu za razvojem i primenom novih lekova za snižavanje lipida. PCSK-9 inhibitori redukuju LDL holesterol za oko 60% kada se koriste kao monoterapija i čak 85% u kombinaciji sa statinima visokog intenziteta i/ili drugim lekovima za lečenje dislipidemije. Alirokumab i evolokumab su monoklonska antitela koja se efikasno vezuju za LDL receptor ometajući njegovu razgradnju. Inklisiran je mala interferirajuća RNK koja ometa sintezu PCSK-9 molekula. Indikaciona područja za primenu PCSK-9 inhibitora se sve više šire zbog otkrića njihovih plejotropnih efekata. Takođe, u fokusu je otkriće novih mehanizama PCSK-9 inhibicije što bi otvorilo vrata razvoju novih terapijskih agenasa. Studije efikasnosti i bezbednosti oralnih PCSK-9 inhibitora su u toku, kao i rane faze kliničkih ispivanja genske terapije.

Cilj ovog preglednog članka je da predstavi dosadašnja saznanja o primeni PCSK-9 inhibitora.

Ključne reči: dislipidemija, LDL holesterol, PCSK-9

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