SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Non-statin therapy in patients with elevated LDL-C and high platelet reactivity: a narrative review

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ABSTRACT

Introduction: Evidence of an association between elevated LDL-C levels and HRPR - which are highly prevalent separately and both lead to rapid progression of atherosclerosis on ineffective hypolipidaemic therapy - is scarce.

Materials and Methods: We searched electronic databases. All available randomized controlled trials (RCTs) were included, and we considered the scientific novelty of the study, the reliability of the reported study results; the high methodological level of the study of non-statin therapy in patients with dyslipidemia and high residual platelet reactivity, with no language or date restrictions. We did separate random-effects meta-analyses for LDL-C, HRRP on their effects on LDL-C levels and outcomes, taking into account the reliability of the reported study results and the high methodological level of the study. The challenge of achieving target LDL-C levels, their impact on high residual platelet reactivity, and the choice of optimal antiplatelet and lipid-lowering therapy remains unresolved.

Results: The integration of newer therapies, such as inclisiran and PCSK9 inhibitors, may play a critical role in achieving optimal outcomes for patients at high cardiovascular risk.

Conclusion: The necessity of applying an individual multidisciplinary approach in order to determine the best regimen of antiplatelet and lipid-lowering therapy in patients with coronary heart disease, including after revascularization, is shown. This approach will reduce the risk of recurrent cardiovascular events. Few studies on the relationship between LDL-C and HRPR dictate the need for more detailed research in this area.

KEYWORDS:
low-density lipoproteins cholesterol, high residual platelet reactivity, non statin lipid-lowering therapy

INTRODUCTION

Nowadays, cardiovascular diseases, despite the achievements of modern cardiology, are the leading cause of mortality throughout the world. In 2015, it was found that cardiovascular pathology causes one third of all deaths, especially from coronary heart disease (CHD) in economically developed countries. Low-density lipoprotein cholesterol (LDL-C) has been identified as a major risk factor for cardiovascular disease, associated with one in four deaths from CHD in patients with high LDL-C levels.[1,2] In general, elevated LDL-C is considered a modifiable risk factor for the development of cardiovascular diseases, playing a major role in the pathogenesis of atherosclerosis.[3,4]

High residual platelet reactivity (HRPR) is a predictor of many adverse cardiovascular complications, such as myocardial infarction, stent thrombosis in patients with coronary artery disease (CAD), and death from cardiovascular diseases.[5,6] Considering the involvement of platelets and LDL-C in the pathogenesis of atherosclerosis, it can be assumed that high residual platelet aggregation (HRAP) is capable of increasing the proliferation of smooth muscle cells, forming foam cells, which, by absorbing LDL-C, contribute to the formation of atherosclerotic plaque. Therefore, reducing the level of platelet aggregation and LDL-C by prescribing antiplatelet and lipid-lowering therapy can block the process of atherogenesis and subsequent cardiovascular complications.

Patients with elevated LDL-C and high residual platelet reactivity (HRPR) are a difficult group for cardiologists, cardiovascular surgeons and endovascular surgeons. Evidence of an association between elevated LDL-C levels and HRPR - which are highly prevalent separately and both lead to rapid progression of atherosclerosis, high rates of recurrent arterial thrombosis in cerebral and coronary vessels against a background of polymorbidity, including in patients after revascularization procedures- is scarce.

The study provides an overview of modern clinical studies on the treatment of patients with elevated LDL-C in cardiovascular diseases (CVD), as well as their effect on HRPR, achieving target LDL-C levels in very high-risk patients with HRPR during antiplatelet therapy. This study employs a narrative literature review to achieve two main objectives (1) to examine the effect of non-statin therapy on lowering LDL values in atherosclerosis-associated disease, including very

This article was accepted: 13 November 2024
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high-risk patients with high residual platelet reactivity; and (2) to determine the impact of target LDL values on high residual platelet reactivity in very high-risk patients with cardiovascular disease receiving antiplatelet therapy.

The secondary objective is to identify gaps and limitations in the existing literature on LDL lowering in patients with cardiovascular disease and high residual platelet reactivity and to suggest directions for future research, including exploring novel therapeutic interventions in the form of inclisiran, the long-term outcomes of treatment strategies to achieve target LDL levels, and approaches designed for patients at very high risk of cardiovascular events.

MATERIALS AND METHODS

Search strategy

A systematic literature search was conducted in the electronic PubMed, Embase, Scopus and Cochrane Library databases and forward and backward citations for studies published in English between January 10, 2014, and January 10, 2023 (Free full text).

The search strategy utilized relevant keywords and Medical Subject Headings (MeSH) to comprehensively search for studies related to non-statin therapy for cardiovascular disease. The primary keywords included: "low-density lipoproteins cholesterol", "high residual platelet reactivity", "non statin lipid-lowering therapy".

Study selection criteria

The inclusion criteria covered studies that were published in peer-reviewed journals that included adults with dyslipidemia on a background of atherosclerosis-associated disease and/or coronary heart disease. Both observational studies (cross-sectional, cohort, case control) and interventional studies (clinical trials, interventions) were considered. All available randomized controlled trials (RCTs) were included, and we considered the scientific novelty of the study, the reliability of the reported study results; the high methodological level of the study of non-statin therapy in patients with dyslipidemia and high residual platelet reactivity, with no language or date restrictions. We did separate random-effects meta-analyses for LDL-C, HRRP on their effects on LDL-C levels and outcomes, taking into account the reliability of the reported study results and the high methodological level of the study.

Exclusion criteria. The exclusion criteria included studies that were not published in English, studies focused exclusively on non-dyslipidemic populations, and studies with small sample sizes or incomplete data with small sample sizes or incomplete data. Non-original articles, such as commentaries, editorials, reviews, and letters to the editor, were excluded.

Data extraction, synthesis and analysis

Data extraction was conducted independently by three reviewers, using a standardized form. Data extraction fields included study characteristics (author, year, country(s), purpose, design, sample size, patient demographics), non-statin therapy including studies with inclisiran, LDL levels in patients with dyslipidemia, prevalence rates of not achieving treatment goal and cardiovascular events on therapy. A narrative synthesis approach was employed to summarise and integrate the findings across the selected studies.

Quality assessment

The quality of included studies was assessed using established tools such as the Newcastle-Ottawa Scale for Observational Studies and the Cochrane Collaboration Risk of Bias Tool for interventional studies. This assessment helped ensured the validity and reliability of the evidence synthesized. A critical appraisal was conducted for each study by two independent researchers of this paper. Any disagreements were resolved through discussion with the third author.

RESULTS

The selection process is illustrated in the PRISMA flow diagram (Figure 1).

Study characteristics

Several studies have described the indirect effects of lowering LDL-C in atherosclerotic plaque and platelet aggregation. The direct effect of lipid-lowering therapy on platelet function was also examined. In vitro incubation of platelets and lipoproteins shows how high levels of LDL-C activate platelet aggregation. In particular, apoB-100, expressed by LDL-C, binds to and activates the LDL-C receptor expressed by platelets and alters signal transduction. Platelets become more sensitive to activated stimuli and acquire a hyperaggregation phenotype.[7] In addition, platelets with higher mean platelet volume (MPV) are correlated with a higher risk of ischaemic and thrombosis.[7,8] Several studies have demonstrated a significant association between hyperlipidemia and platelet volume indices (PVI), including mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (P-LCR).[8]

In accordance with the Systemic CoronarRisk Estimation (SCORE) scale. which assesses the risk of death from myocardial infarction, heart failure and stroke over the next ten years, patients are divided into four categories: low, moderate, high, very high risk. In recent years, another category has been added - extreme risk. This scale takes into account many modifiable risk factors: arterial hypertension, dyslipidaemia and smoking, as well as non-modifiable risk factors: gender and age.[9] Currently, the European Heart Association, based on its recommendations on atherosclerosis, considers that maintaining adequate lipoprotein control, especially lowering LDL levels, is important for the treatment of dyslipidemia. Lowering LDL-C levels is especially important in patients at high, very high, and extreme risk. The target LDL-C level according to the SCORE scale is: in patients at high risk - less than 1.8 mmol/L, very high risk - less than 1.4 mmol/L and extreme risk - less than 1 mmol/L.

According to European studies, 80% of very high-risk patients do not achieve target LDL-C levels with statin monotherapy.[10] Statin pharmacotherapy is the gold standard in the treatment of hypercholesterolaemia, especially LDL. Moreover, some patients do not achieve target levels even on

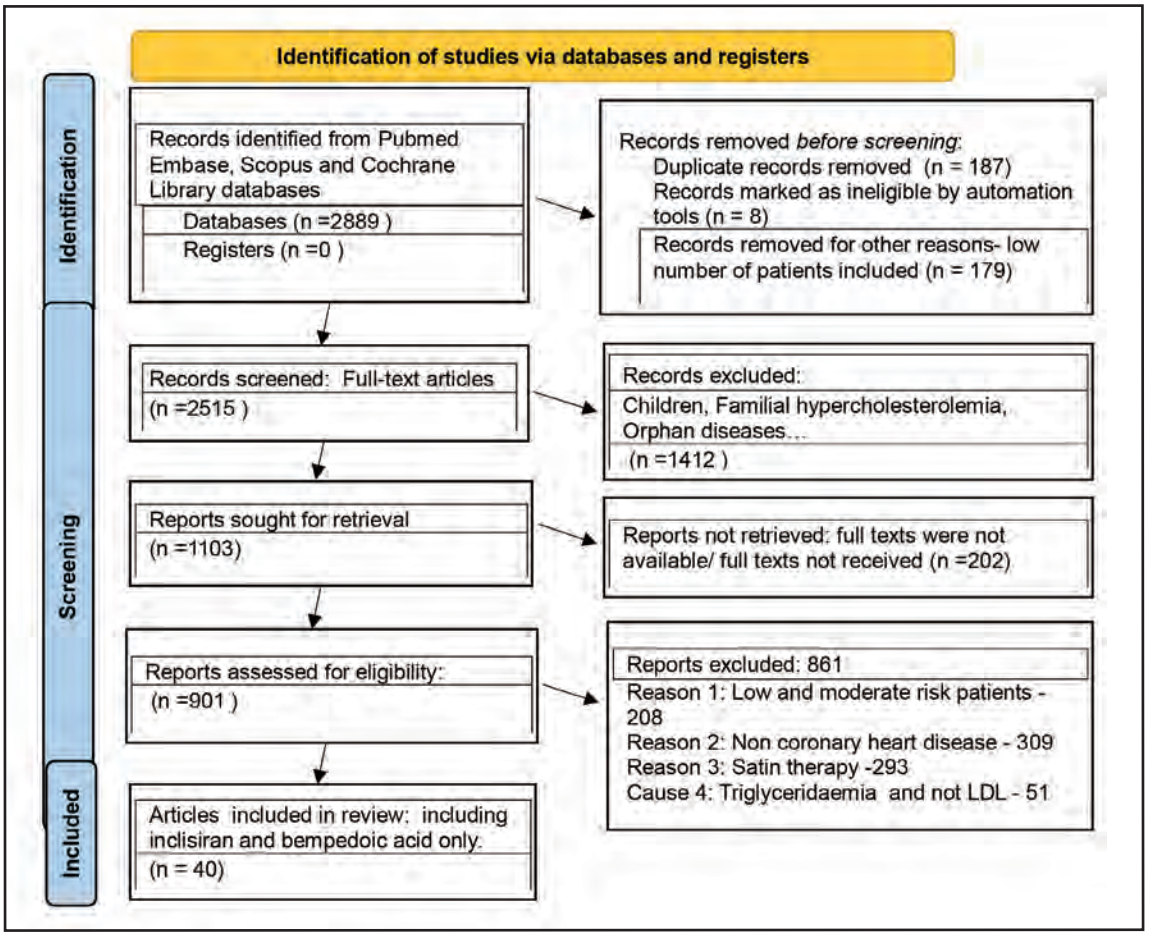

Fig. 1: PRISMA diagram of the screening process

high tolerated doses of statins.[11] In addition, long-term statin therapy is associated with side effects such as fibromyalgia and myopathy, which are the main reasons for stopping of lipid-lowering therapy.[10,12]

Currently, for patients who do not reach the target LDL level, a combination of statins with ezetimibe is recommended; if this combination is not enough to achieve the therapeutic goal, it is necessary to add monoclonal antibodies inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9), in particular alirocumab, evolocumab.[13,14] A study by Murphy et al., which examined the comparative effectiveness of atorvastatin at a dose of 80 mg and pravastatin at a dose of 40 mg in patients with recent acute coronary syndrome, showed the benefits of high-dose statin therapy compared with a moderate dose.[16] PCSK9 inhibitors (evolocumab and alirocumab) reduce LDL levels by approximately 60% and are given once or twice a month subcutaneously.[17,18]

The FOURIER trial compared the efficacy of evolocumab with placebo in 27,564 patients with cardiovascular disease. After 48 weeks of evolocumab therapy, patients experienced a 1.5% reduction in LDL cholesterol levels from 92 to 30 mg/dL, and a 1.5% reduction in absolute risk and cardiovascular events compared with statin therapy ($p < 0.001$).

Moreover, the ODYSSEY trial studied 18,924 high-risk patients who experienced acute coronary syndrome with LDL-C levels ≥1.8 mmol/L despite receiving the maximum dose of statin using alirocumab. Treatment with alirocumab was associated with a 61% reduction in LDL-C levels over 12 months, as well as a 15% reduction in major reversible cardiovascular events (HR, 0.85; 95% CI [0.78, 0.93]) and mortality. (HR, 0.85; 95% CI [0.73,0.98]) over a mean period of 2.8 years.[15,19,20]

The DESCARTES trial (long-term effect of PCSK9 monoclonal antibodies versus placebo study) showed that side effects (increased levels of creatine kinase above normal levels and muscle pain) were observed at similar levels in both groups (placebo and evolocumab).[21,22]

Bempedoic acid (BA) is an oral inhibitor of adenosine triphosphate (ATP) citrate lyase, an enzyme that acts "upstream" of the cholesterol synthesis cascade than HMG-CoA, which is the "target" of statins, catalyzing the production of acetyl coenzyme A, a precursor to the mevalonate pathway of cholesterol synthesis. The results of a 12-week randomized controlled trial indicate a reduction in LDL cholesterol levels by up to 30% with BA monotherapy and up to 50% when BA is combined with ezetimibe.[15,23] The main disadvantages of the drug are the development of gout and high cost.

Inclisiran is a cholesterol-lowering double-stranded small interfering RNA conjugated to an N-acetylgalactosamine (GalNAc) coding strand to facilitate uptake by hepatocytes. In hepatocytes, inclisiran uses the mechanism of RNA interference and triggers the catalytic decay of mRNA, acting on proprotein convertase subtilisin-kexin type 9 (PCSK-9). This helps to increase the recycling of the LDL cholesterol receptor and its expression on the surface of hepatocytes, which leads to an increase in the uptake of LDL cholesterol and a decrease in its concentration in the blood plasma. Inclisiran blocks the transcription of PCSK-9 intracellularly, which leads to a decrease in the production of PCSK-9 in hepatocytes, which leads to an increase in LDL-C receptors on the surface of hepatocytes, which take up LDL and reduce their amount in the blood.[13,24] According to atherosclerosis guidelines, inclisiran is a new non-statin drug that has been approved by the USA Food and Drug Administration and is prescribed twice a year 1,25. The main difference between monoclonal antibodies and inclisiran is that inclisiran acts intracellularly by activating LDL cholesterol receptors, while PCSK9 inhibitors act extracellularly by binding to and blocking circulating PCSK-9 protein.[1,26]

Adverse reactions of inclisiran. All adverse events were mild or moderate in severity and did not require discontinuation of the study in any participant. The main side effects are cough, musculoskeletal pain, headache, back pain, diarrhoea and nasopharyngitis.[21,27] One study participant taking a statin had asymptomatic increases in GGTP and ALT without increases in bilirubin; Enzyme levels returned to normal after stopping statins. In addition, some study participants experienced erythema and pain at the injection site. No changes in corrected QT interval (QTc) were observed.[21,28] The most common adverse events (occurring in >2% of patients) were myalgia, headache, fatigue, nasopharyngitis, back pain, hypertension, diarrhea and dizziness. The incidence of these adverse events was not significant between the inclisiran and placebo groups.

The multicentre, double-blind, placebo-controlled ORION-1 trial included 501 patients with coronary artery disease with high LDL levels. The average age of the participants was 63 years. Overall, 73% of participants were receiving statin therapy. Patients were randomized to receive a single dose of placebo or 200, 300 and 500 mg of inclisiran or two doses of placebo (on days 1 and 90) or 100, 200 and 300 mg of inclisiran. The study assessed the percentage change in LDL cholesterol during treatment with different doses of inclisiran for 180 days. At day 180, there was a decrease in LDL cholesterol compared with placebo from 27.9% to 41.9% after a single dose of inclisiran and from 35.5% to 52.6% after a double dose ($p<0.001$ for all comparisons with placebo). The greatest reduction in levels was observed with the 2-dose inclisiran 300 mg regimen, which reduced LDL, PCSK-9, and C-reactive protein levels by 52.6% ($p < 0.001$), 69.1% ($p < 0.001$), and 16.7% ($p < 0.05$), respectively.[24,29]

Serious adverse events occurred in 11% of patients receiving inclisiran and 8% of those receiving placebo. Injection site reactions were observed in 4% and 7% of patients receiving one and two doses of inclisiran. The most common adverse events (occurring in >2% of patients) were myalgia, headache, fatigue, nasopharyngitis, back pain, hypertension, diarrhoea and dizziness. The incidence of these adverse events was not significant between the inclisiran and placebo groups.[24,30]

The ORION-2 study is a pilot study of the effect of inclisiran sodium in patients with familial homozygous hyperlipidaemia.[24] The study included 4 patients who had a genetically confirmed defect in coding the LDL receptor. After two doses of the drug, the duration of observation was 180 days. The decrease after six months in LDL-C ranged from -17.5 to -37.0%, and the decrease in plasma PCSK-9 concentration ranged from -40.5 to -80.5%. Follow-up for up to 10 months did not reveal any adverse events or laboratory abnormalities (except for those characterizing the intervention on lipid metabolism).[31,32]

ORION-3 is an extension study of ORION-1 with a 4-year follow-up period. At day 210 of the ORION-3 study, there was an average 51% reduction in LDL cholesterol and an average 77% reduction in PCSK9. In the ORION-3 study, a stable long-term LDL-lowering effect of a 300 mg dose of inclisiran was observed over approximately 22 months and the mean LDL reduction over time was approximately 60 mg/dL. No changes in the safety profile and laboratory tests of liver and kidney function were observed for at least 3 years. The most common adverse events with inclisiran therapy were nasopharyngitis (19%) and injection site adverse reaction (14%).

ORION-4 is a double-blind, randomized clinical trial that aims to study the effects of inclisiran and the clinical outcome of patients with cardiovascular disease. Approximately 15,000 patients aged ≥55 years were randomized 1:1 to receive inclisiran 300 mg or placebo (subcutaneously every 3 months and every 6 months) for a median follow-up of 5 years. Patients include the following criteria: previous ischemic stroke, peripheral vascular disease, or myocardial infarction. The ORION-4 trial will provide evidence of the effectiveness of inclisiran on major reversible cardiovascular events and overall prognosis in patients with CAD over one year. The results of the study are expected until 2026.[1,33]

ORION-5 was a study of 60 patients with homozygous familial hypercholesterolaemia in North America, Europe and the Middle East. Their primary endpoint was the percent change in LDL cholesterol at day 510 and the percent time-adjusted change between days 90 and 540 (ORION -9), as well as an analysis of the change in LDL level during treatment (ORION -5).[10,33] Responses are pending from the ongoing multinational trials ORION -4 and ORION -5, which evaluate the effect of inclisiran on cardiovascular outcomes in adults with established atherosclerotic cardiovascular disease and homozygous familial hypercholesterolaemia.[26,33]

The phase I study, ORION-7, evaluated the pharmacokinetics, safety, and tolerability of inclisiran in participants with renal impairment. All 31 participants were randomized 1:1:1:1 according to renal function (normal ≥ 90 ml/min; mildly impaired 60–89 ml/min; moderately impaired 30–59 ml/min; severely impaired 15–29 ml/min). min) to receive a single subcutaneous dose of inclisiran

300mg. Participants were followed until day 60, with an extended follow-up period of 180 days. Multiple pharmacokinetic endpoints included the relationship between the degree of renal impairment and the maximum plasma drug concentration (Cmax) of inclisiran, area under the curve (AUC) 0-infinity, and plasma half-life. The percentage change in LDL levels from baseline was assessed at 4 and 48 hours, and on days 4, 7, 30, 60, 120, and 180.[26,34]

The ORION-8 study examined the effect of inclisiran in patients at high risk of cardiovascular complications: «In the largest and longest follow-up to date with >12 000 patient-years exposure, inclisiran demonstrated consistent and effective LDL-C lowering with a favourable long-term safety and tolerability profile. Treatment-emergent adverse events at injection site (all mild/moderate) occurred in 5.9% of the patients. Inclisiran-associated anti-drug antibodies were infrequent (5.5%) and had no impact on the efficacy or safety of inclisiran. No new safety signals were identified. The hypothesis about the effect of the drug on the electrophysiological characteristics of the myocardium was also tested on healthy volunteers, but such an effect was not registered (ORION-12)».[31]

ORION-9 is an 18-month, multicenter, double-blind, randomized clinical trial (RCT) of 482 patients with heterozygous familial hypercholesterolaemia (FHC) treated with statins and ezetimibe. The average age of the patients was 55 years. At day 510, there was a 48% reduction in LDL cholesterol percentage from baseline compared with placebo (95% CI, -54% to -42%, $p < 0.0001$). By day 510, 52.5% of patients with ASCVD in the inclisiran group achieved a target LDL level of <1.8 mmol/L (70 mg/dL) compared to 1.4% with placebo. LDL <2.mmol/(100mg/dL) reached 66.9% of patients in the inclisiran group compared to 8.9% placebo.

ORION-10 is a multicentre, double-blind, month-long RCT involving 1561 patients with associated cardiovascular diseases (ASCVD). The average age of patients is 66 years. At day 510, there was a 52% reduction in LDL cholesterol percentage from baseline compared with placebo (95% CI, -56% to -49%, $p < 0.0001$). By day 510, 84% of patients in the inclisiran group achieved the target LDL level <1.8 mmol/L (70 mg/dL) compared to 18% with placebo.

ORION-11 is a multicentre, month-long, double-blind, RCT of 1617 patients with ASCVD risk equivalents. The average age of patients is 65 years. At day 510, there was a 50% reduction in LDL cholesterol percentage from baseline compared with placebo (95% CI, -53% to -47%, $p < 0.0001$). By day 510, 82% of patients with ASCVD in the inclisiran group achieved a target LDL level of <1.8 mmol/L (70 mg/dL) compared to 16% with placebo. LDL <2.mmol/(100mg/dL) reached 78% of patients in the inclisiran group compared to 31% with placebo.[31]

The ORION-14 study, includes 308 patients from a Chinese population, aimed to evaluate the pharmacokinetics and pharmacodynamics of inclisiran in patients with coronary artery disease or at high risk of developing it in patients with familial hypercholesterolaemia when prescribed maximum tolerated doses of statins. Inclisiran was generally safe and well tolerated. The greatest reductions were observed with the 300 mg regimen of Inclisiran.

The ORION-15 study: Inclisiran sodium 100, 200, and 300 mg demonstrated clinically meaningful and statistically significant LDL-C and PCSK9 reductions at Day 180, which were consistent over 12 months. Inclisiran was effective and well tolerated in Japanese patients with high cardiovascular risk with hypercholesterolaemia, including heterozygous familial hypercholesterolaemia.

In a placebo-controlled, multinational, phase III study, ORION-13 and ORION-16 are recruiting adolescents 12 to 17 years of age with homozygous and heterozygous familial hypercholesterolaemia and high LDL levels on stable lipid-lowering therapy to evaluate the short-term effectiveness of inclisiran.[31,35]

Further study of the effect of inclisiran in hetero-homozygous forms of familial hypercholesterolaemia will be continued in the planned studies ORION-19 (among homozygotes) and ORION-20 (among heterozygotes).[31,35]

Effect of PCSK-9 inhibitors and inclisiran on platelet function. The PCSK9-REACT study presents an associated association between PCSK9 and platelet activity in patients with acute coronary syndrome receiving dual antiplatelet therapy (DAPT). High levels of PCSK9 were associated with high platelet reactivity ($p=0.004$) and decreased effectiveness of antiplatelet drugs. Moreover, the results of this study showed a strong association between major adverse cardiovascular events and high levels of PCSK9.[7,36] The main limitations of in vivo studies are the combined use of statins and antiplatelet agents.

Wang et al assessed the relationship between PCSK9 and platelet reactivity in vitro to exclude the influence of other drugs (statins and antiplatelet agents) on the results. Subsequently, an in vivo study in healthy subjects without statins and antiplatelet drugs found that subjects with high levels of PCSK9 had higher platelet reactivity.[7] Frankie et al assessed the effect of evolocumab on platelet reactivity. Low LDL cholesterol levels were achieved at 30 days in all patients receiving evolocumab. Although evolocumab was associated with a statistically significant reduction in platelet reactivity units in the first 14 days, there was no change in platelet reactivity units (PRU) compared with placebo after 30 days ($p = 0.161$).[36]

The production of PCSK9 and Ox-LDL is increased in patients with hypercholesterolemia. High levels of PCSK9 in the blood activate platelet receptors CD36, which induce platelet activation through SRK and JNK kinases involved in the mechanism of thromboxane A2 production. PCSK9 increases ROC production by activating NOX2 on the platelet surface. This increases the formation of Ox-LDL, which enhances platelet activation through binding to CD36 and LOX1 receptors. This triggers platelet aggregation and thrombogenesis through the expression of p-selectin, CD40L and release of granules. PCSK9 inhibitors help reduce the activation of NOX2, CD36 and LOX1. Specifically, they demonstrated a reduction in oxidative stress by reducing

NOX2. In addition, a decrease in platelet aggregation is associated with a decrease in circulating platelet factors (thromboxane, PAF-4, CD62, CD40L and p-selectin), which was observed after 6 months of treatment.[7,37,38]

The ORION-1 study showed that the drug does not cause immunogenicity in relation to platelets, cells of the immune system (lymphocytes and monocytes) and immune markers (IL-6 and TNF-α).[7,39] PCSK9 protein is involved in proinflammatory and prothrombotic effects. In addition, high levels of PCSK9 enhance platelet aggregation.

Thus, an indirect, mediated effect of inclisiran on platelets is possible. Inclisiran, due to its highly specific hepatic absorption, acts only at the hepatic level. Consequently, inclisiran has no direct effect on PCSK9, which is present in other tissues such as intestinal cells, pancreatic cells, adipocytes, kidneys and brain.[7,40]

DISCUSSION

High residual platelet reactivity (HRPR) is a significant predictor of adverse cardiovascular outcomes, including myocardial infarction and stent thrombosis, particularly in patients with coronary artery disease. This underscores the importance of managing platelet aggregation and LCL-C levels to mitigate the progression of atherosclerosis. Elevated platelet aggregation is believed to enhance smooth muscle cell proliferation and foam cell formation, which contributes to atherogenesis by promoting LDL-C accumulation within atherosclerotic plaques.

Numerous studies highlight the interrelationship between lipid levels and platelet function. Specifically, elevated LDL-C levels have been shown to activate platelet aggregation, primarily through the binding of apolipoprotein B-100 to LDL receptors on platelets, resulting in altered signaling pathways and increased platelet sensitivity to stimuli. Higher mean platelet volume (MPV) has also been linked to an increased risk of ischemic events and thrombosis, suggesting that platelet volume indices are valuable markers in assessing cardiovascular risk.

According to the SCORE scale, which stratifies patients based on their 10-year risk of cardiovascular events, effective management of LDL-C levels is crucial, especially for individuals categorized as high, very high, or extreme risk. The European Heart Association emphasizes the importance of achieving target LDL-C levels—less than 1.8 mmol/L for high-risk patients and under 1 mmol/L for those at extreme risk. However, evidence indicates that a significant proportion of very high-risk patients fail to reach these targets, even with maximally tolerated statin therapy. This highlights the need for additional therapeutic strategies.

Recent advancements in lipid-lowering therapies, including the combination of statins with ezetimibe and the incorporation of monoclonal antibodies targeting proprotein convertase subtilisin/kexin type 9 (PCSK9), such as alirocumab and evolocumab, show promising results in reducing LDL-C levels substantially. For instance, trials have demonstrated that evolocumab can lower LDL-C levels by approximately 60% and significantly decrease major cardiovascular events.

Bempedoic acid (BA) and inclisiran are emerging as novel agents with distinct mechanisms of action in LDL-C reduction. BA inhibits adenosine triphosphate (ATP) citrate lyase, leading to reduced LDL levels by up to 30% with monotherapy and 50% in combination with ezetimibe. Inclisiran employs RNA interference to decrease PCSK9 levels, enhancing LDL receptor recycling in hepatocytes and facilitating LDL uptake. Clinical trials have shown inclisiran to significantly reduce LDL-C levels and associated cardiovascular events, further establishing its role in managing dyslipidemia.

The relationship between PCSK9 and platelet reactivity is an area of ongoing investigation. Studies suggest that elevated PCSK9 levels are associated with increased platelet reactivity, potentially leading to worse cardiovascular outcomes. While PCSK9 inhibitors have shown promise in reducing oxidative stress and platelet aggregation, further research is necessary to delineate their direct effects on platelet function.

Overall, the collective evidence underscores the multifaceted nature of cardiovascular disease management, necessitating a comprehensive approach that includes aggressive lipid-lowering strategies and careful monitoring of platelet function. The integration of newer therapies, such as inclisiran and PCSK9 inhibitors, may play a critical role in achieving optimal outcomes for patients at high cardiovascular risk.

CONCLUSION

Most studies indicate the ineffectiveness of high-intensity statins in patients at high and extreme SCORE risk. Despite combination therapy with statins and ezetimibe or monoclonal antibodies, target LDL-C levels are not achieved in some cases. In addition, long-term therapy with statins, ezetimibe and monoclonal antibodies can lead to the development of side effects such as fibromyalgia and increased liver enzymes.

Inclisiran is the latest technology to lower LDL-C and PCSK-9 levels. From the above data, it is known that high LDL-C promotes increased platelet aggregation and the development of high platelet reactivity. Moreover, high levels of PCSK-9 protein are associated with high platelet reactivity in patients with CAD despite antiplatelet therapy. Inclisiran acts intracellularly, unlike monoclonal antibodies, reducing the production of the PCSK-9 protein and the uptake of LDL-C from the circulatory system. Since there is an association between high levels of PCSK-9, LDL-C and high platelet reactivity, it can be assumed that reducing PCSK-9 and LDL-C with inclisiran will help reduce platelet aggregation and reduce the incidence of cardiovascular complications in the long term. Thus, inclisiran represents a promising strategy for optimizing lipid control and reducing platelet activity in patients at high risk for cardiovascular diseases.

ACKNOWLEDGEMENTS

The authors would like to thank the JSC "Research Institute of Cardiology and Internal Medicine", Almaty, Republic of Kazakhstan, for support and encouragement in writing the manuscript.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

FUND

This study was funded by a grant from the Ministry of Science and Higher Education of the Republic of Kazakhstan "Improving the outcomes of surgical myocardial revascularization based on the development of comprehensive innovative management of patients after intervention", IRN AR19680319.

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