Review

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Hypercholesterolemia: a literature review on management using tafolecimab: a novel member of PCSK9 monoclonal antibodies

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Background: Cardiovascular diseases (CVD) persist as the leading cause of mortality globally, with atherosclerotic cardiovascular disease (ASCVD), including hypercholesterolaemia, being a significant contributor. Hyperlipidemia management includes various lipid-lowering drugs, including statins, Bempedoic acid, inclisiran, Lomitapide, ANGPTL3 inhibitors, and PCSK9 inhibitors. Statins have traditionally dominated lipid management therapies; however, a subset of patients remains unresponsive or intolerant to this therapy, necessitating novel therapeutic approaches. Tafolecimab, a promising and novel PCSK9 monoclonal antibody, demonstrated significant LDL-C reduction and a favourable safety profile in clinical trials.
Objective: This review aimed to discuss the role and efficacy of Tafolecimab in the management of hypercholesterolaemia.
Methods: The authors searched online databases, including PubMed, Scopus, and Embase, for articles related to talofecimab.
Discussion: The efficacy of Tafolecimab in diverse patient populations, including those with comorbid conditions and various lipid disorders, has been explored. Ongoing trials, such as CREDIT-1, CREDIT-2, and CREDIT-4, have provided valuable insights into Tafolecimab's potential as a lipid-lowering agent. Moreover, the drug's extended dosing interval may enhance patient compliance and reduce treatment costs. It has also been found that Tafolecimab has more affinity for PCSK9 and a longer duration of LDL-C reduction than other monoclonal antibody drugs such as evolocumab. Thus, this review focuses on Tafolecimab, a novel PCSK9 monoclonal antibody, its mechanism of action, clinical trial outcomes, safety profile, and potential role in hypercholesterolaemia management. Despite its assuring potential, the long-term impact of Tafolecimab on cardiovascular outcomes remains to be fully elucidated, necessitating further research. Regulatory authorities like the FDA and EMA should also evaluate Tafolecimab's risks and benefits.
Conclusion: In conclusion, Tafolecimab shows potential as an innovative therapeutic option for hypercholesterolaemia, particularly in patients with specific risk factors, but warrants additional research.

Keywords: Cardiovascular disease, hypercholesterolaemia, PCSK9 Inhibition

Introduction and background

The leading cause of death worldwide remains cardiovascular disease (CVD), with the disease burden set to increase in future years[1]. Among CVD causes, atherosclerotic disease remains the highest contributor, with 3.81 million reported deaths in the United States (US) alone[1]. The level of low-density lipoprotein cholesterol (LDL-C) is well established to have a causal relationship with atherosclerotic cardiovascular disease (ASCVD); therefore, its control is of vital interest to cardiac and non-cardiac patients. Along with lifestyle modification, HMG-CoA reductase therapy with 'statins' has been the mainstay of lipid control[2]. However, patient populations unable to reach goal lipid levels, those at high CV risk, and those intolerant to statin therapy have been required additive agents such as bile acid sequestrants, ezetimibe, and/or lipid-lowering novel medicines[2]. Of the novel therapies, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are the most powerful to date[2]. With increasing evidence of a 'lower is better' approach to treatment, their role in hypercholesterolaemia management may become quite important soon[3–6].

The PCSK9 gene was discovered in patients with familial hypercholesterolaemia who did not possess mutations in either the LDL receptor gene or the apolipoprotein B (ApoB) gene. Genetic researchers then proved that mutations in the PCSK9 gene on chromosome 1 are the culprit[7]. These drugs have since proven effective in treating hypercholesterolaemia patients with few reported adverse effects, although the question of long-term safety remains[8]. While the efficacy and safety of drugs such as alirocumab and evolocumab are well established, data on novel medicines from the PCSK9 inhibitor family, namely talofecimab, is limited. Pre-clinical investigations have revealed that

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tafolecimab exhibits a greater affinity for PCSK9 and a longer duration of LDL-C reduction in comparison to evolocumab[9]. Therefore, we decided to conduct this review to discuss the efficacy and safety profile of Tafolecimab in light of recent trials. The other objectives of this review include summarizing the past knowledge of hyperlipidemia, the mechanisms, role, and protocols for using PCSK9 inhibitors, and the implications for cardiac and non-cardiac patients treated with talofecimab.

Methods

We searched online databases, including PubMed, Scopus, and Embase, for articles related to talofecimab. We included review articles, editorials, clinical trials, meta-analyses, and conference abstracts.

PCSK9 monoclonal antibodies—structure, function, and regulation

PCSK9 is a protease from the proprotein convertase family. The molecule cleaves itself into a prosegment and an inactive protein that remains complex[10]. This complex then binds to and interacts with the LDL receptor (LDLR) on the hepatocyte cell surface, leading to its internalization and degradation via lysosome merger[11]. Fewer LDLR molecules in liver cells mean less LDL is removed from the blood, resulting in higher LDL-C levels[12,13]. Corroboration of this mechanism is presented in the form of PCSK9 gene gain-of-function mutations, which resulted in hypercholesterolaemia and loss-of-function mutations, which were associated with hypocholesterolemia[14–16]. As a result, inhibition of these molecules has been targeted using monoclonal antibodies, siRNAs, anti-sense oligonucleotides, vaccines, and mimetics[17–21]. PCSK9, found on chromosome 1 in humans, is regulated by the sterol regulatory element binding protein-2 (SREBP2) through a promoter region and a transcription regulator motif. Its regulation transcription and endogenous levels have largely proven to be sterol-dependent, with sterol depletion gradually increasing transcription levels[22]. Depleted intracellular cholesterol by statins and bile acid binding resins has been found to raise PCSK9 transcription activity, while fenofibrate has been found to downregulate expression[23,24].

Alirocumab and evolocumab are monoclonal, human immunoglobulin-G subtype (IgG) antibodies that bind both the catalytic and prodomains of PCSK9 protein, stopping its binding to LDLR[17]. Absent PCSK9 allows LDL bound to the LDLR to be degraded without internalization of the receptor. This allows for a faster rate of LDL clearance from the blood and reduced atheroma volumes[25]. Suppression of circulating PCSK9 protein can occur as quickly as 4-8 hours after injection, and newly secreted PCSK9 within a few days[25–27]. The lipid-lowering effect starts just a day after injection[25].

PCSK9 inhibition as a therapy for lowering LDL-C

PCSK9-inhibiting monoclonal antibodies are a new and powerful addition to lipid-lowering regimens[28]. Current trends in hyperlipidemia management according to the 'lower is better' guidelines in both the 2018 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines as well as 2019 European Society of Cardiology guidelines (down to <1 mmol/l) will favour their use for ASCVD patients with the only drawback being the higher cost of treatment compared to statins[2,29–31].

Evolocumab in the FOURIER trial and alirocumab in the ODYSSEY-OUTCOMES trial were associated with 59% and 54% reductions in LDL-C, respectively[32,33]. A 20% risk reduction in stroke, myocardial infarction, and CV death was also observed for evolocumab compared to placebo[32]. In an acute setting, 95.7% and 80.5% of patients with acute coronary syndrome (ACS) on evolocumab reached AHA/ACC LDL-C goals at the end of treatment (the EVACS and EVOPACS trials)[34,35]. Alirocumab and evolocumab have also shown promise for plaque regression, improved endothelial function, reduced CV events, and even stroke prevention, paving the way for their increased use among CVD patients[36–39]. While numerous studies point to their efficacy in the short-term, long-term data attesting to their sustained effects is coming to light[40–43]. Two new randomized controlled trials (RCTs) and a phase 3 clinical trial evaluated the use of evolocumab or alirocumab in paediatric familial hypercholesterolaemia (FH) with sustained reductions in LDL and few reported side effects[44–46]. This adds to current guidelines recommending them for heterozygous FH patients (HeFH) who cannot achieve therapeutic targets with standard therapy (LDL-C of <70 mg/dl) and homozygous FH (HoFH) patients. However, this depends on the type of mutation present[47,48].

The 2018 AHA/ACC guidelines recommend these antibodies for secondary prevention of ASCVD patients at very high risk that being multiple major ASCVD events, one major ASCVD event, and two primary high-risk conditions if LDL remains greater than 70 mg/dl or non-HDL-C remains greater than

HIGHLIGHTS

- Cardiovascular disease patient populations who are resistant to standard statin therapy require novel lipid-lowering medications.
- PCSK9 inhibitors are monoclonal antibodies that have powerful lipid-lowering effects by increasing the recycling of low-density lipoprotein receptors (LDLR) and indirectly lowering circulating LDL cholesterol levels by increasing LDL cholesterol uptake.
- Tafolecimab, a novel recombinant fully human immunoglobulin G2 (IgG2) PCSK9 monoclonal antibody, has been recognized as a potent drug for lowering LDL-C concentration.
- The CREDIT trials offer a valuable understanding of the potential of Tafolecimab in managing hypercholesterolaemia in various patient populations, including those with non-familial hypercholesterolaemia and HeFH.
- Based on the study results of three-phase clinical trials (CREDIT-1, CREDIT-2, and CREDIT-4), China's National Medical Products Administration (NMPA) has approved Innovent Biologics Inc. Sintiblo (Tafolecimab), which is the first locally developed PCSK9 monoclonal antibody to be approved in China.
- Hence, the Food & Drug Administration (FDA) and European Medicines Agency (EMA) should also conduct scientific research to evaluate the risks and benefits of Tafolecimab.

100 mg/dl with maximally tolerated statin and ezetimibe therapies. Primary prevention guidelines recommend their use in patients of heterozygous FH with LDL-C greater than 100 mg/dl or patients with baseline LDL-C greater than 220 mg/dl on top of maximally tolerated statin and ezetimibe therapies. European guidelines differ slightly as they recommend them for primary prevention of FH with another significant risk factor, severe CKD, diabetes mellitus with target organ damage, or prolonged duration (>20 years) type 1 diabetes mellitus. For secondary prevention, they are indicated for patients with documented ASCVD, imaging findings of ASCVD, or if target LDL-C less than 55 mg/dl or 50% LDL reduction isn't achieved with max statin and ezetimibe therapies[49,50]. This shows a more aggressive treatment protocol overall in the European guidelines. Data from all RCTs have found them well tolerated, with few reported side effects. While early trials reported significant increases in neurocognitive side effects in treatment arms, subsequent targeted studies such as the EBBINGHAUS trial and large meta-analysis found no such correlation[51,52].

Classification of hyperlipidemia

According to the 1972 Fredrickson classification, Dyslipidemias are classified based on electrophoresis and centrifugation to separate cholesterol and triglyceride disorders into 5 phenotypes (Types I–V). These include Type I, familial hyperchylomicronemia, and Type II, familial hypercholesterolaemia. Type III is dysbetalipoproteinemia. Type IV is primary hypertriglyceridemia, and Type V is mixed hyperlipoproteinemia[53]. Although many other classification schemes have since been suggested, the Fredrickson classification still holds the most diagnostic and therapeutic significance. This is a result of its grouping according to lipid type, wherein certain types of lipids are more atherogenic and require more intensive treatment protocols (such as very low density lipid)[54,55]. The WHO has widely adopted it, and is still clinically used[55].

Drugs used in hyperlipidemia management

Figure 1 shows a summary of lipid-lowering medications.

Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (Statins)

Statins are the most widely used and studied drugs for lipid-lowering[56]. These are hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, a rate-limiting enzyme in the cholesterol synthesis pathway in the liver, which increases the hepatocyte LDL receptor expression and LDL removal from the blood[56]. They reduce LDL-C levels by 20–65%[57,58]. Treatment regimens are divided into high-intensity for ASCVD patients and those at high CV risk (lowers LDL-C by >50%), moderate-intensity for those between 40 and 75 years with diabetes mellitus (lowers LDL-C by 30–49%), and low power (lowers LDL-C by <30%)[2,59]. However, complaints of muscle-related side- effects, elevated creatine kinase, and mild muscle injury have been reported in about 5–20% of patients. They may cause non-compliance in as many as 30% of prescribed patients[60,61]. Most side effects require monitoring of CK levels and can be avoided by changing the type of statin administered[62]. Rarely seen side effects include rhabdomyolysis, myositis, and new-onset diabetes mellitus, which require statin cessation[54,63].

Non-statin therapies

Additive agents included ezetimibe, bile acid sequestration, and PCSK9 inhibition. These may be indicated in patients who cannot reach goal LDL-C levels (<70 mg/dl or >50% LDL-C reduction) on high-intensity statin and/or are intolerant to statin therapy. Ezetimibe inhibits intestinal cholesterol absorption at the jejunal brush border and increases hepatic LDLR expression[64]. Ezetimibe has been shown to lower LDL levels and the relative risk of MI and stroke when added to statin therapy[65]. It is beneficial as a sole agent for reducing CV outcomes in patients with non-atherosclerotic CVD[66]. Bile acid sequestration agents such as colesevelam and cholestyramine have been shown to further lower LDL-C levels by 15–30% when added to statin therapy, respectively[2]. Among novel non-statin therapies, inclisiran is a synthetic interfering RNA (siRNA) that binds to the RNA-induced silencing complex (RISC), causing the hydrolysis of PCSK9 mRNA[66]. It has the added benefit of requiring bi-annual 300 mg subcutaneous injection, making it useful for patients with compliance issues with statin or PCSK9 inhibitor therapies[67]. While phase 1 trials and pooled data from meta-analysis have provided evidence for its efficacy, data from long-term studies such as the ORION-4 trials is still needed[67].

The orally bioavailable PCSK9 inhibitor MK-0616 is currently being developed and may be indicated for patients who cannot comply with monoclonal antibody and inclisiran injection subcutaneously[68]. It has passed phase 1 trials in 60 healthy volunteers with no adverse effects and shown up to 60% reductions in LDL-C after eight weeks in step 2a trials[69,70]. Other PCSK9 targeting therapies also include anti-sense oligonucleotides (SPC5001), which were found to reduce PCSK9 levels by greater than 80% at steady state and reduction in LDL-C by 0.72 mmol/L; however, these have since been associated with acute kidney injury (AKI)[19,71,72].

Bempedoic acid is an oral inhibitor of adenosine triphosphate citrate lyase, an enzyme of the cholesterol synthesis pathway[73]. It has since been found to be safe and efficacious in patients intolerant to statins and those using them as an add-on to high-intensity statin therapy[73–75]. It was associated with a lower rate of major adverse CV events (defined as death from CVD causes, non-fatal MI, non-fatal stroke, and coronary revascularization) as monotherapy in statin-intolerant patients as well as an additive agent to maximally tolerated statin therapy[76,77]. Angiopoietin-like three protein (ANGPTL3) inhibitors such as evinacumab are another potential therapy currently targeted for treating homozygous FH. The ANGPTL3 protein inhibits endothelial lipases; loss-of-function mutations of this gene are known to cause lower serum cholesterol and triglyceride levels[78]. It benefits patients with null LDLR variants of HoFH, differentiating it from PCSK9 inhibitors, which are of limited importance in such cases[79,80]. Furthermore, evolocumab phase 1 studies have shown peak mean reductions of up to 81.6% after 4 days in patients with severe hypertriglyceridemia. However, phase 2 trials have demonstrated only decreases of up to 27.1% after 12 weeks[81,82]. If more extensive trials have published favourable results, it may be a candidate for acute pancreatitis treatment. It has also shown LDL-C reductions of 38–56% in HeFH patients with refractory hypercholesterolaemia and reported low rates of adverse effects (3–16%)[83]. Lomitapide is another

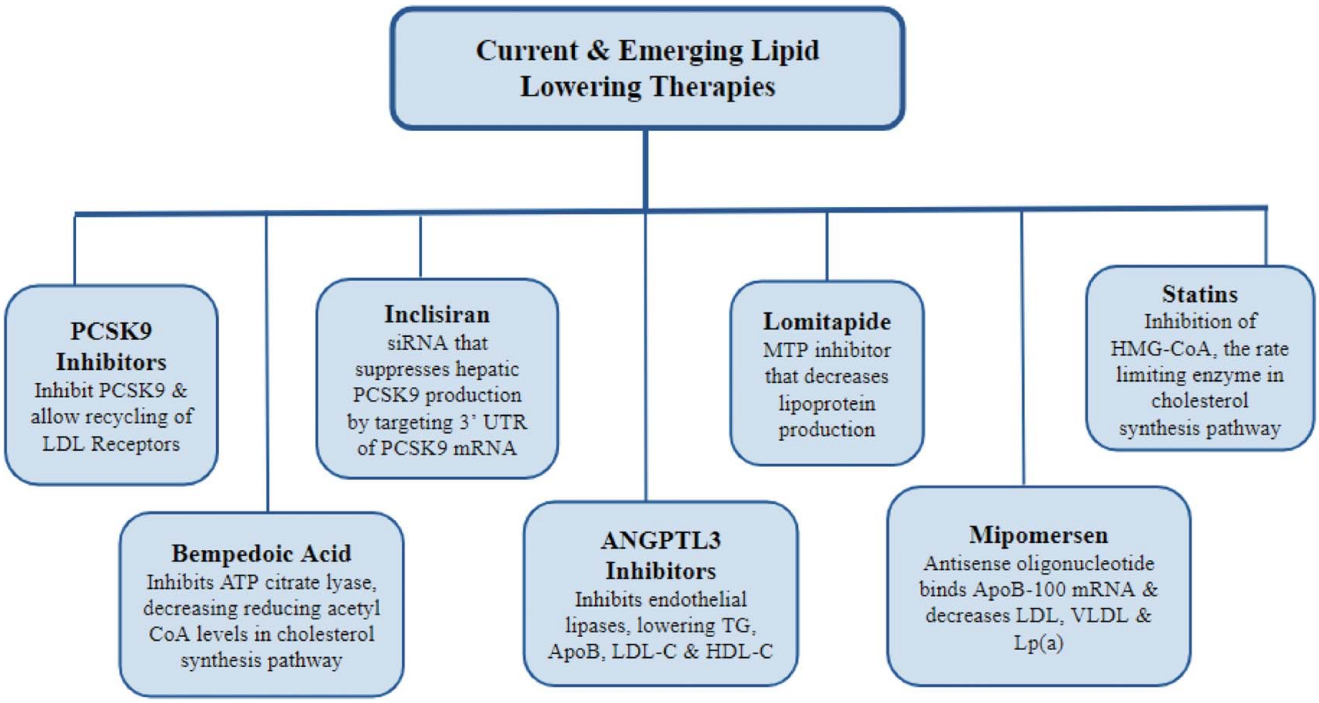

Figure 1. Drugs used in hyperlipidemia management. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MTP, microsomal triglyceride transfer protein; VLDL, Very low density lipoprotein.

targeted therapy for HoFH. It is a microsomal triglyceride transfer protein (MTP) inhibitor that decreases the formation of very low density lipid chylomicrons and reduces LDL-C levels[84]. Adverse effects are primarily gastrointestinal events, with rare cases of hepatic injury being reported[85,86]. Evidence of its long-term safety and efficacy for HoFH patients in European and Japanese studies has been published, although more extensive phase 3 trials are still required[87–89].

Mechanism of action of tafolecimab

PCSK9 plays a vital role in regulating LDL-C levels in the blood, acting as a critical regulator in the complex mechanisms of cholesterol homoeostasis. PCSK9 is synthesized in hepatocytes and subsequently released into the circulation, where it affects the circulating LDL-C levels through its inhibitory action on the recycling of LDLR[90]. Under normal conditions, LDLR on the hepatocyte surface binds to LDL, and the resultant LDLR–LDL complex is internalized into the cell. After internalization, LDLR is typically recycled back to the cell surface, engaging in multiple rounds of LDL binding and internalization[91]. However, secreted PCSK9 disrupts this cycle by binding to LDLR on the hepatocyte surface, orchestrating the internalization and degradation of LDLR within lysosomes. This action reduces the number of LDLRs available on the cell surface, thereby diminishing the cellular uptake of LDL-C[92].

PCSK9 inhibitors, such as alirocumab and evolocumab, are a new generation of lipid-lowering drugs that have shown encouraging LDL cholesterol-lowering results in clinical trials[93]. PCSK9 plays a vital role in LDL receptor downregulation, and when the PCSK9 protein binds to the LDLR, it initiates the receptor's degradation process, thus increasing LDL cholesterol levels[94] (Fig. 2). Monoclonal antibodies inhibit PCSK9 binding to LDLRs, increase LDLR recycling, and indirectly lower circulating LDL cholesterol levels by increasing LDL cholesterol uptake[95] (Fig. 2). Tafolecimab, a novel recombinant fully human immunoglobulin G2 (IgG2) PCSK9 monoclonal antibody, has been recognized as a potent drug for lowering LDL-C concentrations[96]. It is produced through affinity maturation by chain shuffling and complementarity determining region mutagenesis on candidate antibodies discovered from a synthetic human antibody library. Tafolecimab (IBI306) is a human IgG2κ antibody that binds PCSK9, preventing PCSK9′s interaction with its receptor LDLR, thereby restoring LDLR recycling and LDL-C uptake[96].

Concomitant risk factors and their effect on lipid-lowering agents

Treatment of hypercholesterolaemia is essential for reducing the risk of ASCVD, with statins traditionally being the basis for the prevention and treatment of ASCVD. However, even under optimal statin therapy[97], a significant risk remains, necessitating the search for additional lipid-lowering agents, considering various associated risk factors that may influence the efficacy of these agents. Patients with hypercholesterolaemia often present with other risk factors such as diabetes, hypertension, and a family history of premature CVD, which can exacerbate the condition and potentially influence the effectiveness of lipid-lowering agents. Familial hypercholesterolaemia (FH), a genetic disorder characterized by high plasma LDL-C levels from birth, poses a particular challenge due to the congenital defect in LDLR, rendering traditional therapies like statins less effective[98]. PCSK9 inhibitors, such as evolocumab and alirocumab, have

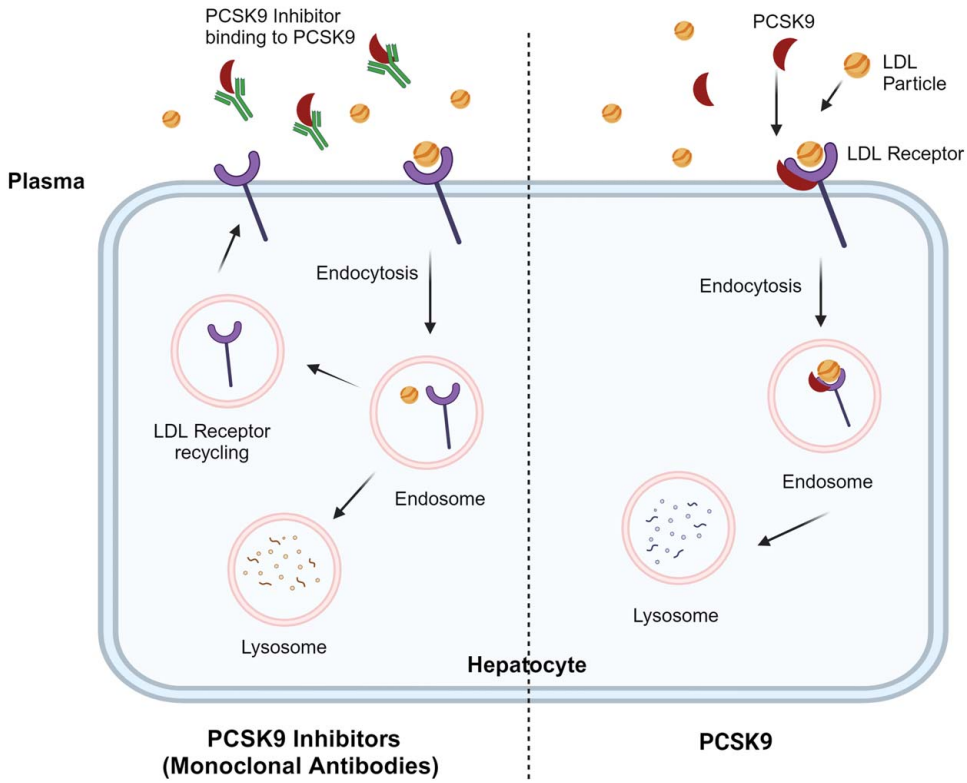

Figure 2. Mechanism of action. LDL, low-density lipoprotein.

demonstrated significant efficacy in reducing LDL-C levels, especially in heterozygous FH (HeFH) patients. However, their effectiveness in homozygous FH (HoFH) patients depends on residual LDLR activity[99]. ANGPTL3 inhibitors, such as evolocumab, have shown promise in reducing LDL-C levels even in HoFH patients carrying null LDLR mutations, owing to their LDLR-independent mechanism of action, present a potential alternative for patients who do not respond to PCSK9 inhibitors due to null mutations in LDLR[100]. Furthermore, novel lipid-lowering agents, including inclisiran, a small interfering RNA targeting PCSK9, have shown comparable effects to PCSK9 monoclonal antibodies[101]. Bempedoic acid, an ATP citrate lyase inhibitor, offers a valuable treatment option for statin-intolerant patients[102]. Additionally, fenofibrate, a selective peroxisome proliferator-activated receptor alpha modulator, and high-dose icosapent ethyl, a modified eicosatetraenoic acid preparation, have demonstrated CV benefits[103].

Tafolecimab effects in patients with diabetes mellitus, hypertension, and high LDL-C levels

In hypercholesterolaemia management, particularly among patients with diabetes mellitus, hypertension, and elevated LDL-C levels, Tafolecimab has become a crucial therapeutic drug. Patients with diabetes mellitus often exhibit dyslipidemia, characterized by high triglycerides, reduced high-density lipoprotein cholesterol (HDL-C), and increased LDL-C, significantly increasing their CV risk[104]. Connelley and colleagues investigated the prevalence of high plasma triglycerides combined with low HDL-C levels in a Canadian population. They found that most of these lipid abnormalities were increased in groups who were cigarette smokers, diabetic, hypertensive, obese, or sedentary, or who had higher LDL-C levels in both sexes[105]. Moreover, the coexistence of hypertension and hypercholesterolaemia increases the risk for ASCVD, highlighting the importance of aggressively managing LDL-C levels. While PCSK9 inhibitors, including Tafolecimab, have demonstrated efficacy in reducing LDL-C levels, particularly beneficial for patients who do not achieve optimal LDL-C reduction with statin therapy alone[9], specific data on Tafolecimab in patients with diabetes mellitus and hypertension remains limited. Tafolecimab, similar to established PCSK9 monoclonal antibodies such as alirocumab and evolocumab, not only significantly reduced LDL-C concentration by approximately 70% but at the same time lowered non-HDL-C, ApoB, and lipoprotein (a) [Lp(a)] levels[33]. These lipid-related markers, which have recently become novel lipid targets in the prevention and treatment of ASCVD, coupled with Tafolecimab's extended period of LDL-C concentration reduction (an injection every 4 weeks as opposed to every 2 weeks with alirocumab and evolocumab)[106], present a promising treatment approach. This extended dosing interval increases patient medication compliance and reduces both the frequency of injections and treatment costs, which is especially relevant for patients in developing countries within Asia[107]. Figure 3 shows detailed insights into the effects of PCSK9 inhibition.

Tafolecimab role in primary hypercholesterolaemia and mixed dyslipidemia

Hypercholesterolaemia, defined by elevated LDL-C levels, is a dominant risk factor for the onset of CVD. Patients with familial hypercholesterolaemia, predisposed to early CV risks, often find

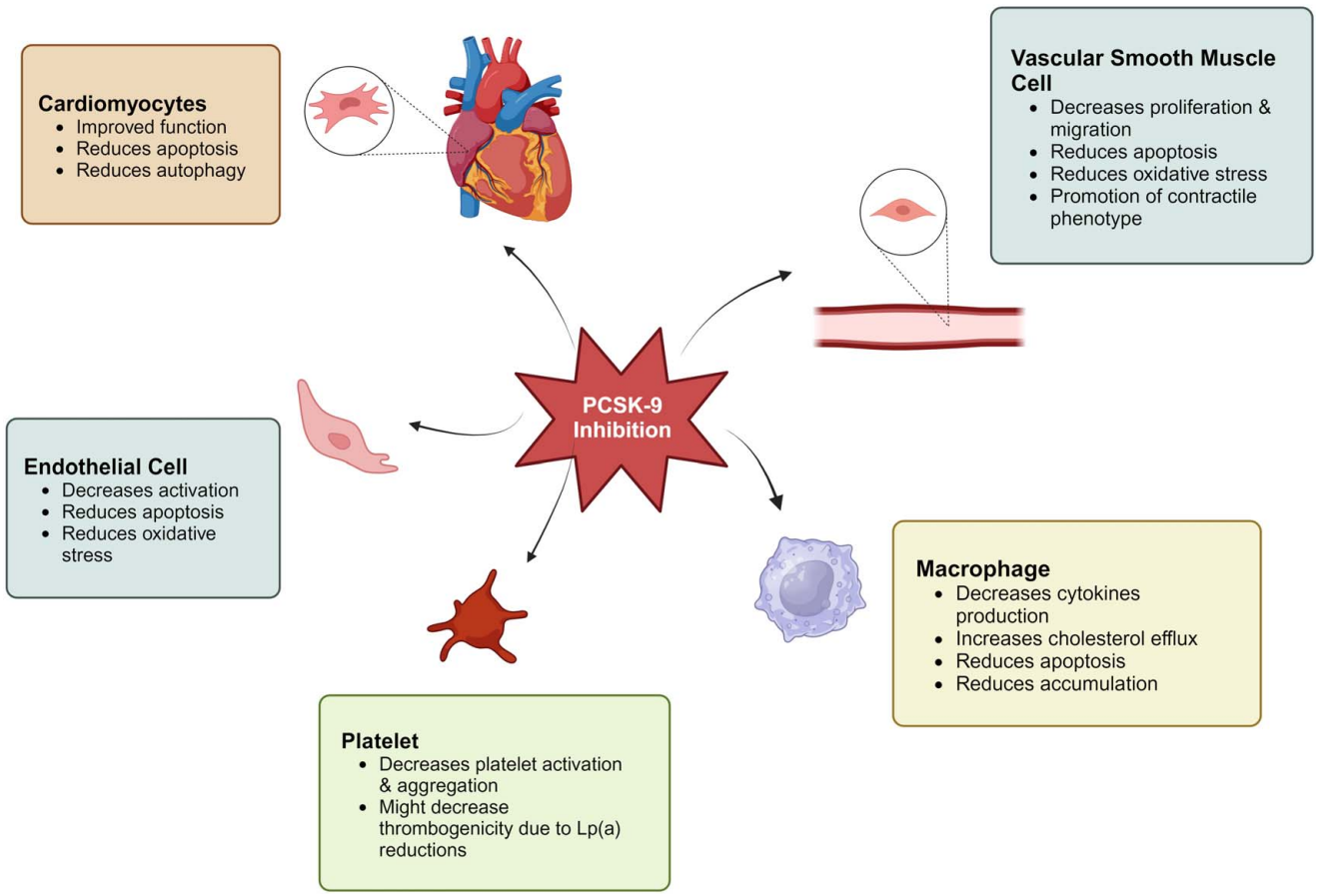

Figure 3. Effects of PCSK9 inhibition.

conventional therapies, like statins combined with ezetimibe, insufficient[108]. PCSK9 inhibitors, such as evolocumab, have demonstrated significant efficacy in reducing LDL-C levels in patients with primary hypercholesterolaemia and mixed dyslipidemia[108]. Hong and colleagues evaluated the efficacy and safety of evolocumab in Chinese patients with primary hypercholesterolaemia and mixed dyslipidemia. They revealed significant reductions in LDL-C levels, highlighting the potential of PCSK9 inhibitors to treat these conditions[109]. Antonioand colleagues evaluated the fixed-dose combination of rosuvastatin and ezetimibe. They demonstrated efficacy and tolerability in Brazilian patients with primary hypercholesterolaemia or mixed dyslipidemia, indicating the potential of combining lipid-lowering agents to achieve optimal lipid control[110]. From the broad therapeutic perspective, while statins remain the mainstay in LDL-C reduction, for high-risk patients, the combination of statins with adjunct therapies like ezetimibe or PCSK9 inhibitors is often recommended to achieve optimal LDL-C levels. PCSK9 Inhibitor, Tafolecimab has demonstrated significant reductions in LDL-C concentration, non–high-density lipoprotein cholesterol, apoB, and Lp(a) levels, highlighting its potential as a potent lipid-lowering agent. Moreover, Tafolecimab has the advantage of a longer dosing interval than other PCSK9 monoclonal antibody agents, which may improve medication compliance, reduce the number of injections, and potentially lower treatment costs, especially for patients in developing countries[111].

Ongoing trials of tafolecimab

Tafolecimab (PCSK9), a monoclonal antibody, has undergone investigation in clinical trials for its efficacy and safety in managing hypercholesterolaemia. The CREDIT trials are essential for understanding its role in managing different patient populations with hypercholesterolaemia.

CREDIT-1 trial: non-familial hypercholesterolaemia

The CREDIT-1 trial aimed to assess the efficacy and safety of Tafolecimab in Chinese patients with non-familial hypercholesterolaemia. Patients were randomized to receive either Tafolecimab 450 mg every four weeks, Tafolecimab 600 mg every 6 weeks, or placebo for 48 weeks. The primary endpoint was the percent change in LDL-C levels from baseline to week 48. Tafolecimab significantly reduced LDL-C levels and showcased a favourable safety profile in Chinese patients with non-familial hypercholesterolaemia[112].

CREDIT-2 trial: heterozygous familial hypercholesterolaemia (HeFH)

The CREDIT-2 trial focused on Chinese patients diagnosed with HeFH according to the Simon Broome criteria and on a stable lipid-lowering therapy. Patients were randomized to receive Tafolecimab 150 mg every 2 weeks, Tafolecimab 450 mg every four weeks, or placebo in a 12-week double-masked treatment

period, followed by a 12-week open-label period with Tafolecimab. The primary endpoint was the percent change in LDL-C levels from baseline to week 12. Tafolecimab induced significant reduction in LDL-C levels and was associated with a higher proportion of patients achieving greater than or equal to 50% LDL-C reductions or LDL-C less than 1.8 mmol/l at week 12 compared to placebo[113].

CREDIT-4 trial: high or very high cardiovascular risk patients

The CREDIT-4 trial aimed to assess the efficacy and safety of Tafolecimab in Chinese patients at high or very high CV risk with hypercholesterolaemia. Patients who were either diagnosed with HeFH by the Simon Broome criteria or at high or very high CV risk with non-familial hypercholesterolaemia, with screening LDL-C level greater than or equal to 1.8 mmol/l, were randomized to receive Tafolecimab or placebo 450 mg every four weeks in a 12-week double-blind treatment period. The primary endpoint was the percent change in LDL-C levels from baseline to week 12. Tafolecimab significantly reduced LDL-C levels from baseline to week 12 and markedly reduced non-HDL-C, apoB, and Lp(a) levels[114].

The CREDIT trials offer a valuable understanding of the potential of Tafolecimab in managing hypercholesterolaemia in various patient populations, including those with non-familial hypercholesterolaemia and HeFH. The significant reductions in LDL-C levels and favourable safety profiles observed in these trials suggest that Tafolecimab may be a useful treatment option for hypercholesterolaemia. Further research and ongoing trials will be crucial in establishing Tafolecimab's long-term efficacy, safety, and impact on CV outcomes.

Tafolecimab side-effect profile

PCSK9 inhibitors, such as alirocumab and evolocumab, showed a favourable safety profile in clinical trials. Commonly reported side effects include injection site reactions, nasopharyngitis, and upper respiratory tract infections[115]. Furthermore, no causal relationship has been proven between the inhibition of PCSK9 and neurocognitive or glycemic adverse events[116]. In the study by Litong and colleagues, the incidence of adverse events was lower in the Tafolecimab group than in the placebo group (41.5% with Tafolecimab versus 54.1% with placebo). The most reported adverse events in the Tafolecimab group were urinary tract infection (5.9% versus 4.1%) and hyperuricemia (3.4% versus 4.1%)[114].

Additionally, the commonly reported treatment-emergent adverse events (TEAEs) in the Tafolecimab groups included upper respiratory tract infection, increased blood creatine phosphokinase, alanine aminotransferase, aspartate aminotransferase and hypertension[106]. Gürgöze *et al*.[115] found similar rates of muscle-related adverse events and hypersensitivity between the Tafolecimab and placebo groups (5.0% with Tafolecimab vs. 6.3% with placebo). Serious adverse events, including urinary tract infection, pneumonia, unstable angina, angina pectoris, and oedema, were reported in one (0.5%) patient each in the Tafolecimab group, all of which were judged by the investigator to be unrelated to the study drug[113].

While Tafolecimab has demonstrated a favourable safety profile in clinical trials, it is essential to note that the impact of Tafolecimab on CV outcomes still needs to be improved; further study is warranted. The detailed side effect profile, especially in diverse populations and over extended periods, must be elucidated in future studies to ensure the safe and effective use of Tafolecimab in managing hypercholesterolaemia.

Drug approval and future implications

Most research on Tafolecimab has been conducted in China[108,114–116], where pharmaceutical products are regulated by the National Medical Products Administration (NMPA). Based on the study results of three-phase clinical trials (CREDIT-1, CREDIT-2, and CREDIT-4), China's NMPA has approved Innovent Biologics Inc. Sintiblo (Tafolecimab), the first locally developed PCSK9 monoclonal antibody, has been approved in China[117,118]. The approval is for treating patients with hypercholesterolaemia (both heterozygous familial and non-familial hypercholesterolaemia) as well as mixed dyslipidemia[117,118].

Further research should be conducted to evaluate the efficacy and safety profile of Tafolecimab with varying regimens in different populations, especially in the US, because it is estimated that over 50% of American adults have elevated LDL levels[119]. Hence, the Food & Drug Administration (FDA) and European Medicines Agency (EMA) should also conduct scientific research to evaluate the risks and benefits of Tafolecimab. Future studies should be based on trials with larger sample sizes and longer follow-up durations for better results and understanding. Additionally, it has been found that Tafolecimab has a greater affinity for PCSK9[9], therefore, the comparative efficacy of Tafolecimab should be assessed with traditional therapies, such as other PCSK9 inhibitors in the market, to explore the best therapeutic approach with the most promising safety profile for the patients.

Conclusion

Tafolecimab is an emerging intervention that has shown promising lipid-lowering efficacy and a well-tolerated safety profile in the Chinese population, indicating that it can be a potentially innovative therapeutic alternative for hypercholesterolaemia patients. However, further research is encouraged with varying dosage regimens in different people.

Ethical approval

Ethical approval was not required for this review.

Consent

Informed consent was not required for this review.

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Author contribution

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