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REVIEW ARTICLE

Long-Term Efficacy and Tolerability of PCSK9 Targeted Therapy: A Review of the Literature

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Abstract

Increased plasma levels of low-density lipoprotein cholesterol (LDL-C) are causally associated with atherosclerotic cardiovascular disease (ASCVD), and statins that lower LDL-C have been the cornerstone of ASCVD prevention for decades. However, guideline-recommended LDL-C targets are not achieved in about 60% of statin users. Proprotein convertase subtilisin/kexin type 9 (PCSK9)-targeted therapy effectively lowers LDL-C levels and has been shown to reduce ASCVD risk. A growing body of scientific and clinical evidence shows that PCSK9-targeted therapy offers an excellent safety and tolerability profile with a low incidence of side effects in the short term. In this review, we present and discuss the current clinical and scientific evidence pertaining to the long-term efficacy and tolerability of PCSK9-targeted therapy.

Key Points

PCSK9-targeted therapy demonstrates effectiveness and safety in reducing LDL-C levels, making it a valuable option for high-risk patients with atherosclerotic cardiovascular disease.

The balanced adverse event profile, positive effects on plaque burden, and anticipated user-friendly formulations hold promise for wider accessibility in the global fight against atherosclerosis cardiovascular disease.

1 Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality and morbidity worldwide. Hypercholesterolemia is a major and causal risk factor for ASCVD [1]. Lowering LDL-C is therefore an established and effective pharmacological approach to reduce the risk of ASCVD. The use of lipid-lowering therapies has led to a significant reduction in the occurrence of major adverse cardiovascular events (MACE), making them a fundamental pillar in current preventive treatment [2]. The expected benefit for reducing ASCVD risk is correlated to the magnitude of LDL-C reduction [3]. This emphasizes the importance of initiation of potent LDL-C-lowering therapies combined with good medication adherence. The latter is often compromised by adverse effects attributed to lipid lowering treatment (mostly in statin users), and loss of adherence is more common in female patients and in those with a low socioeconomic status [4]. Real-world studies have reported that after 2 years, only 50% of patients continue statin therapy [5, 6], resulting in a significant residual ASCVD risk [6–8].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a relatively new target to lower LDL-C. Pharmacological reduction of circulating PCSK9 enhances the clearance of LDL-C from circulation through LDL receptor-mediated mechanisms [9]. At present, evolocumab and alirocumab, fully humanized monoclonal antibodies (mAbs) targeting PCSK9, as well as inclisiran, a synthetic small interfering RNA (siRNA) which inhibits translation of PCSK9 mRNA, have been approved for clinical use as injectable lipid lowering therapies (LLT). PCSK9-targeted therapy is recommended by the European (ESC/EAS) and American (ACC/AHA) guidelines as additional lipid-lowering agents in adult patients with familial hypercholesterolemia (FH)

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or established ASCVD requiring additional LDL-C lowering to reduce the risk of myocardial infarction, stroke, and coronary revascularization [10–12].

Monoclonal antibodies directed against PCSK9 have been shown to reduce the risk of recurrent cardiovascular events in patients who were on statin therapy [13, 14]. Also, among patients with coronary artery disease, the addition of PCSK9-targeted therapy to high-intensity statin therapy resulted in significant coronary plaque regression [15, 16]. However, there are conflicting secondary reports about the long-term tolerability of these efficacious agents [17, 18]. This review presents and discusses the current clinical and scientific evidence regarding the long-term efficacy and tolerability of PCSK9-targeted therapy.

2 Lipid Metabolism and PCSK9-Targeted Therapy

LDL receptors (LDLR) on the surface of liver hepatocytes primarily control plasma LDL-C levels and are responsible for eliminating approximately 70% of circulating LDL-C particles [19]. PCSK9 is a proteolytic enzyme produced mainly in the liver and a major regulator of LDL-C metabolism [20]. Circulating PCSK9 binds the LDLR, leading to endocytosis of the LDLR–PCSK9 complex into the hepatocyte and ensuing degradation of the LDLR in lysosomes [20]. Premature degradation of the LDLR leads to fewer LDLRs present on the cell surface, which invariably gives rise to increased serum LDL-C levels [9, 21]. In Fig. 1, an overview of existing PCSK9-targeted therapies is provided along with their respective mechanisms of action, which are further described below.

Alirocumab and evolocumab are fully humanized monoclonal antibodies that specifically bind PCSK9, resulting in an increased recycling of LDLR, accelerated clearance of LDL-C particles, and, thereby, lower levels of circulating LDL-C [21, 22]. Alirocumab and evolocumab are administered by a subcutaneous injection once every 2 weeks or once a month. This subcutaneous injection introduces an excess of antibodies that capture all free plasma PCSK9 [9]. Together, evolocumab and alirocumab are hereafter referred to as PCSK9 mAbs.

Inclisiran is a long-acting synthetic small-interfering RNA (siRNA) directed against the mRNA encoding the PCSK9 protein. Targeting PCSK9-mRNA in the liver reduces intracellular and extracellular PCSK9 concentrations, leading to a significant LDL-C reduction [23, 24]. Its effect lasts longer than other lipid lowering agents, which translates into a dosing scheme of only two injections per year.

3 Pharmacological Efficacy

3.1 Lipid Levels

The potent lipid-lowering efficacy of evolocumab [25–28] and alirocumab [29–32] was shown in many clinical trials with reductions in LDL-C levels by at least 60% when used in combination with statins and 50–60% when used as monotherapy. Inclisiran has been shown to reduce mean PCSK9 plasma protein levels by 70% and LDL-C levels by up to

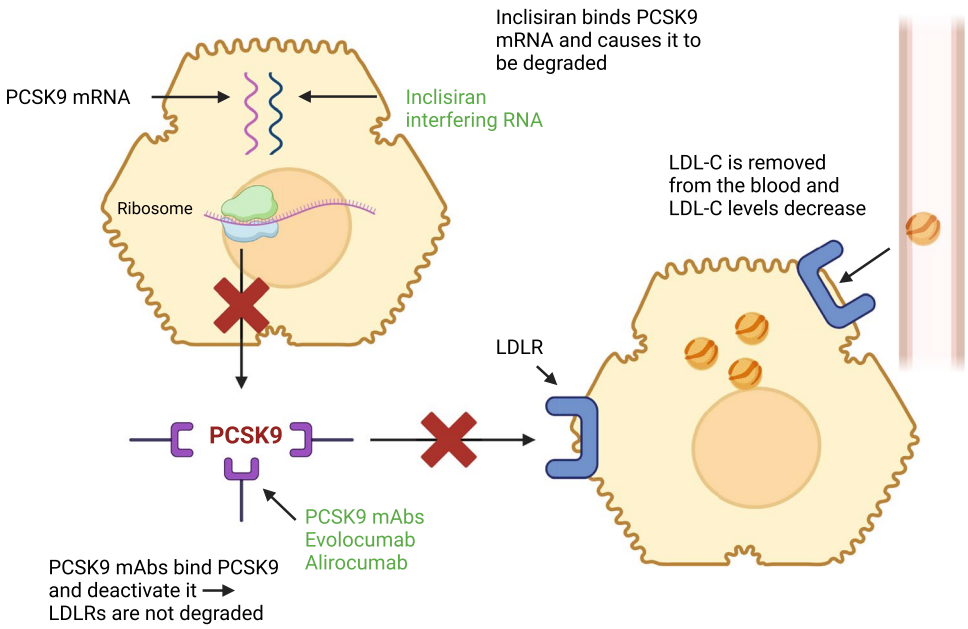

Fig. 1 Mechanism of action of current PCSK9 targeted therapy: evolocumab, alirocumab and inclisiran

56% [24, 33, 34]. The results of plasma LDL-C lowering remained consistent across various high-risk clinical subgroups (such as patients at high ASCVD risk, patients with statin intolerance, and patients with FH) and independent of baseline plasma PCSK9 levels [35, 36]. PCSK9-targeted therapy was also shown to be highly effective in patients with FH or statin-intolerant patients, representing an important therapeutic option for these high-risk patients [26, 37, 38]. Moreover, PCSK9-targeted therapy lowers apolipoprotein B levels and non-HDL cholesterol, both important markers of ASCVD risk [39]. Unlike statins, evolocumab and alirocumab also reduce lipoprotein(a) levels by up to 25%. However, the molecular mechanism underlying this effect has not yet been fully elucidated [40, 41]. Interestingly, in a recent meta-analysis concerning statins, a significant reduction in high-sensitive CRP (hs-CRP) levels was observed among patients with ASCVD, with a reduction of −0.97 mg/L [95% confidence interval (CI): − 1.26, − 0.68 mg/L; $P < 0.001$), whereas a meta-analysis on PCSK9-targeted therapy did not show a reduction (weighted mean difference: 0.002 mg/L, CI: – 0.017, 0.021; $P = 0.807$; $I^2 = 37.26\%$) in hs-CRP levels compared with the placebo, irrespective of the type of drug, dosing frequency, changes in LDL-C levels, or cumulative dosage [42, 43]. The difference between PCSK9-targeted therapy and statins on hs-CRP raises the question to what extent attenuation of inflammation drives cardiovascular disease reduction for both agents. However, it should be mentioned that most PCSK9-targeted therapy trials were performed in patients that were already using statins, making it hard to untangle any fundamental differences.

3.2 Atherosclerotic Disease

PCSK9-targeted therapy offers the prospect of positive effects on atherosclerotic plaque burden and plaque characteristics (Table 1). The association between serum PCSK9 levels and the extent of atherosclerotic plaque burden has been assessed in a number of imaging studies. Elevated PCSK9 levels are independently associated with coronary artery calcification (CAC) [44], the fraction and amount of necrotic core tissue in coronary atherosclerosis [45], and overall atherosclerotic extent as measured by intima media thickness or total plaque volume [46–48].

Evolocumab in addition to moderate- or high-intensity statin treatment resulted in a significant decrease (− 1.0%; 95% CI − 1.8% to − 0.64%) of percent atheroma volume and (−4.9 mm^3; 95% CI − 7.3 to − 2.5) of total atheroma volume measured by intravascular ultrasound (IVUS; GLAGOV trial) and an increase in fibrous cap thickness (+ 42.7 µm versus + 21.5 µm; $P = 0.015$) and decrease in lipid arc (−57.5° versus −31.4°; $P = 0.04$) measured by IVUS and optical coherence tomography (OCT; HUYGENS trial) in patients with ASCVD and non-ST elevated acute coronary syndrome (ACS) after treatment for 52–76 weeks [15, 49]. In a separate study, coronary plaque regression, lipid core reduction, and plaque stabilization measured with IVUS and OCT in noninfarct-related arteries was found in post-ACS patients treated for 52 weeks with alirocumab in addition to high-intensity statin [16]. Furthermore, a more stable plaque phenotype and plaque regression, measured with either IVUS [50] or OCT [51, 52], were observed in patients with ASCVD who were treated for 36 weeks with alirocumab in addition to maximally tolerated statin therapy. Evolocumab also significantly reduced the area of coronary atherosclerotic stenosis in nontarget lesions (− 13.6%) measured with quantitative coronary angiography 1 year after treatment following a primary percutaneous coronary intervention for ACS [53]. For intracranial atherosclerosis, evolocumab, in addition to moderate statin therapy, resulted in plaque stabilization and significantly reduced stenosis degree (74.2–65.5%, $P = 0.010$) of carotid arteries measured by high-resolution magnetic resonance imaging (MRI) [54]. Similar effects were observed in patients treated with alirocumab, where regression in plaque lipid content (20%) and neovasculature (17%) were observed after treatment with alirocumab in addition to low-dose statin therapy after 12 months [55].

A phase IV open-label single-arm clinical trial in patients with FH without clinical ASCVD showed that treatment with alirocumab for 78 weeks, in addition to high-intensity statin therapy, resulted in regression of total coronary plaque volume (34.6% at entry to 30.4% at follow-up; $P < 0.001$) and changes in coronary plaque characteristics; an increase of calcified (+0.3%; $P < 0.001$) and fibrous (+6.2%; $P < 0.001$) plaque volume, accompanied by a decrease of fibrofatty (–3.9%; $P < 0.001$) and necrotic plaque volume (–0.6%; $P < 0.001$), were shown on coronary computed tomographic angiography (CCTA) [56]. These findings suggest that coronary imaging using CCTA may serve as a sensitive marker for therapeutic response and could potentially hold more clinical significance than measured LDL-C reduction alone.

3.3 Cardiovascular Risk Reduction

Monoclonal antibodies directed against PCSK9 provide an extra tool in the therapeutic armamentarium to reduce MACE, which encompasses cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The efficacy of PCSK9 mAbs, exemplified by the FOURIER and ODYSSEY OUTCOMES trials investigating evolocumab and alirocumab in high-risk patients receiving maximally tolerated statins and/or ezetimibe, has been studied extensively [13, 57]. The FOURIER trial was a randomized, double-blind, placebo-controlled trial that evaluated the clinical efficacy and safety

Table 1 Effect on atherosclerotic plaque burden after treatment with PCSK9 targeted therapy in patients on standard of care background therapy

First author, year (study name)	Population, *N*	Intervention	Endpoint	Results
Nicholls, 2016 (GLAGOV)	ASCVD, $N = 968$	Evolocumab versus placebo	PAV and TAV measured by IVUS after 78 weeks	PAV: + 0.05% with placebo and − 0.95% with evolocumab (difference, − 1.0% (95% CI − 1.8% to −0.64%); $P < 0.001$); TAV: −0.9 mm^3 with placebo and − 5.8 mm^3 with evolocumab (difference, − 4.9 mm^3 (95% CI − 7.3 to − 2.5); $P < 0.001$)
Nicholls, 2021 (HUYGENS)	ACS, non-ST-elevated, $N = 161$	Evolocumab versus placebo	Plaque phenotype measured by OCT + IVUS after 50 weeks	Minimum FCT + 42.7 mm vs. + 21.5 mm, maximum lipid arc decrease 57.5 mm versus 31.4 mm, and decrease macrophage index 3.17 mm versus 1.45 mm
Lepor, 2021	NCP carotid, $N = 27$	Alirocumab	Plaque lipid core, fibrous tissue, and neovasculature measured with carotid MRI after 12 months	Percent lipid core reduced from 9.8% to 7.2% ($P = 0.014$); percent fibrous tissue increased from 87.8% to 90.2% ($P = 0.009$); neovasculature reduced from 0.069 ± 0.019 to 0.058 ± 0.020 ($P = 0.029$)
Li, 2022	Post-ACS, $N = 17$	Evolocumab or alirocumab	Plaque regression measured by QCA after 12 months	Plaque regression from 61.18% ± 14.55% to 52.85% ± 15.5% ($P < 0.001$)
Wu, 2023	ICAS, $N = 49$	Evolocumab versus SOC	Stenosis degree measured with high-resolution MRI after 12 weeks	Stenosis degree decreased from 74.2% to 65.5%
Perez de Isla, 2023 (ARCHITECT)	FH, ASCVD-, Spanish, $N = 104$	Alirocumab	Coronary plaque volume and characteristics measured with CCTA after 78 weeks	Plaque volume regression from 34.6% to 30.4% ($P < 0.001$). Increased calcified (+0.3%; $P < 0.001$) and fibrous (+6.2%; $P < 0.001$) plaque. Decreased fibro-fatty (–3.9%; $P < 0.001$) and necrotic (–0.6%; $P < 0.001$) plaque
Raber, 2022 (PACMAN-AMI)	AMI, European countries, $N = 300$	Alirocumab versus placebo	PAV and plaque phenotype measured with IVUS, NIRS and OCT after 52 weeks	PAV regression 2.13% versus 0.92% ($P < 0.001$); maximum lipid core regression 79.42 mm versus 37.60 mm ($P = 0.006$); increased FCT 62.67 µm versus 33.19 µm ($P = 0.001$)
Gao, 2021	ASCVD, $N = 64$	Alirocumab versus SOC	Plaque phenotype measured with OCT after 36 weeks	Increased FCT 18.0 µm versus 13.2 µm ($P = 0.029$); increased minimum lumen area 0.20 mm^2 versus 0.13 mm^2 ($P = 0.006$); decreased maximum lipid arc 15.1° versus 8.4° ($P = 0.008$)
Ako, 2019 (ODYSSEY J-IVUS)	ACS, Japanees, $N = 206$	Alirocumab versus SOC	TAV/PAV measured with IVUS after 36 weeks	PAV regression 1.4% versus 1.3%; $P = 0.79$ TAV regression 4.8% versus 3.1%; $P = 0.23$
Sugizaki, 2020 (ALTAIR)	CAD, Japanese, $N = 24$	Alirocumab versus SOC	Plaque phenotype measured with OCT after 36 weeks	Increased FCT 140 µm versus 45 µm ($P = 0.002$); decreased lipid core 26.2% versus 2.8% ($P < 0.001$); decreased macrophage rate 28.4% versus 10.2% ($P = 0.033$)

ACS acute coronary syndrome, *AMI* acute myocardial infarction, *CAD* coronary artery disease, *CCTA* coronary computed tomographic angiography, *FCT* fibrous cap thickness, *ICAS* Intracranial atherosclerotic stenosis, *IMT* intima-medial wall thickness, *IVUS* intravascular ultrasound, *NIRS* near-infrared spectroscopy, *OCT* optical Coherence Tomography, *PAV* percent atheroma volume, *QCA* Quantitative Coronary Angiography, *SoC* standard of care, *TAV* total atheroma volume

of evolocumab in 27,564 patients with clinically evident ASCVD. Evolocumab, in addition to maximally tolerated statin therapy, led to a significant reduction of MACE after a follow-up period of 2.2 years [hazard ratio (HR): 0.85, 95% CI 0.79–0.92; $P < 0.001$) [3, 57]. The FOURIER-OLE trial, involving 6,559 patients who were switched to open-label evolocumab regardless of their initial treatment allocation in the FOURIER trial, reaffirmed the results observed in the original FOURIER trial during an extended median follow-up period of 4.8 years [58].

The ODYSSEY OUTCOMES trial was a randomized, double-blind, placebo-controlled trial that evaluated long-term safety and efficacy of 18,924 patients who were randomly assigned in a 1:1 ratio with an acute coronary syndrome (ACS) within the prior 12 months [13]. Alirocumab on top of high-intensity statin therapy reduced the risk of MACE (9.5% patients compared with 11.1% of placebo-treated patients; HR: 0.85, 95% CI 0.78–0.93; $P < 0.001$) over a median follow-up time of 2.8 years. Cardiovascular outcome-trials for inclisiran are ongoing. Nevertheless, a meta-analysis encompassing three double-blinded, randomized, placebo-controlled phase 3 clinical trials (ORION-9, ORION-10, and ORION-11), which primarily investigated its lipid-lowering effects and were not specifically powered for assessing ASCVD risk reduction, demonstrated that inclisiran therapy indeed led to a 32% reduction in myocardial infarction incidence [relative risk (RR): 0.68, 95% CI 0.48–0.96, $P = 0.03$) [59]. However, it did not exhibit a statistically significant reduction in the risk of MACE (RR: 0.81, 95% CI 0.65–1.02; $P = 0.07$) or stroke (RR: 0.92, 95% CI 0.54–1.58; P = 0.76) [60]. Subsequent studies are anticipated to offer additional insights into the impact of inclisiran on MACE (NCT03705234, NCT05030428, and NCT05739383).

4 Safety and Tolerability

Accumulating evidence suggests that PCSK9-targeted therapy is safe and well tolerated. Typical side effects associated with PCSK9-targeted therapy are generally mild and encompass symptoms such as nasopharyngitis, injection site reactions, and upper respiratory tract infections [61]. Fortunately, the number of adverse events (AEs), serious adverse events (SAEs), and AEs leading to PCSK9-targeted therapy discontinuation was similar in the intervention and control groups in most randomized clinical trials. Interestingly, unlike statins and other lipid lowering therapies, PCSK9-targeted therapy had no adverse effects on liver function and muscle enzymes [62]. Below, we explore in more detail the impact of PCSK9-targeted therapy on diabetes mellitus risk, the occurrence of myalgia, neurocognitive effects, and serum levels of hydrophobic vitamins, with a particular focus on vitamin E. These studies are summarized in Table 2.

4.1 PCSK9-Targeted Therapy in Patients with Myalgia/Statin Intolerance

Statin intolerance, characterized by muscle-related symptoms, represents the most frequent cause for patients discontinuing statin therapy and has a prevalence of 9.1% (95% CI 8.0–10%) [63]. Of note, the occurrence of statin intolerance in RCTs was lower compared with cohort and observational studies [4.9% (95% CI 4.0–6.0%) versus 17% (95% CI 14–19%)] [63]. The threefold difference may be attributed to pretrial tolerance or intolerance to statins, and this discrepancy represents a significant obstacle to achieving long-term adherence and a sufficient reduction in LDL-C levels. Clinical trials have examined whether PCSK9-targeted therapy is associated with myalgia, especially in statin-intolerant patients.

The ODYSSEY LONG TERM trial, which studied 2341 patients on maximum tolerated LLT over a 78-week follow-up period, found an increased incidence (5.4% versus 2.9%, $P = 0.006$) of myalgia in the alirocumab group versus the placebo group [64]. However, no difference in muscle-related adverse events between the PCSK9-targeted therapy and the placebo group were noted in other studies with PCSK9 mAbs [58, 65, 66], and some studies even reported a beneficial impact of PCSK9-targeted therapy on muscle-related adverse events [25, 29, 67], which are described in more detail below.

The DESCARTES trial, a phase 3, multicenter, randomized, double-blinded study, investigated 901 statin-intolerant patients over a 52-week follow-up period [65]. A comparable incidence of elevated creatinine kinase (CK) levels, defined as exceeding five times the upper limit of normal range, and a comparable incidence of myalgia between the evolocumab and placebo groups were observed. No significant difference or marked trend between lower LDL-C levels and muscle-related events in the evolocumab group versus the placebo group was found in the FOURIER-OLE and a post hoc analysis of the FOURIER trial [3, 58].

Results from the GAUSS-3 trial support these findings and investigated evolocumab in statin-intolerant patients due to muscle-related adverse events over a 24-week follow-up period. Statin intolerance was defined as the inability to tolerate at least two different statins because of muscle pain or weakness. Treatment with evolocumab reduced the occurrence of muscle-related side effects (incidence 20.7% versus 28.8%) and the rate of discontinuation due to these side effects (0.7% versus 6.8%) when compared with ezetimibe [25]. The findings of the GAUSS-3 trial were substantiated by the OSLER open-label extension studies [67]. Patients underwent a 2:1 randomization, receiving either evolocumab

Table 2 Tolerability/safety of PCSK9-targeted therapy

Clinical trial	Study treatment and follow-up period	Diabetes	Myalgia/myositis	Cognitive functions	Vitamin E and other fat-soluble vitamins
Evolocumab					
FOURIER	Evolocumab versus placebo for 2.2 years	8.1% versus 7.7%	5.0% versus 4.8%	1.6% versus 1.5%	NA
OSLER-1 Extension Study	Evolocumab + SOC versus SOC alone for 2.2 years	2.8% versus 4.0%	4.7% versus 8.5%	0.4% versus 0%	NA
GLAGOV	Evolocumab versus placebo for 76 weeks	3.6% versus 3.7%	7.0% versus 5.8%	1.4% versus 1.2%	
BERSON	Evolocumab + atorvastatin versus atorvastatin alone for 12 weeks	No difference in HbA1c and FPG	NA	NA	No difference after normalization for serum lipid levels
FOURIER-OLE	Evolocumab for 5 years	Incidence 0.66 LDL-C: < 20 mg/dL versus 0.43 LDL-C > 70 mg/dL; $P = 0.13$	Incidence 0.67 LDL-C < 20 mg/dL versus 0.56 LDL-C > 70 mg/dL; $P = 0.84$	Incidence 0.50 LDL-C < 20 mg/dL versus 0.43 LDL-C > 70 mg/dL; P = 0.35	NA
DESCARTES	Evolocumab versus placebo for 52 weeks	NA	4.0% versus 3.0%	NA	1.0 mmol/L versus −0.2 mmol/L after normalization for serum lipid levels
OSLER-1/2	Evolocumab + SOC versus SOC alone for 2.2 years	1.1% versus 0.7%	6.4% versus 6.0%	0.9% versus 0.3%	NA
OSLER OLE studies	Evolocumab + SOC versus SOC alone for 2 years	NA	10.8% versus 16.0%	1.4% versus 0.0%	NA
EBBINGHAUS	Evolocumab versus placebo for 19 months	NA	NA	3.4% versus 3.5%	NA
HAUSER-RCT	Evolocumab versus placebo for 24 weeks	Decrease of FPG: −2.0mg/dL versus −1.2mg/dL	NA	NA	No difference after normalization for serum lipid levels; 0.0009 mg/dL versus 0.0002 mg/dL
GAUSS-3	Evolocumab versus placebo for 24 weeks	NA	20.7% versus 28.8%	NA	NA
Alirocumab					
ODYSSEY LONG TERM	Alirocumab versus placebo for 78 weeks	1.8% versus 2.0%	5.4% versus 2.9%	1.2% versus 0.5%	No significant difference levels of fat-soluble vitamins (A and D) and cortisol
ODYSSEY FH	Alirocumab versus placebo for 78 weeks	2.1% versus 2.5%	3.9% versus 6.3%	0.6% versus 1.2%	NA
ODYSSEY OUTCOMES	Alirocumab versus placebo for 2.8 years	9.6% versus 10.1%	NA	1.5% versus 1.8%	NA
ODYSSEY COMBO II	Alirocumab versus placebo for 104 weeks	8.4% versus 9.3%	4.3% versus 5.0%	1.3% versus 2.2%	NA

Table 2 (continued)

Clinical trial	Study treatment and follow-up period	Diabetes	Myalgia/myositis	Cognitive functions	Vitamin E and other fat-soluble vitamins
ODYSSES DM-INSULIN	Alirocumab versus placebo for 24 weeks	HbA1c change DMII 0.2% versus 0.1% and HbA1c change DMI: 0.0% versus −0.2%	4.4% versus 1.8%	1.2% versus 0%	NA
ODYSSEY ALTERNATIVE	Alirocumab versus ezetimibe versus atorbastatin for 24 weeks	NA	32.5% versus 41.1% vs. 46.0%	NA	NA
Janik et al. 2021	Alirocumab versus placebo for 96 weeks	9.0% versus 8.8%		1.3% versus 1.7%	NA
Inclisiran					
ORION-10	Inclisiran versus placebo for 540 days	15.4% versus 13.9%	NA	NA	NA
ORION-11	Inclisiran versus placebo for 540 days	10.9% versus 11.7%	NA	NA	NA

DMI diabetes mellitus I, *DMII* diabetes mellitus II, *FPG* fasting plasma glucose, *SOC* standard of care, *NA* not applicable

in addition to standard of care (SOC) or SOC alone. From the second year onward, all participants received evolocumab in combination with SOC. These studies demonstrated that the addition of evolocumab to standard-of-care (SOC) treatment resulted in a reduced occurrence of muscle-related adverse events (10.8% versus 16.0%) when compared with SOC alone. Furthermore, these studies found that evolocumab was well-tolerated and effective over a 2.2-year follow-up period in patients with statin intolerance.

The ODYSSEY ALTERNATIVE trial, which compared alirocumab with ezetimibe in 314 statin-intolerant patients at moderate to high ASCVD risk over a 24-week follow-up period, showed that musculoskeletal adverse events were less frequent in patients randomized to alirocumab (HR: 0.61; 95% CI 0.38–0.99). Intolerance was defined as the inability to take at least two different statins because of muscle-related adverse events, one at the lowest approved starting dose [29].

In the ORION phase 3 trials, investigating inclisiran versus placebo, no data concerning muscle-related adverse events were provided [33].

4.2 PCSK9-Targeted Therapy and Diabetes Mellitus

Diabetes mellitus represents a chronic metabolic disorder characterized by an elevated risk of cardiovascular and neurological complications. Due to its growing prevalence, it is rapidly evolving into a global health crisis. Its inflammatory pathophysiology accelerates atherosclerosis, making diabetes a prevalent risk factor for atherosclerotic cardiovascular disease (ASCVD). To mitigate this risk, since many patients with diabetes have dyslipidemia, lipid-lowering therapies (LLT) are essential for ASCVD prevention in patients with diabetes. However, there is compelling evidence that statin use may disrupt glycemic control and increase the risk of new-onset diabetes [68]. Hence, a critical assessment was necessary to determine the safety, efficacy, and potential effects on glucose metabolism of PCSK9-targeted therapy in patients with diabetes.

In the FOURIER trial, patients with diabetes mellitus, patients with prediabetes, and patients without diabetes mellitus were studied. The incidence of new-onset diabetes in patients randomized to evolocumab was not statistically different from the patients randomized to placebo (HR: 1.05; 95% CI 0.94–1.17) after 2.2 years. Also, HbA1c and fasting plasma glucose levels did not differ between active and placebo treatment in patients with diabetes, prediabetes, or normoglycemia. Importantly, evolocumab significantly reduced ASCVD risk in patients with diabetes (HR: 0.83; 95% CI: 0.75–0.93) and without diabetes (HR: 0.87; 95% CI 0.79–0.96) [57, 69]. In the aforementioned FOURIER-OLE trial, 1604 patients with markedly low LDL-C levels (< 20 mg/dL) exhibited a somewhat higher annualized incidence

of new-onset diabetes (0.66; 95% CI 0.32–1.39) as compared with the annualized incidence of 811 patients with LDL-C levels exceeding 70 mg/dL (0.43; 95% CI 0.20–0.95). However, routine assessments for diabetes were not conducted, and reliance was placed on adverse event reports. Periodic collection of fasting plasma glucose and HbA1c levels by a central laboratory was not carried out, potentially resulting in the oversight of some cases. Finally, this observation occurred while all patients were taking a PCSK9-targeted therapy, and thus, it was not directly associated with PCSK9 inhibition itself [58]. Furthermore, the OSLER-1 extension study found an incidence of new-onset diabetes of 4% in the standard of care group versus 2.8% in the evolocumab plus SOC group after a follow-up period of 2.2 years [70]. Evolocumab on top of statin therapy in the BANTING trial [71] and BERSON trial [72] showed no notable effect on glucose metabolism in patients with type 2 diabetes after 12 weeks. The GLAGOV trial showed no increased incidence of new-onset diabetes (3.6% versus 3.7%), nor worsening of hyperglycemia in 968 patients presenting for coronary angiography in the evolocumab group after a follow-up period of 76 weeks [15]. In the ODYSSEY OUTCOMES trial, those treated with alirocumab showed no elevated risk of new-onset diabetes (9.6% versus 10.1%) over a median follow-up period of 2.8 years when compared with the placebo group. Importantly, patients with diabetes exhibited a notably larger absolute risk reduction with alirocumab treatment (2.3%; 95% CI 0.4–4.2) when compared with patients with prediabetes (1.2%; 95% CI 0.0–2.4) or normoglycemia (1.2%; 95% CI −0.3 to 2.7) [73]. This shows that diabetic patients achieve most benefit of treatment with alirocumab. In addition, the ODYSSEY DM-INSULIN trial investigated alirocumab versus placebo in patients with both type 1 and 2 diabetes for 24 weeks. Alirocumab treatment resulted in significant LDL-C reductions in patients with both type 1 and 2 diabetes receiving insulin treatment, with no apparent effect on measures of glycemic control [74]. The ODYSSEY LONG TERM and ODYSSEY FH trial showed no notable effect of alirocumab on fasting plasma glucose and HbA1c levels, nor on increasing numbers of new-onset diabetes or worsening hyperglycemia after a follow-up period of 78 weeks [31, 64]. The ODYSSEY COMBO II showed the same results after a follow-up period of 104 weeks [75].

A similar nondiabetogenic effect of PCSK9 lowering was observed in clinical trials evaluating the effects of inclisiran. The ORION-10 and ORION-11 trials showed no significant increase in new-onset diabetes among 3178 patients with either ASCVD or an ASCVD risk equivalent after 540 days of treatment with inclisiran [33].

Research on the relationship between PCSK9-targeted therapy and insulin secretion remains inconclusive. Targeting the LDLR may impact diabetes development, as statin therapy correlates with impaired insulin secretion leading to incident diabetes [76]. Genetic studies link LDLR variants to reduced diabetes risk, but PCSK9 loss-of-function variants are associated with higher diabetes risk [77]. One recent meta-analysis [78] indicated a slight increase of HbA1c after PCSK9 inhibition, whereas another meta-analysis [79] reported no effect on new-onset diabetes or glucose metabolism. We found one study cautiously concluding that PCSK9 expression in human beta cells regulates LDLR abundance without directly impacting insulin secretion in response to glucose, indicating the safety of PCSK9-targeted therapy concerning beta cell function. However, a potential broader influence of PCSK9 deficiency on glucose homeostasis beyond pancreatic islets is suggested, as plasma PCSK9 levels correlate positively with markers of insulin resistance, prompting further investigation to unravel the precise role of PCSK9 in diabetes risk [80].

Existing evidence substantiates the efficacy and safety of PCSK9-targeted therapy, as they confer a substantial cardiovascular benefit in patients with diabetes and are not associated with new-onset diabetes or worsening of parameters of glucose metabolism. Additional clinical trials with even longer follow-up are needed to confirm these findings.

4.3 PCSK9-Targeted Therapy and Neurocognitive Events

The brain is the most cholesterol-rich organ and almost contains a quarter of the total amount of cholesterol present in a human. Under normal circumstances, cholesterol, the PCSK9 protein, and PCSK9 mAbs are unable to cross the blood–brain barrier [81]. However, some diseases can alter the permeability of the blood–brain barrier, allowing compounds to diffuse through it. The debate continues regarding whether this translates into clinically meaningful effects with respect to PCSK9-targeted therapy. Some studies have reported a slight increased rate of adverse neurocognitive events within the PCSK9-targeted therapy group when compared with the placebo or other treatments, raising some concerns regarding the long-term neurological safety of PCSK9-targeted therapy [18, 82, 83].

In both the ODYSSEY LONG TERM trial (with 2341 patients randomly assigned in a 2:1 ratio) and the OSLER-1 and OSLER-2 trials (with 4465 patients randomly assigned in a 2:1 ratio), neurocognitive events occurred more frequently in the groups receiving PCSK9 mAbs compared with the placebo or standard therapy groups. In the ODYSSEY LONG TERM trial, alirocumab exhibited an incidence of 1.2%, whereas the placebo group had an incidence of 0.5%. In OSLER-1 and OSLER-2, evolocumab showed an incidence of 0.9%, while the standard therapy group had an incidence of 0.3%. However, it is important to clarify that the increased incidence was not evaluated using a

validated measure to establish clinically meaningful differences [82, 83]. Moreover, other well-conducted and randomized controlled studies have contradicted the findings in the ODYSSEY LONG TERM and OSLER trials, with no significant differences in the rate of neurocognitive adverse events between patients treated with PCSK9-targeted therapy versus placebo [15, 31, 57, 58, 73–75, 84, 85]. This discrepancy is possibly explained by the lack of standardized cognitive testing and potential reporting bias by the patients, which may have contributed to a distorted picture of the neurocognitive adverse events observed in the earlier studies and especially the OSLER open-label studies. To better elucidate this issue, the EBBINGHAUS trial was conducted. EBBINGHAUS was a randomized, double-blind, multicenter trial which consisted of a subgroup of 1204 patients from the FOURIER trial. Patients were monitored for a median duration of 19 months, during which their cognitive function was assessed using the Cambridge Neuropsychological Test Automated Battery. Patients received either evolocumab or placebo in addition to maximal-tolerated statin therapy. No significant differences in neurocognitive functions, nor an association between LDL-C levels and cognitive changes between the evolocumab and placebo group, were observed [84]. These results were supported by the findings in the GLAGOV [15] and FOURIER-OLE [58] trials, in which no significant neurodegenerative adverse events and no trend between lower achieved LDL-C levels and an increased risk of neurocognitive events was found in the evolocumab group over a follow-up period of at least 76 weeks (GLAGOV) and up to 5 years (FOURIER-OLE). These finding are in line with the results from the ODYSSEY OUTCOME trial, where no significant difference in the rate of adverse neurocognitive events occurred between patient randomized to alirocumab versus placebo over a median follow-up period of 2.8 years [73]. These results for alirocumab were supported by the findings in the ODYSSEY FH [31], ODYSSEY DM-INSULIN [74] and ODYSSEY COMBO II [75] trials. Finally, alirocumab showed no effect on neurocognitive function over a 96-week follow-up period evaluated by Cambridge Neuropsychological Test Automated Battery, in 2176 patients with heterozygous FH or non-FH at high or very-high cardiovascular risk [85].

Based on current studies, PCSK9 mAb therapy is widely considered not to cause serious adverse neurocognitive side effects. Nonetheless, it remains unclear whether this holds true for extended follow-up durations (> 10 years) or whether it can be extrapolated to older patients or those with a history of cerebrovascular events. For this reason, longer follow-up studies within various vulnerable subpopulations are needed [86].

4.4 PCSK9-Targeted Therapy and Vitamin E and Other Fat-Soluble Vitamins

Some vitamins are hydrophobic and are transported within lipoproteins. Among these, vitamin E is an essential fat-soluble micronutrient known for its diverse biological activities, primarily attributed to its potent antioxidant activity. The main clinical features of vitamin E deficiency are neuromuscular disorders, retinopathy, impaired immune response, and anemia [87]. Rare genetic diseases that lead to abetalipoproteinemia are marked by exceptionally low levels of lipoproteins, potentially leading to severe deficiencies in fat-soluble vitamins, including vitamin E [88]. Therefore, some clinical trials investigated whether intensive lowering of LDL-C with PCSK9-targeted therapy leads to severe deficiencies of fat-soluble vitamins, including vitamin E. As apolipoprotein-B particles serve as carriers for vitamin E, both free vitamin E and cellular vitamin E content hold physiological significance. Consequently, the term "vitamin E after lipid correction" is utilized.

In the DESCARTES trial, vitamin E levels were measured in 738 patients over a 52-week study period. The results showed that treatment with evolocumab did not result in a significant change in serum and lipoprotein vitamin E levels when normalized for cholesterol content. Also, no changes in steroid hormone of gonadotropin levels were observed [65]. In the BERSON trial, which studied evolocumab in 981 patients with type 2 diabetes and dyslipidemia over a 12-week follow-up period, no effect of evolocumab on vitamin E levels were found upon correction for normalized plasma lipid concentrations [72]. Furthermore, the HAUSER-RCT, a randomized clinical trial to evaluate the safety and efficacy of evolocumab in 157 pediatric patients with heterozygous FH during a 24-week follow-up period, did not observe any differences in levels of steroid hormones and fat-soluble vitamins (vitamin A, D, E, and K) between the evolocumab and placebo group [89]. Finally, the aforementioned ODYSSEY LONG TERM trial did found more patients in the alirocumab group with vitamin E and vitamin K levels below the lower limit of the normal range, but these changes were not meaningful when corrected for LDL-C levels. No significant effects were found in other fat-soluble vitamins (vitamin A and vitamin D) or cortisol [82].

To summarize, PCSK9-targeted therapies are unlikely to exert clinically significant impacts on fat-soluble vitamin levels or steroid hormone synthesis, and none of the studies have reported an increase in the symptoms related to vitamin E deficiency.

5 Persistence/Adherence

Current guidelines recommend intensive LDL-C lowering in patients with high ASCVD risk. With advancing insights about the continuous and causal relationship between LDL-C levels and ASCVD outcomes, guideline recommended LDL-C targets have decreased over time. The 2019 ESC/EAS guidelines therefore lower LDL-C treatment targets for patients at high-risk (< 1.8 mmol/L) or very high risk (< 1.4 mmol/L) of developing ASCVD [12]. However, there is a large discrepancy between recommended treatment as studied in clinical trials and real-world treatment data with regards to LDL-C target achievement. In less controlled real-world settings, these objectives are often unattained as a result of clinical inertia exhibited by healthcare providers and poor patient adherence [90, 91]. The sustained utilization of PCSK9-targeted therapy has been shown to be promising, with 92% to 98% of patients still using PCSK9-targeted therapy after 1 to 2 years after initiation of therapy [92–96]. The extent of adherence to PCSK9-targeted therapy is relatively under-investigated, with one single country, multicenter, observational retrospective study reporting 95.2% adherence, defined as medication adherence ratio > 80% among 798 patients after up to 18 months [96]. In addition, only a very small proportion of patients discontinue PCSK9-targeted therapy due to adverse drug reactions [9]. While long-term follow-up studies on inclisiran adherence (e.g., NCT05399992) are still ongoing, the convenience of its biannual administration schedule is expected to significantly enhance treatment adherence, potentially leading to improved clinical outcomes in a substantial population of high-risk patients [97]. In conclusion, PCSK9-targeted therapy is very effective and well tolerated in routine clinical practice, leading to high adherence. This will result in more patients achieving their recommended LDL-C targets and decrease the global burden of ASCVD.

6 Conclusions

PCSK9-targeted therapy is effective and well tolerated. The number of adverse events in RCTs are well balanced between patients receiving PCSK9 lowering agents and placebo, which justifies the statement that PCSK9-targeted therapies are safe. While there is compelling evidence that further lowering LDL-C reduces the risk of ASCVD, achieving recommended LDL-C targets remains challenging. Despite the use of statins, many high-risk patients do not achieve sufficient LDL-C reduction and remain at elevated ASCVD risk. PCSK9-targeted therapy offer potent LDL-C reduction potential for high-risk patients, with documented positive effects on plaque burden and characteristics. In general, there is no heightened incidence of adverse events of particular interest, including diabetes, neurocognitive effects, and vitamin deficiency, observed among patients undergoing PCSK9-targeted therapy. Anticipated advancements in user-friendly formulations (e.g., oral pills or one-time gene editing) [98] and also the emergence of new subcutaneous PCSK9-targeted therapies such as lerodalcibep and recaticimab [99], alongside forthcoming long-term clinical studies, are expected to confirm its favorable efficacy and safety profile. Hopefully, PCSK9-targeted therapy will become more accessible worldwide in the fight against atherosclerotic cardiovascular disease.

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