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Review

Exploring the benefits of alirocumab as lipid-lowering therapy in people with diabetes and very high cardiovascular risk

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ABSTRACT

People with diabetes mellitus (DM) are at a higher risk (2–4 times) for cardiovascular (CV) death and atherosclerotic CV disease (ASCVD) than the general population. A multifactorial approach is recommended to reduce CV risk. Since low-density lipoprotein cholesterol (LDL-C) is a major causal and cumulative risk factor for ASCVD, the management of lipids is a fundamental element in global risk reduction. Intensive lipid lowering therapy (LLT), such as the addition of a proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i), to achieve LDL-C goals and reduce the risk of first or recurrent CV events in people with DM at very high CV risk (VHCVR) of ASCVD (i.e. acute coronary syndrome, coronary artery disease, peripheral artery disease) is often required. Alirocumab, a monoclonal antibody against PCSK9, as lipid-lowering therapy offers significant CV benefits and a favourable safety profile in people with DM and a VHCVR, with or without previous CV events. This review highlights the role of LDL-C in the complex pathogenesis of atherosclerosis, summarises the guidelines for CV risk reduction related to LDL-C in patients with DM and a VHCVR, and focuses on the role of alirocumab in managing LDL-C and consequent CV risk reduction in these patients.

1. Introduction

Diabetes mellitus (DM) is a group of metabolic disorders characterised by hyperglycaemia, among which type 1 diabetes (T1D) and type 2 diabetes (T2D) are the most frequent forms, each with unique characteristics [1]. T1D results from the autoimmune destruction of pancreatic β-cells leading to a complete loss of endogenous insulin production [2]. T2D accounts for ~ 96 % of all cases of DM and occurs when insulin secretion is insufficient to overcome insulin resistance, which is initially countered by increased insulin production; however, over time, insulin production decreases and is associated with β-cell dysfunction, leading to β-cell failure [1–3].

Cardiovascular disease (CVD) accounts for 50–60 % of deaths among diabetic patients; when considering people in the same risk category, those with DM live up to 6 years less than their non-diabetic counterparts [4]. As DM progresses, the risk of CVD and the prevalence of cardiovascular (CV) complications increase, as does the risk of morbidity and mortality [5–8]. DM frequently manifests as macrovascular (myocardial infarction [MI], stroke and peripheral arterial disease [PAD]) and microvascular (retinopathy, nephropathy and neuropathy) complications [9]. Dyslipidaemia significantly contributes to microvascular and macrovascular complications among individuals with DM, thus placing this group of patients at very high CV risk (VHCVR) irrespective of any prior CV events that may have occurred [10].

In 2021, 529 million people lived with DM globally; this number is expected to rise to 1.3 billion in 30 years [3]. The growing incidence of T2D, linked to increasing childhood obesity in low- and middle-income countries, is seen as a global epidemic [11]. In Europe, 61 million adults have DM, a number projected to reach 69 million by 2045 [12]. In Italy, over 4 million people had DM between 2021 and 2022, representing 5 % of the population, with high rates of concurrent hypertension and

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hypercholesterolemia [13]. The 2023 registry of the Association of Medical Diabetologists (AMD) in Italy reported on 573,164 patients with T2D and 42,611 with T1D [14]. Only 6.6 % of patients with T2D and 3.5 % of those with T1D reached the composite outcome of glycated haemoglobin (HbA1c) $\leq$ 7.0 % + low-density lipoprotein cholesterol (LDL-C) < 70 mg/dL + blood pressure (BP) < 130/80 mmHg [14].

Importantly, a diagnosis of CVD has been reported in 15 % of people with DM aged 18–64 years and in 42 % of those aged $\geq$ 65 years in Italy [13]. Epidemiological data from the Italian RIACE study show that CV complications are very frequent among people with T2D [15]. Specifically, among patients attending diabetes clinics, 11.2 % had a MI, 10.0 % had undergone reperfusion or coronary revascularization, 3.3 % had a stroke, 5.5 % had carotid revascularization and 29 % had lower limb revascularization [15].

The leading cause of morbidity and mortality among people with DM is atherosclerotic CVD (ASCVD), which includes acute coronary syndrome (ACS), coronary artery disease (CAD), cerebrovascular disease and PAD [16,17]. Several pathological mechanisms are linked to the development of ASCVD, such as the formation of advanced glycation end products, overproduction of reactive oxygen species (ROS), protein kinase C (PKC) activation resulting from increased glucose uptake by vascular cells and chronic vascular inflammation [16]. The direct implication of LDL-C in the development of ASCVD has been well established [18]. Studies have demonstrated that LDL-C is an important causal risk factor in the development and progression of ASCVD [18,19].

The individual and simultaneous control of CV risk factors has been proven crucial to prevent or slow down ASCVD specifically in people with DM. Therefore, therapies aimed at controlling glycaemia, BP and lipids, together with the incorporation of specific therapies to improve CV and kidney outcomes, are fundamental to lowering the global risk in patients with DM [20]. Thus, a safe, multifactorial and risk-reducing approach is recommended to manage DM-related complications [21]. Management of LDL-C, especially with statins, has proven to be of great benefit in the prevention of clinical CVD [22]. Because many patients fail to attain the low levels of LDL-C recommended by the guidelines with statins alone, supplemental therapy with a proprotein convertase subtilisin kexin type 9 (PCSK9) monoclonal antibody (mAb) inhibitor (mAb PCSK9i) such as alirocumab, is often required to reach LDL-C goals [23].

This review focuses on alirocumab as a lipid-lowering strategy to be used in people with DM, in particular, those with ASCVD and a VHCVR, with or without previous CV events.

2. Pathogenesis of atherosclerosis in DM

Atherosclerosis is a progressive disease where a clinically unapparent build-up of plaque occurs in the coronary artery over a prolonged latent phase [24]. Most acute events occur because of plaque rupture, which represents the last stage of the disease, and is preceded by an intermediate and modifiable step of plaque progression [24].

The pathogenesis of atherosclerosis in DM involves metabolic and inflammatory processes [25]. Being a multifactorial process, ASCVD is regulated by a complex interplay between several risk factors, including hyperglycaemia and increased plasma LDL-C levels [8,21,25].

Endothelial dysfunction is a key driver of atherosclerosis in both T1D and T2D; both high blood glucose levels and endothelial insulin resistance can lead to endothelial dysfunction in DM [26,27]. In atherogenesis, endothelial dysfunction is characterised by impaired endothelium-dependent vasodilation due to reduced nitric oxide bioavailability [27,28], as well as increased permeability [29] and inflammatory adhesion molecule expression [30]. In addition, non-enzymatic glycation of proteins and lipoproteins, favoured by chronic hyperglycaemia, activates the receptor for advanced glycation end products, which in turn drives oxidative stress and inflammation, thus exacerbating atherosclerosis further [25,31]. The risk of CVD is significantly accelerated by poor glycaemic control in T2D [32], and the impairment of pancreatic β-cell function; the resultant decrease of peripheral glucose uptake caused by insulin resistance may contribute to the development of dyslipidaemia [33].

The impact of DM on lipid metabolism causes a typical dyslipidaemia profile and accelerates the occurrence of atherogenesis [34]. Hypertriglyceridaemia, low high-density lipoprotein-C (HDL-C) levels, and elevated small and dense LDL-C levels, along with different lipoprotein subclass accumulation, are the main lipid disorders associated with DM [35,36]. Uncontrolled lipid abnormalities give rise to micro- and macrovascular issues [37,38]. The risk of dyslipidaemia and atherosclerosis is higher in patients with versus without DM, which can lead to a proatherogenic lipid profile in patients with DM [39].

Taken together, evidence from numerous studies (preclinical investigations, genetic studies, epidemiological cohort studies, Mendelian randomisation studies and randomised trials of LDL-C-lowering medications including more than 2 million participants with over 20 million person-years of follow-up and over 150,000 CV events) show a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL-C and the risk of ASCVD, highlighting the causal role of LDL-C in the pathogenesis of ASCVD [40]. As such, the effect exerted by LDL-C on the risk of ASCVD appears to be both causal and cumulative over time [18]. Retention and accumulation of cholesterol-rich apolipoprotein B (apoB)-containing lipoproteins (which can enter and exit the arterial intima) within the arterial intima at sites of predilection for plaque formation are the key events in ASCVD initiation; the initiation and progressive development of atherosclerotic plaques (caused by intimal retention of LDL-C) increases in a dose-dependent manner when LDL-C concentration rises above 20–40 mg/dL [18,40].

Lipid abnormalities are more prominent in T2D because insulin resistance exacerbates the atherogenic lipid profile [41]. Atherogenesis is further accelerated by hyperglycaemia through lipoprotein oxidation and increased very low density lipoprotein cholesterol (VLDL-C), thus lowering HDL-C levels [42].

Several classes of lipids and lipoproteins influence the buildup of plaque in arteries [43]. The formation of small dense LDL-C and HDL-C particles (caused by large VLDL-C particles) can cause the initiation of events leading to aggravated atherosclerosis in T2D [43]. A functional role in atherogenesis is exerted by, for example, prostaglandin I2, thromboxane A2 and their receptors, emphasising the significance of lipid-mediated pathways in CVD [34].

3. Diabetes in patients with VHCVR

Patients with DM are at higher risk (2 to 4 times) for death and adverse CV outcomes than the general population [44]. When compared with the non-diabetic population, diabetic patients have a two-fold increased risk of death from CV causes and a two- to four-fold increased risk of MI, stroke and PAD [9].

National and international guidelines for the management of CVD and/or dyslipidaemia stratify people with DM by CV risk; those with a VHCVR are identified if one of the following is present [20,45–51]:

- documented ASCVD (either clinical or unequivocal on imaging; ACS, stroke, transient ischaemic attack, a multivessel coronary disease with two major epicardial arteries having > 50 % stenosis, CAD, PAD) with and without previous acute ischaemic events, or
- organ damage (i.e. microvascular disease: neuropathy, retinopathy, micro/macroalbuminuria), or
- at least three CV risk factors (i.e. hypertension, obesity, smoking), or
- T1D for > 20 years.

In the AMD Annals initiative among patients from 258 Italian diabetes centres with a total of 473,740 patients with T2D, 78.5 % were at VHCVR, 20.9 % were at high CV risk, and 0.6 % were at moderate CV risk (according to European Society of Cardiology [ESC] 2019 guidelines [48]) [52]. Among individuals with VHCVR, 26.4 % had retinopathy,

39.5 % had albuminuria, 18.7 % had a previous major CV event, 39.0 % had organ damage and 89.1 % had three or more risk factors [52].

The American Diabetes Association has recommended a comprehensive and multifactorial approach to reduce the risk of diabetes-related complications and microvascular outcomes, including kidney, retinopathy, neurological and CV complications [1]. Four fundamental elements in the global risk reduction of DM are the management of glycaemia, BP and lipids, as well as the incorporation of specific therapies that improve CV and kidney outcomes [20].

4. LDL-C lowering therapy in diabetic patients with VHCVR

In people with DM and a VHCVR, intensive lipid-lowering therapy (LLT) can halt plaque progression and reduce CV events [24]. LDL-C–lowering therapy occupies a central role in international guidelines for the prevention and management of CV risk, and includes the following medication classes: statins, cholesterol absorption inhibitors (ezetimibe), mAb PCSK9is (alirocumab, evolocumab), small interfering RNA (siRNA) PCSK9is (inclisiran), and an ATP citrate lyase inhibitor (bempedoic acid) [53,54] (Table 1).

5. PCSK9is

PCSK9, a protein that is involved in the metabolism of LDL-C, binds to the low-density lipoprotein receptor (LDL-R), where it promotes degradation of the LDL-R (Fig. 1.A) [55]. An increase in the plasma PCSK9 concentration results in an elevated LDL-C concentration because uptake of LDL-C is reduced due to a decreased number of LDL-Rs on the cell surface.

The mAB PCSK9is were developed to specifically target PCSK9, which is found either circulating freely in plasma or bound to the LDL-R [55]. Immediately after a mAb PCSK9i injection, the antibody rapidly binds to free PCSK9, leading to the prompt depletion of plasma PCSK9 levels. This increases the availability of LDL-Rs on cell surfaces, enhancing LDL-C particle uptake and lowering LDL-C levels (Fig. 2) [55].

The rapid and significant reduction of LDL-C by mAb PCSK9is assists in achieving LDL-C goals and impacts on CV outcomes. In large CV outcomes trials, the mAb PCSK9is alirocumab and evolocumab were proven to significantly reduce major acute CV events [56,57].

The ODYSSEY studies assessed the effectiveness and safety of different doses of alirocumab in patients with high CV risk and elevated LDL-C levels [56,58–68]. The findings indicated that alirocumab not only reduces circulating LDL cholesterol but also helps prevent CV events. Similarly, the FOURIER trial reported a reduction in CV events in patients who previously experienced major CV events treated with evolocumab, compared to the placebo group [57].

siRNA PCSK9is represent another strategy for controlling LDL cholesterol. They are rapidly and specifically taken up by hepatocytes, where they promote the degradation of PCSK9 mRNA by preventing synthesis of the encoded protein, thereby leading to a decrease of circulating LDL-C levels [70].

Real-world evidence has demonstrated that the ‘Strike early–strike strong’ lipid-lowering strategy of adding a mAb PCSKi to the statin-ezetimibe combination achieves the LDL-C target of < 55 mg/dL in the majority of patients and is associated with significant reduction of major CV events, including all-cause death [69]. Therefore, mAb PCSK9is are notably safe and effective in clinical practice and associated with a reduction of CV risk.

Table 1
Lipid-lowering agents and mean expected low-density lipoprotein cholesterol reduction.

Agent	Mechanism of action	LDL-C reduction
Statins	Lowers cholesterol synthesis in the liver and increases LDL-R activity by inhibiting HMG-CoA reductase to enhance LDL-C clearance	Moderate intensity statin: ~30 % High intensity statin: ~50 % High intensity statin combined with ezetimibe: ~65 %
Ezetimibe	Inhibits intestinal absorption of cholesterol	20–25 % added to baseline statin therapy
Bempedoic acid	Inhibits ACLY (a cytosolic enzyme upstream of HMG-CoA reductase)	16–18 % added to baseline statin therapy
mAb PCSK9i	Inhibits the activity of PCSK9, resulting in decreased degradation of the LDL-R	~75 % added to baseline statin therapy
siRNA PCSK9i	Inhibits the hepatic synthesis of PCSK9	~50 % added to baseline statin therapy

ACLY, ATP citrate lyase; HMG-CoA, β-hydroxy β-methylglutaryl-coenzyme A; LDL-C, low-density lipoprotein cholesterol; LDL-R, low-density lipoprotein receptor; mAb, monoclonal antibody; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; siRNA, small interfering ribonucleic acid.

6. Alirocumab

Alirocumab is a fully human anti-PCSK9 mAb that significantly lowers LDL-C levels, thereby reducing the risk of CV events [56]. Alirocumab is indicated to treat adults with primary hypercholesterolaemia (heterozygous familial and non-familial), mixed dyslipidaemia and/or established ASCVD [71]. Solutions for injection are available in 75 mg and 150 mg doses to be administered every 2 weeks and 300 mg to be administered once monthly [71]. A pharmacokinetic and pharmacodynamic study has shown that following single injections of alirocumab 75 mg, 150 mg and 300 mg, the mean free PCSK9 levels decreased within 4 h and remained as such for 10, 14 and 28 days, respectively [72]. The maximum mean reduction in LDL-C was observed on days 8 (55.3 %), 15 (63.7 %) and 22 (73.7 %), respectively (Fig. 3) [72].

The SYDNEY study employed the use of the auto-injector to administer alirocumab 300 mg once monthly [73]. This auto-injector (without an activation button) provides feedback on administration (tactile, auditory and visual feedback) and is simple to use through a two-step, self-administration process that takes < 20 s. No product technical issues were reported during supervised injections; most patients were confident when using this auto-injector and found them “very easy” to use. The mean LDL-C reduction from baseline at week 4 was 66.2 % (Table 2) [73].

6.1. *Use of alirocumab in DM*

Alirocumab to manage dyslipidaemia or hypercholesterolaemia and reduce CV risk has been extensively studied in the ODYSSEY clinical programme, as well as in several other clinical and real-world studies. Taken together, these studies have demonstrated significant efficacy and safety in reducing LDL-C levels and the risk of major adverse CV events (MACE) in patients with hypercholesterolaemia, ASCVD, high CV risk or VHCVR (with and without previous ischaemic events) in a number of settings, including patients with DM [23,56,58–68,74,75].

6.2. *Pivotal trials*

The ODYSSEY DM-INSULIN study evaluated the efficacy and safety of alirocumab (75 mg or 150 mg) in patients with T1D or T2D who were at high CV risk and had elevated LDL-C levels despite statin therapy [62]. The study included both patients with and without ASCVD; the latter presented with three or more CV risk factors. A significant reduction in LDL-C was observed in patients with insulin-treated DM, regardless of diabetes type. The treatment was well tolerated, and concomitant administration of alirocumab and insulin did not raise any safety concerns [62].

The ODYSSEY DM-DYSLIPIDEMIA study assessed the efficacy and safety of alirocumab (75 mg or 150 mg every 2 weeks) compared with traditional LLTs (ezetimibe, fenofibrates, omega-3 fatty acids or

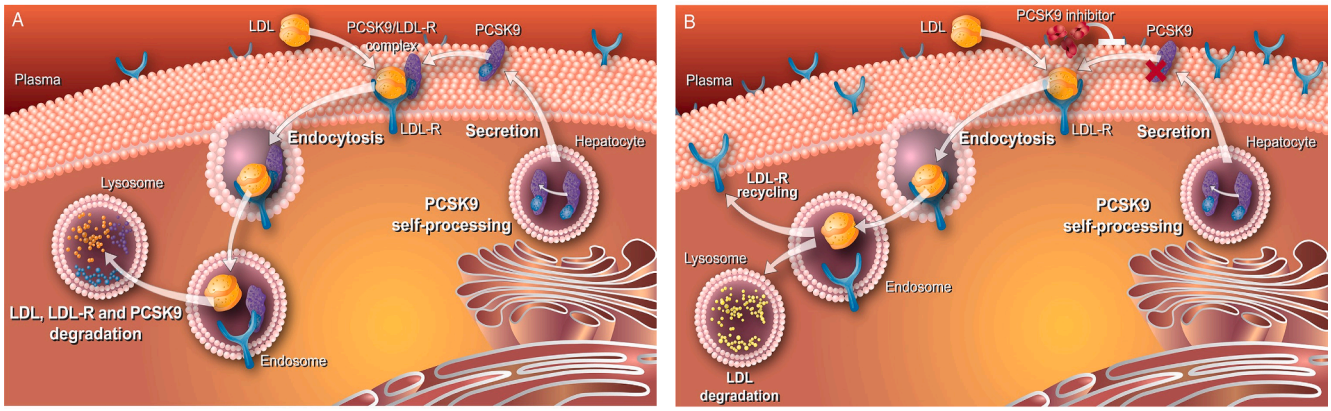

Fig. 1. Mechanism of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors by (a) PCSK9 regulation of hepatic low-density lipoprotein (LDL) receptor expression and (b) reduction of LDL-cholesterol levels by PCSK9 blockade [55].

nicotinic acid) in 413 patients with T2D and mixed dyslipidaemia (MDL) at high CV risk and VHCVR, whose non-HDL-C was not adequately controlled despite being treated with the maximum tolerated dose of a statin [66]. The study included patients with ASCVD and/or at least one CV risk factor. In this study, alirocumab showed superiority to usual care in non-HDL-C reduction and was generally well tolerated [66].

The ODYSSEY LONG TERM study (78 weeks) evaluated 150 mg alirocumab treatment every 2 weeks in patients at high CV risk who were receiving statins at the maximum tolerated dose, with or without other LLTs [76]. In the T2D ODYSSEY LONG TERM *post hoc* analysis (812 individuals with T2D with or without MDL), alirocumab reduced LDL-C by 62.6 % at 24 weeks (vs − 6.0 % with placebo) in patients with MDL, and by 56.1 % (vs − 5.6 % with placebo) in patients without MDL, with no significant difference between the with versus without MDL treatment groups (P = 0.0842) (Table 2) [68]. The reduction in LDL-C was maintained consistently through to week 78 [68].

A *post hoc* analysis of nine studies from the ODYSSEY clinical development programme assessed the efficacy and safety of alirocumab in 984 patients with DM and ASCVD [59]. The analysis included 984 patients with a clinical history of T1D or T2D and ASCVD, which was defined as the presence of CAD, ischaemic stroke or PAD. In the subgroup of patients with DM and ASCVD treated with alirocumab 150 mg in combination with statins, LDL-C was reduced by 61.5 % at week 24 (Table 2). A higher percentage of patients achieved LDL-C levels < 55 mg/dL at week 24 in the alirocumab group versus the control group [59].

The ODYSSEY CHOICE I study evaluated the administration of alirocumab 300 mg once monthly in patients at moderate-to-VHCVR on either maximally tolerated statin doses or no statin therapy, with or without other LLTs [23,67]. In the T2D subgroup who had received statins at the maximally tolerated dose, mean LDL-C was reduced from baseline to week 24 in the alirocumab group (−57.4 % (standard error [SE] 3.3 %) and increased in the placebo group (4.2 %, SE 4.5 %; P < 0.0001) [23]. The change from baseline to the mean of week 21 (−61.6 %) to week 24 (–68.8 %) was –67.9 % (SE 2.8 %) in the alirocumab group and 10.9 % (SE 3.8 %) in the placebo group (P < 0.0001 vs placebo); LDL-C reductions were significantly greater with alirocumab versus placebo [23]. In alirocumab-treated individuals, LDL-C reductions were observed from week 4 and were maintained up to week 48 [23].

ODYSSEY OUTCOMES reported on 18,924 patients who had ACS 1–12 months prior to study enrolment and inadequate atherogenic lipoprotein control despite treatment with the maximum tolerated dose of statins [56,75]. The primary endpoint was a composite of death from coronary heart disease, non-fatal MI, fatal/non-fatal ischaemic stroke or unstable angina requiring hospitalisation for MACE, which occurred in 9.5 % of patients in the alirocumab group and 11.1 % in the placebo group (relative risk reduction [RRR]: 15 %, hazard ratio [HR] 0.85; 95 % CI 0.78–0.93; P < 0.001) [56]. Notably, the incidence of death from all causes was 3.5 % with alirocumab versus 4.1 % with placebo (RRR: 15 %, HR 0.85; 95 % CI 0.73–0.98; nominal P = 0.03) [56,75].

ODYSSEY OUTCOMES has shown that alirocumab is associated with a reduction in the risk of all-cause mortality [75]. In a prespecified analysis conducted on 8,242 patients with a follow-up of 3–5 years,

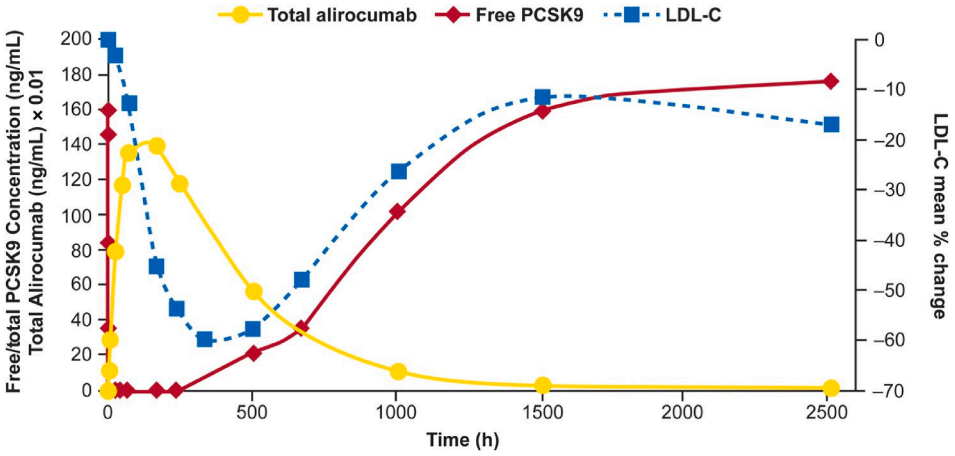

Fig. 2. Relationship between anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibody, plasma free PCSK9, and low-density lipoprotein cholesterol levels [55].

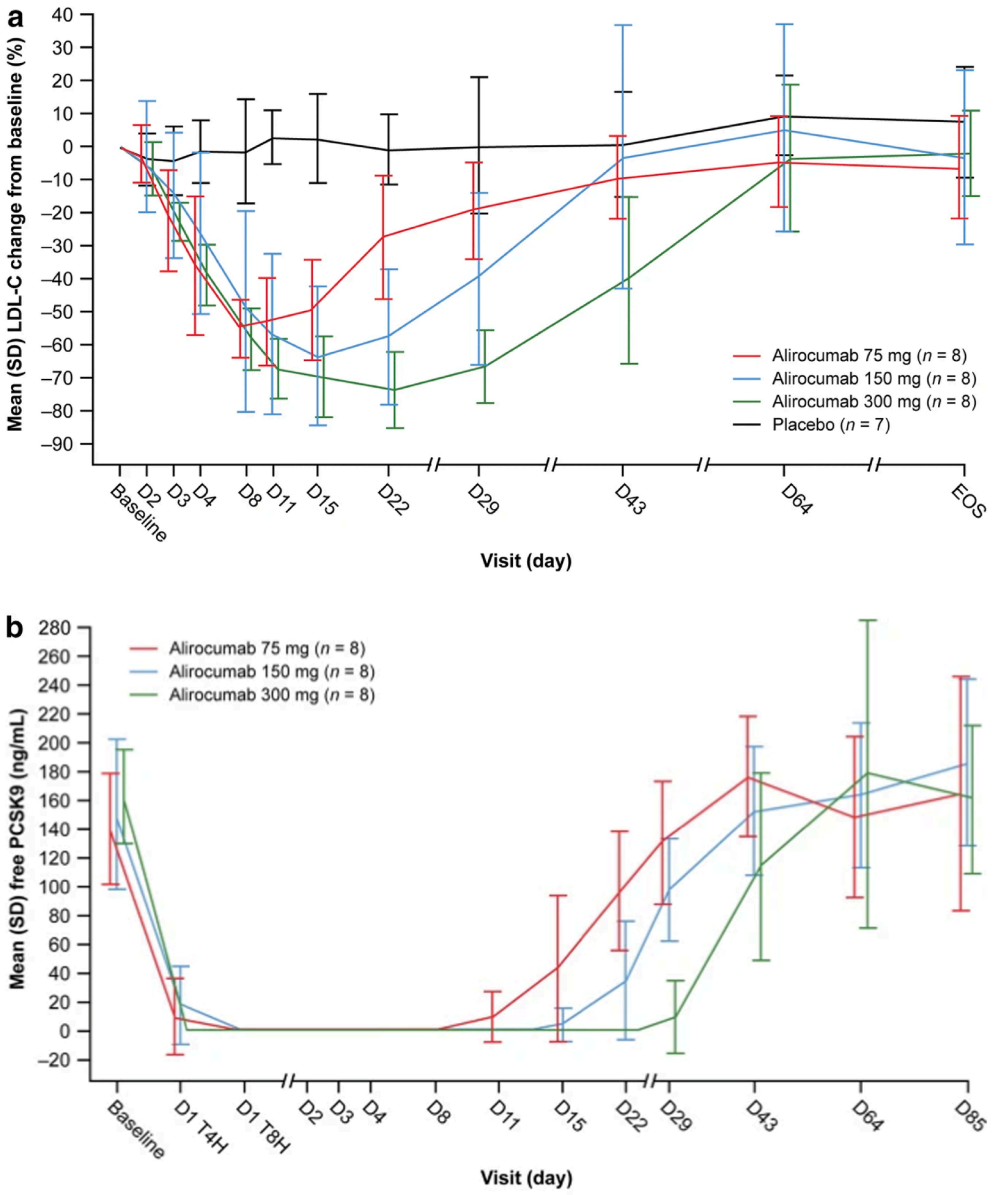

Fig. 3. Mean (a) percentage and (b) absolute change from baseline in low-density lipoprotein cholesterol (LDL-C) to end of study (EOS) after single-dose alirocumab or placebo administration [72]. Baseline = day 1 pre-dose assessment. SD standard deviation.

alirocumab treatment was associated with a 22 % reduction in the risk of death from all causes (HR 0.78; 95 % CI 0.65–0.94; P = 0.01) [75]. The treatment benefit on mortality increased and was evident after the first year (HR 0.79; 95 % CI 0.66–0.94; P = 0.0073). The lower mortality was, therefore, potentially related to the duration of alirocumab treatment [75].

In another *post hoc* ODYSSEY OUTCOMES analysis, which described the efficacy, safety and tolerability of alirocumab versus placebo in a prespecified subgroup of patients eligible for ≥ 3 years of follow-up, the efficacy of alirocumab in reducing the risk of MACE and CV death was further confirmed [61]. Alirocumab also reduced the risk of MACE (–17 %, HR 0.83 [95 % CI, 0.74–0.94]; P = 0.003) and CV death (–19 %, HR 0.81 [95 % CI 0.65–1.01]; P = 0.06) in patients with follow-up to 5 years [61]. The results show that the risk reduction for all-cause mortality may be driven by a reduction in CV death [61]. Alirocumab reduced the risk of CV death in ODYSSEY OUTCOMES, and the effect was maintained for > 3 years [61].

In a prespecified analysis of ODYSSEY OUTCOMES, the reduction of LDL-C from baseline to month 4 was 64 % in patients with normoglycaemia and prediabetes, and 65 % in patients with DM [64]. The CV protective effect (absolute risk reduction of MACE) of alirocumab was amplified in patients with DM, with a greater RRR in the incidence of the primary endpoint being similar in patients with diabetes (RRR: –16 %, HR 0.84; 95 % CI 0.74–0.97), prediabetes (RRR: –14 %, HR: 0.86; 95 % CI 0.74–1.00) or normoglycaemia (RRR: –15 %, HR: 0.85, 95 % CI 0.70–1.03; P interaction = 0.019 among the three glycaemic categories). The substantially higher absolute risk among patients with diabetes resulted in a greater absolute risk reduction with alirocumab treatment (2.30 %, 95 % CI 0.40–4.20) compared with patients with prediabetes (1.20 %, 0.00–2.40) or normoglycaemia (1.20 %, –0.30 to 2.70; P = 0.0019), with a highly favourable number needed to treat of 43 [64].

6.3. *Safety profile*

Assessment of the safety profile of alirocumab showed consistency across the presented studies [23,56,58–68,73–75]. AEs were generally similar between alirocumab and control groups, except for injection site

Table 2
Low-density lipoprotein cholesterol reduction and cardiovascular outcomes in selected studies.

Study name	Alirocumab dose	Reduction in LDL-C in patients with DM	CV outcomes in patients with DM
ODYSSEY LONG TERM (DM post-hoc analysis of the ODYSSEY LONG TERM Trial) [72,74]	150 mg every 2 weeks	↓62.6 % (week 24)	
ODYSSEY DM post-hoc analysis of 9 phase 3 studies [62]	150 mg every 2 weeks	↓61.5 % (week 24)	
ODYSSEY CHOICE I (DM analysis of CHOICE I) [23]	300 mg once monthly	↓67.9 % (week 21–24)	
ODYSSEY OUTCOMES (DM prespecified analysis) [70]	75/150 mg	↓65 % (month 4)	16 % ↓ in RR of MACE up to 5 years
Study name	**Alirocumab dose**	**Reduction in LDL-C**	**CV outcomes**
SYDNEY [61]	300 mg once monthly	↓66.2 % (week 4)	–
ODYSSEY OUTCOMES [56,63,71]	75/150 mg	↓62,7% (month 4)	15 % overall ↓ in RR of MACE 15 % overall ↓ in all-cause mortality* 17 % ↓ in RR of MACE up to 5 years 22 % ↓ in all-cause mortality up to 5 years

CV, cardiovascular; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; RR, relative risk; MACE, major adverse cardiovascular events.
*Nominal P-value of 0.03.

Table 3
Guidelines on mAb PSK9i therapy for patients with DM at VHCVR.

Guideline	LDL-C goal	mAb PSK9i therapy
ESC/EAS 2019 [47]	Reduction of ≥ 50 % from baseline and an LDL-C goal of < 55 mg/dL	• For patients at VHCVR who have not achieved their goals despite a maximum tolerated dose of a statin and ezetimibe, add a mAb PCSK9i • If a statin-based regimen is not tolerated at any dosage (even after rechallenge), add a mAb PCSK9i to ezetimibe
ESC/EASD 2019 [48]	Reduction of ≥ 50 % from baseline and an LDL-C goal of < 55 mg/dL	• mAb PCSK9i should be added in patients with VHCVR with high LDL-C levels despite maximum tolerated statin doses combined with ezetimibe or in statin-intolerant patients
ADA 2025 [20]	Reduction of ≥ 50 % from baseline and an LDL-C goal of < 55 mg/dL	• For people with DM and ASCVD (VHCVR), the addition of ezetimibe or a mAb PCSK9i is recommended if this goal is not achieved on maximum tolerated statin therapy • For people with DM and ASCVD (VHCVR) intolerant to statin therapy, mAb PCSK9i should be considered as an alternative cholesterol-lowering therapy
ESC 2023 [49]	Reduction of ≥ 50 % from baseline and an LDL-C goal of < 55 mg/dL	• A mAb PCSK9i is recommended in patients at VHCVR, with persistently high LDL-C levels above the target, despite treatment with a maximum tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance • If a statin-based regimen is not tolerated at any dosage (even after rechallenge), consider adding a mAb PCSK9i to ezetimibe

ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; DM, diabetes mellitus; EAS, European Atherosclerosis Society; EASD, European Association for the study of Diabetes; ESC, European Society of Cardiology; LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; VHCVR, very high cardiovascular risk.

reactions in the alirocumab group. Notably, there was no significant increase in HbA1c or fasting blood glucose levels, and non-diabetic patients treated with alirocumab showed no increased risk of new-onset diabetes [65].

7. Therapeutic recommendations

Guidelines recommend the addition of mAb PCSK9is for patients with DM at VHCVR with or without previous acute CV events who are not achieving the target LDL-C goals while receiving a maximally tolerated dose of statins and ezetimibe (Table 3).

The 2023 ESC guidelines for the management of CVD in patients with DM offer evidence-based recommendations to manage CV risk and provide guidance for the treatment of ASCVD in this patient population [49]. These guidelines introduce a novel, dedicated, T2D-specific 10-year CVD risk score (SCORE2-Diabetes) for patients with T2D without ASCVD or severe target-organ damage (TOD) [49]. According to the previous ESC/EAS and ESC/EASD guidelines, patients with DM and ASCVD or TOD were classified as patients with VHCVR for whom a reduction in LDL-C of ≥ 50 % from baseline and an LDL-C goal of < 55 mg/dL were recommended [49].

Statins remain the first-line treatment for reducing LDL-C levels in people with T2D and dyslipidaemia, and high-intensity statins (rosuvastatin and atorvastatin) are recommended for people in the high- or very high- CV risk categories [49]. Furthermore, the 2023 ESC guidelines state that LDL-C reduction can be intensified with ezetimibe or mAb PCSK9is, and recommend mAb PCSK9is for VHCVR patients with elevated LDL-C despite maximum tolerated statin doses or in combination with ezetimibe or for statin-intolerant patients [49].

8. Implications for clinical practice

The use of alirocumab as an effective LLT is supported by evidence from studies in patients with DM at VHCVR, particularly in those who do not achieve adequate lipid control with statin treatment alone or who are intolerant to statins. Significant reductions of LDL-C (up to 73.7 %) [72] and other lipid parameters, coupled with favourable CV outcomes, suggest a crucial role for alirocumab in the management of people with

DM with ASCVD or who are at VHCVR, and with or without previous acute CV events. The safety profile of alirocumab, especially its neutral impact on glycaemic control, is reassuring for clinicians who are concerned about the potential negative metabolic effects of LLTs in this patient group.

The authors suggest that physicians act early in patients with DM and ACS, and even earlier if patients with DM have ASCVD without previous ischaemic events (i.e. CAD, PAD, severe TOD, more than three CV risk factors) to achieve the recommended LDL-C goal of < 55 mg/dL. This approach may ultimately benefit this patient population by preventing either a first or a recurring acute CV event.

9. Conclusion

Patients with DM are at a higher risk for ASCVD and CV death than the general population. Several pathological mechanisms are linked to the development and progression of ASCVD, and LDL-C has been identified as causal factor for CVD. For patients with DM who are at VHCVR (i.e. ACS, CAD, PAD or TOD, three or more CV risk factors), and therefore at greater risk of a first acute or relapse of a CV event, clinical practice guidelines recommend a target LDL-C of < 55 mg/dL. If individuals do not achieve LDL-C targets, treatment can be intensified with LLTs, such as mAb PCSK9is. Alirocumab is effective in the management of dyslipidaemias by enabling significant reductions in LDL-C levels, providing significant CV benefits and offering a favourable safety profile. These features underscore the potential of alirocumab as a valuable addition to the therapeutic arsenal for the management of LDL-C, CV risk reduction and prevention of the first or relapse of a CV event in patients with DM and VHCVR.

CRediT authorship contribution statement

Angelo Avogaro: Writing – review & editing, Supervision, Data curation, Conceptualization. **Raffaella Buzzetti:** Writing – review & editing, Supervision, Conceptualization. **Riccardo Candido:** Writing – review & editing, Supervision, Conceptualization. **Salvatore De Cosmo:** Writing – review & editing, Supervision, Conceptualization. **Lucia Notarianni:** Writing – review & editing, Data curation. **Eleonora Consolo:** Writing – review & editing, Data curation. **Myriam Luciano:** Writing – review & editing, Data curation.

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Declaration of competing interest

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