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REVIEW ARTICLE

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Editor's Choice

Very low LDL-C levels may safely provide additional clinical cardiovascular benefit: the evidence to date

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Summary

Background: Cardiovascular disease (CVD) is the leading cause of death in Europe and increased low-density lipoprotein cholesterol (LDL-C) is a major contributor to CVD risk. Extensive evidence from clinical studies of statins has demonstrated a linear relationship between LDL-C levels and CVD risk. It has been proposed that lower LDL-C levels than those currently recommended may provide additional clinical benefit to patients.

Aim: This review summarises the genetic and clinical evidence on the efficacy and safety of achieving very low LDL-C levels.

Methods: Relevant epidemiological and clinical studies were identified using PubMed and by searching abstracts published at major congresses.

Results: Genetic evidence demonstrates that individuals with naturally very low LDL-C levels are healthy and have a low risk of CVD. Clinical evidence has shown that those patients who achieve very low LDL-C levels through using lipid-lowering therapies (LLTs), such as statins, have reduced CVD risk compared with patients who only just achieve recommended target LDL-C levels. These data show that the incidence of adverse events in patients achieving very low LDL-C levels using LLT is comparable to those reaching the recommended LDL-C targets.

Conclusions: Genetic and clinical evidence supports the concept that reduction in LDL-C levels below current recommended targets may provide additional clinical benefit to patients without adversely impacting patient safety. Statin add-on therapies, such as ezetimibe and the recently approved proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors alirocumab and evolocumab, allow patients to achieve very low LDL-C levels and are likely to impact on future treatment paradigms.

1 | INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in Europe. Over 4 million deaths occur from CVD in Europe each year and, on average, one death occurs every 8 seconds.[1] Prevention is a key to reduce the incidence and impact of CVD, and is a lifelong process.[2]

Major risk factors for CVD include genetics, age, gender, obesity, hypertension, smoking, type 2 diabetes, chronic kidney disease and high low-density lipoprotein cholesterol (LDL-C) levels.[2] Cardiovascular (CV) risk for individuals can be estimated using risk charts such as Systematic COronary Risk Evaluation (SCORE) or the QRISK2 risk assessment tool, which incorporate information on an individual's age, gender, smoking history, systolic blood pressure and total cholesterol. Current European Society of Cardiology (ESC) and UK National Institute for Health and Care Excellence (NICE) guidelines recommend using the SCORE system or QRISK2 tool, respectively, to assess CV risk only in apparently healthy individuals.[3,4] The American College of Cardiology (ACC)/American Heart Association (AHA) recommends using Pooled Cohort Equations to estimate 10-year atherosclerotic CVD (ASCVD) risk in individuals without clinical ASCVD.[5]

The World Health Organization has stated that the majority of CVD cases could be prevented by changes in lifestyle, such as promoting a healthy diet, physical activity and smoking cessation.[6] These should be recommended for all patients regardless of CV risk. However, those deemed to be at highest risk require immediate intervention to reduce all CV risk factors. This includes both lifestyle changes, as described above, and medical interventions to control risk factors such as high blood pressure and cholesterol levels. The precise definition of patients who require immediate medical intervention differs between guidelines, but includes those with a history of CVD, type 2 diabetes or familial hypercholesterolaemia (FH).[2,4,5]

Review criteria

This narrative review describes epidemiological studies of individuals with genetically determined very low low-density lipoprotein cholesterol (LDL-C) levels and clinical studies of lipid-lowering therapies, where patients achieved LDL-C levels below recommended targets. The articles discussed were identified using PubMed and by searching abstracts published at major cardiovascular (CV) congresses. Only clinical studies were included where post hoc analyses evaluated the effect of achieving very low LDL-C levels on CV outcomes and safety.

Message for the clinic

Approximately, half of individuals with hypercholesterolaemia do not reach the current recommended LDL-C goals and remain at high risk for cardiovascular disease (CVD). Emerging genetic and clinical evidence supports the concept that LDL-C levels lower than the current recommended targets may provide additional clinical benefit to patients, without additional safety concerns. Physicians should ensure that patients receive optimal lipid-lowering therapy to ensure adequate LDL-C regulation and minimise CVD risk.

2 | METHODS

A search was conducted using PubMed and by searching abstracts published at major CV congresses to identify epidemiological and clinical studies where very low LDL-C levels were achieved. Search terms included *low cholesterol*, *safety* and *cardiovascular*, and Phase 3 clinical studies of statins, ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors evaluating CV outcomes were identified. Relevant articles, abstracts and related literature were selected for inclusion, but only clinical studies where post hoc analyses evaluated the effect of achieving very low LDL-C levels on CV outcomes and safety were included in this narrative review article.

3 | LDL-C AND CVD

Increased total plasma cholesterol is a major risk factor for CVD.[2] The majority of cholesterol in plasma is transported by LDL particles as LDL-C, which plays a central role in the pathogenesis of CVD. LDL-C is deposited in artery walls when levels are high and undergoes oxidation. This promotes inflammation and attracts monocytes and macrophages to the site of cholesterol deposition. Together this causes the development of atherosclerotic plaques.[7,8]

Extensive clinical evidence has demonstrated that increased LDL-C levels are a major contributor to CVD risk. Statins reduce LDL-C levels by inhibiting HMG-CoA reductase (HMGCR) function in the liver, thereby reducing cholesterol synthesis.[9] Statin treatment is the current standard of care to lower LDL-C levels and prevent CVD.[2,4,5] Regression of atherosclerotic plaques has also been demonstrated in a limited number of studies, where patients were treated with high-intensity statins.[10–12]

In multiple large, secondary prevention studies of statins, LDL-C levels showed a linear relationship with the risk of CV events; the lower the level of LDL-C, the lower the risk of CV events.[13–15] Consequently, current ESC CVD prevention guidelines recommend an LDL-C goal of <2.5 mmol/L (<100 mg/dL) or a reduction of at least 50% if baseline levels are 2.6–5.1 mmol/L (100–200 mg/dL) for high-risk patients and <1.8 mmol/L (<70 mg/dL) or a reduction of at least 50% if baseline levels are 1.8–3.5 mmol/L (70–135 mg/dL) in very high-risk patients.[2] However, both the ACC/AHA and UK NICE guidelines found no evidence to recommend LDL-C titration and instead recommend treating patients based on their individual level of CV risk.[4,5] For the purposes of this review, LDL-C goals refer to those stated in the ESC guidelines.[2]

4 | UNDERACHIEVEMENT OF LDL-C GOALS IS A MAJOR PROBLEM IN CVD PREVENTION

Despite treatment with lipid-lowering therapy (LLT), individuals with high LDL-C levels often do not achieve the ESC-recommended LDL-C goals.[16] For example, in the pan-European CEPHEUS study of 14 478 patients with hypercholesterolaemia on LLT for at least 3 months, only 55% achieved their LDL-C target. Multivariate analyses identified several factors that predicted achievement of LDL-C goals including treatment adherence.[16] Treatment adherence is a concern in the prevention of CVD. The reasons for this are multifactorial, and include medication side effects and lack of physical symptoms from the disease.[2]

Even when patients adhere to treatment, LDL-C goals are often still not reached. Results from the EUROASPIRE IV study of 6648 patients with coronary heart disease (CHD) showed that 86% of patients (n=5717) received LLT (predominantly statins) and 33% of patients (n=2176) received high-intensity LLT at the time of interview. Of the patients receiving high-intensity LLT, only 68% achieved LDL-C levels below 2.5 mmol/L (100 mg/dL) and 27% achieved LDL-C

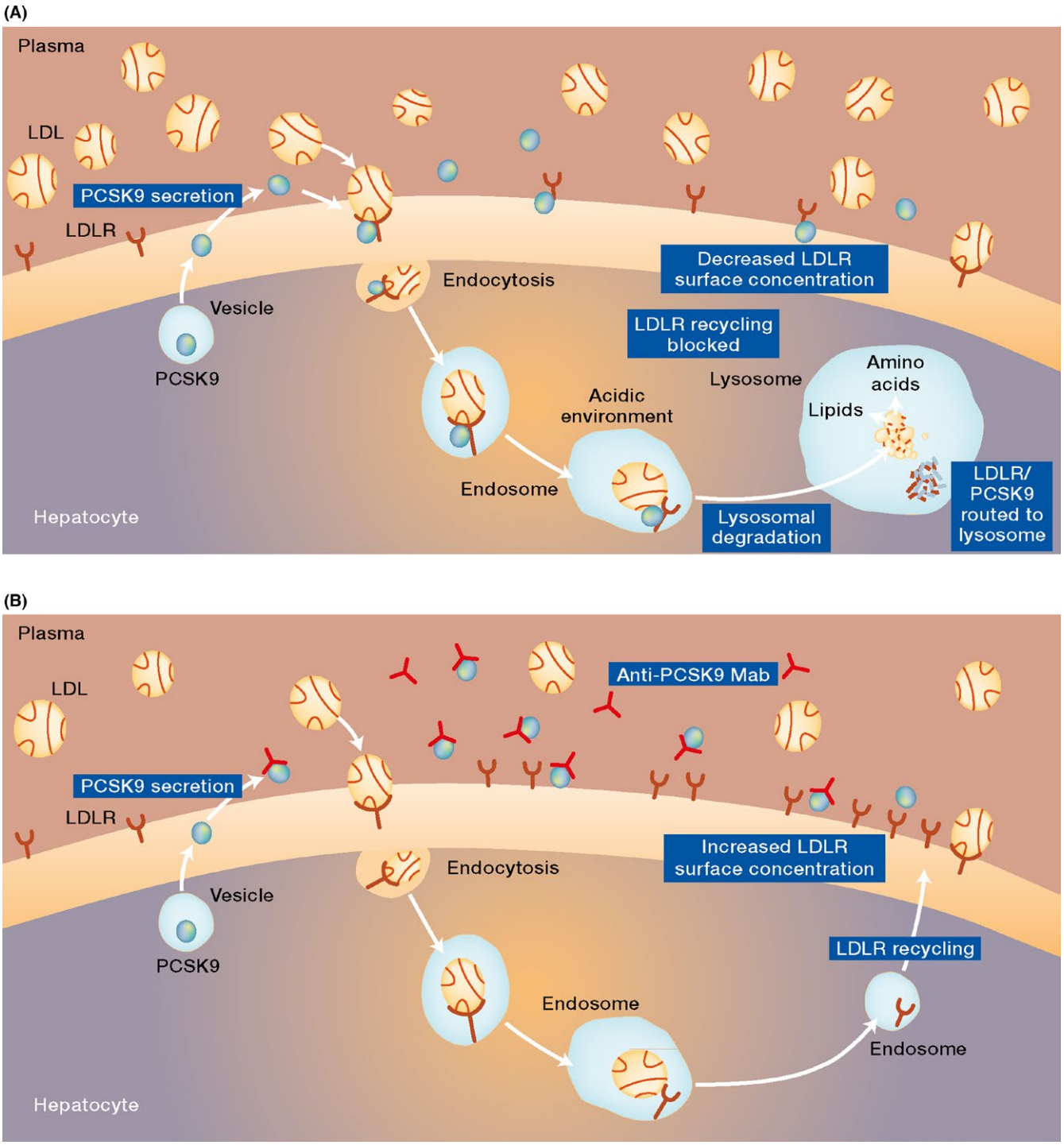

FIGURE 1 PCSK9 role in the liver (A) and mechanism of action of anti-PCSK9 monoclonal antibodies (mAbs) (B). (A) The low-density lipoprotein receptor (LDLR) expressed on the cell surface of hepatocytes binds to low-density lipoprotein (LDL) particles and undergoes endocytosis. When proprotein convertin subtilisin/kexin type 9 (PCSK9) is secreted from hepatocytes and binds to the LDLR on the cell surface, LDLR recycling to the cell surface is blocked and the LDLR instead traffics to the lysosome where it is degraded. In the acidic environment of the endosome, LDL dissociates from the LDLR and both are degraded in the lysosome to their component lipids and amino acids. The ability of PCSK9 to promote LDLR degradation results in decreased LDLR levels at the cell surface and consequently an increase in serum LDL levels. (B) The interaction between PCSK9 and LDLR can be prevented by anti-PCSK9 mAbs that specifically bind to PCSK9. In the absence of PCSK9 bound to LDLR, the complex formed by LDLR and LDL is internalised in an endosome that allows LDLR recycling to the cell surface instead of its lysosomal degradation. LDLR recycling results in increased LDLR levels at the cell surface, allowing further rounds of LDL uptake and degradation, and consequent reduction in serum LDL levels

levels below 1.8 mmol/L (70 mg/dL).[17] Furthermore, a separate cross-sectional study of 1249 patients with heterozygous FH (HeFH) in The Netherlands showed that the treatment goal of LDL-C of <2.5 mmol/L (<100 mg/dL) was only achieved in 21% patients despite 96% of patients being on statin treatment. A major problem identified in this study was that only 27% of patients not at LDL-C target used the maximum LLT. The main reason for individuals not using the maximum LLT was acceptance of higher LDL-C levels by the treating physician.[18] Complacency with LLTs is a major problem in CVD prevention. Patients are often started on low statin doses and stay at these levels despite LDL-C levels remaining high.[3]

Many patients are not achieving current ESC-recommended LDL-C goals due to a combination of reasons including lack of treatment adherence by patients, failure by physicians to prescribe the maximum LLT and the inability of standard LLTs to reduce LDL-C levels adequately in certain high-risk patient populations.[2,3,16–19] For example, patients with HeFH have been exposed to higher than average LDL-C levels over the course of their lives, which puts them at high risk of CV events. However, even with maximum statin treatment, HeFH patients are currently unlikely to achieve more than a 50% reduction in LDL-C levels, which may not be sufficient to meet current targets.[19] Despite large numbers of high-risk and very high-risk individuals not achieving current recommended LDL-C goals, it has been proposed that LDL-C levels even lower than current recommended ESC targets may be clinically beneficial. The data to support this proposal will be discussed, including results indicating that very low LDL-C levels are not associated with additional safety concerns. Currently, no formal definition for very low LDL-C levels exists and the studies cited in this review use varying levels as cut-offs for their analyses.[20–25] For the purposes of this review, we define very low LDL-C levels as below 1.3 mmol/L (50 mg/dL).

5 | INDIVIDUALS WITH NATURALLY VERY LOW LDL-C LEVELS ARE HEALTHY AND HAVE REDUCED CVD RISK

Individuals with naturally very low LDL-C levels have been identified carrying mutations in genes associated with the regulation of LDL-C levels including *low-density lipoprotein receptor* (*LDLR*), *HMGCR*, *apolipoprotein E* (*APOE*) and *PCSK9*.[26,27] Individuals with loss of function mutations in *PCSK9* have been of particular interest as these mutations occur in 1–3% of the human population and are associated with naturally low LDL-C levels in these individuals.[28–31] The *PCSK9* gene encodes a protein that regulates the LDLR in hepatocytes by targeting it for degradation instead of allowing recycling to the plasma membrane (Fig. 1A).[28,29] In individuals with loss of function mutations in *PCSK9*, cell surface LDLR levels are raised, allowing increased cellular uptake of LDL-C, thereby reducing plasma LDL-C levels.[28,29,32]

Individuals carrying *PCSK9* loss of function mutations not only have naturally low LDL-C levels but also have reduced CVD risk.[31,33] The Dallas Heart Study followed 12 887 individuals for 15 years, including carriers of specific *PCSK9* loss of function mutations that in this study were associated with absolute LDL-C levels of approximately 2.5 mmol/L (100 mg/dL). These *PCSK9* loss of function mutation carriers exhibited a low incidence of CHD. Compared with non-carriers, the CHD risk reduction was 88% and 47% in Black and White *PCSK9* loss of function mutation carriers, respectively. No changes were observed in overall mortality rates in this study and the incidence of cancer or haemorrhagic stroke was not reported.[31] The Myocardial Infarction Genetics Consortium has also reported that individuals carrying the *PCSK9* R46L missense mutation have a 60% reduced risk of myocardial infarction (MI) compared with non-carriers.[33] The *PCSK9* R46L mutation is associated with an absolute LDL-C level of 2.2 mmol/L (86 mg/dL).[29]

Several studies have suggested a link between low LDL-C levels and an increased risk of adverse events (AEs). An observational trial in diabetics treated with statins hypothesised a higher risk of cancer in individuals with both low and high LDL-C levels.[34] In addition, the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial reported a higher incidence of cancer in the simvastatin/ezetimibe-treated arm compared to placebo.[35] However, long-term follow-up of the SEAS trial participants showed this not to be the case.[36] The larger Study of Heart and Renal Protection (SHARP) study and IMProved Reduction of Outcomes: Vytorin Efficacy International Trial [IMPROVE-IT (TIMI 40)], using the same medication in differing patient populations, showed no relationship between the more intensively treated patients and cancer rates.[37,38]

In the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) and treating to new targets (TNT) studies, higher discontinuation rates due to AEs, elevation of liver enzyme levels and increased diagnoses of new-onset diabetes were reported in patients receiving high-dose statins, who achieved LDL-C levels of approximately 2.1 mmol/L (80 mg/dL).[13,39,40] However, increased liver enzymes and onset of type 2 diabetes are known side effects of statin treatment regardless of achieved LDL-C level and can contribute to statin intolerance.[41]

Observational research has also suggested that very low LDL-C levels are associated with increased risks of haemorrhagic stroke and mortality.[42–44] However, genetic analyses indicate that naturally occurring very low LDL-C levels do not appear to negatively impact on health.[28,31] An individual with total *PCSK9* deficiency has been identified with extremely low LDL-C levels of 0.4 mmol/L (15 mg/dL) and no reported health problems.[45]

6 | DO VERY LOW LDL-C LEVELS PROVIDE ADDITIONAL CLINICAL BENEFIT?

Post hoc analyses from several studies of LLTs in which patients achieved very low LDL-C levels have analysed the impact of these very low LDL-C levels on CV outcomes.[20–23] The results provide support to the concept that very low LDL-C levels may provide additional clinical benefit to patients compared with current ESC-recommended LDL-C targets (Tables 1 and 2).

TABLE 1 Overview of key trials with efficacy data from patients with very low LDL-C levels

Study name	N	Patient population and study duration	Treatment regimen	Baseline LDL-C level, mmol/L (mg/dL)	Achieved LDL-C level, mmol/L (mg/dL)	Rate of CV end-point, % (n)[a]	HR[b] (95% CI)
Statin monotherapy studies							
TNT[13,20]	10 001	Coronary heart disease LDL-C <3.4 mmol/L (130 mg/dL) Median follow-up: 4.9 years	Atorvastatin 80 mg Atorvastatin 10 mg	2.5 (97)[c] 2.5 (98)[c]	2.0 (77)[c] 2.6 (101)[c]	8.7 (434) 10.9 (548)	0.78 (0.69–0.89), *P* < .001
PROVE IT-TIMI 22[21,46]	4162	Post-ACS Total cholesterol <6.2 mmol/L (240 mg/dL) Mean follow-up: 2 years	Atorvastatin 80 mg Pravastatin 40 mg	2.7 (106)[d] 2.7 (106)[d]	1.6 (62)[d] 2.5 (95)[d]	22.4 (470) 26.3 (543)	0.84 (0.74–0.95), *P*=.005
JUPITER[22,47]	17 802	Healthy individuals hs-CRP ≥2.0 mg/L Median follow-up: 1.9 years	Rosuvastatin 20 mg Placebo	2.8 (108)[d] 2.8 (108)[d]	1.4 (55)[d] 2.8 (110)[d]	1.6 (142) 2.8 (251)	0.56 (0.46–0.69), *P* <.00001
Statin + ezetimibe combination study							
IMPROVE-IT[23,38]	18 144	Post-ACS LDL-C 1.3–2.6 mmol/L (50–100 mg/dL) with LLT or 1.3–3.2 mmol/L (50–125 mg/dL) with no LLT Median follow-up: 6 years	Simvastatin 40 mg + ezetimibe 10 mg Simvastatin 40 mg + placebo	2.43 (94)[c] 2.43 (94)[c]	1.4 (53)[c] 1.8 (70)[c]	32.7 (2965) 34.7 (3150)	0.94 (0.89–0.99), *P* = .016
Statin + PCSK9 inhibitor combination studies							
ODYSSEY LONG TERM[24]	2341	High CV risk LDL-C ≥1.8 mmol/L (70 mg/dL) Receiving statin treatment at maximum tolerated dose Mean follow-up: 1.5 years	Alirocumab 150 mg Q2W Placebo	3.2 (123)[c] 3.2 (122)[c]	1.2 (48)[c] 3.1 (119)[c]	1.7 (27) 3.3 (26)	0.52 (0.31–0.90), *P*=.02
OSLER-1 and OLSER-2[25]	4465	Varying Median follow-up: 0.9 years	Evolocumab 140 mg Q2W or 420 mg QM + ST Placebo + ST	3.1 (120)[d] 3.1 (121)[d]	1.2 (48)[d] NR	1.0 (28) 2.2 (32)	0.47 (0.28–0.78), *P*=.003

ACS, acute coronary syndrome; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; MI, myocardial infarction; NR, not reported; PCSK9, proprotein convertin subtilisin/kexin type 9; Q2W, every 2 weeks; QM, every month; ST, standard therapy; UA, unstable angina. [a]In the TNT study, the primary end-point was defined as death from coronary heart disease, non-fatal non-procedure-related MI, resuscitation after cardiac arrest or stroke; in the PROVE IT-TIMI 22 study, the primary end-point was defined as a composite of death, MI, stroke, revascularisation and UA requiring hospitalisation; in the JUPITER study, the primary end-point was defined as a composite of MI, stroke arterial revascularisation, UA or death from CV causes; in the IMPROVE-IT study, the primary end-point was defined as a composite of CV death, MI, UA, coronary revascularisation after 30 days and stroke; in the OSLER studies, the CV end-point was defined as the incidence of CV events including death, coronary events (MI, UA requiring hospitalisation or coronary revascularisation), cerebrovascular events (stroke or transient ischaemic attack) and heart failure requiring hospitalisation; in the OSYSSEY LONG TERM study, the CV end-point was defined as a composite of death from coronary heart disease, non-fatal MI, fatal or non-fatal ischaemic stroke or UA requiring hospitalisation. [b]HR associated with CV end-point. [c]Mean. [d]Median.

6.1 | Statin monotherapy studies

The TNT study was designed to prospectively assess the impact of reducing LDL-C levels below 2.6 mmol/L (100 mg/dL) on efficacy and safety in a secondary prevention setting.[13,20] Patients with CHD (N=10 001) were randomly assigned to receive either 10 or 80 mg atorvastatin. In the atorvastatin 80 mg group, mean baseline LDL-C levels were 2.5 mmol/L (97 mg/dL) and mean LDL-C levels achieved during the study were 2.0 mmol/L (77 mg/dL). The primary end-point was the occurrence of a major CV event defined as death from CHD,

TABLE 2 Overview of key efficacy and safety outcomes in studies where patients achieved very low LDL-C levels

Study name	Proportion of patients achieving very low LDL-C	Key efficacy outcomes in patients achieving very low LDL-C	Key safety outcomes in patients achieving very low LDL-C
Statin monotherapy studies			
TNT[20]	• 9769 of 10 001 patients enrolled in the study had LDL-C measurements at 3 months • These patients were stratified into quintiles according to achieved LDL-C • LDL-C <1.7 mmol/L (<64 mg/dL): 19% of patients • LDL-C <1.0 mmol/L (<40 mg/dL): 1% of patients	• The lowest rate of primary end-point[a] occurred in the <1.7 mmol/L quintile (*P*<.0001 for trend) • For the total TNT cohort, each 1 mg/dL reduction in LDL-C was associated with a 0.7% reduction in the relative risk of primary end-point (*P*<.0001)	• No difference in the treatment-associated AE profile (including muscle-related AEs) across LDL-C levels • No significant trend in the incidence of mortality, suicide, haemorrhagic stroke or cancer deaths across LDL-C levels • Haemorrhagic stroke: 0.3% in <1.7 mmol/L quintile vs. 0.3–0.4% in other quintiles
PROVE IT-TIMI 22[21]	• 1949 of 4162 patients enrolled in the study had LDL-C measurements at 4 months • These patients were stratified into groups according to achieved LDL-C • LDL-C ≤1.0 mmol/L (<40 mg/dL): 10% of patients	• Patients in the LDL-C ≤1.0 mmol/L and >1.0–1.6 mmol/L groups had the lowest rate of primary end-point[b] (*P*=.1 for trend) • Risk of primary end-point compared with the >2.1–2.6 mmol/L group: o ≤1.0 mmol/L group: HR=0.61 (95% CI, 0.40–0.91) o 1.0–1.6 mmol/L group: HR=0.67 (95% CI, 0.50–0.92)	• No differences in safety parameters (including muscle and liver side effects, haemorrhagic stroke, retinal AEs and mortality) across LDL-C levels • Haemorrhagic stroke: one case recorded in each of the 1.6–2.1 and 2.1–2.5 mmol/L groups
JUPITER[22,63]	• 8154 patients who received rosuvastatin were stratified into groups according to achieved LDL-C • LDL-C <1.3 mmol/L (<50 mg/dL): 51% of patients • LDL-C <0.8 mmol/L (<30 mg/dL): 5% of patients	• Risk of primary end-point[c] compared with the placebo group: o LDL-C ≥1.3 mmol/L: HR=0.76 (95% CI, 0.57–1.00) o LDL-C <1.3 mmol/L: HR=0.35 (95% CI, 0.25–0.49) o *P*<.0001 for trend	• Increases in the risk of type 2 diabetes, haematuria and certain musculoskeletal, hepatobiliary and psychiatric AEs in patients with LDL-C <0.8 mmol/L • No differences in the incidence of renal failure, cancer, memory impairment or haemorrhagic stroke across LDL-C levels • Haemorrhagic stroke: eight cases recorded in the placebo group vs. five in the rosuvastatin group; only one case recorded in the <1.3 mmol/L group
Statin + ezetimibe combination study			
IMPROVE-IT[23]	• 15 191 of 18 144 patients enrolled in the study had LDL-C measurements at 1 month • These patients were stratified into groups according to achieved LDL-C • LDL-C 0.8 to <1.3 mmol/L (30–<50 mg/dL): 30% of patients • LDL-C <0.8 mmol/L (<30 mg/dL): 6% of patients	• The risk of primary end-point[d] was significantly reduced in patients with LDL-C <1.3 mmol/L vs. ≥1.3 mmol/L (HR=0.90; 95% CI, 0.85–0.96; *P*=.002)	• No increase in AEs (including muscle, liver, gall bladder and neurocognitive AEs), cancer, haemorrhagic stroke or non-CV death across LDL-C levels
Statin + PCSK9 inhibitor combination studies			
ODYSSEY LONG TERM[24]	• 1553 patients received alirocumab • LDL-C <0.6 mmol/L (<25 mg/dL): 37% of patients	N/A	• Rates of AEs were similar in patients with LDL-C <0.6 mmol/L compared with the overall alirocumab group • Fatal or non-fatal ischaemic stroke: 0.6% in alirocumab group vs. 0.3% in placebo group • Incidence of haemorrhagic stroke not reported

(continues)

TABLE 2 (continued)

Study name	Proportion of patients achieving very low LDL-C	Key efficacy outcomes in patients achieving very low LDL-C	Key safety outcomes in patients achieving very low LDL-C
OSLER-1 and OSLER-2[25]	• 2976 patients received evolocumab • LDL-C <0.6 mmol/L (<25 mg/dL): 26% of patients	N/A	• Rates of AEs (including muscle and neurocognitive AEs) and elevations in aminotransferase and creatine kinase levels were similar across LDL-C levels • Stroke: 0.1% in either group • Transient ischaemic attack: 0% in evolocumab group vs. 0.3% in control group • Incidence of haemorrhagic stroke not reported

AE, adverse event; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; N/A, not applicable; PCSK9, proprotein convertin subtilisin/kexin type 9; UA, unstable angina.
[a]In the TNT study, the primary end-point was defined as death from coronary heart disease, non-fatal, non-procedure-related MI, resuscitation after cardiac arrest or fatal or non-fatal stroke.
[b]In the PROVE IT-TIMI 22 study, the primary end-point was defined as a composite of death, MI, stroke, revascularisation and UA requiring hospitalisation.
[c]In the JUPITER study, the primary end-point was defined as a composite of MI, stroke arterial revascularisation, UA or death from CV causes.
[d]In the IMPROVE-IT study, the primary end-point was defined as a composite of CV death, MI, UA, coronary revascularisation ≥30 days after randomisation or stroke.

non-fatal, non-procedure-related MI, resuscitation after cardiac arrest or stroke. A primary event occurred in 8.7% of patients (n=434) in the atorvastatin 80 mg group vs 10.9% (n=548) in the atorvastatin 10 mg group [hazard ratio (HR): 0.78; 95% confidence interval (CI): 0.69–0.89; *P*<.001) over a median follow-up of 4.9 years. No difference in overall mortality was observed between the atorvastatin 10 and 80 mg groups.[13] In a post hoc analysis of results from the TNT study, 1836 patients (19%) achieved LDL-C levels below 1.7 mmol/L (64 mg/dL). While the LDL-C cut-off used in this post hoc analysis was greater than 1.3 mmol/L (50 mg/dL), these patients had a reduced rate of major CV events compared with those who achieved LDL-C levels of 1.7 mmol/L (64 mg/dL) or greater (*P*<.0001 for trend), although the number of events were not reported. Finally, 98 patients (1%) achieved LDL-C levels below 1.0 mmol/L (40 mg/dL) and during the study, three major CV events (two non-fatal MIs and one non-fatal stroke) occurred in this group of patients.[20]

The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) study assessed the impact of intensive vs. moderate LLT in the secondary prevention setting.[21,46] Patients who had been hospitalised after acute coronary syndrome (ACS; N=4162) were randomised to receive either atorvastatin 80 mg (intensive LLT) or pravastatin 40 mg (moderate LLT).[46] Of the 2099 patients randomised to the intensive LLT group, 1949 patients (93%) had LDL-C levels measured after 4 months of treatment. Among these patients, baseline LDL-C levels were 2.3–3.0 mmol/L (89–115 mg/dL) and 1756 patients (90%) had an LDL-C level below 2.6 mmol/L (100 mg/dL) at 4 months.[21] The primary end-point of this study, a composite of death, MI, stroke, revascularisation and unstable angina requiring hospitalisation, was reduced by 16% in the intensive LLT group (470 patients in the intensive LLT group vs. 543 in the moderate LLT group experienced events over a mean follow-up of 2 years; *P*=.005).[46] In further analysis of the results from the intensive LLT group, 193 patients achieved LDL-C levels of below 1.0 mmol/L (40 mg/dL; 10% of the 1949 patients with LDL-C levels measured at 4 months). Patients with LDL-C levels below 1.0 mmol/L (40 mg/dL) and between 1.0 and 1.6 mmol/L (40–60 mg/dL) had the lowest rate of the primary end-point [20.4% for both the below 1.0 mmol/L (n=39) and 1.0–1.6 mmol/L (n=129) groups vs. 22.2% for the 1.6–2.1 mmol/L group (n=128) and 26.1% for the 2.1–2.5 mmol/L group (n=67); *P*=.1 for trend].[21]

The Justification for the Use of statins in primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) was designed to test if individuals without hyperlipidaemia, but with elevated high-sensitivity C-reactive protein levels would benefit from statin therapy.[22,47] Apparently, healthy individuals (N=17 802) were randomly assigned to receive either rosuvastatin 20 mg or placebo. Baseline median LDL-C levels were 2.8 mmol/L (108 mg/dL) in both groups. Median LDL-C levels at 1 year were 1.4 mmol/L (55 mg/dL) and 2.8 mmol/L (110 mg/dL) in the rosuvastatin and placebo groups, respectively. The primary end-point was a composite of MI, stroke, arterial revascularisation, unstable angina or death from CV causes. The primary end-point occurred in 1.6% of patients in the rosuvastatin group (n=142) vs. 2.8% (n=251) of patients in the placebo group (HR: 0.56; 95% CI: 0.46–0.69; *P*<.00001) over a median of 1.9 years follow-up.[47] In a post hoc analysis of results from the JUPITER study, 4154 individuals (51%) in the rosuvastatin group achieved LDL-C levels below 1.3 mmol/L (50 mg/dL). Compared with individuals in the placebo group, those in the rosuvastatin group achieving LDL-C levels below 1.3 mmol/L (50 mg/dL) had a larger risk reduction for the primary end-point (*P*<.0001 for trend). The number of events in each group was not reported.[22]

6.2 | Statin and ezetimibe combination study

Results from the IMPROVE-IT study showed that the linear relationship between LDL-C levels and CVD risk extends below the current ESC-recommended LDL-C goals.[23] These data strongly support the

concept that very low LDL-C levels provide additional clinical benefit with regard to reducing CVD risk.

IMPROVE-IT was designed to test whether the addition of ezetimibe, a cholesterol absorption inhibitor, to statins can further reduce the incidence of CV events.[23,38] Patients recruited after hospitalisation for ACS (N=18 144) received simvastatin 40 mg and were randomised to receive either ezetimibe 10 mg or placebo. In both treatment groups, mean LDL-C levels at the time of hospitalisation for ACS were 2.4 mmol/L (94 mg/dL). The mean LDL-C level after 1 year of treatment was 1.4 mmol/L (53 mg/dL) in the ezetimibe-simvastatin group and 1.8 mmol/L (70 mg/dL) in the placebo-simvastatin group. The primary end-point was a composite of CV death, MI, unstable angina, coronary revascularisation after 30 days and stroke. The Kaplan–Meier event rates for the primary end-points at 7 years were 32.7% in the ezetimibe-simvastatin group (n=2965) vs 34.7% in the placebo-simvastatin group (n=3150; HR: 0.94; 95% CI: 0.89–0.99; *P*=.016).[38] Analysis of results from the IMPROVE-IT study showed that when both treatment groups were combined, 975 of 15 191 patients (6%) achieved LDL-C levels below 0.8 mmol/L (30 mg/dL) and 5578 patients (37%) achieved LDL-C levels below 1.3 mmol/L (50 mg/dL) after 1 month of treatment. The risk of the primary end-point was significantly reduced in patients with LDL-C levels below 1.3 mmol/L (50 mg/dL) compared with those of 1.3 mmol/L and above (HR: 0.90; 95% CI: 0.85–0.96; *P*=.002). The number of events in each group was not reported.[23]

6.3 | Statin and PCSK9 inhibitor combination studies

The PCSK9 inhibitors, alirocumab and evolocumab, have recently been approved to reduce LDL-C levels, in combination with statins or as monotherapies, in selected patients at high CV risk.[48,49] Alirocumab and evolocumab are monoclonal antibodies (mAbs) against PCSK9 that block PCSK9 binding to the LDLR.[29,48,49] This prevents the degradation of LDLR and consequently reduces plasma LDL-C levels (Fig. 1B). Multiple Phase 3 studies of PCSK9 inhibitors administered subcutaneously in combination with statins have allowed patients to achieve very low LDL-C levels,[50–57] but only those with preliminary CV outcome data are described here.[24,25]

The ODYSSEY LONG TERM study was a large study to analyse the efficacy and safety of long-term alirocumab treatment. Patients at high risk of CV events and receiving statin treatment (N=2341) were randomised to receive alirocumab 150 mg or placebo every 2 weeks for 78 weeks. In the alirocumab group, mean baseline LDL-C levels were 3.2 mmol/L (123 mg/dL) and absolute LDL-C levels at week 24 were 1.2 mmol/L (48 mg/dL). Overall, 575 patients (37%) in the alirocumab group achieved an LDL-C level below 0.6 mmol/L (25 mg/dL). Post hoc analysis of results from the ODYSSEY LONG TERM study evaluated the rate of major adverse CV events defined as death from CHD, non-fatal MI, ischaemic stroke or unstable angina requiring hospitalisation. The rate of CV events over 78 weeks was lower in patients receiving alirocumab [1.7% (n=27)] compared with those receiving placebo [3.3% (n=26); HR: 0.52; 95% CI: 0.31–0.90; nominal *P*=.02].[24]

The Open-Label Study of Long-Term Evaluation against LDL-C (OSLER-1) and OSLER-2 studies were extension studies encompassing differing patient populations from Phase 2 or 3 trials, and designed to obtain long-term safety and efficacy data for evolocumab treatment. Between October 2011 and June 2014, 4465 patients who had completed one of 12 Phase 2 or 3 studies chose to enrol in the OSLER-1 or -2 extension studies. At the start of the OSLER extension programme, all patients received standard therapy based on local guidelines and were randomly assigned to receive evolocumab 140 mg every 2 weeks, evolocumab 420 mg every month or placebo for an extended 52-week follow-up. In the OSLER-1 study, the evolocumab group received a monthly dose of 420 mg. In the OSLER-2 study, patients assigned to evolocumab could choose their dosing regimen, 140 mg every 2 weeks or 420 mg once a month, which was known to be clinically equivalent in this patient population. At the start of the parent study, 80% of patients in either group had at least one CV risk factor. In the evolocumab group, median baseline LDL-C levels in the parent studies were 3.1 mmol/L (120 mg/dL). At Week 12 of the OSLER-1 and OSLER-2 studies, median LDL-C levels were 1.2 mmol/L (48 mg/dL) in patients receiving evolocumab. This LDL-C reduction was sustained throughout 48 weeks. Overall, 773 patients (26%) in the evolocumab group achieved LDL-C levels below 0.6 mmol/L (25 mg/dL). A pre-specified, exploratory outcome of the OSLER-1 and OSLER-2 studies was the incidence of CV events including death, coronary events (MI, unstable angina requiring hospitalisation or coronary revascularisation), cerebrovascular events (stroke or transient ischaemic attack) and heart failure requiring hospitalisation. The rate of CV events at 1 year was reduced from 2.2% (n=32) in the standard therapy group to 1.0% in the evolocumab plus standard therapy group (n=28; HR: 0.47; 95% CI: 0.28–0.78; *P*=.003).[25]

6.4 | Study limitations

Measurement accuracy is a challenge when LDL-C levels are very low. In standard clinical practice LDL-C levels are estimated using the Friedewald equation. However, this tends to underestimate LDL-C levels when they are very low, especially when triglycerides are above 1.7 mmol/L (150 mg/dL).[58] Consequently, direct measurements of LDL-C using ultracentrifugation are more accurate when LDL-C levels are very low. The method of LDL-C measurement was not reported in the TNT, PROVE IT-TIMI 22 and JUPITER studies.[13,20–22,46,47] The OSLER-1 and OSLER-2 studies used the Friedewald equation.[25] The ODYSSEY LONG TERM study used a mixture of both techniques.[24] The IMPROVE-IT study used the Friedewald equation, except where triglyceride levels were above 4.5 mmol/L (400 mg/dL).[38] The method of LDL-C measurement should be considered when interpreting study results where patients achieve very low LDL-C levels.

It should be noted that there are several limitations associated with the post hoc analyses of patients achieving very low LDL-C levels in the TNT, PROVE IT-TIMI 22, JUPITER and IMPROVE-IT studies. In each study, all patients received a fixed dose of the study drug and titration to achieve specific LDL-C goals was not a prespecified end-point.[13,24,25,38,46,47] Moreover, post hoc analyses of baseline characteristics of patients achieving the lowest LDL-C levels in the TNT, PROVE IT-TIMI 22, JUPITER and IMPROVE-IT studies showed that they were more likely to be older males with diabetes and a lower

baseline LDL-C level.[20–23] To fully elucidate the clinical impact of very low LDL-C levels, studies specifically designed to test this hypothesis are required.

Results from the ODYSSEY LONG TERM and OSLER-1 and OSLER-2 studies demonstrated the same trend in reduction in MACE in both studies. However, these studies were not designed or powered for CV outcome analysis.[24,25] The event-driven analyses were based on small number of events in both studies and the treatment duration in the OSLER-1 and OSLER-2 studies was only 48 weeks. Consequently, further data are required to determine the impact of PCSK9 inhibitor treatment on CV outcomes. Results from the long-term alirocumab ODYSSEY outcomes study and the evolocumab Further cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk [FOURIER (TIMI 59)] study are anticipated in 2017 and are expected to provide additional efficacy and safety data in patients who achieve LDL-C levels below recommended targets.[59,60]

Finally, while some patients in all the studies described did achieve very low LDL-C levels, the clinical impact may be masked by high lipoprotein(a) levels, a known risk factor for CVD.[61,62] This could provide an explanation for the residual CV events that occur in patients who achieve very low LDL-C levels and would suggest that targeting LDL-C alone is not sufficient to eradicate CV risk. Studies of PSCK9 inhibitors have reported reductions in lipoprotein(a) levels of 26% (P<.001).[24,25] Consequently, these novel agents may provide additional clinical benefit to patients by simultaneously reducing the levels of multiple atherosclerotic lipoproteins.

7 | ARE VERY LOW LDL-C LEVELS SAFE?

Results from the studies described here provide evidence that LDL-C levels lower than recommended by the current guidelines further reduce CV risk and may provide additional clinical benefit to patients.[20–25] Although some reports have suggested that very low LDL-C levels are associated with an increased risk of AEs and deaths,[34,42–44] genetic evidence indicates that individuals with naturally very low LDL-C levels have reduced CVD risk and are apparently healthy.[28,31,45] Clinical evidence from the studies described also supports the concept that achieving very low LDL-C levels does not pose additional safety concerns.

In the JUPITER study, 767 patients (5%) who were treated with rosuvastatin 20 mg achieved LDL-C levels below 0.8 mmol/L (30 mg/dL). In those patients, an increase in the risk of physician-reported type 2 diabetes and haematuria was observed, as was an increased risk of certain musculoskeletal, liver and psychiatric AEs. No difference in the risk of renal failure, cancer, memory impairment or haemorrhagic stroke were reported.[63] In the PROVE IT-TIMI 22 study, 193 patients (10%) achieved LDL-C levels below 1.0 mmol/L (40 mg/dL). No differences in safety parameters including muscle and liver side effects, haemorrhagic stroke and mortality were observed in patients regardless of achieved LDL-C level.[21] In the TNT study, 1836 patients (19%) achieved LDL-C levels below 1.7 mmol/L (64 mg/dL). No difference in the AE profile or incidence of suicide, cancer deaths or haemorrhagic stroke was observed in patients regardless of achieved LDL-C level.[20] In the IMPROVE-IT study, 975 patients (6%) achieved LDL-C levels below 0.8 mmol/L (30 mg/dL). No increase in AEs, including muscle, liver, gall bladder and neurocognitive AEs, cancer, haemorrhagic stroke or non-CV death were reported in patients who achieved LDL-C levels below 0.8 mmol/L (30 mg/dL) compared with patients with LDL-C levels at recommended targets.[23] In the ODYSSEY LONG TERM study, 575 patients (37%) achieved LDL-C levels below 0.6 mmol/L (25 mg/dL). Rates of AEs were similar between patients with LDL-C below 0.6 mmol/L and the overall alirocumab group.[24] In the OSLER-1 and OSLER-2 studies, 773 patients (25%) achieved LDL-C levels below 0.6 mmol/L (25 mg/dL). Rates of AEs, including muscle and neurocognitive AEs, and elevations in aminotransferase and creatine kinase levels were similar in patients across all achieved LDL-C levels.[25]

Increased incidence of haemorrhagic stroke in patients with very low LDL-C levels has been previously reported.[42–44] In the studies described above, no significant differences in the rate of haemorrhagic stroke across LDL-C levels were reported (Table 2),[20–23,63] indicating that the incidence of haemorrhagic stroke is not increased in patients who achieve very low LDL-C levels.

Cholesterol is essential for synaptic formation and function, and there has been concern regarding dramatically lowering cholesterol levels and cognitive impairment.[64] Formal studies of cognitive impairment in statin users have provided conflicting evidence, but these events have been reported rarely.[65–70] In studies of PCSK9 inhibitors, higher rates of neurocognitive events have been reported, which has led to concern about the impact of these novel agents on neurocognition, although the definitions of neurocognitive AEs varied between studies and were not prospectively assessed.[24,25] ApoE, another lipoprotein that binds to LDLR, is associated with dementia risk and in preclinical studies the functional interaction between ApoE and LDLR has been demonstrated to influence this risk.[64,71] It could be hypothesised that increased LDLR levels mediated by PCSK9 inhibitors could affect ApoE levels in the brain and, therefore, cognitive function. However, as mAbs cannot cross the blood–brain barrier, LDLR levels in the brain are not expected to be altered in PCSK9 inhibitor-treated patients. Regardless of mechanism, some patients treated with PCSK9 inhibitors experienced neurocognitive AEs and this is being further explored in EBBINGHAUS, a substudy of the evolocumab FOURIER study that will use a battery of tests to assess cognitive function.[24,25,60]

Long-term studies of statin treatment have demonstrated their manageable safety profile.[2,41] But, it has been suggested that the combination of statins and PCSK9 inhibitors may pose an additional safety concern due to their differing mechanisms of action. Both increase LDLR levels which may have unintended safety consequences.[28,29] However, multiple studies combining PCSK9 inhibitors and statins in a variety of patient populations have been performed to date and no new safety issues have come to light.[24,25,50–57] Another concern associated with increased LDLR levels is that of its potential role as a receptor for the hepatitis C virus (HCV).[72,73] There is also conflicting data suggesting that PCSK9 may target CD81, an essential component of the HCV receptor, for degradation.[74,75] Together these data have led

to concerns that the use of PCSK9 inhibitors may increase susceptibility to HCV infection. Long-term safety data for alirocumab and evolocumab are not yet available, but results from the ongoing ODYSSEY outcomes and FOURIER studies are expected to address this issue.[59,60]

8 | CONCLUSIONS

To reduce CVD risk, current ESC guidelines recommend that LDL-C targets [high-risk individuals: <2.5 mmol/L (<100 mg/dL) or a reduction of at least 50% if baseline levels are 2.6–5.1 mmol/L (100–200 mg/dL); very high-risk individuals: <1.8 mmol/L (<70 mg/dL) or a reduction of at least 50% if baseline levels are 1.8–3.5 mmol/L (70–135 mg/dL)] be achieved using a combination of lifestyle and medical interventions as required. This may include smoking cessation, a healthy diet, regular physical activity, maintaining a body mass index of 20–25 kg/m^2 and waist circumference less than 94 cm in men and 80 cm in women and keeping blood pressure below 140/90 mm Hg. In patients with type 2 diabetes, HbA_{1c} is recommended to be less than 7% (53 mmol/mol).[2] However, as noted previously ACC/AHA and UK NICE guidelines do not support treating patients to achieve specific LDL-C targets and instead recommend treatment based on an individual's CV risk.[4,5]

Medical interventions to control LDL-C levels include LLTs, with statins being the standard recommended treatment.[2,4,5] Recommendations regarding other LLTs differ between guidelines. The ACC/AHA guidelines do not recommend any LLT other than statins,[5] while the NICE guidelines recommend the use of ezetimibe in patients whose condition is not appropriately controlled by a statin alone.[4] The ESC guidelines recommend ezetimibe in combination with statins when statin monotherapy is not sufficient to reach LDL-C targets.[2] The recent European Commission's approval of alirocumab and evolocumab is likely to change future treatment recommendations.[48,49] However, mAbs are complex and more costly to produce than generic statins. Consequently, economic considerations may restrict access to these drugs. For example, NICE has only approved alirocumab and evolocumab in the primary prevention setting for patients with FH and LDL-C levels above 5.0 mmol/L (193 mg/dL) and in the secondary prevention setting for patients with LDL-C levels above 3.5 or 4.0 mmol/L (135 or 155 mg/dL), depending on their CV risk.[76,77]

In conclusion, high levels of plasma LDL-C are associated with increased CVD risk. Lowering of LDL-C levels using a combination of standard and novel LLTs can allow high-risk individuals to reach ESC-recommended LDL-C targets and reduce CVD risk. A growing body of evidence supports the concept that LDL-C levels lower than the current ESC-recommended targets may provide additional clinical benefit to patients without additional safety concerns. CVD prevention guidelines may take this into account when deciding to recommend LDL-C targets in the future.

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AUTHOR CONTRIBUTIONS

All authors contributed to the interpretation of the collected literature, and in the writing, revision and final approval of the manuscript.

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