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Lipid management

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About the Expert

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Abbreviations used in this review
ApoB = apolipoprotein B
ASCVD = atherosclerotic cardiovascular disease
EAS = European Atherosclerosis Society
eGFR = estimated glomerular filtration rate
ESC = European Society of Cardiology
HMG-CoA = hydroxymethylglutaryl-coenzyme A
PCSK9 = proprotein convertase subtilisin kexin type 9

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This publication is an educational resource for cardiologists and general practitioners in NZ highlighting recent changes in lipid management recommendations. Specifically, it emphasises the need to aggressively lower LDL-C levels in patients with high CV risk in accordance with international guidelines. This review is sponsored by an educational grant from Sanofi.

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in New Zealand, accounting for almost 1 in 3 deaths and 12.5% of the total health expenditure.[1,2] CVD also contributes substantially to health inequalities due to Māori, Pacific and Indian people having a 13-48% increased risk, compared to Europeans.[3] Despite the burden of CVD, it is the most pharmacologically undertreated long-term condition in New Zealand.[4]

The major risk factors for atherosclerotic CVD (ASCVD) include advancing age, smoking, hypertension, dysglycaemia, and dyslipidaemia (including familial and non-familial hypercholesterolaemia).[5,6] Numerous epidemiological studies have demonstrated that non-high-density lipoprotein (HDL) cholesterol, of which low-density lipoprotein cholesterol (LDL-C) is the major component, demonstrates a log-linear relationship with incidence of ASCVD (**Figure 1**).

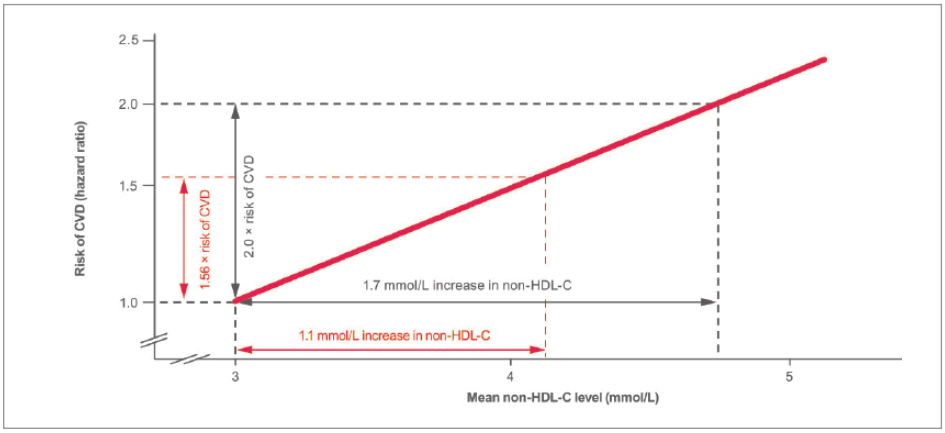


Figure 1: Non-HDL-C and the risk of atherosclerotic CVD, adapted from Packard *et al* (2021)[7]

The relationship between LDL-C and ASCVD is replicated in genetic studies and outcome trials (**Figure 2**) that provide convincing evidence that LDL-C is causally associated with the risk of ASCVD, and that lowering LDL-C reduces the risk of ASCVD proportionally to the reduction in LDL-C achieved.[7]

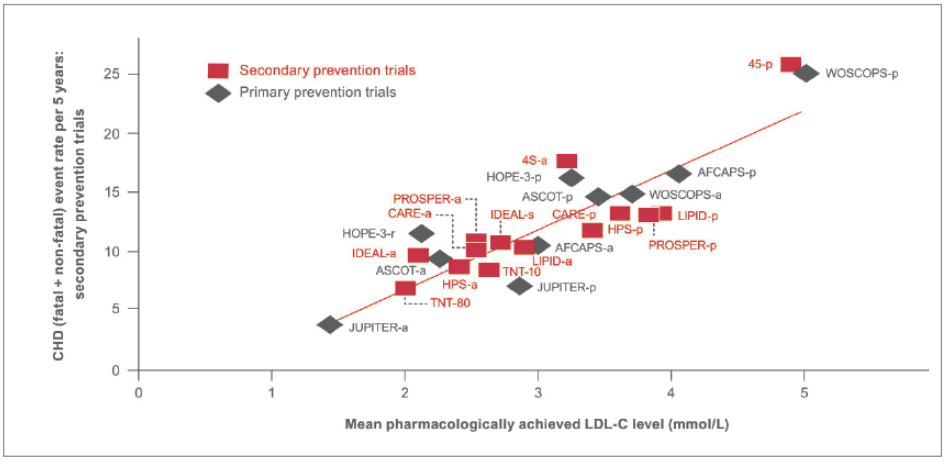


Figure 2: Relationship between achieved LDL-C and coronary artery disease event rate in lipid lowering trials, adapted from Packard *et al* (2021)[7]

CVD risk management

Assessment of total CV risk is central to CVD management and is recommended internationally by all current guidelines.[5,6,8–10] The overarching principle guiding CVD risk management is that the higher the patient's CVD risk, the more intense interventions should be because the treatment benefit is greatest in those with the highest risk.[6] Management of CVD risk should involve shared decision making with the patient, aided by risk prediction tools, to determine the level of risk at which treatments will be initiated.[6]

Currently in New Zealand, CVD risk assessment and management for people aged 30 to 74 years without prior CVD is based on 5-year CVD risk calculated using the NZ Primary Prevention Equations, derived from the local PREDICT study.[3] Those with prior CVD, familial hypercholesterolaemia (FH), chronic kidney disease (CKD) with an eGFR < 30 mL/min/1.73 m^2, diabetes with overt nephropathy or other renal disease (eGFR < 45 mL/min/1.73 m^2) are estimated to have a 5-year risk of 15% or more. A 5-year CVD events risk of ≥15%, as used in the NZ risk prediction calculators, approximates to a SCORE (Systematic Coronary Risk Estimation system, 10-year fatal CVD) risk of ≥ 10% used in the ESC/EAS guidelines.

Familial hypercholesterolaemia

FH is an inherited autosomal dominant disorder resulting in markedly elevated LDL-C and, if untreated, premature atherosclerosis and coronary artery disease (CAD).[11] The risk of CAD is approximately 20-fold higher in untreated patients with FH than in individuals without FH.[12,13]

The majority of people with FH are undetected and inadequately treated.[11] FH is highly probable in patients with an LDL-C > 5 mmol/L, or an LDL-C 4-5 mmol/L in those with parents with a history of hypercholesterolaemia or premature ASCVD, or an LDL-C > 3.5 mmol/L if a parent carries a pathogenic or likely pathogenic gene.[11] CV risk prediction equations from the general population are not appropriate for people with FH and these patients are assumed to have a 5-year CV risk > 15% requiring intensive individualised lipid management.[6,9,11]

Whereas funding for the newer LDL-lowering agents would be desirable for FH, by far the greatest health benefit would accrue through higher FH detection rates and treatment with high-dose statins and ezetimibe.

LDL-C treatment targets

Several large trials and meta-analyses have demonstrated that the greater the absolute reduction in LDL-C, the greater the reduction in CV risk.[14–17] Furthermore, the benefit of reducing LDL-C levels is not restricted to patients taking statins and there is no LDL-C level identified below which benefit ceases or harm occurs.[6,10] The ESC/EAS therefore now recommend reducing LDL-C levels as far as possible, at least for patients with a high CV risk, with a minimum reduction in LDL-C of 50%, in combination with the patient's individual goal (**Table 1**).[6,10] These lower LDL-C targets have recently been endorsed by the New Zealand Regional Committee of the Cardiac Society of Australia and New Zealand.[18]

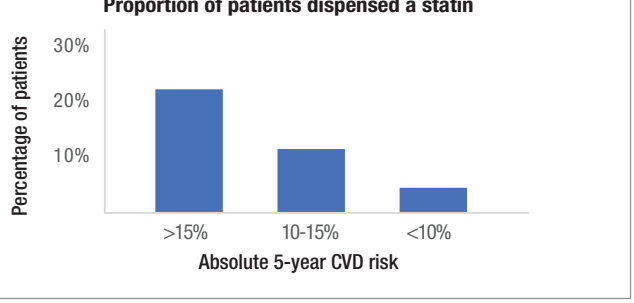


Figure 3: Proportion of PREDICT subsample aged 55-74 years (without CVD) who were dispensed a statin, by CV risk level (2007-2014).[20]

To align with international best practice, health professionals will need to increase the intensity of LDL-C lowering interventions in those at very high risk, as previous New Zealand treatment targets recommend a ≥ 40% reduction in LDL-C and an LDL goal < 1.8 mmol/L for the highest risk patients.[9] Dispensing data shows that statin prescribing is already not commensurate with the CVD risk of the New Zealand population as all patients with a 5-year CVD risk >15% should be taking a statin, unless they are intolerant to treatment (**Figure 3**).[9,19]

Table 1: 2019 ESC/EAS lipid management and CV disease prevention recommendations by patient group[6,10]

All risk categories:

- For high-risk* patients an LDL-C reduction ≥ 50% from baseline and an LDL-C < 1.8 mmol/L is recommended
- In primary prevention, for very-high risk† patients (without FH) an LDL-C reduction ≥ 50% from baseline and an LDL-C < 1.4 mmol/L is recommended
- If the treatment goal is not being met with a maximum tolerated dose of a statin, combination treatment with ezetimibe should be considered
- For patients at very-high risk† who are not achieving their treatment goal on a maximum tolerated statin and ezetimibe dose, combination treatment with a PCSK9 inhibitor should be considered

Diabetes:

- In patients with T2D at high risk*, an LDL reduction ≥ 50% of baseline and an LDL-C < 1.8 mmol/L is recommended
- In patients with T2D at very-high risk†, an LDL-C reduction ≥ 50% of baseline and LDL-C < 1.4 mmol/L is recommended

Secondary prevention:

- For secondary prevention in very-high risk† patients, an LDL reduction ≥ 50% of baseline and LDL-C < 1.4 mmol/L is recommended; an LDL-C < 1.0 mmol/L may be considered if the patient has a second vascular event in 2 years while taking maximal statin therapy
- For patients presenting with an ACS whose LDL-C levels are not at target, despite a maximally tolerated statin and ezetimibe dose, a PCSK9 inhibitor early after the event (in hospital, if possible) should be considered

Familial hypercholestrolaemia:

- For primary prevention in patients with FH and very-high risk† or established ASCVD, an LDL reduction ≥ 50% of baseline and LDL-C goal < 1.4 mmol/L is recommended
- For patients with FH and very-high risk† who are not achieving their treatment goal on a maximum tolerated statin and ezetimibe dose, a PCSK9 inhibitor is recommended
- For secondary prevention in patients with FH who are not achieving their treatment goal on a maximum tolerated statin dose and ezetimibe, combination treatment with a PCSK9 inhibitor is recommended

*High risk is defined as markedly elevated single risk factors (total cholesterol > 8 mmol/L, LDL-C > 4.9 mmol/L, or blood pressure ≥ 180/110 mmHg), or type 2 diabetes (T2D) with target organ damage (with duration ≥ 10 years or another risk factor), or moderate CKD (eGFR 30-59 mL/min/1.73m^2), or FH without major risk factors, or a 10-year risk of fatal CVD ≥ 5% and <10%.

†Very-high risk is defined as documented ASCVD, or T2D with target organ damage (or ≥ 3 major risk factors, or early onset type 1 diabetes of long duration), or severe CKD (eGFR <30mL/min/1.73m^2), or FH with another major risk factor, or a 10-year risk of fatal CVD ≥ 10% (approximates as NZ PREDICT 5-year CVD events risk ≥15%).

N.B. Baseline is the LDL-C level in a patient not taking lipid-lowering medication or the extrapolated baseline value for those currently taking lipid-lowering medication.

Managing cardiovascular risk

A healthy lifestyle is recommended for everyone to reduce CV risk including smoking cessation, regular physical activity, maintaining an optimal bodyweight, and a diet low in saturated fat and rich in wholegrain foods, vegetables, fruit, and fish.[6,9] The American Heart Association recently released a scientific statement which provides evidence-based dietary pattern guidance to promote cardiometabolic health.[21]

Statins

Statins are the first-line lipid-lowering therapy for reducing CV risk, and statin intensification should be considered before initiating combination therapy.[6,9] Statins competitively inhibit the enzyme HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis. Reduction of cholesterol synthesis in the liver and reduction in intracellular cholesterol promotes increased LDL receptor expression on the surface of hepatocytes which leads to increased uptake of LDL from the blood. The degree of LDL-C reduction varies between statins and is dose-dependent.[6] Statin therapy has also been shown to lower triglycerides, raise HDL-C, have anti-inflammatory and antioxidant effects as well as resulting in plaque stabilisation.[6,22]

The evidence supporting the use of statins to reduce LDL-C and CV risk is substantial.[5,6,8,9,23] For example, in the large CTT meta-analysis, a 1.07 mmol/L statin-induced reduction in LDL-C was associated with a 22% reduction in first major vascular events, compared to controls (p<0.0001).[15] This proportional benefit was seen in all subgroups, irrespective of the patient's starting cholesterol. Patients with highest base-line risk experienced the greatest absolute risk-reduction.

The MRC/BHF Heart Protection Study (HPS) enrolled 20,536 adults aged 40-80 years with coronary disease, other occlusive artery disease or diabetes, and randomised them to 40 mg simvastatin daily or placebo.[24] Over the 5-year treatment period there was an 18% relative reduction in coronary death in patients treated with simvastatin, compared to placebo (p=0.0005). For the first occurrence of any major vascular event there was a 24% reduction over the treatment period, compared to placebo (p<0.0001, **Figure 4**). Furthermore, the benefits of simvastatin were additional to any other cardioprotective interventions. It was calculated that among similar high-risk populations, 5 years of treatment with a statin would prevent 70-100 major vascular events per 1000 people treated, regardless of age, sex, or baseline cholesterol.

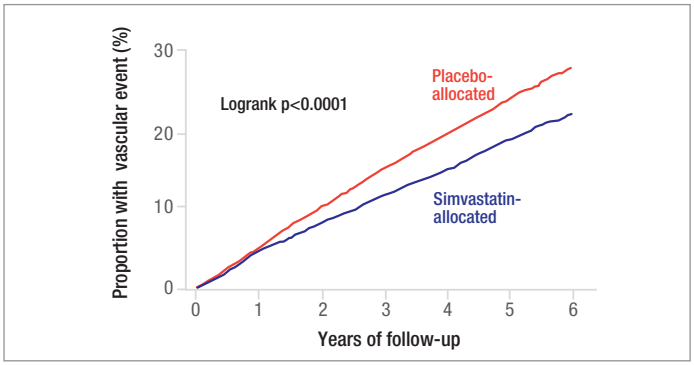


Figure 4: Effects of simvastatin treatment on percentage of patients having major vascular events, compared to placebo, adapted from HPS Collaboration Group (2002)[24]

Standard vs high-intensity statin therapy

Standard statin regimens (e.g. 20–40 mg simvastatin daily) typically reduce LDL-C concentrations by approximately one third, but higher doses of newer, more potent statins (e.g. 40–80 mg atorvastatin or 10–20 mg rosuvastatin daily) can halve LDL-C.[25–28] The CTT Collaboration performed a meta-analysis using individual data from trials comparing intensive versus standard statin regimens.[15] They found in the trials of more versus less intensive statin therapy, the weighted mean further reduction in LDL-C at 1 year was 0·51 mmol/L. Compared with less intensive regimens, more intensive regimens produced a significant 15% (95% CI 11–18; p<0.0001) further reduction in major vascular events, consisting of separately significant reductions in coronary death or non-fatal myocardial infarction (MI) of 13% (95% CI 7–19; p<0.0001), in coronary revascularisation of 19% (95% CI 15–24; p<0.0001), and in ischaemic stroke of 16% (95% CI 5–26; p=0.005).

Rosuvastatin funded with Special Authority

Rosuvastatin is a more potent statin that is capable of greater cholesterol lowering than currently funded statins. From 1 December, 2021, any relevant practitioner, will be able to apply for a Special Authority to prescribe rosuvastatin. Special Authority is available for the following criteria:[29]

- **Reducing CV risk** if the patient is considered at risk of CV disease and is of Māori or any Pacific ethnicity, OR they have a calculated 5-year CV risk ≥ 15% and their LDL-C is not less than 1.8 mmol/L following the maximum tolerated dose of atorvastatin and/or simvastatin.
- **Familial hypercholestrolaemia** if the patient has FH (Dutch Lipid Clinic Network score ≥ 6), AND their LDL-C is not less than 1.8 mmol/L following the maximum tolerated dose of atorvastatin and/or simvastatin.
- **Established CV disease** if the patient has proven coronary artery disease or proven peripheral artery disease or experienced an ischaemic stroke, AND their LDL-C is not less than 1.4 mmol/L following the maximum tolerated dose of atorvastatin and/or simvastatin.
- **Recurrent major CV events** if the patient has experienced a recurrent major CV event in the last two years, AND their LDL-C is not less than 1.0 mmol/L following the maximum tolerated dose of atorvastatin and/or simvastatin.

N.B. A major CV event is defined as MI, ischaemic stroke, coronary revascularisation, or hospitalisation for unstable angina.

Statins and the elderly

Statins are effective for the prevention of CVD in older patients, including those aged >75 years. The CTT collaboration recently provided a comprehensive assessment of the randomised evidence on the effects of statin therapy at different ages.[30] Among 186,854 participants in 28 trials, 14,483 (8%) were aged >75 years at randomisation. Overall, statin therapy produced a 21% relative reduction (RR) in major vascular events (RR 0.79, 95% CI 0.77-0.81) per 1.0 mmol/L reduction in LDL-C, with evidence of significant benefit in all age groups. Of course, patient co-morbidities, frailty, and overall potential to benefit should be considered when prescribing statins and other cholesterol-lowering medications in the elderly.

Statins, adverse effects and adherence

The benefits of statins will only be seen if patients adhere to treatment. In randomised controlled trials (RCTs) there is little difference between statin therapy and placebo in the rates of withdrawal due to adverse events of any kind. These findings suggest that nearly all patients should be able to tolerate statins. The recently published SAMSON study found that the majority of adverse effects caused by statins were nocebo.[31] The nocebo effect is a decrease in subjective benefit, a worsening of symptoms or onset of adverse effects due to an expectation or perception of harm associated with a medicine or other treatment. Clinicians should therefore not interpret symptom intensity or timing of symptom onset or offset (on starting or stopping statin tablets) as indicating pharmacological cause, because the pattern is identical for placebo. Large cohort studies have provided valuable information on withdrawal and reinitiating statins. In one study of 6,579 patients who stopped statins because of an adverse event, statin therapy could be reinitiated in 92% when they were rechallenged.[32] Similarly, a review of 1,605 patients referred to a specialist clinic because of statin intolerance found that statin therapy could be reinitiated in 73% of patients.[33]

Ezetimibe

Ezetimibe inhibits cholesterol absorption in the small intestine through the Niemann-Pick C1-like protein 1 receptor, resulting in an indirect increase in LDL receptor synthesis.[6,10,34] Ezetimibe should be considered if patients with high CV risk are unable to reach their LDL-C treatment goal, despite a maximally tolerated statin dose.[5,6,10] Ezetimibe may also be considered as an alternative LDL-C lowering treatment for patients who cannot tolerate statins.[6,10]

The IMPROVE-IT trial enrolled 18,144 patients who had been hospitalised in the preceding 10 days with an acute coronary syndrome (ACS) with LDL-C levels of 1.3 to 2.6 mmol/L, if they had been taken lipid-lowering treatment, or 1.3 to 3.2 mmol/L

if they had not been taking lipid-lowering treatment.[35] Patients were randomised to either once daily simvastatin 40 mg plus ezetimibe 10 mg, or simvastatin 40 mg plus placebo. The primary endpoint was a composite of CV death, non-fatal MI, unstable angina requiring hospitalisation, coronary revascularisation, or non-fatal stroke, and the median follow-up was 6 years. The median time-weighted average LDL-C during the study in the simvastatin-ezetimibe arm was 1.4 mmol/L, compared to 1.8 mmol/L in the simvastatin monotherapy arm (p<0.001). The primary endpoint event rate at 7 years was 32.7% in the simvastatin-ezetimibe arm, compared to 34.7% in the simvastatin monotherapy arm (p=0.016).

A meta-analysis of 8 RCTs found that ezetimibe monotherapy was associated with a mean reduction in LDL-C of 18.58%, compared to placebo (p<0.00001).[36] Ezetimibe monotherapy was also associated with a 13.46% reduction in total cholesterol, an 8.06% reduction in triglyceride levels, and a 3% increase in HDL-C levels (p<0.00001).[36] In combination with a statin, daily ezetimibe 10 mg was associated with greater reductions in LDL-C, total cholesterol, non-HDL-C, ApoB, and lipid ratios, compared to statin monotherapy (p<0.0001).[37]

Ezetimibe 10 mg tablets are funded under Special Authority for patients with an absolute 5-year risk of CV disease ≥ 15% and whose LDL-C ≥ 2 mmol/L and who have experienced statin induced rhabdomyolysis, or who are intolerant to simvastatin and atorvastatin, or who have not reduced their LDL-C < 2 mmol/L with the maximal tolerated dose of atorvastatin.

Ezetimibe 10 mg + simvastatin (10 mg, 20 mg, 40 mg, 80 mg) tablets are also funded under Special Authority for patients with an absolute 5-year CVD risk ≥ 15% and whose LDL-C ≥ 2 mmol/L and who have not reduced their LDL-C < 2 mmol/L with the maximal tolerated dose of atorvastatin. Ideally, the Special Authority criteria for ezetimibe should be revised to be in line with the new rosuvastatin Special Authority criteria.

PCSK9 inhibitors

A new pathway to reduce LDL-C levels involves inhibiting PCSK9, a protein that is involved in the control of LDL receptors. PCSK9 binds to the LDL receptor preventing it recycling to the cell surface, instead routing it to lysosomes for destruction.[6] Inhibition of PCSK9 therefore increases the number of LDL receptors on hepatocytes that are available to clear circulating LDL-C, thereby lowering LDL-C levels.[6]

To date, the most experience is with the monoclonal antibodies alirocumab (Praluent®) and evolocumab (Repatha®) which inhibit this pathway. More recently, a long-acting small interfering RNA (siRNA) that inhibits the translation of PCSK9 has been developed and is under investigation. Alirocumab and evolocumab are both registered in New Zealand, but currently only alirocumab is available, unfunded, for prescription at a cost of approximately $9000 a year.

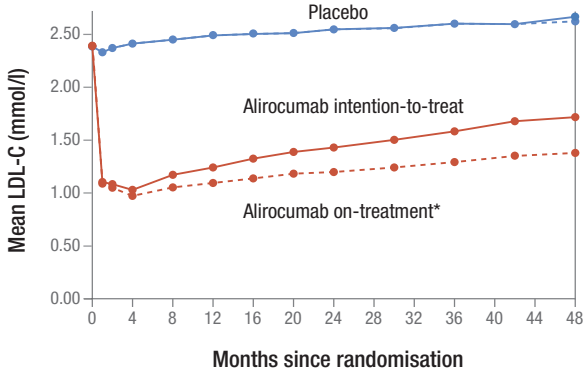
PCSK9 inhibitors are effective in reducing LDL-C levels as monotherapy for those who are intolerant to statins or in combination with other lipid-lowering medicines for patients who are not meeting treatment targets.[6,10] The average reduction in LDL-C levels is approximately 60% in patients receiving monotherapy, 75% in combination with a high-intensity statin, and 85% in combination with a high-intensity statin plus ezetimibe.[10]

Clinical trials of PCSK9 inhibitors

The ODYSSEY OUTCOMES trial was a multicentre RCT that enrolled 18,924 patients with an ACS in the past 1-12 months and a LDL-C ≥ 1.8 mmol/L, a non-HDL-C ≥ 2.6 mmol/L or an ApoB ≥ 80 mg/dL, and were receiving high-intensity statin treatment or statin treatment at the maximum tolerated dose.[38] Patients were randomised to either subcutaneous alirocumab 75 mg, every two weeks, or matching placebo injections. The primary endpoint was a composite of death from coronary heart disease, non-fatal MI, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospitalisation. The median duration of follow-up for the study was 2.8 years. The primary end-point occurred in 9.5% of the alirocumab group and 11.1% of the placebo group (p<0.001).[38]

On-treatment analysis in the alirocumab group revealed LDL-C levels at 4, 12 and 48 months to be on average 62.7%, 61% and 54.7% lower than the respective time points in the placebo group (**Figure 5**). In a post hoc analysis the absolute risk reduction in the primary endpoint was greatest in patients with a baseline LDL-C ≥ 2.6 mmol/L treated with alirocumab (3.4%, p<0.001).

Subgroup analysis of patients with diabetes or polyvascular disease in the ODYSSEY trial showed that the patients with the highest CV risk benefit the most from aggressive lipid management.[39,40]



*Excluding values measured after discontinuation of alirocumab and after blinded substitution of placebo for alirocumab

Figure 5: LDL-C levels during the ODYSSEY OUTCOMES trial, adapted from Schwartz *et al* (2018)[38]

The FOURIER trial enrolled 27,564 patients with ASCVD and LDL-C levels ≥ 1.8 mmol/L who were taking statins.[14] Patients were randomised to evolocumab (140 mg every 2 weeks or 420 mg a month) or placebo subcutaneous injections, with a median follow-up of 2.2 years.[14] The composite primary end point was CV death, MI, stroke, hospitalisation with unstable angina, or coronary revascularisation.[14] The key secondary composite end point was CV death, MI, or stroke. The least-squares mean percentage reduction in LDL-C at 48 weeks associated with evolocumab was 59%, compared to placebo (p<0.001). The primary end point occurred in 9.8% of patients taking evolocumab, compared to 11.3% in the placebo group (p<0.001). The key secondary end point occurred in 5.9% of patients taking evolocumab, compared to 7.4% in the placebo group (p<0.001). The benefits of lowering LDL-C were consistent regardless of the baseline LDL-C. In patients with the lowest quartile for baseline LDL-C, there was a 22% reduction in the risk of the key secondary end point following a reduction in LDL-C from 1.9 mmol/L to 0.57 mmol/L.

While there is no doubt that the currently available monoclonal antibodies that inhibit PCSK9 are effective, cost remains a significant issue. The cost-effectiveness of these drugs at current prices has been debated. The groups where these drugs are most likely to be cost effective are those at highest absolute risk, such as patients with FH and those with ACS and diabetes or polyvascular disease.

HDL

The inverse relationship between plasma HDL-C and the risk of ASCVD has been consistently observed.[41] However, no study to date has indicated that raising HDL-C with currently available therapies reduces the risk of ASCVD events.[42,43]

Triglycerides

Elevations in plasma triglycerides are associated with an increasing risk of ASCVD.[6] However, plasma triglycerides reflect the concentration of ApoB-containing triglyceride-rich lipoproteins.[6] Multiple studies strongly suggest that the causal effect of triglyceride-rich lipoproteins on ASCVD risk is mediated by the concentration of ApoB-containing particles, rather than by triglyceride concentration *per se*.[6]

TAKE-HOME MESSAGES

- Assessment of total CVD risk is the cornerstone of CV risk management
- Statins and other lipid-lowering therapies are substantially under-prescribed in those with high and very high CV risk
- The lower a patient's LDL-C level, the lower their CVD risk, and there is no LDL-C level identified below which benefit ceases or harm occurs
- Recent international guidelines have reduced LDL-C targets for patients with very high CVD risk, recommending an LDL-C reduction ≥ 50% of baseline and LDL-C < 1.4 mmol/L in this group
- Statins are the first-line lipid-lowering medicine for reducing CV risk
- High-intensity statins with the addition of ezetimibe, where necessary, should be prescribed in those with high CV risk to achieve their LDL-C goal
- Long-term adherence to statins remains a major problem with recent research suggesting the majority of adverse effects caused by statins were nocebo
- Statin therapy can be safely reinitiated in the majority who have stopped treatment due to perceived adverse effects
- PCSK9 inhibitors are very effective and can be considered in those with very high CVD risk who are not meeting their LDL-C targets. However, alirocumab is the only PCSK9 inhibitor available in New Zealand. It is unfunded and cost will limit its use.

EXPERT'S CONCLUDING REMARKS

Therapeutic targets for LDL-C have progressively lowered over the years reflecting the development and availability of new drugs that can achieve these targets and accumulation of a large body of evidence that confirms the dose-dependent relationship with greater absolute LDL-C reduction, the greater the CVD risk reduction. The most recent international guidelines on the management of dyslipidaemia from the ESC/ESA have recommended more aggressive treatment with a further lowering of LDL-C targets, particularly in those at the highest risk. These guidelines have recently been endorsed by the New Zealand Regional Committee of the Cardiac Society of Australia and New Zealand.

The challenge of lipid management is now three-fold. Firstly, to identify patients at high CV risk early and initiate appropriate treatment. Secondly, to achieve recommended treatment targets by prescribing high intensity statin therapy, including recently funded rosuvastatin along with ezetimibe and PCSK9 inhibitors, where appropriate. Thirdly, strategies for improving adherence and rechallenging those patients with perceived adverse effects in the absence of biochemical disturbance are required.

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