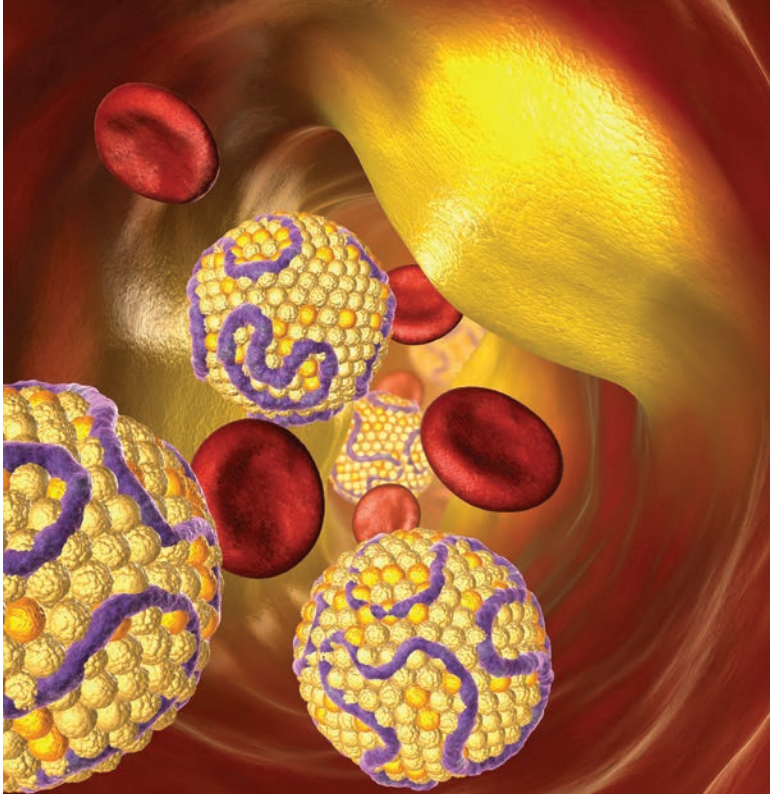

Advances in lipid management
Current challenges and new horizons

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Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide, with elevated low-density lipoprotein cholesterol being a major modifiable risk factor. Effective lipid management is crucial for CVD prevention, yet a substantial proportion of patients do not achieve guideline-recommended lipid goals. This treatment gap underscores the need for implementation strategies to optimise the use of currently available therapies for lipid lowering. Furthermore, the landscape of lipid management is rapidly evolving, with several novel therapies showing promise in clinical trials.

KEY POINTS

- Treatment gaps exist between guideline recommendations for lipid goals and clinical practice.
- There has been a significant evolution of lipid-lowering therapies in the past decade.
- Several safe and effective therapies are available in clinical practice to achieve lipid goals.
- Implementation strategies are needed to optimise lipid management.
- Novel therapies in clinical trials could expand options for lipid-modifying treatment in the future.

Despite being preventable, cardiovascular disease (CVD) continues to be one of the leading causes of death in Australia.[1] Although smoking and diabetes are often the focus of CVD prevention in clinical practice, high cholesterol remains an overlooked yet treatable condition. The INTERHEART study showed that elevated cholesterol and apolipoprotein B (apoB) levels are leading CVD risk factors, accounting for about 50% of the population-attributable risk for myocardial infarction worldwide.[2] Long-term exposure to high plasma levels of apoB-containing lipoproteins, such as low-density lipoprotein (LDL), significantly increases the risk of CVD.[3,4] Randomised controlled trials of LDL-cholesterol (LDL-C)-lowering therapies have shown that every 1 mmol/L reduction in LDL-C safely reduces CVD risk by 20 to 25%, with reductions in risk that accumulate over time.[5] Intensive LDL-C lowering can also stabilise atherosclerotic plaque.[6,7] Therefore, current guidelines recommend lipid goals or thresholds for lipid-lowering therapies that are more intensive than prior guidelines.[8] Similar to the management of hypertension, combination therapies (including polypills for improving adherence to treatments) may be needed to achieve effective lipid lowering in patients at high and very high risk of CVD.[9]

This review discusses the current challenges, treatment options, implementation strategies and new horizons for lipid-focused CVD prevention in Australia.

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The scope of the problem

Several studies have shown gaps between guideline recommendations for lipid lowering and clinical practice. Most patients at high risk of CVD in Australia are not prescribed cholesterol-lowering therapies.[10] Moreover, almost two-thirds of statin-treated patients are not meeting LDL-C goals.[11] In patients with acute coronary syndrome, almost half do not meet lipid goals within 12 months of the event, leaving them at increased residual risk.[12] Despite ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors being safe and effective therapies for LDL-C lowering, their use remains low in patients with CVD, even in tertiary care.[10] There is also scope to improve lipid management in older patients, in Indigenous Australians and in people living in rural or remote areas.[13-15] Furthermore, patients with familial hypercholesterolaemia (FH), a genetic condition affecting about one in 250 people, remain largely undiagnosed and undertreated.[16-18] Patients with FH have an estimated threefold increased risk of premature coronary artery disease.[19] Yet, the roughly 100,000 Australians diagnosed with FH are thought to represent only 10% of the actual burden of this disease.[16]

This current state of undertreatment exists despite the increasing number of safe and effective lipid-lowering therapies. Several factors contribute to suboptimal LDL-C-goal attainment at the clinician, patient and health system level. At the clinician level, contributing factors may include clinician time pressure, competing priorities, therapeutic inertia and limited familiarity with new guidelines and therapies.[20] At the patient level, misinformation about medications, cost, difficulty accessing or adhering to medication, and side effects are important factors.[21,22] At the health system level, lack of multidisciplinary lipid clinics, lack of standardised procedures and health alerts, and delays in accessing healthcare are potential factors.[22] There is also a need to improve access to effective lipid-lowering therapies through the PBS.[21]

The current state of play

The European Society of Cardiology (ESC) 2019 Guidelines recommend that patients at very high risk of CVD achieve at least a 50% reduction in LDL-C from baseline, with an LDL-C goal of less than 1.4 mmol/L.[8] Patients at high risk should aim for at least a 50% reduction in LDL-C from baseline and an LDL-C goal of less than 1.8 mmol/L.[8]

The wider acceptance of nonfasting blood samples for lipid assessment may make lipid testing more acceptable to patients, leading to more routine testing to meet lipid goals.[23] Although more therapies are now available for lipid lowering, lifestyle management with dietary modifications and increased physical activity remains the cornerstone of treatment.[8] In addition, addressing secondary causes of dyslipidaemia like obesity, diabetes mellitus and alcohol excess is imperative.

This current state of undertreatment exists despite the increasing number of safe and effective lipid-lowering therapies

Statins remain the mainstay of lipid-lowering therapy, having been proven safe and effective in lowering LDL-C levels and reducing CVD events in primary and secondary prevention.[8] However, there has been new emphasis on a high-intensity lipid-lowering therapy strategy, particularly in patients at high and very high risk of CVD.[9] Available therapies in Australia that can be added to statins for LDL-C lowering include ezetimibe, bile-acid sequestrants and PCSK9-directed therapies (Table 1).[18,24,25]

Ezetimibe is well tolerated and has been shown to reduce CVD events.[26] Upfront combination of moderate doses of statins plus ezetimibe in patients at high risk may improve outcomes and has fewer adverse effects compared with high-dose statin monotherapy.[9,27] The PBS has recently removed the authority restrictions on prescribing ezetimibe, which allows for earlier use of combination therapy (https://www.pbs.gov.au/pbs/search?term=ezetimibe).

Bile-acid sequestrants are rarely used owing to their gastrointestinal side effects, impact on fat-soluble vitamin absorption and medication interactions.[28]

Statin intolerance is an important issue, with ezetimibe and PCSK9-directed therapies being alternative options. Nutraceutical regimens (such as plant sterols, red yeast rice and berberine) have a modest effect in lowering LDL-C levels and are another alternative for patients with statin intolerance.[8]

The PCSK9-directed therapies currently available in Australia are the monoclonal antibody evolocumab and the small interfering RNA (siRNA) inclisiran. Evolocumab is administered subcutaneously every two or four weeks by the patient and can reduce LDL-C by 50 to 60% when added to a statin.[8] The triple combination of a high-intensity statin, ezetimibe and a PCSK9 monoclonal antibody can achieve, on average, an 85% reduction in LDL-C from baseline.[8] Inclisiran can reduce LDL-C by 50% in patients on statin therapy and was listed on the PBS in April 2024.[29] It reduces the hepatic production of PCSK9 at the RNA level and is highly specific to the hepatocyte, leading to few off-target effects. With its long duration of action, inclisiran is administered subcutaneously by a healthcare professional every six months after the day 1 and day 90 doses. Longer-term data for PCSK9-directed therapies have shown safety and efficacy.[30,31]

Fibrates have a role in reducing triglyceride levels, especially in preventing pancreatitis in patients with extreme hypertriglyceridaemia (>10 mmol/L).[32] Fenofibrate can reduce the progression of microvascular disease in patients with diabetes.[32] However, a recent CVD outcome trial of pemafibrate (not available in Australia) did not show a reduction in CVD events in patients with diabetes, hypertriglyceridaemia, low high-density lipoprotein-cholesterol (HDL-C) levels and well-controlled LDL-C.[33] Niacin and mixed formulations of omega-3 fatty acids

TABLE 1. CURRENTLY AVAILABLE LIPID-LOWERING PHARMACOTHERAPIES IN AUSTRALIA[18,24,25]

Drug/drug group	Target/mode of action	Dosing	Availability on PBS*	Main effects	Examples of potential adverse effects
Statin	HMG-CoA reductase inhibitor	Oral, daily	Several agents available	LDL-C • 25–55% reduction Triglycerides • 10–20% reduction	Elevated liver enzymes, statin-associated muscle symptoms, GI symptoms, risk of diabetes
Ezetimibe	NPC1L1 inhibitor	Oral, daily	Monotherapy or combination therapy with rosuvastatin, atorvastatin or simvastatin	LDL-C • 15–25% reduction	GI symptoms, higher incidence of elevated liver enzymes, dizziness
Colestyramine	Bile-acid sequestrant	Oral, daily	PBS restriction: primary hypercholesterolaemia with GP Management Plan/Team Care Arrangement	LDL-C • 15–25% reduction Triglycerides • May increase levels	GI symptoms, impaired absorption of fat-soluble vitamins, decreased absorption of medications
Evolocumab (note alirocumab is no longer available in Australia)	PCSK9 monoclonal antibody	Subcutaneous injection every 2 weeks	PBS authority: • Homozygous FH • Heterozygous FH • Non-FH with symptomatic CVD, high CV risk and LDL-C >1.8 mmol/L on maximal tolerated statin + ezetimibe	LDL-C • 50–60% reduction Lp(a) • 20–30% reduction	Injection site reactions, flu-like symptoms, nasopharyngitis, back pain
Inclisiran	PCSK9 small interfering RNA	Subcutaneous injection on day 1, day 90 and then 6-monthly	PBS authority: • Heterozygous FH • Non-FH with symptomatic CVD, high CV risk and LDL-C >1.8 mmol/L on maximal tolerated statin + ezetimibe	LDL-C • About a 50% reduction Lp(a) • 20–30% reduction	Injection site reactions, bronchitis/nasopharyngitis
Fibrate (fenofibrate, gemfibrozil)	PPAR alpha agonist	Oral, daily	Available on PBS	Triglycerides • 25–50% reduction HDL-C • 10–30% increase	GI symptoms, gallstones, elevated liver enzymes, higher incidence of myopathy when used with statin
Icosapent ethyl (purified eicosapentaenoic acid)	Triglycerides	Oral, twice a day	PBS authority: • Established CVD, on statin treatment, LDL-C of 1.0–2.6 mmol/L and fasting triglycerides of 1.7–5.6 mmol/L	Triglycerides • About a 20% reduction	Atrial fibrillation, GI symptoms, bleeding

Abbreviations: CV = cardiovascular; CVD = cardiovascular disease; FH = familial hypercholesterolaemia; GI = gastrointestinal; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NPC1L1 = Neimann-Pick C1-like 1 protein; PCSK9 = proprotein convertase subtilisin/kexin type 9; PPAR alpha = peroxisome proliferator-activated receptor alpha.
* Refer to the Schedule for full details.

have also not been shown to reduce CVD events and are therefore not routinely recommended for CVD prevention.[34-38]

Conversely, icosapent ethyl (IPE), a highly purified eicosapentaenoic acid, has been shown to reduce CVD events in patients with established CVD or diabetes and additional risk factors and with residual hypertriglyceridaemia despite statin therapy.[24] It has been approved by the Therapeutic Goods Administration and was listed on the PBS in October 2024 (https://www.pbs.gov.au/pbs/search?term=icosapent+ethyl). It is cost-effective and recommended by international guidelines for hypertriglyceridaemia.[25,32,39] Although IPE can increase the risk of atrial fibrillation and bleeding, these potential adverse events are outweighed by the benefits of treatment in reducing total CVD events.[40] Notably, IPE also has antithrombotic and anti-inflammatory effects and its CVD benefits are independent of triglyceride lowering.[24,41]

TABLE 2. EXAMPLES OF LIPID-LOWERING PHARMACOTHERAPIES IN CLINICAL TRIALS TARGETING LIPOPROTEIN(A) OR TRIGLYCERIDE-RICH LIPOPROTEINS[46,47]

Target	Mechanism	Drug(s)	Dosing	Effect*
Lp(a)	ASO that inhibits mRNA and synthesis of apo(A)	Pelacarsen	Subcutaneous injection every 4 weeks	About an 80% reduction in Lp(a)
	siRNA that inhibits mRNA and synthesis of apo(A)	Olpasiran Lepodisiran Zerlasiran	Subcutaneous injection ranging from every 12-24 weeks depending on the therapy	>80–90% reduction in Lp(a)
	Small molecule inhibitor of apo(a) binding to apoB	Muvalaplin	Oral, daily	>80% reduction in Lp(a)
ApoC3	ASO that inhibits mRNA and synthesis of apoC3	Olezarsen	Subcutaneous injection every 4 weeks	40–50% reduction in triglycerides
	siRNA that inhibits mRNA and synthesis of apoC3	Plozasiran	Subcutaneous injection every 12 weeks	50–60% reduction in triglycerides (80% reduction in patients with chylomicronaemia)
ANGPTL3	siRNA that inhibits mRNA and synthesis of ANGPTL3	Zodasiran	Subcutaneous injection every 12 weeks	50–60% reduction in triglycerides
		Solbinsiran	Awaiting results of phase II trial results	Awaiting results of phase II trial

Abbreviations: ANGPTL3 = angiopoietin-like 3; apoA = apolipoprotein A; apoB = apolipoprotein B; apoC3 = apolipoprotein C3; ASO = antisense oligonucleotide; Lp(a) = lipoprotein(a); mRNA = messenger ribonucleic acid; siRNA = small interfering ribonucleic acid.
* Adverse effect profile to be reported in longer/larger studies.

The promise of novel lipid-lowering therapies

LDL-C currently remains the primary target in clinical practice. However, there are other apoB-containing lipoproteins, such as triglyceride-rich lipoproteins and lipoprotein(a) [Lp(a)], that are causally associated with CVD.[42-45] Genetic studies and advances in drug development have led to several novel lipid-lowering therapies that target these atherogenic apoB-containing lipoproteins and are in clinical trials (Table 2).[46,47] CVD outcome trials, as well as safety, acceptability and cost-effectiveness data, are crucial to enable such therapies to enter clinical practice. The long duration of action, especially with siRNA therapies, allows less frequent dosing regimens and potentially greater patient convenience.

In terms of targeting LDL-C, bempedoic acid has been shown to reduce CVD events compared with placebo in patients with statin intolerance.[48] It is another alternative for patients with statin intolerance. It is available in the USA and Europe but currently not available in Australia. The future of LDL-C lowering also includes oral PCSK9 inhibitors.[49] Other highly targeted therapies against PCSK9, such as vaccines and gene editing using CRISPR-Cas9, are in development.[50,51] Further research is needed to resolve questions on bioethical issues, safety and costs, especially for gene editing therapies.

Lp(a) is an LDL-like particle that is genetically determined and its levels can be modestly lowered by PCSK9-directed therapies but are not lowered by statins.[43] In the absence of specific Lp(a)-lowering therapies, current guidelines recommend intensive CVD risk-factor management in patients with elevated Lp(a) levels.[43,52] RNA therapies that reduce the hepatic production of apolipoprotein(A) and which reduce Lp(a) level by more than 80 to 90% are currently in clinical trials. These therapies include the antisense oligonucleotide (ASO) therapy, pelacarsen, and siRNA therapies, such as olpasiran, zerlasiran and lepodisiran.[53-56] CVD outcome trials of pelacarsen, olpasiran and lepodisiran are ongoing and will answer whether Lp(a) lowering reduces CVD events. Oral Lp(a) inhibitors such as muvalaplin are also in clinical trials.[57]

The future of triglyceride lowering includes agents that target apolipoprotein C3 (apoC3) and angiopoietin-like protein 3 (ANGPTL3), as these proteins regulate triglyceride-rich lipoprotein metabolism. Agents in clinical trials targeting apoC3 include the ASO therapy, olezarsen, and the siRNA therapy, plozarisan, both of which can reduce triglyceride levels by more than 50 to 60%.[58,59] The monoclonal antibody against ANGPTL3, evinacumab, is approved overseas for homozygous FH, but is not available in Australia, while siRNA therapies against ANGPTL3, zodasiran and solbinsiran are in clinical trials.[60-62]

Familial chylomicronaemia syndrome, another under-recognised inherited lipid disorder affecting about one to 10 in one million people and causing severe hypertriglyceridaemia, increases the risk of pancreatitis and is inadequately treated by current lipid-lowering therapies.[63] Agents targeting apoC3 can significantly reduce triglycerides and the risk of pancreatitis in patients with chylomicronaemia.[64,65]

HDL-C, the so-called 'good cholesterol' because of its inverse association with CVD, remains another potential therapeutic target. However, trials evaluating therapies that increase HDL-C levels have not shown reductions in CVD events.[66] In addition, a recent trial evaluating CSL112, a therapy that increases cholesterol efflux, found that it did not significantly improve CVD outcomes when administered after acute myocardial infarction.[67] Obicetrapib, an oral inhibitor of cholesteryl ester transfer protein (CETP), which increases HDL-C levels, is currently being studied in a CVD outcomes trial in patients at high risk of CVD.[66,68] However, the potential impact of CETP inhibitors on CVD events may be mediated by the associated reductions in LDL-C.[66,68] The care of people with genetically very low HDL-C levels, who are at increased risk of CVD, remains an unmet need and requires further clinical trials of HDL-targeted therapies.[66]

What needs to change

Updated guidelines on lipid management are overdue given that the last Australian guideline on overall care of patients with lipid disorders was published in 2005.[69] The recently published 2025 Heart Foundation and Cardiac Society of Australia and New Zealand (CSANZ) guidelines on managing acute coronary syndrome provides more guidance on lipid lowering for secondary prevention.[70] The FH Australasia Network published a guideline on enhancing the care of FH in 2020 and the Australian Atherosclerosis Society published a position statement on elevated Lp(a) in 2023.[16,52] Furthermore, the International Atherosclerosis Society consensus statement on triglyceride management was published in 2024.[25] As we are now in 2025, broader national guidelines for lipid management that reflect contemporary evidence are needed. Provision of short focused 'how to' articles for practical lipid management in the Australian context specifically for primary care is also important. The impact of the new Heart Foundation's 2023 CVD risk calculator could be enhanced with updated guidelines for lipid management as well as updated guidelines for hypertension.[71]

The growing availability of lipid-lowering therapies offers clinicians and patients more options and flexibility, enabling personalised care plans. However, in Australia many of these new therapies are not accessible for routine clinical use (e.g. bempedoic acid and evinacumab) or are accessible only through clinical trials. Nonetheless, it is crucial to make full use of currently available therapies and ensure better adherence to both lifestyle changes and medications, as many patients who could benefit from available treatments are still not receiving them. To address these gaps, implementation strategies with a comprehensive, multifaceted and interdisciplinary approach is needed.[21,22] In 2022, the Global Heart World Federation Cholesterol Roadmap laid out priorities for lipid management in CVD prevention, with the aim of lowering lifetime exposure to LDL-C at a population level.[72,73] Strategies include:

- screening for FH
- recognising at-risk individuals with CVD risk scoring
- prioritising LDL-C lowering with lifestyle and pharmacotherapy
- improving access to therapies
- educating patients and clinicians
- promoting public policy.[72,73]

The currently available lipid-lowering therapies can potentially enable the attainment of guideline-recommended lipid goals. However, a clear action plan for the care of patients with lipid disorders in Australia needs to be developed and implemented nationally with key policy makers to further reduce the burden of CVD.[73] The action plan requires further investment and collaboration at the patient, GP, specialist, allied health, health system and policy levels.

Conclusion

Despite the crucial role of lipid lowering in CVD prevention, many patients are not achieving guideline-recommended lipid goals, highlighting the need for a clear action plan on management of lipid disorders. The current armamentarium of lipid-lowering therapies is underutilised, and further strategies are required at every level of healthcare to optimise their use. Looking ahead, the addition of novel lipid-modifying therapies against a broad range of targets heralds a new era of precision preventive medicine. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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