Evolving worldwide approaches to lipid management and implications for Australian general practice

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Background
Guidelines on lipid disorders are constantly evolving. General practitioners regularly face critical decisions about the best treatment strategies for individual patients. Cardiovascular disease (CVD) is common, with most morbidity and mortality due to atherosclerosis. Raised low-density lipoprotein cholesterol (LDL-C) is the most atherogenic component – lowering it lowers the risk of future cardiovascular events.

Objective
The aim of this article is to provide an evidence-informed summary of national guidelines and recent research to help clinicians reduce the risk of atherosclerotic CVD and improve health service delivery through improved lipid management strategies.

Discussion
Elevated plasma lipids, especially LDL-C, increase the likelihood of a CVD event over time. Knowledge of family and personal histories plus other risk factors for CVD should alert clinicians to the need for treatment. The greater the overall burden of combined risk factors, the greater the lifetime risk. This update provides new information that informs future approaches for improving lipid management in Australian general practice.

GUIDELINES on assessing and managing lipid disorders are constantly evolving as new knowledge and treatments emerge to help health professionals and patients decide the best course of disease management.

As the point of first contact with the health system, general practitioners (GPs) are uniquely placed to see, assess and prevent disease in the early stages of development.[1] The care provided by GPs can extend to families and communities and involves contact across multiple generations, yielding opportunities for unique insights into the family histories and the biopsychosocial dynamics affecting individual patient risk and disease presentations.[2]

Lipid disorders are commonly managed in general practice but their severity and optimum treatment options may not always be appreciated or updated. As patients progressively age, many develop multiple chronic conditions, with multimorbidity the norm as people progress beyond their middle years.[3,4]

Younger people gain most if signs and risk factors of cardiovascular disease (CVD) are detected early and preventive actions tailored to their overall risk are enacted.[5] Lower-risk patients can be advised of diet and other lifestyle strategies to maintain their status quo while those with lipid disorders often need additional strategies.[6,7]

CVD accounted for 14% of Australia's total burden of disease in 2015, with 27% of deaths attributed to CVD in 2017.[8] Raised blood lipids are just one of multiple modifiable risk factors for CVD, all of which deserve appropriate consideration for treatment.[9]

The aim of this article is to review international lipid management guidelines focusing on recommendations of relevance to the primary care management of lipid disorders.

Lipid disorders

Lipid disorders are increasingly prevalent in the modern world, due primarily to poor diet and unhealthy, sedentary lifestyles; they can also be secondary to other disease conditions and treatments. Left untreated, lipid disorders can progress to severe CVD and predispose to other conditions such as diabetes, non-alcoholic fatty liver disease, chronic kidney disease (CKD) and pancreatitis.

Lipids are a component of plasma lipoproteins and can be subject to abnormalities in their metabolism due to genetic and environmental factors resulting in elevated levels of cholesterol or triglycerides. Such abnormalities can occur at any stage of the continuum, from synthesis through processing and

clearance, resulting over time in increased risk of CVD.[10]

Cholesterol and triglyceride are the two major forms of lipid found in the body. Both are carried in lipoproteins in the blood. Cholesterol is used mainly in cell membrane formation as well as in bile acids and in steroid hormones.

Hypertriglyceridaemia has strong environmental and genetic causes. High triglyceride levels can lead to increased CVD risk, pancreatitis and hepatic steatosis.[11] Levels up to 1.7 mmol/L are normal while >10 mmol/L increases risk of pancreatitis and hepatic steatosis. It is important that fasting blood levels are taken, as levels are highest after meals. After a trial period of diet and exercise, it is recommended that a fasting triglyceride test is repeated.[11]

Common causes are sugary foods, inactivity, excess alcohol/binge drinking, smoking, certain conditions (eg diabetes, kidney and thyroid disorders), medications such as thiazide diuretics, steroids, oestrogen and tamoxifen, and inheritance. Obesity and the metabolic syndrome are other complicating factors that need to be considered.[11,12]

Among the inherited hypercholesterolaemias, heterozygous familial hypercholesterolaemia (HeFH) is an often-missed, autosomal dominant, hereditary disorder with high phenotypic penetrance that is present in approximately 1:250 people in the general population.[5,13,14] Dominant forms of familial hypercholesterolaemia are also caused by *APOB* mutations and proprotein convertase subtilisin/kexin type 9 (PCSK9) gain-of-function mutations causing markedly elevated low-density lipoprotein cholesterol (LDL-C) levels related to defective LDL receptor activity in liver cells, leading to premature CVD and death if untreated.[13–16] HeFH is recognised worldwide as a major public health problem[13,14] with 50% of first-degree relatives harbouring the disease.

Homozygous familial hypercholesterolaemia (HoFH) is a much more serious condition affecting 1:300,000 people. It results from the union of two HeFH carriers, with 25% of their offspring inheriting the homozygous form.[13,14] Such children have markedly elevated LDL-C from birth and rarely survive beyond teenage years unless aggressively treated from infancy.[5,13,14]

Elevated lipoprotein(a) is a dominantly inherited disorder leading to accumulation in plasma of lipoprotein(a) particles[17,18] affecting 20% of the population. A high level (>50 mg/dL) increases the risk of coronary and peripheral artery disease, calcific aortic stenosis and strokes. Testing is not listed on the Medical Benefits Schedule in Australia and is currently undertaken mostly by lipid specialists if there is a family history of heart disease.

Up to 30% of patients with HeFH have elevated lipoprotein(a).[17] There is currently no specific treatment other than lipoprotein(a) apheresis but RNA-based therapies that target the hepatic over-production of apolipoprotein(a) and the formation of lipoprotein(a) particles are under investigation.[17,18]

A comparison of heritable lipid disorders, including prevalence, mutations and epidemiology, is presented in Table 1.

Cardiovascular disease risk assessment

Approaches to assessing cardiovascular risk have moved from determining individual risk factors to a more global perspective involving absolute risk calculations.[6,19] Absolute risk determines the percentage probability of an individual having a major cardiovascular event in the next 5–10 years. The target group are

Table 1. Summary of inherited lipid disorders

Type	Heterozygous (Homozygous familial hypercholesterolaemia)	Lipoprotein(a)	Familial combined hyperlipidaemia	Familial hypertriglyceridaemia	Type III familial dysbetalipoproteinaemia	Familial chylomicronaemia syndrome
Inheritance	Monogenic co-dominant		Polygenic with variable penetrance and secondary causes, environmental factors			Monogenic, recessive
Prevalence	1 in 250 (1 in 300,000)	1 in 5	1 in 100	1 in 500	1 in 5000	13 per million
Effect on lipids	Elevated LDL	Elevated lipoprotein(a)	Elevated LDL-C, triglyceride, ApoB	Elevated VLDL	Elevated intermediate density lipoprotein	Elevated chylomicrons
Clinical features	Premature CAD	CAD	Premature CAD	CAD, acute pancreatitis	CAD	Recurrent acute pancreatitis
Gene variants	*LDLR, APOB, PCSK9*	*APOA*	Several gene variants	*APOE2/E2*		Deficiency lipoprotein lipase or *APOC-II*

APO, apolipoprotein; CAD, coronary artery disease; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; VLDL, very low-density lipoprotein

those with no known or overt CVD and usually in the 45–74 years age range.

Risk calculators were originally developed using specific variables based on Framingham data to estimate 10-year risk of developing coronary heart disease.[20] The original cohort involved patients to age 70 years, but other versions have been developed to cater for different population and ethnic groups.[21,22]

Apart from patients with known high-risk conditions, the absolute cardiovascular risk assessment tool found at www.cvdcheck.org.au[23,24] should be used for Australian patients aged over 45 years (35–75 years if Aboriginal or Torres Strait Islander) to assess the individual's overall risk. Young Aboriginal patients may need clinical CVD assessment from age 18 years.[25]

Absolute risk assessment uses an algorithm to evaluate the probable impact on CVD events of multiple risk factors.[22] While an absolute risk assessment is more accurate than clinician or patient judgement,[26] relying on the outcome may cause high-risk patients to be mislabelled if an accurate family history is not considered.[2]

Young patients are not accurately assessed with CVD risk calculators developed from patient cohorts aged over 40 while inherited risk (eg familial hypercholesterolaemia) may exist but remain undetected. Postmenopausal women are also at increased risk.[12]

The risk calculator is not appropriate for assessing patients with already known high CVD risk (eg familial hypercholesterolaemia) for absolute CVD risk.[5,13] Their relative risk from the pre-existing condition immediately places them in the highest risk category with atherosclerosis risk present from birth.[5,13,15,16]

Risk enhancers

The role of coronary artery calcium scores (CACs) is receiving increasing attention in guidelines[9,15,16,22,26,27] and can help patient–doctor understanding of an individual's risk. The Cardiac Society of Australia and New Zealand acknowledges a role for CACs in guiding decisions for patients at intermediate risk where a high CAC score re-classifies them at higher risk, whereas a zero score reflects low disease probability.[28]

As well as elevated LDL-C, lipid disorders (apolipoprotein B and lipoprotein(a)) are attracting increasing attention in overall risk estimation and treatment approaches due to synergistic effects on CVD risk.[9,15,16,26]

Inherited factors and secondary causes

It is important to consider the risk of serious hereditary conditions (eg familial hypercholesterolaemia) in patients with a total cholesterol level above 7.5 mmol/L, especially those with a family history of premature coronary artery disease and death.[5,13] An unexpected high total cholesterol level is a prompt for further exploration of the patient's family history.[2,29]

It is important to exclude potential secondary causes of raised cholesterol levels such as hypothyroidism, uncontrolled diabetes, excess alcohol intake, liver disease and nephrotic syndrome.[13,15,16]

A family history of premature CVD or death in a younger patient (age <45 years) should alert the treating doctor to the potential for hereditary factors[16,30] and prompt consideration of random lipid profile (total cholesterol, LDL-C and triglyceride) to assess future CVD risk. Fasting lipids are not required, but it is recommended that a repeat check be fasted if initial results are high.

International approaches to risk assessment

A summary of lipid risk assessment approaches for Australia,[6,7] New Zealand,[27] Canada,[26] UK,[31,32] USA[9,16] and Europe[15] is presented (Appendix 1, available online only).

Evidence from human Mendelian randomisation studies,[33] the Cholesterol Treatment Trialists Collaboration analysis,[34] the Improve-IT[35] and the PCSK9-mAb trials (FOURIER and ODYSSEY)[36,37] on the role of LDL-C in atherogenesis, plaque formation and future cardiovascular events now influences dosage and timing of treatment.

The risk of CVD is no longer seen as an 'LDL-hypothesis' as the evidence increasingly shows LDL-C values are causally related to CVD, and the lower the LDL-C level achieved, the better the outcome.[15,38,39] For each 1 mmol/L reduction in LDL-C achieved, there is a 22% relative risk reduction in cardiovascular events over five years.[34]

In the UK, the National Institute for Health and Care Excellence (NICE) CVD risk guidelines recommend 50% lowering of total cholesterol levels. This is aligned with average fall in large trials.[40] The NICE guidelines,[31] which formerly recommended 'fire and forget', now emphasise more precise clinical practice.

European guidelines originally proposed their target should be to a specific cholesterol level (in other words 'treat to target') based on evidence that the lower the cholesterol levels, the better the health outcomes.[41] More recently, there has been discussion of individualising treatment on the basis of the person's risk status.[40]

While many countries, including Australia, previously favoured a percentage reduction approach, there has been a debate about what cholesterol target should be achieved with lipid lowering treatment. The targets were originally based on LDL-C (<2.6 mmol/L and <1.8 mmol/L for primary and secondary prevention, respectively), but increasingly non-HDL has gained favour.[31,32]

It is important that intensity of treatment reflects the patient's total cardiovascular risk. Increasing age is the most potent driver representing the individual's exposure over time to multiple risk factors. This inherent limitation in CVD risk estimation means that older patients progressively move into high risk categories irrespective of other risk factors.[15,16] Younger people have greater cumulative risk over time[5,15,19] but this may not become manifest until later in life when their CVD may have progressed.

Any lowering of LDL-C brings benefit, even if targets are not reached.[15] Duration of treatment brings cumulative benefit, especially when started early in life.[5,15,42,43] Future medications that target

PCSK9[44] are expected to facilitate LDL-C levels <1.0 mmol/L and this may provide additional cardiovascular benefits.

Risk communication

Risk communication is seen as the critical element in allowing for shared decisions between clinician and patient about future risk management.[9,15,26,27] It is vital that results of risk assessments are delivered to patients and their families/carers at a level appropriate to their circumstances. It is important to stress heart-healthy lifestyle interventions and compliance reinforcement throughout all recommendations.[7,9,26,27] This is enhanced by opportunistic health promotion by GPs at routine consultations.[1]

Increasing age, sex and inheritance are key immutable risk factors.[15,19] Patients aged >75 years who are already on statins should continue.[15,45] It is recommended that children with HeFH commence lifelong treatment from the age of 8–10 years,[5] while statins should be avoided in pregnancy.[13] High-risk adults with HeFH should commence maximally tolerated doses of high potency statins on diagnosis and continue for life.[15,43] It is recommended that relevant specialist advice is sought for the care of children and pregnant women.[5,13]

Other important and potentially modifiable risk factors include smoking; obesity, especially central obesity; poor diet; lack of exercise; social deprivation and isolation; raised blood pressure; diabetes; and lipid disorders.[9,46]

Chronic kidney disease (eGFR <45 mL/min/m^2),[47] severe mental illness (depression, bipolar affective disorder and schizophrenia), use of antipsychotic medications or steroids, obstructive sleep apnoea, atrial fibrillation, heart failure and non-alcoholic fatty liver disease are also important risk factors.[27]

Management

Risk assessment approach

Most patients without overt CVD can have risk assessment undertaken using a global risk calculator. Those with known CVD are already at increased risk and benefit from management with aggressive treatment. In Australia, all patients with absolute risk >15% for a CVD event in the next five years should be similarly treated, while those with absolute risk of 10–15% plus additional risk factors should also be targeted.[6,7]

Secondary causes for increased lipid levels (hypothyroidism, CKD, poorly controlled diabetes, alcohol abuse and liver disease) require individual assessment and management.

Lifestyle modifications

A healthy lifestyle is encouraged for all patients for both primary and secondary prevention. This includes regular physical exercise, a heart-healthy diet, avoidance of obesity and smoking cessation.[7]

It is important that support for smoking cessation be central to lifestyle modification. All guidelines recognise smoking as a key risk factor in CVD minimisation,[5–7,9,15,26,27,31] particularly for young patients with hereditary disorders, HeFH and HoFH.[5]

A key dietary approach is the use of mono- and poly-unsaturated fats and wholegrains instead of saturated fats and refined carbohydrates to help reduce LDL-C levels. A Mediterranean-style diet,[48] which includes nuts and olive oil, can complement medication in achieving treatment goals.

Exercise recommendations consist of 150 minutes per week of moderate exercise or 75 minutes of more vigorous exercise together with muscle strengthening exercises twice weekly. Joining group classes or clubs to encourage swimming, walking, cycling, dancing or gym attendance can be helpful.[2,6,7]

Weight management targets body mass index of 25 kg/m^2 with waist circumferences of <94 cm in men and <80 cm in women.

Alcohol intake should be a maximum of two standard drinks per day, with two to three alcohol-free days per week encouraged.

The active support of GPs can be critical to ensure patients adhere to agreed treatment plans and help to guarantee the sustainability of the approach.[2,6,49]

Cholesterol targets and pharmacotherapies

A summary of international approaches to treating elevated cholesterol levels is shown (Appendix 2, available online only). A comparison of medications and their effects is also included (Table 2).

Patients requiring help with raised lipids can be advised that statin treatment has the most powerful evidence from robust clinical trials based on outcomes research.[50,51]

Statins

Statins have been for decades the main primary prevention treatment for CVD in patients with significant hypercholesterolaemia as well as for patients aged 40–75 years with diabetes or higher CVD risk.[6,7,9,13,15,16,26,27,32] LDL-C is the dominant form of atherogenic cholesterol and the mainstay of treatment.

Lipid management for secondary prevention of CVD will involve pharmacotherapy with high intensity statins at doses higher than used for primary prevention.[13,15–16]

There is increasing evidence that high intensity statins (atorvastatin 80 mg and rosuvastatin 40 mg) are capable of more substantial lowering of LDL-C levels, resulting in greater reductions in CVD.[39] The new approach from European and American guidelines is the lower the LDL-C level, the better the outcome for the patient.[9,15,16,34]

Intolerance

Patient resistance to statins can occur but major side effects, especially in randomised trials, are rare.[13,15,34] Potential statin adverse effects include myopathy, mild elevation of alanine aminotransferase and some medication interactions involving cytochrome P450 pathways. It is important to avoid statins in combination with gemfibrozil, while combination with fenofibrate carries very low myopathy risk.[15] Statin treatment can precipitate new-onset diabetes mellitus, linked to medication potency and concomitant obesity and insulin resistance.[9] For patients with an adverse reaction to statin, 70% will tolerate an alternative regimen.[13]

Non-statins

Non-statin lipid-lowering medications include ezetimibe and PCSK9 inhibitors.[52] Ezetimibe, which inhibits cholesterol absorption from the gut, has a low incidence of side effects and can be used in combination with a statin[13,35] or alone to achieve a 13–20% LDL-C lowering. Patients resistant to statin treatment can try ezetimibe prior to re-introducing a low dose statin later.[9,13,16]

PCSK9 inhibitors evolocumab and alirocumab have been registered in Australia with evolocumab on the Pharmaceutical Benefits Scheme[53] according to strict revised criteria for both familial hypercholesterolaemia and non–familial hypercholesterolaemia patients from 1 May 2020.

If PCSK9 inhibitors are added to a statin, the overall effect can produce reductions of 43–64% in LDL-C levels.[36,37] Because PCSK9 inhibitors cross the placenta, they are not suitable for use in pregnancy and are not licensed for use in children. A downside to their use is cost plus 2–4-weekly injections. No adverse effects for diabetes or neurocognition have been found.[54]

Some newer medications undergoing clinical trials include inclisiran, which targets PCSK9 via small interfering RNA.[44]

Table 2. Comparison of lipid-lowering drugs

Medication/ class	Typical effect on lipids	Tolerability	Dose frequency	Comments
Statins	Reduce LDL 25–55% Reduce triglycerides 10–20%	Well tolerated	Once daily	Medications of choice; most effective oral LDL-lowering agents with best supporting evidence Reduce risk of MI, stroke and mortality in patients at high risk of cardiovascular disease (with or without coronary heart disease) A 1 mmol/L decrease in LDL reduces rates of coronary death by 20% and non-fatal MI by 27%
Colestyramine (bile acid binding resin)	Reduces LDL 15–25% May increase triglycerides	GI disturbances common Poorly tolerated	1–4 times daily	May be used in combination treatment (in low dose), for example when a statin alone is inadequate
Ezetimibe	Reduces LDL 15–25%	Well tolerated	Once daily	Option when statins are contraindicated or not tolerated May be added to a statin when statin alone is insufficient
Fibrates	Reduce LDL 5–15% (>25% with fenofibrate) Increase HDL 10–30% Decrease triglycerides 40–80%	GI disturbances common Gallstones	1–2 times daily	Used in severe hypertriglyceridaemia (triglycerides >10 mmol/L) to prevent pancreatitis LDL may increase in pure hypertriglyceridaemia
Fish oils (omega-3 fatty acids)	Lower triglycerides when taken daily in doses containing 2–4 g omega-3 fatty acids Do not reduce LDL	Few adverse effects High doses may increase bleeding time	1–3 times daily	Used in hypertriglyceridaemia or with LDL-lowering medications in mixed hyperlipidaemia Content varies between products To obtain 2–5 g omega-3 fatty acids daily may require >6 capsules daily
Nicotinic acid	Reduces LDL 15–30% Reduces triglycerides 25–40% Increases HDL 20–35%	Poorly tolerated Flushing	3 times daily	May be used for hypertriglyceridaemia or in combination therapy for mixed hyperlipidaemia (if tolerated)
PCSK9 inhibitors	Reduce LDL 60% (alone or with statins) Evolocumab reduces LDL 20–30% in homozygous familial hypercholesterolaemia Increase HDL	Appear well tolerated Injection site reactions may occur	Once every 2–4 weeks	SC injection, reduce ischaemic cardiovascular events (when used with statins) in patients with cardiovascular disease Option in familial hypercholesterolaemia, usually in combination with maximally tolerated statins Use is limited by high cost Long-term safety data are lacking

GI, gastrointestinal; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; SC, subcutaneous
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These medications offer considerable hope for the future, especially potential reduced costs and twice annual dosage requirements.

Bile acid sequestrants act indirectly by binding to bile acids in the intestine to prevent the reabsorption of both the medication and cholesterol into the blood.[15] They can reduce LDL-C by 15–30% but cause constipation and risk increasing triglyceride levels if baseline levels are raised.[15]

Fibrates produce small reductions in LDL-C levels among patients with normal triglycerides and have benefits for some patients with severe hypertriglyceridemia.[16] Triglyceride levels >10 mmol/L are associated with increased risk of pancreatitis[11] with levels <1.7 mmol/L advised. In addition to dietary and lifestyle advice, statins are the optimum medication treatment and can be combined with fenofibrate[15] to reduce hepatic production of very low-density lipoproteins and hasten removal of hypertriglyceridaemia from the blood.

Fish oil supplements[15] (2–4 g daily) can lower hypertriglyceridemia. They do not reduce LDL-C and have few side effects but may require more than six capsules daily to achieve effective dose levels (Table 2).

Niacin is now rarely used[26] because of adverse effects including liver damage and strokes.

Other areas of interest

Nutraceuticals are food-type products that may have potential as fourth-line adjuncts to standard lipid pharmacotherapy or in patients with statin resistance or statin-associated muscle symptoms[55,56] but to date there is no evidence they reduce atherosclerotic CVD events. Their mode of action is not well defined.

Apheresis is used in specialist lipid centres for difficult-to-manage, high-risk patients (eg HoFH, severe HeFH or those with high lipoprotein(a) levels) to separate disease-provoking components from their plasma, with the remaining blood then returned to the patient.[14,17]

Bempedoic acid is a novel therapy to inhibit cholesterol synthesis that recently completed phase 3 trials. It has been approved by the US Food and Drug Administration for LDL-C reduction therapy for established atherosclerotic CVD and HeFH and is expected to help statin-resistant patients.[57]

Adherence

Adherence to optimum management can be problematic, and a patient-centred approach addressing concerns about medications and potential side effects is recommended. Statin adherence and persistence is often poor, lacking patient benefit if not taken.[42] Initial patient–doctor discussion should seek consensus on treatment need, stratification of risk involved as well as planned approach involving diet, regular exercise, lifestyle changes and potential pharmacotherapy. Supportive counselling from pharmacists as well as new electronic reminder devices, including texting, can also help adherence.[15]

Understanding patient and family health literacy is essential because reinforcement in follow-up visits about the nature of the underlying problem plays a critical part in management outcomes.

Conclusion

Evolving worldwide guidelines and research on lipid management and CVD mitigation show consensus towards tighter control of LDL-C with higher-risk patients requiring earlier diagnosis and more aggressive treatments. Close adherence to diet, lifestyle and medications is underscored and remains a challenge in practice. New lipid treatment targets beyond LDL-C for which specific therapies are being tested are triglyceride-risk, lipoprotein remnants and lipoprotein(a).

Future directions in primary healthcare delivery will need to focus on increasing awareness of how to improve CVD risk assessment among GPs, practice nurses and their patients; early identification of those at highest risk; plus an ability to adjust and meet management strategies as newer, more focused and personalised treatments become available. The new findings presented in this article can positively influence GP clinical decision making and provide a foundation for developing new lipid management guidelines for Australia.

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References

1. Stott NC, Davis RH. The exceptional potential in each primary care consultation. J R Coll Gen Pract 1979;29(201):201–05.
2. Qureshi N, Armstrong S, Dhiman P, et al. Effect of adding systematic history enquiry to cardiovascular disease risk assessment in primary care: A matched-pair, cluster randomized trial. Ann Intern Med 2012;156(4):253–62. doi: 10.7326/0003-4819-156-4-201202210-00002.
3. Brett T, Arnold-Reed DE, Popescu A, et al. Multimorbidity in patients attending 2

Australian primary care practices. Ann Fam Med 2013;11(6):535–42. doi: 10.1370/afm.1570.

4. Starfield B. Challenges to primary care from co- and multi-morbidity. Prim Health Care Res Dev 2011;12(1):1–2. doi: 10.1017/S1463423610000484.
5. Weigman L, Gidding SS, Watts GF, et al. Familial hypercholesterolaemia in children and adolescents: Gaining decades of life by optimizing detection and treatment. Eur Heart J 2015;36(36):2425–37. doi: 10.1093/eurheartj/ehv157.
6. Jackson R. Guidelines on preventing cardiovascular disease in clinical practice. BMJ 2000;320(7236):659–61. doi: 10.1136/bmj.320.7236.659.
7. Tonkin A, Barter P, Best J, et al. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Position statement on lipid management – 2005. Heart Lung Circ 2005;14(4):275–91. doi: 10.1016/j.hlc.2005.10.010.
8. Australian Institute of Health and Welfare. Cardiovascular disease. Canberra, ACT: AIHW, 2020. Available at www.aihw.gov.au/reports/heart-stroke-vascular-disease/cardiovascular-health-compendium/contents/deaths-from-cardiovascular-disease [Accessed 16 December 2020].
9. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;74(10):e177–e232. doi: 10.1016/j.jacc.2019.03.010.
10. Mahley RW, Weisgraber KH, Bersot TP. Disorders of lipid metabolism. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, editors. Williams textbook of endocrinology. 11th edn. Philadelphia, PA: Saunders Elsevier, 2008.
11. Tsuang W, Navaneethan U, Ruiz L, Palascak JB, Gelrud A. Hypertriglyceridemic pancreatitis: Presentation and management. Am J Gastroenterol 2009;104(4):984–91. doi: 10.1038/ajg.2009.27.
12. Watts GF, Ooi EM, Chan DC. Demystifying the management of hypertriglyceridaemia. Nat Rev Cardiol 2013;10(11):648–61. doi: 10.1038/nrcardio.2013.140.
13. Watts GF, Sullivan DR, Poplawski N, et al. Familial hypercholesterolaemia: A model of care for Australasia. Atheroscler Suppl 2011;12(2):221–63. doi: 10.1016/j.atherosclerosissup.2011.06.001.
14. Pang J, Sullivan DR, Brett T, Kostner KM, Hare DL, Watts GF. Familial hypercholesterolaemia in 2020: A leading tier 1 genomic application. Heart Lung Circ 2020;29(4):619–33. doi: 10.1016/j.hlc.2019.12.002.
15. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J 2020;41(1):111–88. doi: 10.1093/eurheartj/ehz455.
16. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73(24):e285–e350. doi: 10.1016/j.jacc.2018.11.003.
17. Tsimikas S. In search of patients with elevated Lp(a): Seek and ye shall find. J Am Coll Cardiol 2019;73(9):1040–42. doi: 10.1016/j.jacc.2018.12.036.
18. Viney NJ, van Capelleveen JC, Geary RS, et al. Anti-sense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): Two randomised, double-blind, placebo-controlled dose-ranging trials. Lancet 2016;388(10057):2239–57. doi: 10.1016/S0140-6736(16)31009-1.
19. Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. N Engl J Med 2012;366(4):321–29. doi: 10.1056/NEJMoa1012848.
20. Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: A historical perspective. Lancet 2014;383(9921):999–1008. doi: 10.1016/S0140-6736(13)61752-3.
21. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and Wales: Prospective derivation and validation of QRISK2. BMJ 2008;336(7659):1475–82. doi: 10.1136/bmj.39609.449676.25.
22. Cooney MT, Dudina A, D'Agostino R, Graham IM. Cardiovascular risk-estimation systems in primary prevention: Do they differ? Do they make a difference? Can we see the future? Circulation 2010;122(3):300–10. doi: 10.1161/CIRCULATIONAHA.109.852756.
23. Australian Chronic Disease Prevention Alliance. Australian absolute cardiovascular disease risk calculator. Sydney, NSW: ACDPA, 2012. Available at www.cvdcheck.org.au [Accessed 16 December 2020].
24. Zomer E, Owen A, Magliano DJ, Liew D, Reid C. Validation of two Framingham cardiovascular risk prediction algorithms in an Australian population: The 'old' versus the 'new' Framingham equation. Eur J Cardiovasc Prev Rehabil 2011;18(1):115–20. doi: 10.1097/HJR.0b013e32833ace24.
25. Agostino JW, Wong D, Paige E, et al. Cardiovascular disease risk assessment for Aboriginal and Torres Strait Islander adults aged under 35 years: A consensus statement. Med J Aust 2020;212(9):422–27. doi: 10.5694/mja2.50529.
26. Allan GM, Lindblad AJ, Comeau A, et al. Simplified lipid guidelines: Prevention and management of cardiovascular disease in primary care. Can Fam Physician 2015;61(10):857–67, e439–50.
27. Ministry of Health. Cardiovascular disease risk assessment and management for primary care. Wellington:NZ: Ministry of Health, 2018.
28. Chua A, Blankstein R, Ko B. Coronary artery calcium in primary prevention. Aust J Gen Pract 2020;49(8):464–69. doi: 10.31128/AJGP-03-20-5277.
29. Bell DA, Hooper AJ, Bender R, et al. Opportunistic screening for familial hypercholesterolaemia via a community laboratory. Ann Clin Biochem 2012;49(Pt 6): 534–37. doi: 10.1258/acb.2012.012002.
30. Brett T, Qureshi N, Gidding S, Watts GF. Screening for familial hypercholesterolaemia in primary care: Time for general practice to play its part. Atherosclerosis 2018;277:399–406. doi: 10.1016/j.atherosclerosis.2018.08.019.
31. National Institute for Health and Care Excellence. Cardiovascular disease: Risk assessment and reduction, including lipid modification. London, UK: NICE, 2016.
32. JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart 2014;100 Suppl 2:ii1–ii67. doi: 10.1136/heartjnl-2014-305693.
33. Ference BA, Majeed F, Penumetcha R, Flack JM, Brook RD. Effect of naturally random allocation to lower low-density lipoprotein cholesterol on the risk of coronary heart disease mediated by polymorphisms in NPC1L1, HMGCR, or both: A 2 × 2 factorial Mendelian randomization study. J Am Coll Cardiol 2015;65(15):1552–61. doi: 10.1016/j.jacc.2015.02.020.
34. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376(9753):1670–81. doi: 10.1016/S0140-6736(10)61350-5.
35. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372(25):2387–97. doi: 10.1056/NEJMoa1410489.
36. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376(18):1713–22. doi: 10.1056/NEJMoa1615664.
37. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379(22):2097–107. doi: 10.1056/NEJMoa1801174.
38. Sabatine MS, Wiviott SD, Im K, Murphy SA, Giugliano RP. Efficacy and safety of further lowering of low-density lipoprotein cholesterol in patients starting with very low levels. JAMA Cardiol 2018;3(9):823–28. doi: 10.1001/jamacardio.2018.2258.
39. Kostner K, Nicholls S, Amerena J, et al. Intensive LDL reduction post acute coronary syndromes: A catalyst for improved outcomes. Heart Lung Circ 2016;25(11):1051–54. doi: 10.1016/j.hlc.2016.09.005.
40. Leibowitz M, Cohen-Stavi C, Basu S, Balicer RD. Targeting LDL cholesterol: Beyond absolute goals toward personalised risk. Curr Cardiol Rep 2017;19(6):52. doi: 10.1007/s11886-017-0858-6.
41. Nayor M, Vasan RS. Recent update to the US cholesterol treatment guidelines: A comparison with international guidelines. Circulation 2016;133(18):1795–806. doi: 10.1161/CIRCULATIONAHA.116.021407.
42. Simons LA. An updated review of lipid modifying therapy. Med J Aust 2019;211(2):87–92. doi: 10.5694/mja2.50142.
43. Ference BA, Yoo W, Alesh I, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: A Mendelian randomisation analysis. J Am Coll Cardiol 2012;60(25):2631–39. doi: 10.1016/j.jacc.2012.09.017.
44. Ray KK, Landmesser U, Leiter LA, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. N Engl J Med 2017;376(15):1430–40. doi: 10.1056/NEJMoa1615758.
45. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: A meta-analysis of individual participant data from 28 randomised controlled trials. Lancet 2019;393(10170):407–15. doi: 10.1016/S0140-6736(18)31942-1.
46. Australian Institute of Health and Welfare. Key indicators of progress for chronic disease and associated determinants: Data report. Cat. no. PHE 142. Canberra, ACT: AIHW, 2011.

47. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351(13):1296–305. doi: 10.1056/NEJMoa041031.
48. Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368(14):1279–90. doi: 10.1056/NEJMoa1200303.
49. Garrahy E, Davison K, Hardcastle S, O'Brien J, Pedersen S, Williams A, Radford J. Exercise as medicine for cardiovascular disease. Aust J Gen Pract 2020;49(8):483–87. doi: 10.31128/AJGP-03-20-5294.
50. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: A systematic review and meta-analysis. JAMA 2016;316(12):1289–97. doi: 10.1001/jama.2016.13985.
51. Boekholdt SM, Hovingh GK, Mora S, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: A meta-analysis of statin trials. J Am Coll Cardiol 2014;64(5):485–94. doi: 10.1016/j.jacc.2014.02.615.
52. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 focused update of the 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: A report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol 2017;70(14):1785–822. doi: 10.1016/j.jacc.2017.07.745.
53. Department of Health. Pharmaceutical benefits scheme (PBS). Canberra, ACT: DoH, 2015. Available at www1.health.gov.au/internet/main/publishing.nsf/content/pharmaceutical+benefits+scheme+(PBS)-1 [Accessed 16 December 2020].
54. Colhoun HM, Ginsberg HN, Robinson JG, et al. No effect of PCSK9 inhibitor alirocumab on the incidence of diabetes in a pooled analysis from 10 ODYSSEY phase 3 studies. Eur Heart J 2016;37(39):2981–89. doi: 10.1093/eurheartj/ehw292.
55. Ward NC, Pang J, Ryan JDM, Watts GF. Nutraceuticals in the management of patients with statin-associated muscle symptoms, with a note on real-world experience. Clin Cardiol 2018;41(1):159–65. doi: 10.1002/clc.22862.
56. Rosenson RS, Baker S, Banach M, et al. Optimizing cholesterol treatment in patients with muscle complaints. J Am Coll Cardiol 2017;70(10):1290–301 doi: 10.1016/j.jacc.2017.07.752.
57. Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: The CLEAR wisdom randomized clinical trial. JAMA 2019;322(18):1780–88. doi: 10.1001/jama.2019.16585.

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