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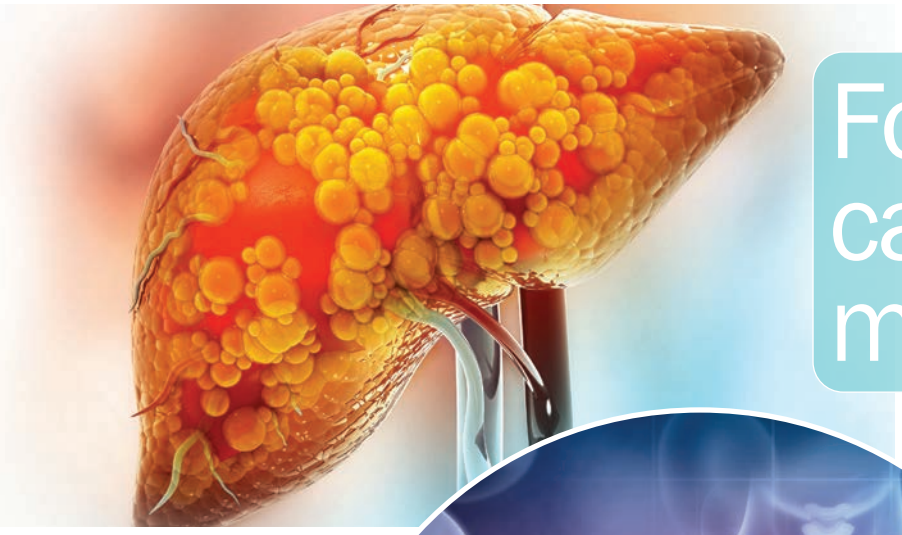
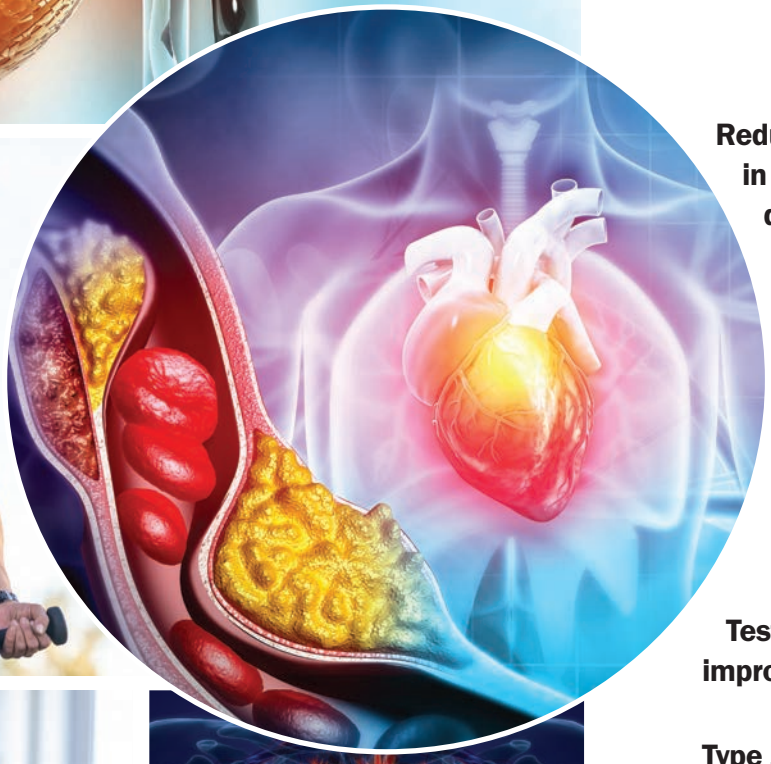
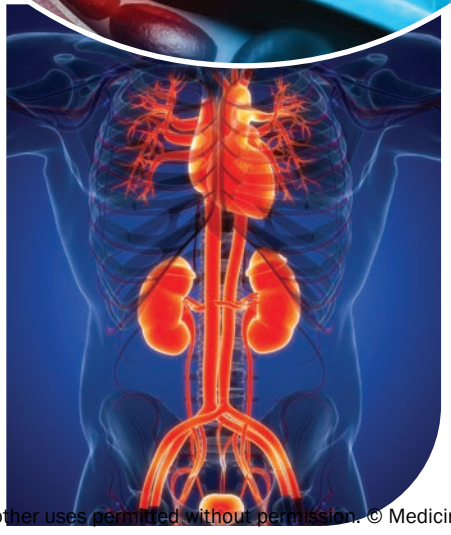


Focus on cardiometabolic matters





Reducing cardiovascular risk in people with chronic kidney disease

Metabolic dysfunction-associated fatty liver disease: the crucial link to CVD

Familial hypercholesterolaemia: improving the health of individuals and families

Testosterone, incretins and improving cardiometabolic health

Type 1 diabetes: reducing cardiovascular risk

Cardiovascular health in transgender people

Formerly MODERN MEDICINE

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FOCUS ON CARDIOMETABOLIC MATTERS
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FOREWORD FROM THE SUPPLEMENT EDITORS

Cardiometabolic diseases are a group of common but often preventable conditions and are a leading cause of morbidity and mortality globally. Advances in screening and investigation to identify predisposing and contributing risk factors pave the way for preventive management. The emergence of new therapies in diabetes, hypercholesterolaemia and kidney disease has improved our armamentarium in the fight against cardiometabolic disease.

This supplement discusses ways to reduce cardiovascular risk in people with chronic kidney disease or type 1 diabetes, highlights the need to 'look beyond the liver' in those with metabolic dysfunction-associated fatty liver disease and outlines the important role of GPs in identifying and managing people with familial hypercholesterolaemia. It also considers the importance of exercise compared with testosterone and incretin-based weight loss therapy for improving cardiometabolic health and reviews how to mitigate the potential cardiovascular risk in the transgender population.

We hope that this supplement, written by diverse expert authors, will provide GPs and other healthcare professionals with a clinically relevant update to enhance the cardiometabolic health of their patients.

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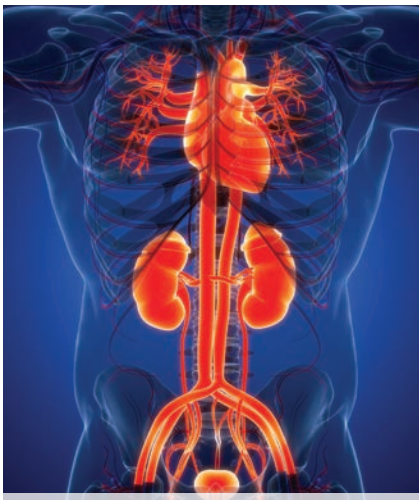

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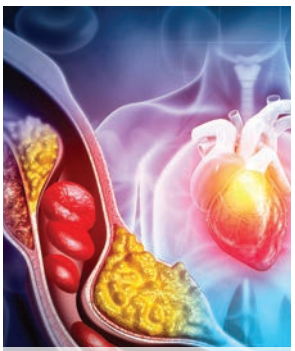

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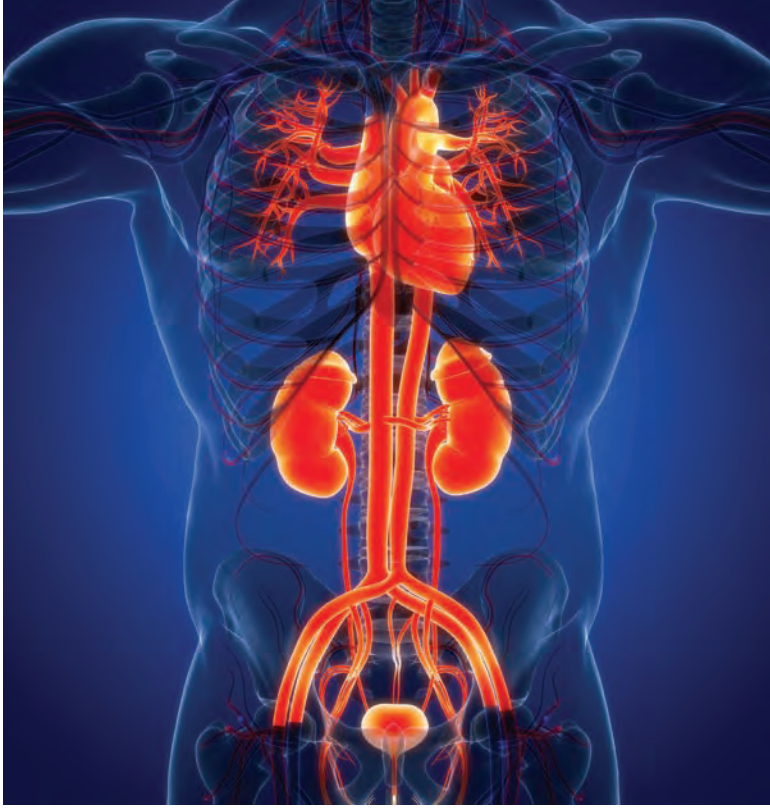
Reducing cardiovascular risk in people with chronic kidney disease

DANA KIM MB BS; **SRADHA KOTWAL** BhB, MBChB, FRACP, PhD



People with chronic kidney disease are at an increased risk of cardiovascular disease. The early recognition of this risk and implementation of effective risk-lowering strategies can be initiated in primary care using a multidisciplinary approach.

Chronic kidney disease (CKD) affects over 10% of the global population and is unequivocally associated with increased risks of cardiovascular disease (CVD) and cardiovascular mortality.[1-4] Specifically, a reduced estimated glomerular filtration rate (eGFR) and the presence of albuminuria or proteinuria portend greater cardiovascular events independent of one another and in addition to other potential confounding factors, such as the presence of diabetes and hypertension.[1,5] Compared with individuals with normal kidney function, the risk of cardiovascular death is twice and three times as high in those with eGFR 30 to 59 mL/min/1.73 m^2 and 15 to 29 mL/min/1.73 m^2, respectively. CVD is the main cause of death in people with kidney failure requiring kidney replacement therapy (maintenance dialysis or kidney transplantation).[6,7]

KEY POINTS

- Chronic kidney disease (CKD) is associated with an increased risk of cardiovascular disease (CVD) and CVD-related death independent of other traditional risk factors.
- Individuals with moderate-to-severe CKD have an estimated five-year CVD risk of at least 10%, placing them in the highest risk category.
- GPs play a key role in the multidisciplinary care required to reduce cardiovascular risk in individuals with CKD, which includes lifestyle modifications, the management of traditional risk factors (e.g. hypertension, diabetes mellitus, hyperlipidaemia) and preventing progressive CKD.
- First-line pharmacotherapy includes renin–angiotensin–aldosterone system (RAAS) inhibitors and sodium-glucose cotransporter-2 (SGLT-2) inhibitors.
- Adjunct therapy for diabetic kidney disease includes nonsteroidal mineralocorticoid receptor antagonists (MRAs) and glucagon-like peptide-1 receptor agonists.
- If medications such as RAAS inhibitors, SGLT-2 inhibitors and MRAs have been ceased in patients with CKD consider recommencing as soon as appropriate to maximise their long-term cardioprotective effects.

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The strong association between CKD and CVD, alongside prevalent shared comorbidities highlight the importance of adopting a multidisciplinary approach to cardiovascular risk reduction. GPs play a pivotal role in fostering patient engagement and facilitating effective care co-ordination. Individuals with early stages of CKD do not require specialist involvement and usually present in primary care settings; thus, understanding the risk of CVD and implementing long-term risk-reducing treatments remain crucial. As more efficacious therapeutic

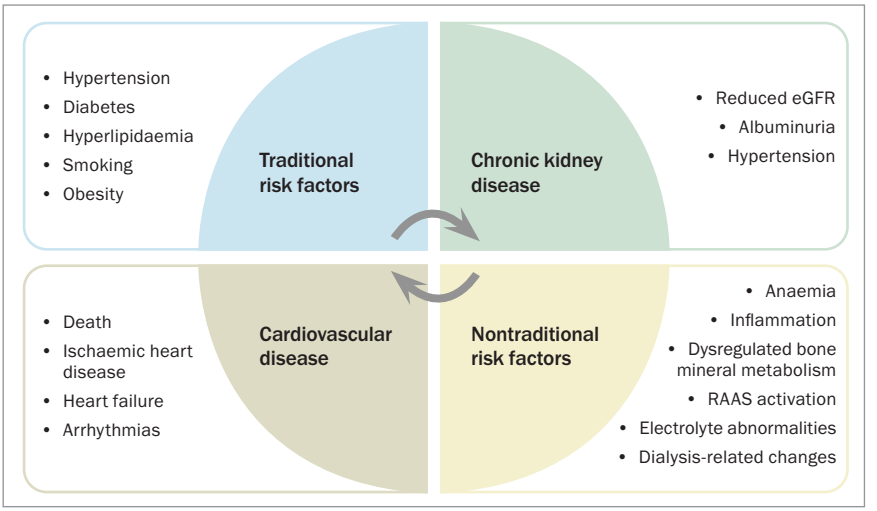


Figure 1. Association between CKD and the risk of developing cardiovascular disease, including shared traditional risk factors and additional nontraditional risk factors specific to CKD.
Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RAAS = renin–angiotensin–aldosterone system.

options become available to curb cardiovascular events and delay CKD progression, it becomes increasingly important to ensure they are used appropriately. This article summarises the underlying mechanisms linking CVD and CKD, discusses screening for CVD in people with CKD and outlines lifestyle modifications and pharmacological interventions aimed at mitigating CVD risk in those with CKD. Additionally, two clinical vignettes illustrate the practical application of these strategies in real-world scenarios.

Risk factors for cardiovascular disease in chronic kidney disease

CKD is associated with a range of CVD subtypes resulting in outcomes such as ischaemic heart disease, heart failure, arrhythmias, sudden cardiac death, peripheral vascular disease, cerebrovascular disease and venous thrombosis.[8,9] This spectrum reflects the number of underlying mechanisms contributing to CVD in people with CKD, which include shared traditional risk factors such as hypertension and diabetes (the two leading causes of CKD), as well as nontraditional factors unique to patients with CKD, such as those listed below and illustrated in Figure 1.

- Anaemia: this is a significant complication of CKD that can lead to adverse cardiovascular outcomes (e.g. heart failure)
- Inflammation: CKD can induce inflammation, reflected by elevated levels of inflammatory markers (e.g. ferritin, C-reactive protein, interleukin-6, tumour necrosis factor), which is associated with cardiac remodelling and fibrosis, cardiomyopathy, left ventricular hypertrophy and diastolic dysfunction
- Dysregulation in bone mineral metabolism: elevated levels of fibroblast growth factor 23, seen even in early stages of CKD, and elevated parathyroid hormone and phosphate levels; in addition, 1,25-dihydroxyvitamin D deficiency drives vascular calcification and increases arterial stiffness and potentially the risk of cardiac fibrosis and heart failure
- Overactivation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system: this contributes to hypertension, vasoconstriction and an increased risk of CVD
- Electrolyte abnormalities: hyperkalaemia is particularly prevalent in advanced CKD and can lead to an increased risk of cardiac arrhythmias
- Dyslipidaemia: patients with CKD typically exhibit hypertriglyceridaemia and low levels of HDL cholesterol, with increased atherogenic qualities of these lipids
- Dialysis-related shifts: patients with kidney failure receiving chronic haemodialysis are at particular risk of sudden cardiac death, precipitated by intradialytic hypotension, hypoxaemia and rapid electrolyte and volume shifts.[8,10,11]

Assessment of cardiovascular risk in chronic kidney disease

Screening

There are insufficient data to support routine screening for coronary artery disease in asymptomatic patients with CKD, as there is no evidence it improves cardiovascular outcomes or alters management.[9,12] This is further emphasised by the results of the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches-Chronic Kidney Disease (ISCHEMIA-CKD), which found no difference in a composite outcome of death or nonfatal myocardial infarction in patients with advanced CKD (eGFR <30 mL/min/1.73 m^2) and moderate-to-severe ischaemia on stress testing randomised to medical therapy compared with invasive coronary revascularisation.[13] Therefore, CVD risk assessment and appropriate risk factor modification in all patients with CKD are recommended in the first instance.

Risk assessment of cardiovascular disease

Most cardiovascular risk prediction calculators do not consider the eGFR or presence of albuminuria and, thus, largely underestimate CVD risk in patients with

TABLE. CVD RISK STRATIFICATION IN CHRONIC KIDNEY DISEASE[14]

eGFR (mL/min/1.73 m^2)	uACR (mg/mmol)	Recommendation
≥60	Men: <2.5 Women: <3.5	Assess CVD risk using validated CVD risk prediction tools
45 to <60	Men: 2.5 to 25 Women: 3.5 to 35	CVD risk may be underestimated when using standard prediction tools; consider reclassifying to a higher risk category
<45	Men: >25 Women: >35	Do not use CVD risk prediction tools; manage as high risk for CVD

Abbreviations: CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; uACR = urine albumin-to-creatinine ratio.
Adapted from: Commonwealth of Australia as represented by the Department of Health and Aged Care. Australian Guideline for assessing and managing cardiovascular disease risk; 2023.[14]

CKD. These calculators are not validated for use in people with advanced CKD or kidney failure requiring dialysis or transplantation.[5,9] As such, current Australian guidelines recommend individuals with an eGFR less than 45 mL/min/1.73 m^2 or macroalbuminuria (urine albumin-to-creatinine ratio [uACR] >25 mg/mmol in men and >35 mg/mmol in women) be regarded at high CVD risk with a five-year risk of 10% or greater (Table).[14]

Approach to reducing cardiovascular risk in chronic kidney disease

The management approach to reducing cardiovascular risk in patients with CKD should include a multidisciplinary team to address lifestyle modifications and common traditional risk factors, such as hypertension, hyperlipidaemia and diabetes, and consider additional pharmacological therapies where appropriate. As CKD itself is a significant cardiovascular risk factor, efforts to prevent kidney disease progression by reducing albuminuria and slowing the rate of eGFR decline should also be prioritised in mitigating CVD risk. It must be recognised that in an increasingly comorbid and elderly population, the treatment targets and recommendations are general in nature. A holistic, patient-centred approach is advised, taking into consideration factors such as tolerability, safety and polypharmacy.

Lifestyle factors

Clear and effective communication of an individual's cardiovascular risk, along with behavioural strategies and continual patient engagement, are essential for the successful implementation of lifestyle modifications. There are limited data regarding lifestyle modifications aimed at reducing cardiovascular risk specifically in CKD populations, so these guidelines are largely extrapolated from studies conducted in general populations and expert opinions. Some recommended lifestyle modifications are listed in Box 1.

Diet

A well-balanced diet with increased fruit and vegetable intake and limited intake of processed meats, refined carbohydrates and sweetened beverages is recommended.[15-17] Dietary interventions, such as consuming a Mediterranean diet, increasing plant-based intake and restricting carbohydrate intake, appear to lower blood pressure and are associated with improved kidney function.[18] Salt restriction in patients with CKD has been shown to significantly lower blood pressure and albuminuria, as well as increase the efficacy of RAAS inhibitors.[19] Therefore, a sodium intake of less than 2 g/day is recommended.

Exercise

Regular exercise in adults with CKD reduces albuminuria, increases aerobic capacity, lowers blood pressure and improves quality of life.[20,21] Moderate-intensity physical activity is recommended for 30 minutes, five times per week, or 150 minutes per week; however, this should be tailored to the individual patient's tolerance and cardiovascular fitness levels.[22,23]

Smoking cessation

Chronic smoking is associated with an increased risk of irreversible proteinuria independent of the daily or cumulative number of cigarettes smoked, and an increased risk of kidney failure in CKD.[24,25] On this basis, along with robust evidence indicating that smoking cessation is associated with a reduction in cardiovascular risk in the general population, the cessation of smoking and tobacco products is recommended in patients with CKD.[22]

1. RECOMMENDED LIFESTYLE MODIFICATIONS TO REDUCE CARDIOVASCULAR RISK IN ADULTS WITH CHRONIC KIDNEY DISEASE

Diet
- Consume a well-balanced diet
- Increase fruit and vegetable intake
- Consume a combination of whole grains, fibre, legumes, plant-based proteins, unsaturated fats and nuts in diet
- Limit intake of processed meats, refined carbohydrates and sweetened beverages
- Aim for a sodium intake <2 g/day
- Conduct dietitian review in patients with advanced kidney disease and patients on dialysis

Exercise
- Engage in moderate-intensity physical activity for 30 minutes, five times per week, or 150 minutes per week
- Tailor to the patient's overall health and cardiovascular fitness level

Smoking
- Cease smoking and tobacco products

Obesity
- Consider losing weight if body mass index >25 kg/m^2

2. RISK FACTOR MANAGEMENT TARGETS TO REDUCE CARDIOVASCULAR RISK IN ADULTS WITH CHRONIC KIDNEY DISEASE

Hypertension
- Systolic blood pressure <120 mmHg
- Consider a higher blood pressure target of <130/80 mmHg, or higher depending on the risk of hypotension and falls and patient's overall health

Type 2 diabetes
- HbA_{1c} level ≤7.0%
- Consider HbA_{1c} target levels ranging from <6.5% to <8.0%, depending on the patient's overall health and risk of hypoglycaemia

Hyperlipidaemia
- Commence statin therapy if:
  - age ≥50 years and not on dialysis
  - age <50 years, at high risk of cardiovascular disease and not on dialysis
- No specific recommended LDL cholesterol targets

Abbreviations: BMI = body mass index; HbA_{1c} = glycated haemoglobin.

Obesity

Obesity is associated with an increased risk of CKD and CVD. People with a body mass index greater than 25 kg/m^2 should be encouraged to lose weight, taking into consideration their other medical comorbidities, overall health and physical activity levels.[23]

Management of traditional risk factors

The treatment targets of traditional risk factor management are outlined in Box 2.

Blood pressure control

The lowering of blood pressure in patients with hypertension significantly reduces the risk of CVD and mortality in patients with CKD; however, optimal treatment targets remain contentious.[26-28] Current international CKD guidelines suggest aiming for a systolic blood pressure less than 120 mmHg, but to consider a more liberal approach depending on the patient's overall health, frailty and risk of postural hypotension and falls.[29] Other guidelines, including the Kidney Health Australia *CKD Management in Primary Care* handbook, recommend higher targets of blood pressure (<130/80 mmHg).[17] These guidelines do not apply to patients on dialysis, in whom ideal blood pressure targets are even more unclear.

Glycaemic control

Type 2 diabetes is a significant shared risk factor of CKD and CVD. Australian guidelines recommend a glycated haemoglobin (HbA_{1c}) target of 7.0% or less in patients with CKD.[9] Tight glycaemic control has not been shown to reduce the risk of kidney failure or cardiovascular death in CKD, although it may help reduce microalbuminuria and nonfatal myocardial infarction.[30] The safety of tight glycaemic control has also not been confirmed in CKD, particularly in frail patients with comorbidities. International guidelines have more recently recommended individualised treatment parameters, with HbA_{1c} targets ranging from less than 6.5% to less than 8.0% to balance the risk of hypoglycaemia and long-term benefits of glycaemic control depending on the patient.[15] Of note, HbA_{1c} measurements can be unreliable in people with advanced CKD or end-stage kidney disease because of anaemia and anaemia treatments including erythropoietin-stimulating agents, iron replacement and blood transfusions.[15] Specific medications, such as sodium-glucose cotransporter-2 (SGLT-2) inhibitors, nonsteroidal mineralocorticoid receptor antagonists (MRAs) and glucagon-like peptide 1 (GLP-1) receptor agonists, may reduce the risk of cardiovascular events and slow CKD progression in type 2 diabetes.

Lipid management

The Study of Heart and Renal Protection (SHARP) trial clearly demonstrated that primary prevention with simvastatin plus ezetimibe reduced the risk of major atherosclerotic events in patients with CKD compared with placebo.[31] The cardiovascular effects of statin therapy do not appear to extend to patients on dialysis, despite significantly lowering LDL cholesterol levels, and the benefits in terms of major vascular events and mortality diminish as the eGFR declines.[32,33] Specific LDL treatment targets for these populations have not been defined.

Statin-based therapy is currently recommended in adults with CKD:
- aged 50 years and older not treated with chronic dialysis or kidney transplantation
  - in those with an eGFR less than 60 mL/min/1.73 m^2, a statin or statin plus ezetimibe combination should be considered
- younger than 50 years of age at high risk of CVD, defined as having one or more of the following:
  - known coronary disease
  - diabetes mellitus
  - prior ischaemic stroke
  - estimated 10-year risk of coronary death or myocardial infarction greater than 10%.[23,34]

Pharmacotherapy

The landscape of available therapies to reduce cardiovascular risk and slow the rate of eGFR decline in CKD is evolving, with the relatively recent development of drugs including SGLT-2 inhibitors, MRAs and GLP-1 receptor agonists.

Aspirin

Overall, aspirin has been shown to reduce the risk of myocardial infarction in people with CKD when used for both primary and secondary prevention, while also increasing the risk of bleeding.[35] When studied for primary prevention alone, the risk of bleeding from aspirin appeared to outweigh the potential cardiovascular benefits of treatment.[36] Therefore, aspirin is only recommended for the secondary prevention of recurrent ischaemic cardiovascular events in people with CKD and established coronary artery disease.

3. PBS INDICATIONS FOR DAPAGLIFLOZIN AND EMPAGLIFLOZIN IN PATIENTS WITH CKD, TYPE 2 DIABETES OR CHRONIC HEART FAILURE*

CKD
Clinical criteria
- The patient must have a diagnosis of CKD present for at least 3 months AND
- eGFR 25 to 75 mL/min/1.73 m^2 AND
- uACR 22.6 to 565 mg/mmol AND
- The patient must not be receiving treatment with another SGLT-2 inhibitor AND
- The patient must be stabilised on a RAAS inhibitor for at least four weeks, unless medically contraindicated, before starting combination therapy with this drug

Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; HbA_{1c} = glycated haemoglobin; LVEF = left ventricular ejection fraction; RAAS = renin–angiotensin–aldosterone system; SGLT-2 = sodium-glucose cotransporter-2; uACR = urine albumin-to-creatinine ratio.

* Refer to the PBS website for full details.

Type 2 diabetes
Clinical criteria
- The treatment must be used in combination with at least one of metformin, a sulfonylurea and insulin AND
- The condition must be inadequately responsive to at least one of the aforementioned agents AND
- The patient must not be undergoing concomitant PBS-subsidised treatment with a GLP-1 receptor agonist or another SGLT-2 inhibitor
- If using as initial treatment:
  - the treatment must be used in combination with metformin and a dipeptidyl peptidase-4 inhibitor (gliptin) AND
  - HbA_{1c} >7% despite metformin and gliptin treatment OR
  - blood glucose levels >10 mmol/L within 2 weeks before starting treatment

Chronic heart failure
Clinical criteria
- The patient must be symptomatic (New York Heart Association classes II, III or IV) independent of LVEF AND
- If LVEF is ≤40%, the treatment must be an add-on therapy to optimal standard chronic heart failure treatment, including a beta blocker and an ACE inhibitor, angiotensin II antagonist or angiotensin receptor with neprilysin inhibitor combination therapy, unless contraindicated or cannot be tolerated
- If LVEF is >40%, there must be structural changes on echocardiography expected to cause diastolic dysfunction (e.g. left ventricular hypertrophy), and at least one of:
  - diastolic dysfunction with high filling pressures
  - hospitalisation for heart failure in the past 12 months
  - requirement for intravenous diuretic therapy in the past 12 months
  - elevated terminal pro brain natriuretic peptide AND
- The patient must not be receiving treatment with another SGLT-2 inhibitor

Renin–angiotensin–aldosterone system inhibitors

RAAS blockade slows the rate of eGFR decline, lowers proteinuria and reduces the risk of kidney failure and cardiovascular events independent of its blood pressure-lowering effects.[37-40] RAAS inhibition with ACE inhibitors and angiotensin receptor blockers has been the cornerstone of CKD treatment for many years. Discontinuation of RAAS inhibitors in patients with CKD is associated with elevated risks of all-cause mortality and cardiovascular events; thus, these agents should be continued if safe and feasible, or promptly recommenced after any period of discontinuation, such as during acute illness or episodes of acute kidney injury.[41]

RAAS inhibitors are recommended for the following patients with CKD:
- patients requiring first-line treatment for hypertension
- patients with type 2 diabetes and uACR greater than 3 mg/mmol
- patients without type 2 diabetes and uACR greater than 30 mg/mmol
  - consider in patients with uACR between 3 and 30 mg/mmol.[15,29,42]

Sodium-glucose cotransporter-2 inhibitors

The cardio- and renoprotective class effects of SGLT-2 inhibitors demonstrated in studies (e.g. the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation [CREDENCE], Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease [DAPA-CKD] and Study of Heart and Kidney Protection with Empagliflozin [EMPA-KIDNEY] trials) conducted in patients with CKD with and without diabetes are overwhelmingly positive.[43-46] SGLT-2 inhibitors have been shown to lower albuminuria and reduce the risk of kidney failure, acute kidney disease and cardiovascular events, including cardiovascular death and hospitalisation for heart failure.

Although the benefits of SGLT-2 inhibitors may extend beyond these groups and international guidelines recommend their use across broader indications,[23] dapagliflozin and empagliflozin are listed on the PBS for the indications listed in Box 3.

Finerenone

Finerenone is a selective, nonsteroidal MRA that has been shown to reduce the risk of kidney failure and cardiovascular events in patients with type 2 diabetes and CKD in the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trials.[47-49] A class effect has not been confirmed with other selective and nonselective MRAs.

Finerenone is PBS listed for patients who have CKD with type 2 diabetes, plus all the following:
- absence of known significant nondiabetic renal disease
- eGFR 25 mL/min/1.73 m^2 or greater
- uACR of 22.6 mg/mmol or greater
- stabilised on a RAAS inhibitor for at least four weeks unless medically contraindicated, before starting combination therapy with this drug
- treatment must be in combination with an SGLT-2 inhibitor unless medically contraindicated or intolerant

- must not be receiving treatment with another selective nonsteroidal MRA, renin inhibitor or potassium-sparing diuretic
- must not have established heart failure with reduced ejection fraction with an indication for MRA treatment.

Refer to the PBS website for full details.

GLP-1 receptor agonists

GLP-1 receptor agonists reduce the risk of major cardiovascular events in patients with type 2 diabetes, including in those with an

4. CLINICAL VIGNETTES: TWO CASES OF EARLY CKD AND HIGH CVD RISK

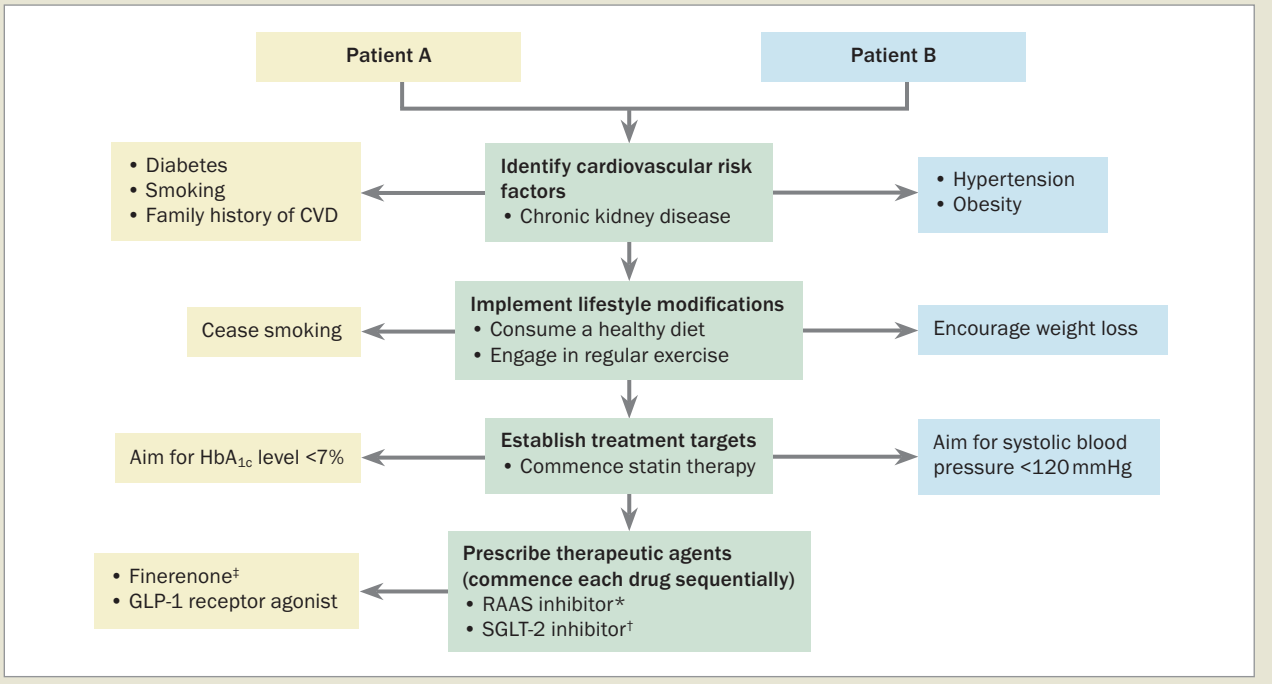
Case presentations

Patient A is a 53-year-old woman with a background of type 2 diabetes for which she has been on single-agent metformin for 10 years. She is a current smoker and has a strong family history of CVD and CKD. She has come to see you for an annual medical check up. Her BMI is 22 kg/m^2 and blood pressure is 121/73 mmHg. You arrange for her to undergo routine blood and urine tests, which show a serum creatinine level of 92 micromol/L, eGFR of 64 mL/min/1.73 m^2, HbA_{1c} level of 7.8% and uACR of 53 mg/mmol.

Patient B is a 64-year-old man with hypertension diagnosed 15 years prior. He has come to see you for the first time to renew his prescription for amlodipine. You perform a comprehensive medical check up. His BMI is 32 kg/m^2 and blood pressure is 162/95 mmHg. Investigation findings show a serum creatinine level of 99 micromol/L, eGFR of 74 mL/min/1.73 m^2 and uACR of 32 mg/mmol.

Management approaches

Both patients present with early CKD and a high risk of CVD. In individuals with a new diagnosis of CKD, it is important to repeat blood and urine tests to monitor the trend in kidney function and confirm persistent albuminuria, and consider renal tract imaging for potential structural abnormalities. At this stage, both patients could continue to be appropriately monitored in the primary care setting unless there are signs of disease progression or abnormal findings such as sustained microscopic haematuria to prompt nephrology referral.[23] The management of cardiovascular risk factors (i.e. optimal glycaemic control in Patient A and blood pressure lowering plus weight loss in Patient B) should be prioritised. The onset of any signs or symptoms of CVD would warrant cardiology referral, keeping in mind that both patients, particularly Patient A (being female and having diabetes), could present with atypical symptoms. Additional specific strategies to reduce cardiovascular risk are outlined below in the Flowchart.



Flowchart. Strategies to reduce cardiovascular risk in Patient A and Patient B.[23] Suggested treatment algorithm to reduce the risk of CVD in two patients with CKD. Strategies specific for Patient A are in yellow. Strategies specific for Patient B are in blue. Strategies applicable to both patients are in green.

* Practice point: Check blood pressure, serum potassium level, creatinine level and eGFR 2 to 4 weeks after initiation and dose increase. Uptitrate to maximal tolerated dose.
† Practice point: No additional monitoring outside of standard of care is required.
‡ Practice point: Check serum potassium level, creatinine level and eGFR 4 weeks after initiation and dose increase. As Patient A is normotensive, confirm blood pressure wil tolerate additional agents.

Abbreviations: BMI = body mass index; CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; HbA_{1c} = glycated haemoglobin; RAAS = renin–angiotensin–aldosterone system; SGLT-2 = sodium-glucose cotransporter-2; uACR = urine albumin-to-creatinine ratio.

eGFR less than 60 mL/min/1.73 m^2.[50] More recently, the findings from the Evaluate Renal Function with Semaglutide Once Weekly (FLOW) trial, specifically studying the effects of semaglutide on renal and cardiovascular outcomes in patients with type 2 diabetes and CKD, have been published.[51] Adults with type 2 diabetes, an HbA_{1c} level of 10% or less and CKD with albuminuria and who were established on maximal tolerated RAAS blockade were included in the study, regardless of treatment with other concomitant glucose-lowering agents. The study found that semaglutide lowered the risk of the primary outcome (a composite of kidney failure, 50% reduction in the eGFR or death from kidney-related or cardiovascular causes) by 24% and major cardiovascular events by 16% compared with placebo over a median follow-up period of 3.4 years.

Long-acting GLP-1 receptor agonists are currently recommended as an additional glucose-lowering agent in patients with CKD and type 2 diabetes who are yet to achieve their individualised glycaemic targets despite use of metformin and SGLT-2 inhibitor therapy, or in those who are unable to use these drugs.[15] However, based on the results of the FLOW trial, the indications for use in CKD may broaden in the future.

Practical prescribing considerations

Considering the acute effects of treatment, it is generally recommended to commence each drug sequentially after establishing a period of stability for at least four weeks. RAAS inhibitors, SGLT-2 inhibitors and finerenone can induce haemodynamic changes resulting in a reversible decline in eGFR, referred to as the 'eGFR dip', which typically occurs within the first four weeks of treatment.[52] If the reduction in the eGFR exceeds 30% or continues to decline beyond the initial dip following drug commencement, alternative causes should be considered. RAAS inhibitors and finerenone may cause hyperkalaemia, particularly in advanced kidney disease (eGFR <30 mL/min/1.73 m^2); therefore, serum potassium levels should be monitored following drug initiation and dose escalation in line with the *Australian Medicines Handbook* guidelines. Notably, concurrent therapy with SGLT-2 inhibitors may lower this risk of hyperkalaemia, and finerenone is not recommended in individuals with an eGFR less than 25 mL/min/1.73 m^2 or serum potassium level greater than 5.0 mmol/L.[53]

All these agents also exhibit blood pressure-lowering effects, which should be monitored. These potential adverse effects are likely to be heightened in the setting of acute illness and hypovolaemic states, and therefore may require additional monitoring or drug suspension during these periods. Two clinical vignettes are presented in Box 4, with management approaches outlined in the Flowchart.[23]

Conclusion

Patients with CKD face a heightened risk of CVD, significantly worsening their health outcomes. Combatting this risk requires a multidisciplinary approach, leveraging various existing and emerging therapies. However, the long-term benefits of some strategies may be limited in advanced CKD. Therefore, early CKD diagnosis, risk assessment and prompt management initiated in primary care are crucial. 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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Reducing cardiovascular risk in people with chronic kidney disease

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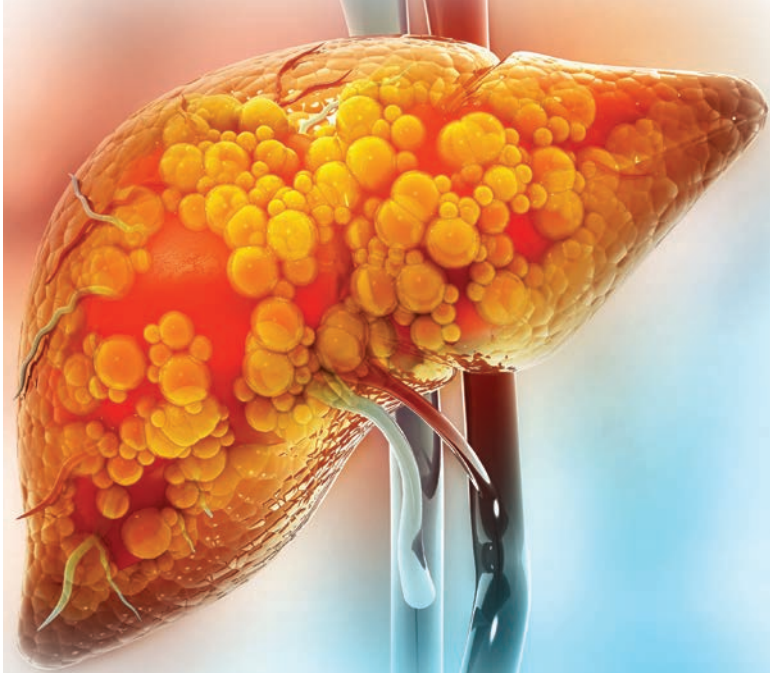
Metabolic dysfunction-associated fatty liver disease

The crucial link to CVD



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Metabolic dysfunction-associated fatty liver disease (MAFLD), which is encountered every day in clinical practice, is a complex disorder that is linked to disease in almost every other organ system. Cardiovascular disease is principal among these, and the most likely cause of death in an individual with MAFLD, highlighting the need to 'look beyond the liver'.

KEY POINTS

- The prevalence of metabolic dysfunction-associated fatty liver disease (MAFLD) is rising in Australia and worldwide. Cardiovascular disease (CVD) remains the single biggest cause of death in individuals with MAFLD.
- Liver fibrosis predicts poor outcomes such as development of cirrhosis, liver cancer and CVD. Liver fibrosis can be estimated with simple calculators using commonly available laboratory results. These tools also identify patients who need specialist referral.
- MAFLD is an independent risk factor for CVD. Commonly used risk calculators may underestimate the risk of CVD in people with MAFLD, especially those with liver fibrosis.
- CVD risk factors should be treated aggressively with pharmacological and nonpharmacological interventions.
- Medications such as statins are safe and tend to be under-prescribed in people with MAFLD.
- Several new medications are likely to become available over the next few years to treat the liver manifestations of MAFLD.

Metabolic dysfunction-associated fatty liver disease (MAFLD, previously known as nonalcoholic fatty liver disease [NAFLD]) is the most prevalent liver disease in Australia and also affects over a third of the global population.[1] In Australia, incident cases of decompensated cirrhosis and primary liver cancer secondary to MAFLD are predicted to increase by 85% and 75%, respectively, this decade, rising in parallel with incident cases of obesity and the metabolic syndrome. Despite this, there is generally low awareness of MAFLD and, when present, it is easy to overlook or simply ignore it. This is likely because of the following factors:

- only a very small proportion of people with MAFLD will experience a liver-related adverse event (i.e. development of cirrhosis or liver cancer)
- there is a lack of effective drugs to improve liver fibrosis and inflammation or prevent liver-related adverse events (although this is hopefully soon set to change)
- the seemingly ubiquitous nature of MAFLD contributes to general desensitisation to the condition.

This therapeutic nihilism is illustrated by some guidelines that have explicitly recommended against routine screening for MAFLD, even in high prevalence settings, such as diabetes clinics, citing 'uncertainties around diagnostic testing and treatment options'.[2] Notably, other guidelines, including our local Asian Pacific Association for the Study of the Liver guidelines, recommend a more proactive approach to screening including in those with overweight or obesity, type 2 diabetes and the metabolic syndrome,[3] whereas universal screening for

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MAFLD in people with type 2 diabetes is now endorsed by some diabetes guidelines, suggesting this lack of interest is shifting.[4]

Importantly, however, MAFLD is not an isolated disorder of the liver, but rather the hepatic manifestation of systemic metabolic dysregulation, and in this regard, the liver can be thought of as a window into a person's general metabolic health. This metabolic dysregulation state, which is integral to MAFLD, is characterised by insulin resistance, dysregulated lipid metabolism and chronic low-grade inflammation. Inter-organ cross-talk results in multiple other affected organ systems including the heart, brain, pancreas, blood vessels, adipose tissue and muscle. A large number of disease associations have been described, including sleep apnoea, cardiovascular disease (CVD), osteoporosis, chronic kidney disease, thyroid disease, polycystic ovary syndrome, mental health disorders and dementia (Figure). In keeping with this, several studies have demonstrated increased all-cause mortality in people with MAFLD compared with the general population, which tends to increase with increasing stages of liver fibrosis.[5,6] However, most of this excess mortality is actually driven by nonliver-related events, most notably CVD, extrahepatic cancer and chronic kidney disease. In fact, despite a rapid rise in MAFLD-associated liver disease in recent decades, liver diseases still account for about one-third of the deaths caused by kidney disease in metabolically unhealthy people with type 2 diabetes in Australia.[7]

CVD warrants special mention as the already leading cause of death in Australia. MAFLD is associated with an increasing risk of fatal or nonfatal CVD events, and CVD is responsible for nearly a third of total mortality in individuals with MAFLD. In fact, upon diagnosis of MAFLD, a clinician's first initial thought should be to consider CVD. In people with MAFLD, the risk of CVD increases along the MAFLD severity spectrum and fibrosis stage. Thus, just as assessing an individual's degree of liver fibrosis predicts the risk of progression to cirrhosis or liver cancer, it likely also predicts the risk of a cardiovascular event.

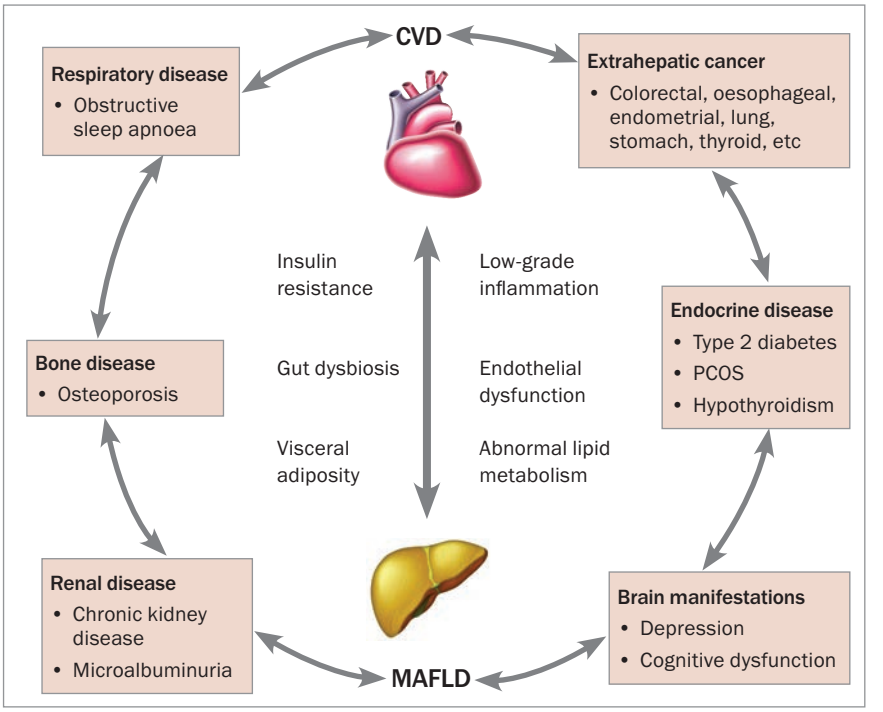


Figure. Multisystem involvement of metabolic dysfunction-associated fatty liver disease (MAFLD).
Abbreviations: CVD = cardiovascular disease; PCOS = polycystic ovary syndrome.

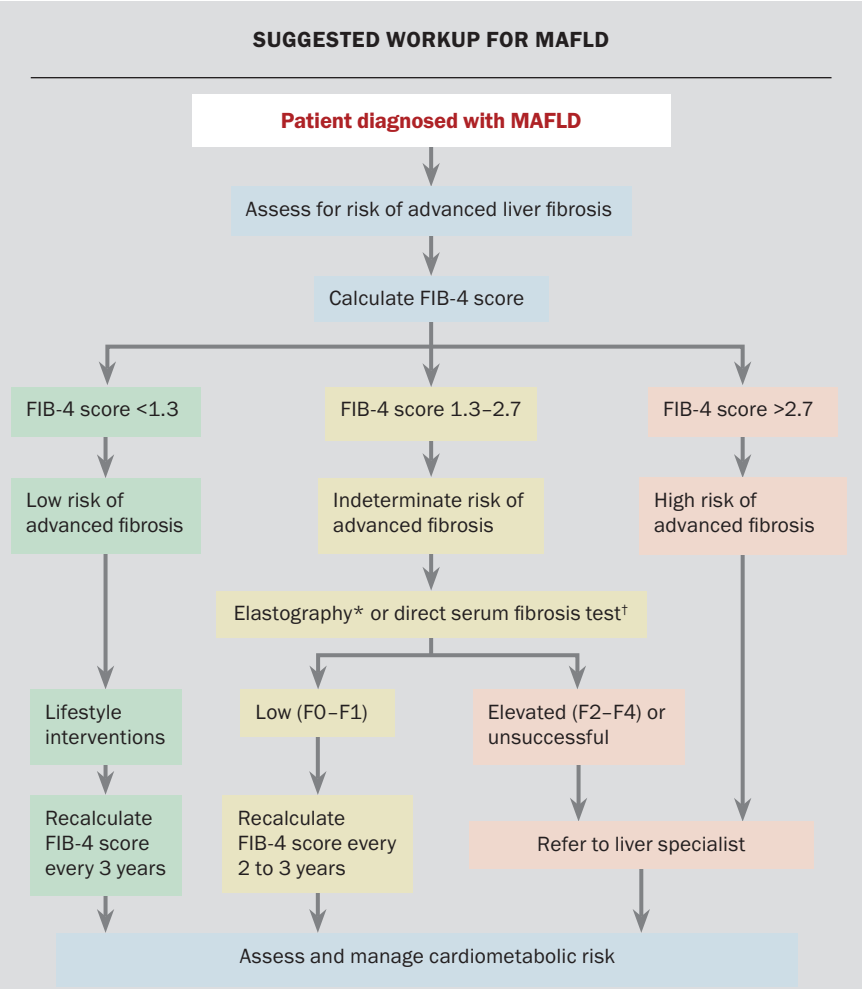
MAFLD: screening, assessment and staging

Australian MAFLD guidelines were presented at the Australian Gastroenterology Week in 2023, and a concise version of the guideline document is expected to be published later this year.

People with obesity, type 2 diabetes or two or more metabolic risk factors (including hypertension, dyslipidaemia, increased waist circumference or prediabetes, regardless of bodyweight) are recommended to undergo screening for MAFLD, with liver ultrasound being the first-line diagnostic test. MAFLD should also be considered in people with unexplained abnormal liver enzyme levels.

In individuals with MAFLD, the single most important prognostic factor is the presence and stage of liver fibrosis, which reflects chronic liver injury and inflammation. Fibrosis is typically reported on a scale of zero (F0; no liver fibrosis), one (F1; mild fibrosis), two (F2; significant fibrosis), three (F3; advanced fibrosis) and four (F4; cirrhosis). Individuals without significant fibrosis in F0 to F1 have a low risk of progressing to cirrhosis, liver decompensation or liver cancer in the short term. Individuals with more advanced fibrosis or cirrhosis (stage F3 to F4) are at significantly higher risk of adverse liver-related outcomes.

Although biopsy is the traditional gold-standard test for assessing liver fibrosis, this is rarely required in practice as several other noninvasive tests can predict the risk of liver fibrosis. The Fibrosis-4 (FIB-4) score is the recommended initial noninvasive test and can be calculated using commonly available clinical and laboratory results (patient age, alanine transaminase and aspartate transaminase levels and platelet count; test available online at: www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis). It



Abbreviations: FIB-4 = fibrosis-4; MAFLD = metabolic dysfunction-associated fatty liver disease.

*Such as vibration-controlled transient elastography (FibroScan) or shearwave elastography.
† Such as Hepascore or enhanced liver fibrosis test.

Adapted from Gastroenterological Society of Australia consensus statement (still in review and expected to be published later this year).

stratifies individuals into low and high risk for significant fibrosis. Individuals with an intermediate FIB-4 score result have an indeterminate risk for advanced fibrosis and should have a second-line test. Second-line testing options include measurement of liver elastography or 'stiffness' (using vibration-controlled transient elastography [FibroScan] or shear wave elastography as an add on to standard ultrasound) or direct serum fibrosis tests, such as Hepascore or the enhanced liver fibrosis test. The choice of second-line test should take into account local availability and cost.

This risk stratification process is an integral part of the initial assessment of individuals diagnosed with MAFLD to ensure they end up on the appropriate care pathway, and that the clinician focus is aligned with treatment priorities. For example, in people without significant fibrosis, care is centred around management of obesity and addressing risk factors for comorbid conditions, including CVD, chronic kidney disease, diabetes and obstructive sleep apnoea. Those with significant fibrosis have an even higher risk of the above conditions, but also have a much higher competing risk of cirrhosis, decompensation and liver cancer and would benefit from liver specialist review. The suggested workup for MAFLD is shown in the Flowchart.

Mechanisms linking MAFLD to CVD

Atherosclerotic cardiovascular disease (ASCVD) is underpinned by the formation of atherosclerotic plaques, consisting of oxidised LDL accumulating within macrophages in the arterial intima in the setting of endothelial dysfunction. Inflammatory cytokines and vascular smooth muscle proliferation makes this plaque vulnerable to rupture and occlusion, particularly in prothrombotic states. MAFLD consists of multiple derangements that make this process more likely to occur.

MAFLD is associated with an atherogenic serum lipoprotein profile (consisting of increased very low LDL and small-dense LDL [the most atherogenic subtype of LDL] and decreased HDL levels), which has an increased propensity to form atherosclerotic plaques.[8] Fat accumulation in hepatocytes induces oxidative stress and the upregulation of a number of proinflammatory signalling cascades. This contributes to the chronic low-grade systemic inflammatory state that mediates many of the extrahepatic complications of MAFLD including CVD. Endothelial dysfunction, referring to the loss of usual homeostatic mechanisms within vascular endothelial cells (which control functions such as regulation of vascular tone, platelet aggregation and immune cell migration), is also known to be a feature of MAFLD and is mediated in part by elevated serum levels of asymmetric dimethyl arginine,[9] a nitric oxide synthase antagonist. Thus, in the milieu of chronic inflammation, endothelial dysfunction, haemostatic alteration and atherogenic dyslipidaemia, an environment primed for the formation of atherosclerotic plaques exists.

In this setting of chronic inflammation and the release of systemic and local proinflammatory mediators, MAFLD is associated with an increased risk of cardiac

arrhythmias, including atrial fibrillation, ventricular arrhythmias and structural heart disease, including left ventricular hypertrophy accompanied by systolic and/or diastolic dysfunction.

MAFLD: an independent risk factor of CVD or an association?

Disentangling the effects of hepatic steatosis on CVD from other features of the metabolic syndrome that invariably accompany MAFLD is challenging. In other words, is hepatic steatosis an independent risk factor for CVD? Or does it simply tend to coincide with other established risk factors? Conflicting data exist reflecting heterogeneity between study populations in the published literature; however, a growing body of evidence suggests liver fat is indeed an independent risk factor. For example, one recent large prospective study with well-phenotyped participants found that baseline steatosis was associated with a 70% increased risk of major adverse cardiovascular events over a two-year follow-up period, even after adjusting for the presence of baseline coronary artery stenosis, ASCVD risk scores, obesity and the metabolic syndrome.[10] Thus, it is likely that assessment of cardiovascular risk using ASCVD risk scores may underestimate risks in the MAFLD population, especially in those with more advanced liver inflammation or fibrosis; both of these factors could be considered when determining an individual's CVD risk.

Management

Nonpharmacological interventions

Lifestyle measures including dietary changes, physical activity and weight loss interventions remain the mainstay of treatment of MAFLD.

Weight loss of a relatively small amount (5% bodyweight) is associated with a 30% improvement in liver fat content and improvement in metabolic parameters,[11] although a greater degree of weight loss (>10%) may be required for regression of liver fibrosis.[12] The benefits of sustained weight loss on cardiovascular risk can be dramatic, and this is well illustrated by bariatric surgery data. A recent large observational study of 650 obese individuals with MAFLD and steatohepatitis who underwent bariatric surgery significantly reduced their risk of major adverse cardiac events by 70% after a median of seven years follow up, compared with a matched control cohort.[13] However, it is essential that weight loss measures be combined with other dietary and exercise interventions in people with MAFLD.

Exercise has beneficial effects on liver fat content and body composition, and promotes an antiatherogenic and anti-inflammatory state, independently of weight loss. Both aerobic exercise and resistance training have beneficial effects on liver fat reduction and, thus, a personalised approach is reasonable. Australian guidelines recommend 150 to 240 minutes of moderate intensity aerobic exercise per week, although as little as 135 minutes per week has been shown to be effective.[14]

High-calorie diets with excess saturated fat and refined carbohydrates are linked to obesity and MAFLD. Reducing caloric intake in line with the Mediterranean style diet is associated with reduced hepatic steatosis and improved cardiometabolic risk parameters.[15,16] This consists of daily consumption of fruit and vegetables, unsweetened fibre-rich cereals, nuts, fish, white meat and olive oil with reduced consumption of saturated fat, processed food and simple sugars. Smoking cessation should also be promoted if relevant, and patients should be encouraged to abstain from alcohol. Coffee consumption appears protective against a variety of liver diseases and may be beneficial in MAFLD.

Pharmacological interventions

Blood pressure- and lipid-lowering therapy is recommended for individuals at high risk of CVD (>10% estimated five-year CVD risk, as determined by the Australian cardiovascular disease risk calculator, which uses age, sex, smoking status, blood pressure, total cholesterol to HDL-cholesterol ratio, diabetes status and use of CVD medications (see: www.cvdcheck.org.au/calculator). These therapies should be considered in people with intermediate (5 to 10%) five-year CVD risk as per Australian guidelines. It is important to bear in mind that existing algorithms do not yet incorporate MAFLD nor the severity of liver disease. Additionally, MAFLD is associated with an atherogenic lipid profile with the presence of highly atherogenic small-dense LDL, low HDL and high triglyceride levels, but often a normal (or only mildly elevated) total LDL-cholesterol level.

Statins are underprescribed in people with MAFLD (and in those with liver diseases more generally) despite substantial evidence to suggest no excess in the risk of hepatotoxicity with their use.[17] Abnormal baseline liver chemistries are not a contraindication to use, and in addition to reducing the risk of cardiovascular events, they have pleiotropic antifibrotic effects on the liver and may reduce the risk of liver cancer (lipophilic statins such as atorvastatin and simvastatin may be more efficacious).[18,19] Although statins are not yet recommended as a primary treatment for people with MAFLD, many of these patients present with other indications for statin use, although they are also underprescribed in these patients.[20]

Despite a previous paucity of pharmacotherapies that can improve liver histology in MAFLD, there are several other medications known to reduce cardiovascular risk that have, at worst, neutral (and possibly beneficial) effects on the liver. These include sodium-glucose cotransporter-2 inhibitors (empagliflozin, dapagliflozin), ACE inhibitors/angiotensin II receptor blockers (e.g. ramipril, perindopril, candesartan) and peroxisome proliferator-activated receptor-gamma agonists (e.g. pioglitazone). Although guidelines generally do not specifically recommend these medications for the sole indication of MAFLD (apart from considering pioglitazone), clinicians should have no hesitation prescribing these if otherwise indicated to do so.

Glucagon-like peptide-1 receptor agonists (liraglutide, dulaglutide, semaglutide) have been shown to improve cardiovascular risk factors, including improving blood pressure and lipid profiles and helping to achieve weight loss, as well as decreasing clinical events in cardiovascular outcome trials. A number of trials have also shown benefits in reducing liver fat, improving steatohepatitis and reducing fibrosis progression.[21] A large phase 3 randomised control trial of semaglutide is currently underway with plans to enrol 1200 participants to assess the impact on liver histology and cardiovascular outcomes (clinicaltrials.gov NCT04822181).

Resmetirom is a new therapy that acts as an oral, liver-directed thyroid hormone receptor beta agonist. In a recent landmark study, the drug was shown to be superior to placebo in inducing steatohepatitis resolution and improving liver fibrosis after 52 weeks of use.[22] On the basis of this study, the drug has just been granted FDA approval for use in the USA in people with noncirrhotic MAFLD with significant fibrosis (in conjunction with diet and exercise interventions), making it the first drug to receive approval for this indication after decades of failed attempts and disappointing trial results (no decision has been made on its approval in Australia at the time of writing this article). Although the trial was not powered to assess cardiovascular outcomes, it was notable that the drug was associated with significant improvements in atherogenic dyslipidaemia, including LDL-cholesterol, non-HDL-cholesterol, triglycerides, apolipoprotein B, apolipoprotein C-III, and lipoprotein(a) levels, thus long-term cardiovascular data are eagerly awaited. Other pharmacotherapies being studied for MAFLD are in late-stage trials, and it is likely that several of the compounds will be approved in Australia over the next five years.

Conclusion

The concept of MAFLD continues to evolve from a 'siloed' liver disease to that of a multisystem disease in which most of the excess morbidity and mortality occurs from extrahepatic events, with CVD being a crucial component. Although the development of drugs specifically targeting liver fibrosis has lagged behind, there are now several effective pharmacological and non-pharmacological interventions to reduce the risk of CVD. Thus, the screening for and identification of MAFLD is an important opportunity for intervention to improve an individual's long-term outcome. 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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Metabolic dysfunction-associated fatty liver disease

The crucial link to CVD

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PEER REVIEWED FEATURE

Familial hypercholesterolaemia

Improving the health of individuals and families

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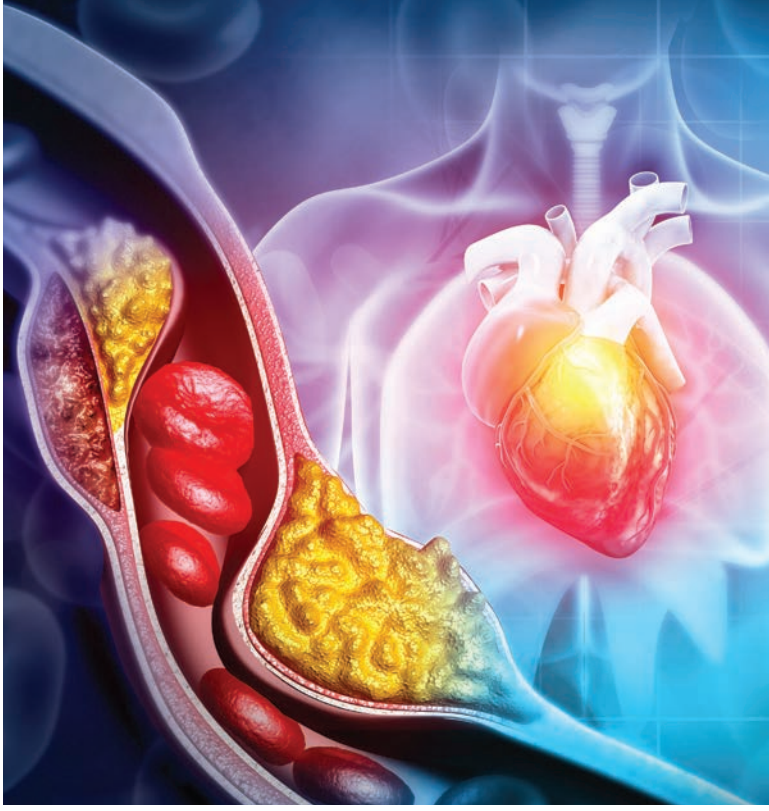

Familial hypercholesterolaemia (FH) is one of the most prevalent, potentially fatal genetic disorders. It causes elevated LDL-cholesterol levels that can lead to premature cardiovascular disease if untreated. Early identification and treatment can substantially improve outcomes. As FH begins at birth and progresses throughout life, GPs are well placed to play an active role in the diagnosis and care of all individuals and families with FH.

KEY POINTS

- Familial hypercholesterolaemia (FH) is a common genetic disorder that leads to premature onset of cardiovascular disease.
- GPs play an important role in identifying people with FH and can access Medicare-rebated genetic testing for the close relative of patients with FH, including their children, before the development of the clinical features of FH.
- The cumulative damaging effect of low-density lipoprotein-cholesterol throughout life justifies the emphasis on early diagnosis and treatment of FH to reduce cardiovascular morbidity and mortality.
- Pathology laboratories need a copy of the genetics report for the first member of a family diagnosed with FH to assist with GP-initiated family cascade screening.

Familial hypercholesterolaemia (FH) is an autosomal dominant genetic disorder caused by pathogenic variants in genes affecting the clearance pathway of low-density lipoprotein (LDL). The condition starts at birth, leading to lifelong elevated levels of LDL-cholesterol, which progress over time. If not treated, FH can accelerate the onset of premature atherosclerotic cardiovascular disease (CVD) by 15 to 30 years.[1] FH is recognised as a tier 1 genomic disorder, meaning it is a preventable cause of premature disease and death with significant potential for a positive impact on public health, supported by high-level evidence-based guidelines and recommendations.[1]

An estimated one in 250 people in Australia have FH. Most remain undetected and unknowingly live with the condition for years, with the risk that the first clinical presentation may be sudden death from cardiac arrest.[2] Fewer than 10% of the more than 100,000 high-risk patients in Australia have been diagnosed. A similar number of their relatives could benefit from having the diagnosis excluded.[1,3,4] Despite an exponential growth in research and strong clinical practice guidelines on FH, it continues to be underdiagnosed and undertreated and remains a significant global health concern.[4]

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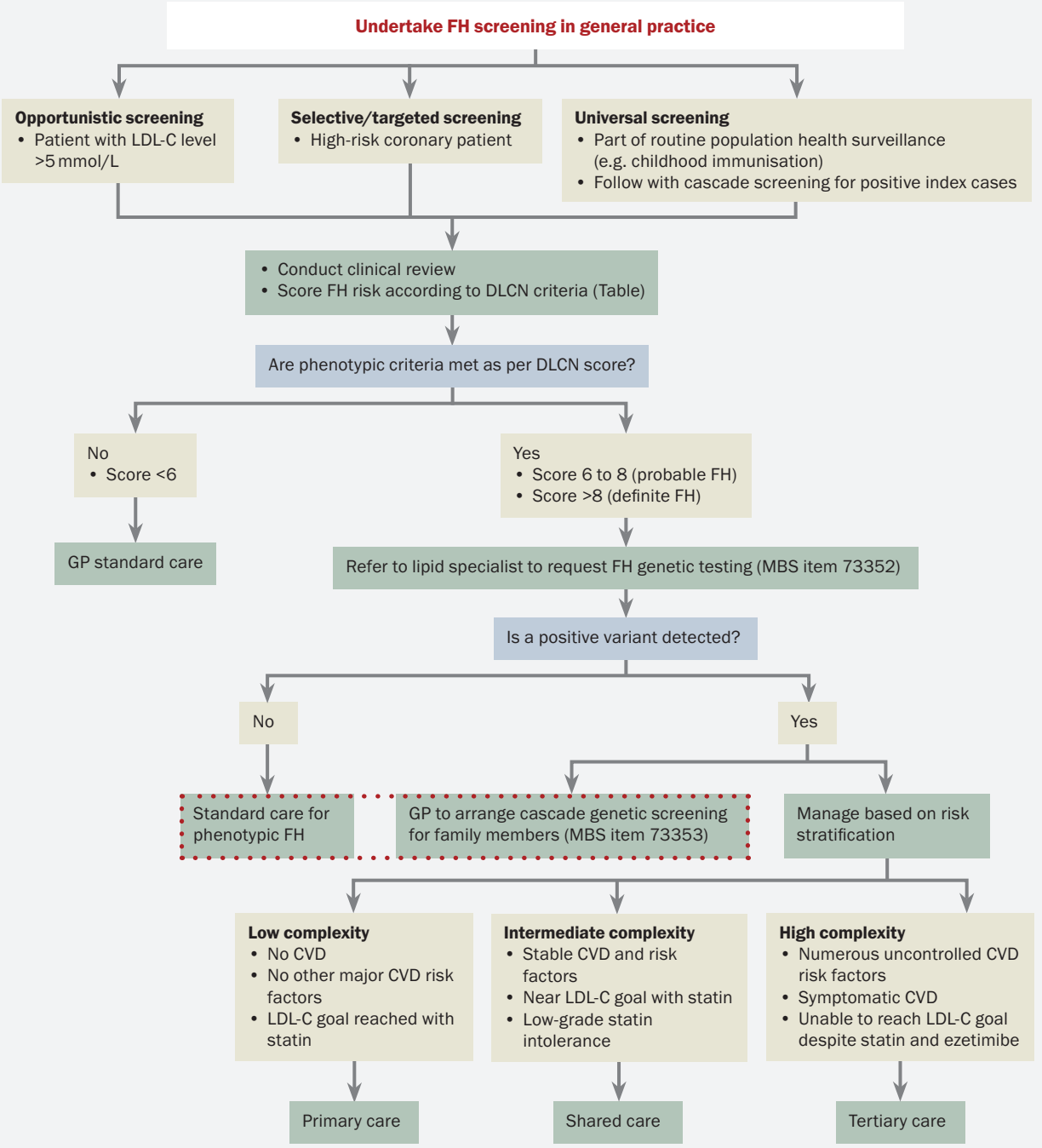
FLOWCHART 1. RECOMMENDED PROCESS FOR SCREENING, DETECTION AND MANAGEMENT OF INDIVIDUALS AT HIGH RISK OF FAMILIAL HYPERCHOLESTEROLAEMIA*



Abbreviations: CVD = cardiovascular disease; DLCN = Dutch Lipid Clinic Network; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein-cholesterol; MBS = Medicare Benefits Schedule.

* The red dashed box represents the GP's role in cascade screening (see Flowchart 2 for details).

Adapted from Brett T, et al. Aust J Gen Pract 2021; 50: 616-621.[11]

As FH is inherited in an autosomal dominant manner, a child born to a parent with FH has a 50% chance of inheriting the disorder, predisposing them to lifelong elevated LDL-cholesterol levels and a high risk of premature atherosclerotic CVD.[5] Entire families can be impacted over generations by the detrimental effects of premature atherosclerotic CVD among so many close relatives. Optimal management includes diagnosing and treating the condition as early in life as possible, as this can significantly reduce cardiac morbidity and mortality.[6] However, most individuals who are diagnosed with FH do not meet optimal management and treatment targets.[5]

As the first point of contact for many individuals seeking healthcare advice, GPs can play an important role in improving the detection and management of FH. Further, the family orientation of general practice can facilitate the expansion of care from the individual to the nuclear family and beyond.

This article outlines how and why GPs play an important role in the identification, diagnosis and management of people with FH. Key strategies and supports are outlined to help GPs take an active and central role in supporting patients and their families with FH.

Why is the GP's role important?

GPs are well placed to help identify, diagnose and manage FH in both patients and their families as almost 90% of people visit their GP at least once a year.[7] Most (90%) LDL-cholesterol tests are ordered through general practice. This provides a perfect opportunity to identify patients who may have FH and initiate screening and diagnosis.[8] After diagnosis, most patients with FH can be managed by their GP; current initiatives aim to facilitate the management of patients with FH by regular GP monitoring in conjunction with specialist support on an 'as needed' basis.[8,9]

It is worth remembering that a predominant increase in LDL-cholesterol level is more specific for FH during childhood. A high LDL-cholesterol level in adulthood is less specific but, when associated with progressive physical signs such as tendon xanthomas or accelerated (before age 45 years) corneal arcus, can suggest a diagnosis of FH. Primary care, supported by improved awareness, guidance and assistance, provides an opportunity to identify more patients with FH.

Screening and detection of FH in primary care

Screening for FH begins by identifying individuals who may be at increased risk. It involves several strategies: opportunistic, selective and universal (followed by cascade family) screening (Flowchart 1).[10,11]

Opportunistic screening

Opportunistic screening can occur during routine medical appointments after a review of family history and cholesterol levels and a physical examination. In primary care, opportunistic screening should be considered for any adult with a plasma LDL-cholesterol level over 5.0 mmol/L.[1] Community laboratories can also support opportunistic screening by flagging elevated cholesterol levels on laboratory reports, alerting the requesting GP of a potential patient with FH. Further, although alerts on laboratory reports can be effective, a direct phone call from the chemical pathologist has been shown to further enhance detection rates.[12]

Selective screening

Selective screening involves identifying patients with premature atherosclerotic CVD (e.g. at age under 55 years in men and under 60 years in women) or a family history of premature atherosclerotic CVD or hypercholesterolaemia. For example, FH should always be considered if a patient has a total cholesterol level greater than 7.5 mmol/L or an LDL-cholesterol level greater than 6.5 mmol/L, especially if there is a family history of premature CVD.[13]

GPs can also conduct selective screening by digitally reviewing electronic health records to detect possible cases using diagnostic criteria such as the Dutch Lipid Clinic Network (DLCN) criteria.[5] The DLCN criteria (Table) are one of the most widely used phenotypic methods for diagnosing adult index cases of FH, involving several risk criteria, and are recommended in several guidelines.[1,8] Primary Health Networks throughout Australia offer assistance to GPs across a range of areas, including supporting health data management and the collection of information.

Universal screening

Several universal screening approaches to improve the detection and diagnosis of FH in patients and their families are under investigation. In general practice, universal screening coupled with reverse cascade screening (i.e. child to parent) would help identify patients at a young age, facilitating optimal treatment, and has the potential to increase detection numbers by flagging the parents of children who are diagnosed. Universal screening should be considered before puberty.[1]

Although Australia does not currently conduct universal screening for FH, it might become standard as a cost-effective approach to increasing detection rates.[14,15] It is important that GPs are ready to manage children who are diagnosed with FH and to reverse cascade test their adult relatives. With an integrated, shared-care approach that includes the patient, GP and other specialists, universal screening combined with cascade screening could be successfully implemented and lead to a substantial increase in the early detection and diagnosis of FH.

Cascade screening of family members

Cascade screening refers to the screening of close family members of index cases who have a known genetic variant. Cascade screening is a highly cost-effective approach. It is one of the key strategies where GPs can have the most impact on increasing detection and diagnostic rates.[16] When an index case is identified, GPs can offer Medicare-rebated genetic cascade

TABLE. DUTCH LIPID CLINIC NETWORK (DLCN) CRITERIA FOR A PHENOTYPIC DIAGNOSIS OF FAMILIAL HYPERCHOLESTEROLAEMIA IN ADULT INDEX CASES*[1]

Criteria	Score
Section 1. Family history	
First-degree relative with known premature coronary or vascular disease (men aged <55 years, women aged <60 years) OR First-degree relative with known LDL-cholesterol level above the 95th percentile for age and sex	1
First-degree relative with tendinous xanthomata or arcus cornealis OR Children aged <18 years with LDL-cholesterol level above the 95th percentile for age and sex	2
Section 2. Clinical history	
Patients with premature coronary artery disease (men aged <55 years, women aged <60 years)	2
Patients with premature cerebral or peripheral vascular disease (men aged <55 years, women aged <60 years)	1
Section 3. Physical examination	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
Section 4. LDL-cholesterol level (mmol/L)†	
≥8.5	8
6.5 to 8.4	5
5.0 to 6.4	3
4.0 to 4.9	1
Diagnosis according to total score‡	**Total score**
Definite FH	>8
Probable FH	6 to 8
Possible FH	3 to 5
Unlikely FH	<3

Abbreviations: FH = familial hypercholesterolaemia; LDL = low-density lipoprotein.
* These criteria should be used to make a phenotypic diagnosis of FH in adults and should not be used for diagnosis in children or adolescents. An online calculator is available from the FH Australasia Network (www.athero.org.au/fh/calculator/).
† If the pretreatment LDL-cholesterol level is not available then a value should be derived from the FH Australasia Network's online calculator (www.athero.org.au/fh/calculator/) by adjusting the value during treatment for cholesterol-lowering medication.
‡ The total score is the sum of the highest score in each section (maximum of 18).

testing to first- and second-degree relatives, provide genetic counselling and work with lipid specialists regarding treatment and management.[17]

Before cascade testing of a relative, GPs should provide a brief summary of FH and discuss the person's risk of inheriting the family variant and the potential benefits and implications of genetic testing, including possible insurance considerations. It is worth noting, Medicare and private health insurance are not affected by genetic testing results. As of June 2024, there is a moratorium that prohibits insurance companies from requesting genetic testing results, where the level of cover requested is less than $500,000 for life and disability insurance, $200,000 for trauma and $4000 a month for income protection insurance. Some insurance companies may consider genetic test results within travel insurance arrangements. For more information on life insurance and genetic testing refer to the Box. Those who test positive for the variant are encouraged to communicate their result to at-risk relatives to allow further cascade testing and should continue to closely monitor their cholesterol levels and manage accordingly. Those who test negative for the variant are advised to follow population screening guidelines.

By supporting the timely treatment of people with FH, cascade screening by GPs has the potential to be a highly effective method for the primary prevention of CVD among families with FH. The greatest opportunity for improved detection and management of FH in current circumstances is expansion of family cascade testing by GPs.

Diagnosis

Irrespective of the approach taken, it is crucial to emphasise that all models of care for FH start with early detection. The sooner a diagnosis is made and treatment commences, the better are the outcomes for patients and their families.

After a patient has been screened and identified as possibly having FH, GPs can apply the DLCN criteria to establish a phenotypic diagnosis of probable FH (score 6 to 8) or definite FH (score over 8) in adult patients (Table). If FH is suspected, the GP is recommended to refer the patient to a lipid specialist, cardiologist or endocrinologist for further evaluation, including consideration of Medicare-rebated genetic testing.

The Medicare-funded genetic test for index cases can be ordered based on any one of the following criteria:

- DLCN score of 6 or more
- LDL-cholesterol level of 6.5 mmol/L or more in the absence of any secondary cause
- LDL-cholesterol level of 5.0 to

6.5 mmol/L with signs of premature or accelerated atherogenesis.

Although genetic testing can be used to confirm a diagnosis, a negative result does not exclude FH. The diagnosis can still be made based on phenotypic criteria (Table).[5]

The DLCN criteria are not suitable for use in children or adolescents because there has not been sufficient time for the development of associated clinical signs. Children who are at risk should be tested between the ages of 5 and 10 years. A probable diagnosis of FH is considered in children if:

- LDL-cholesterol level is over 5.0 mmol/L
- LDL-cholesterol level is 4.0 to 5.0 mmol/L and there is a parental history of hypercholesterolaemia or premature atherosclerotic CVD
- LDL-cholesterol level is over 3.5 mmol/L and a parent has a pathogenic or likely pathogenic gene variant.[18]

Most patients can be successfully managed in an ongoing manner by their GP, with specialist input and support as needed.[16]

Genetic testing for FH

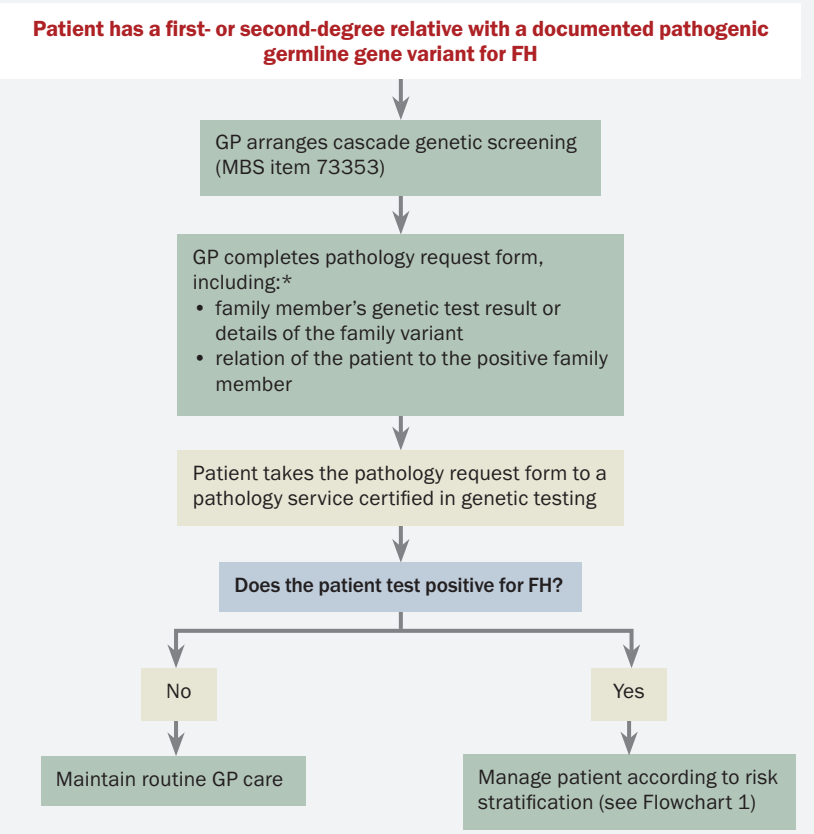
The Medicare Benefits Schedule (MBS) includes genetic testing items that can open the door for enhanced identification:

- item 73352 for index cases (which requires a non-GP specialist)
- item 73353 for cascade testing (which can be ordered by any doctor, including GPs).

Primary care physicians are empowered under Medicare to conduct 'predictive' genetic testing of family members of patients with a genetic diagnosis of FH. This has been available since 2020, but testing numbers suggest cascade testing is underutilised. As a result, family members at risk of FH are missing out on early diagnosis.

Implementation projects are currently underway to support GPs in carrying out family cascade genetic testing through a primary-tertiary shared care model.[19]

FLOWCHART 2. RECOMMENDED CASCADE GENETIC TESTING BY GPS FOR RELATIVES OF A PATIENT WITH A GENE VARIANT FOR FAMILIAL HYPERCHOLESTEROLAEMIA



Abbreviations: FH = familial hypercholesterolaemia; MBS = Medicare Benefits Schedule.
* FH cascade testing can be done with saliva or blood.

These projects are seeking ways to provide counselling and other support measures that will assist family cascade screening to be used for more patients and, thereby, allow more people, in particular young children and adolescents, to be diagnosed. As the burden of elevated LDL-cholesterol accumulates over time, younger individuals have the most to gain from an early diagnosis of FH and prevention of CVD.[20]

GPs can lead the way in enhancing detection rates with the new Medicare-funded cascade genetic testing, which should be offered to FH family members regardless of cholesterol levels. The transition from index case detection to widespread cascade screening has been the missing link in FH diagnosis. The role of the family GP is seen as the fundamental solution. A recommended process for GPs to arrange FH cascade screening is shown in Flowchart 2.

Why can FH be managed successfully in general practice?

Several features of primary care make this the ideal setting for managing FH. These features include regular patient visits, an established therapeutic relationship, shared decision-making, the potential for seeing multiple family members, continuity of care and the capacity to implement preventive measures and provide comprehensive health care.

The incentive to intervene early and substantially reduce lifetime risk is

RESOURCES TO HELP GPS IDENTIFY AND MANAGE PATIENTS WITH FAMILIAL HYPERCHOLESTEROLAEMIA

- **HealthPathways:** online health information portal that supports GPs at the point of consultation and includes information on FH; it is accessed via the local Primary Health Network (www.health.gov.au/our-work/phn)
- **Dutch Lipid Clinical Network Score (DLCN) Online Calculator:** calculator for adult phenotypic diagnosis available through the Australian Atherosclerosis Society (www.athero.org.au/fh/calculator/)
- **TARB-Ex:** electronic screening tool based on the DLCN criteria to help identify at-risk patients (https://bpsoftware.net/resources/bp-premier-downloads/)
- **Fact sheet on FH:** produced by the Centre for Genetics Education, NSW Health (www.genetics.edu.au/PDF/Familial_hypercholesterolaemia_fact_sheet-CGE.pdf)
- **Cascade genetic testing:** MBS item 73353, can be ordered by GPs (https://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=73353&qt=item)
- **Genetic counselling:** some public and private pathology services in Australia offer access to genetic counselling at no cost to the patient
- **Life insurance products and genetic testing in Australia:** (www.genetics.edu.au/SitePages/Life-insurance-products-and-genetic-testing-in-Australia.aspx)

Abbreviations: FH = familial hypercholesterolaemia; MBS = Medicare Benefits Schedule.

highlighted in the Figure through the concept of 'cholesterol years'. The Figure illustrates how the cumulative burden of LDL-cholesterol typically reaches 160 mmol by about the age of 55 years in the general population, by which stage clinical coronary heart disease may develop. An untreated individual with heterozygous FH will reach this threshold by the age of about 35 years. Starting a low-dose statin early will slow the progression of disease and delay the threshold for coronary heart disease to the age of 53 years, just behind the population

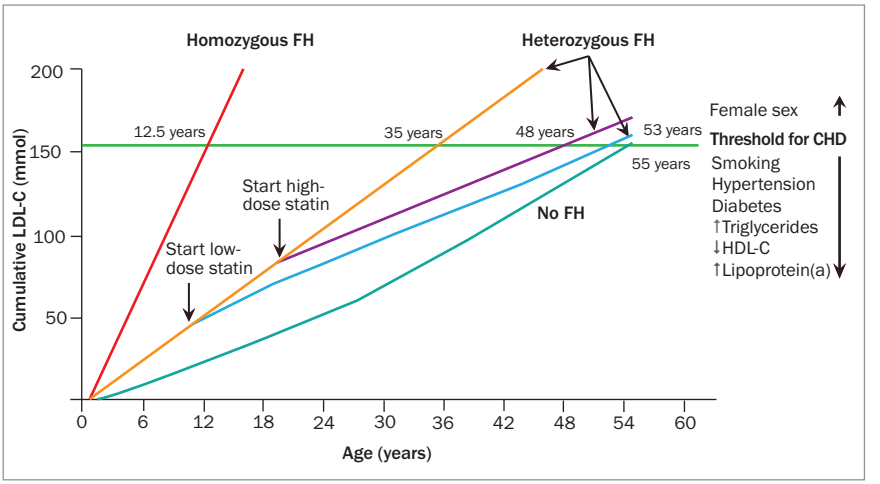


Figure. Lifetime cumulative burden of LDL-cholesterol in people with and without familial hypercholesterolaemia as a function of the age that statin therapy is commenced.

Abbreviations: CHD = coronary heart disease; FH= familial hypercholesterolaemia; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; ↑ = increased; ↓ = decreased.

Adapted from Nordestgaard BG, et al. Eur Heart J 2013; 34: 3478-3490.[9]

age of 55 years.[9] For individuals with FH, improved outcomes are achieved in those who are identified and treated early.

Support for GPs

The optimal care of FH requires patient-centred management that includes a multidisciplinary team.[5] Risk stratification will help identify the best pathway for management and help distribute care across teams depending on risk level (Flowchart 1). The best management approach involves the use of cholesterol-lowering medications, but also includes adherence to a heart-healthy lifestyle and avoiding non-cholesterol risk factors (e.g. smoking, hypertension, obesity and diabetes).[1]

Resources to assist GPs in the identification and management of FH are listed in the Box. GPs are also encouraged to access Health Pathways through their local Primary Health Network (www.health.gov.au/our-work/phn/your-local-PHN) for specific guidance on the diagnosis, treatment, and management of FH.

Conclusion

Considering the highly treatable and preventable nature of FH and its consequences, it is crucial to address gaps and challenges in the early identification and treatment of this common genetic disorder. GPs are well placed to play an important role in the prevention of early onset of CVD through early diagnosis and optimal management. The substantial benefits to individuals and families highlight the importance of addressing these challenges. A multidisciplinary, shared care, patient-centred management approach that includes GPs is important. 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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Testosterone, incretins and improving cardiometabolic health

An endocrinologist's perspective

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Testosterone, an anabolic hormone, can prevent or revert type 2 diabetes in men at high risk. Incretin-based weight-loss therapy is effective in both men and women, but reduces lean mass, as well as fat mass. Exercise may be the vital ingredient for preserving muscle and improving cardiometabolic health.

Treating obesity and preventing type 2 diabetes and cardiovascular disease are major contemporary health priorities. Testosterone treatment, which increases lean mass and reduces fat mass, may prevent or revert type 2 diabetes in high-risk men when used in conjunction with lifestyle intervention. However, other considerations preclude the widespread use of testosterone for this purpose. First- and next-generation incretin-based antiobesity pharmacotherapies are commanding increasing interest, and their advantages and disadvantages are reviewed in this article. The importance of considering changes in lean mass as well as fat mass is highlighted. This article also advises on the benefits of exercise in preference to testosterone treatment in overweight or obese men, and as an adjunct to incretin-based antiobesity pharmacotherapy in women and men.

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KEY POINTS

- Obesity is a gateway condition for type 2 diabetes and cardiovascular disease, and is associated with low testosterone concentrations in men.
- On a background of lifestyle intervention, testosterone treatment, which increases lean mass and reduces fat, can prevent or revert type 2 diabetes in men at high risk.
- Exercise training is more beneficial for overweight or obese men, promptly increasing fitness and muscle mass, and reducing fat, compared with testosterone treatment.
- Incretin-based antiobesity pharmacotherapy results in marked weight loss, primarily reducing fat but also reducing lean mass.
- Optimising body composition (enhancing muscle mass while reducing fat) may be the key to improving cardiometabolic health during ageing.

Testosterone and diabetes prevention

Men with lower testosterone concentrations are more likely to have or develop the metabolic syndrome or diabetes.[1,2] A large Australian multicentre, randomised controlled trial (RCT), Testosterone for the Prevention of Type 2 Diabetes Mellitus in men at high risk (T4DM), has proven this relation is causal.[3] In the T4DM trial, 1007 men aged 50 to 74 years with a waist circumference of 95 cm or above and impaired glucose tolerance or newly diagnosed type 2 diabetes were randomly allocated to two years of treatment with testosterone versus placebo, on a background of lifestyle intervention. At the end of the trial, men on testosterone were 40% less likely to have type 2 diabetes than placebo recipients.[3] A post-hoc mediation analysis concluded that changes in fat mass were the predominant contributor to the testosterone treatment effect.[4] However, a striking finding reported in the primary outcomes paper was the change in body composition: men on testosterone gained on average 0.39 kg of muscle mass and lost 4.6 kg of fat, whereas men in the placebo group lost 1.3 kg of muscle and 1.9 kg of fat.[3] A haematocrit level

greater than 54% occurred in 22% of men in the testosterone group compared with 1% in the placebo group, leading to cessation of treatment in 26 men (25 in the testosterone group or 5% of men in the initial enrolment into that arm of the trial).[3] Prudence is needed when translating the results of the T4DM trial given the requirement for a concomitant lifestyle intervention, uncertainty over the optimal duration of treatment, the need to monitor haematocrit levels and prostate risks (such as abnormal examination findings or elevation of prostate-specific antigen levels).[3,5] Testosterone treatment in this context is only applicable to men and, following cessation of treatment, endogenous hypothalamic–pituitary–testicular axis function typically recovers over six to 12 months (but may take longer), whereas metabolic gains diminish with extended follow up.[6,7]

Testosterone, central adiposity and cardiovascular risk

Excess weight and central adiposity are associated with lower testosterone concentrations, partly from reduced activity of the hypothalamic–pituitary–testicular axis, and from reduced sex hormone-binding globulin concentrations.[8,9] Reducing excess weight results in increased testosterone concentrations.[10] An analysis from the UK Biobank, and a meta-analysis of 11 prospective cohort studies that measured testosterone levels using mass spectrometry, showed no association of endogenous testosterone concentration with incidence of major adverse cardiovascular events in men.[11,12] This is consistent with the recent Testosterone Replacement Therapy for Assessment of Long-Term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) RCT, which was designed as a cardiovascular safety trial. The TRAVERSE trial included 5204 men with cardiovascular disease or cardiac risk factors (mostly overweight, obesity or type 2 diabetes) who received testosterone therapy for a mean duration of 22 months. The trial showed no effect of testosterone treatment on the risk of major adverse cardiovascular events over 33 months of follow up.[13] Of note, in the TRAVERSE trial, men receiving testosterone had a higher incidence of atrial fibrillation,[13] a finding reflected in an observational analysis of healthy older men in which higher endogenous testosterone concentrations were associated with higher incidence of atrial fibrillation.[14] In the TRAVERSE trial, men in the testosterone arm also had a higher incidence of clinical fractures.[15] In the T4DM trial, testosterone treatment increased cortical and total volumetric bone mineral density, and cortical thickness at tibial and radial sites, and increased areal bone mineral density at the lumbar spine.[16] Therefore, the excess of clinical fractures in the TRAVERSE trial is surprising, and warrants further investigation.

To summarise, endogenous testosterone is related to diabetes risk, and exogenous testosterone treatment modulates this risk. However, there appears to be no independent association of testosterone treatment with risk of major adverse cardiovascular events in men.

Testosterone versus exercise in men with overweight or obesity

If the effects of testosterone to reduce the risk of type 2 diabetes in the presence of a concomitant lifestyle intervention are mediated via changes in body composition, a key question is how testosterone compares with exercise to induce metabolically favourable changes in lean and fat mass. A single-centre RCT investigated the effects of testosterone and exercise, alone and in combination, in overweight and obese men aged 50 to 70 years.[17] This testosterone and exercise study showed that a centre-based supervised exercise training program incorporating both aerobic and resistance components, individualised and monitored by an exercise physiologist over 12 weeks, increased cardiorespiratory fitness, increased lean mass and reduced fat, outperforming testosterone.[17] There may be an additive effect of testosterone and exercise on lean mass and strength. Over the 12-week intervention, exercise improved endothelial function and ambulatory blood pressure whereas testosterone treatment did not.[18,19] Therefore, exercise training, provided it is correctly implemented and achieved, should be considered as an initial intervention in the setting of overweight or obesity. In a more general context, exercise is open to, and largely beneficial for, both men and women.

Incretin-based antiobesity pharmacotherapy

Glucagon-like peptide-1 (GLP-1) receptor agonists are a well-established therapy for people with type 2 diabetes, with their use now extended into the setting of obesity. In middle-aged adults with overweight or obesity, treatment with the GLP-1 receptor agonist semaglutide over 68 weeks reduced body weight by 14.9% (–15.3 kg) compared with 2.4% (–2.6 kg) for placebo.[20] A cardiovascular outcomes trial demonstrated a 20% reduction in the risk of major adverse cardiovascular events with semaglutide in people with overweight or obesity over a 40-month duration.[21] Next-generation incretin-based antiobesity pharmacotherapies are now available. In middle-aged adults with overweight or obesity, treatment with tirzepatide, a dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, resulted in 20.9% (–22.1 kg) weight loss after a 72-week intervention compared with 3.1% (–3.2 kg) for placebo.[22] The corresponding RCT of tirzepatide in people with obesity and type 2 diabetes showed a slightly attenuated result, with 15.7% weight loss over 72 weeks.[23] In middle-aged adults with overweight or obesity, treatment with retatrutide, a triple GLP-1, GIP and glucagon receptor agonist, at the highest dose resulted in 24.2% (–26.4 kg) weight loss over 48 weeks (–2.1% for placebo).[24] In these RCTs, although the headline results illustrated average changes in the groups, some individual participants lost substantially more weight. For example, in the retatrutide study, effects were dose-dependent and, at the highest dose, 48% of participants lost 25% or more of their body weight and 26% of participants

lost 30% or more.[24] Retatrutide is currently not available in Australia.

All three agents, semaglutide, tirzepatide and retatrutide, are administered as a weekly subcutaneous injection, demonstrate clear cardiometabolic benefit and provide for the first time effective medical alternatives to bariatric surgery. There are recognised side effects: patients should be warned about risks of nausea, vomiting, diarrhoea and constipation, and advised on how to mitigate or pre-empt these. For example, take small regular meals if nausea occurs, and maintain hydration and fibre intake to ward against constipation. Another increasingly recognised phenomenon is that although large amounts of weight are lost, and most of this is fat, some is lean or muscle mass. In the semaglutide RCT cited earlier, in the subgroup where body composition was analysed using dual energy x-ray absorptiometry, fat mass was reduced by 24.7% (–10.4 kg) and lean mass was reduced on an average by 13.9% (–6.9 kg).[20] In the tirzepatide RCT, in the subgroup studied using dual energy x-ray absorptiometry, 33.9% (about 17 kg) of total fat mass was lost, but also 10.9% (about 6 kg) of lean mass.[22]

Importance of preserving lean mass while losing fat

Muscle, which comprises a large portion of lean mass, is metabolically active and a major contributor to basal metabolic rate.[25] Loss of muscle mass reduces basal metabolic rate, predisposing to weight gain and fat accumulation. On cessation of semaglutide or tirzepatide therapy, more than half of the weight lost was regained after 12 months.[26,27] It is an open question whether or not loss of lean mass contributes to ease of weight regain.[28] Reduced muscle mass also predisposes older adults to sarcopenia and frailty, which carry adverse consequences for health. Thus, it would be prudent to counsel patients receiving incretin therapy to maintain protein intake, but the loss of lean mass remains a potential concern.

In a study of men with obesity who received 10 weeks of a very-low-calorie diet, testosterone therapy until 56 weeks enhanced fat loss and led to regain of lean mass.[29] In another study, following eight weeks of calorie restriction, adults with obesity were randomised to one of four strategies: liraglutide plus exercise group, liraglutide group, exercise group or placebo.[30] The exercise group aimed to achieve aerobic physical activity targets. Liraglutide with or without exercise led to more weight loss, whereas exercise alone increased lean mass and blunted overall weight regain.[30] These studies were designed to examine maintenance of achieved weight loss, and both pre-date the emergence of the newer incretins. Studies of adjunctive interventions applied concomitantly with incretin-based antiobesity pharmacotherapies are awaited. Nevertheless, the scope for interventions that build lean mass is clear. In the testosterone and exercise study discussed earlier, the exercise training regimen comprised a mixture of aerobic and resistance exercise stations.[17] Compared with aerobic exercise, resistance or weight-based exercise training has a greater effect to increase muscle mass and strength.[31] Therefore, pending further studies there is a strong argument to apply resistance exercise training as an adjunct to incretin-based weight loss interventions, to preserve lean mass and enhance fat loss, and possibly reduce weight regain on cessation of pharmacotherapy.[28]

Broader perspectives and conclusion

In men who are hypogonadal because of hypothalamic, pituitary or testicular disease, testosterone treatment is indicated to ameliorate the symptoms and signs of androgen deficiency.[32] Testosterone is not approved for the prevention or treatment of type 2 diabetes, and men who are found to have a low testosterone concentration may be referred to an endocrinologist for assessment. Testosterone treatment should be considered in hypogonadal men in whom no reversible causes or contraindications are present, and where fertility is not an issue, and they should be appropriately supervised and monitored.[33] The T4DM and TRAVERSE trials provide added reassurance with regards to cardiovascular (as well as prostate) safety of testosterone therapy.[3,13] Testosterone is an anabolic hormone, diabetes is a risk factor for dementia, and men with lower testosterone concentrations are at higher risk of dementia.[34] Therefore, the results of the T4DM and TRAVERSE trials provide a foundation for future studies in the general population of men, particularly those aged 70 years and above in whom Leydig cell impairment appears.[9] One such future RCT should be a large multicentre (possibly or necessarily multinational) RCT of testosterone treatment to prevent frailty and dementia in ageing men.

The newer incretin-based antiobesity pharmacotherapies are attracting increasing attention because of their demonstrated efficacy in the setting of cardiometabolic disease.[20-24] Although the potential benefits are substantial, side effects including loss of lean mass and the issue of weight regain on cessation of therapy merit close consideration. Every opportunity to encourage healthy lifestyle behaviours should be taken. In this and other health settings, exercise training should be considered to enhance outcomes and mitigate side effects.[28] Resistance exercise may be an important, nonpharmacological intervention to protect or even enhance muscle mass, thus optimising body composition and longer-term outcomes. A contemporary approach might involve general practitioners working with practice nurses, dieticians, psychologists and exercise physiologists, facilitating exercise and resistance exercise to improve cardiometabolic health in different health settings. 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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Testosterone, incretins and improving cardiometabolic health

An endocrinologist's perspective

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Type 1 diabetes
Reducing cardiovascular risk

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Cardiovascular risk is greatly increased in people with type 1 diabetes. Optimising glycaemic control and managing traditional risk factors, such as hypertension and dyslipidaemia, are the mainstay of treatment. In future, adjunctive noninsulin-based therapies may also have a role; however, these medications currently remain off label for type 1 diabetes, with more evidence needed.

KEY POINTS

- Cardiovascular risk is substantially increased in people with type 1 diabetes.
- Optimal management of blood glucose levels, as well as traditional cardiovascular risk factors, such as hypertension and dyslipidaemia, is the mainstay of management. There is evidence of undertreatment of cardiovascular risk factors in type 1 diabetes, particularly in younger age groups.
- Unique cardiovascular risk factors in type 1 diabetes include glycaemic variability and hypoglycaemia, as well as overall hyperglycaemia.
- Insulin resistance is increased in people with type 1 diabetes due to peripheral hyperinsulinaemia from subcutaneous insulin treatment, even at a lower body mass index.
- The pathophysiology of cardiovascular damage in type 1 diabetes is different from type 2 diabetes, and reliance on risk calculators designed for other patient groups can be misleading.
- Although there is potential for the use of adjunctive therapies such as sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists in type 1 diabetes, their use remains off label at this stage, and evidence for their effectiveness in reducing cardiovascular risk in this cohort is lacking.

Despite advances in the management of cardiometabolic disease in recent decades, premature cardiovascular disease (including coronary artery disease, acute myocardial infarction, stroke and heart failure) remains the greatest cause of mortality in people with type 1 diabetes. People with type 1 diabetes have at least three times the cardiovascular mortality risk of those without diabetes, and this is even more pronounced in people with onset of disease at a young age.[1,2] Further, female sex should not be considered to offer protection against cardiovascular disease in those with type 1 diabetes. Studies show a higher relative rate of cardiovascular disease in women compared with men with type 1 diabetes.[3]

This article explores the important differences in the pathophysiology of cardiovascular disease in type 1 diabetes, options for cardiovascular risk estimation in this cohort and treatment of traditional risk factors.

Pathophysiology of cardiovascular disease in type 1 diabetes

Several mechanisms contribute to cardiovascular damage in type 1 diabetes (Figure). These include traditional cardiovascular risk factors, such as hypertension, dyslipidaemia and excess weight, and there is evidence these are undertreated in people with type 1 diabetes. However, there are also cardiovascular risk factors unique to those with type 1 diabetes, such as glycaemic variability, hypoglycaemia, hyperglycaemia and insulin resistance.

Blood glucose management

Hyperglycaemia is a clear contributor to cardiovascular risk in type 1 diabetes. Likely mechanisms include oxidative stress and endothelial dysfunction caused by generations of damaging substances, such as advanced glycation end products, and

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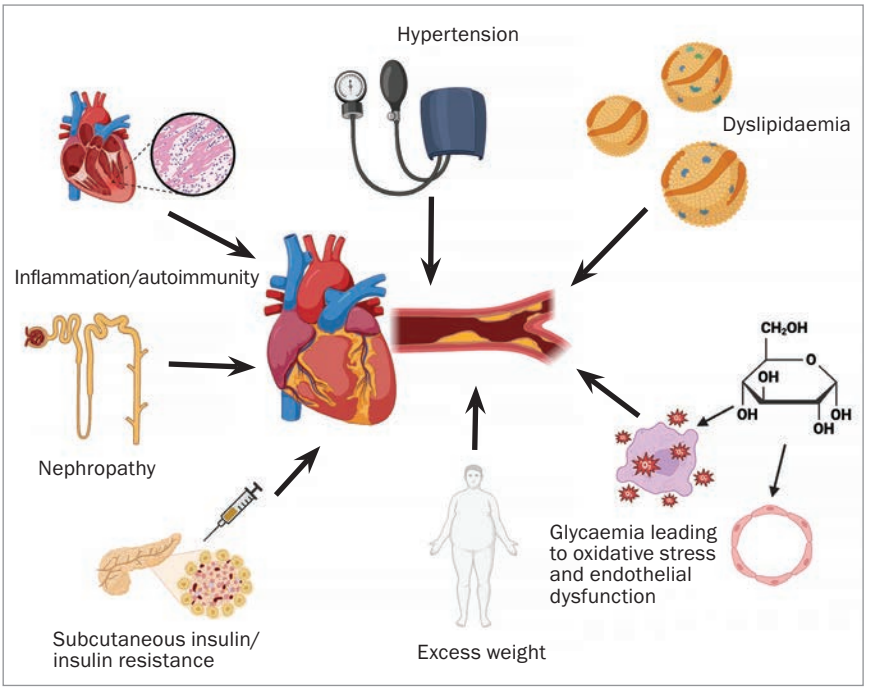

Figure. Mechanisms of cardiovascular damage in type 1 diabetes.
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inhibition of protective factors, such as endothelial nitric oxide synthase.[4]

Robust clinical trial evidence supports the benefits of optimising glycaemia in people with type 1 diabetes. The Diabetes Control and Complications Trial (DCCT), a landmark trial in type 1 diabetes management, showed that intensive glycaemic control over a 6.5-year period reduced the risk of developing cardiovascular disease over the next 10 years. These benefits persisted with follow up for 30 years in the Epidemiology of Diabetes Intervention and Complications (EDIC) study, showing management of glycaemia has ongoing effects or metabolic memory.[5]

With more widespread use of continuous glucose monitoring, variation in blood glucose levels has become easier to identify and study. Physiological studies in type 2 diabetes suggest oscillating blood glucose levels cause greater vascular dysfunction compared with stable levels of hyperglycaemia.[6] In type 1 diabetes, glycaemic variability and hypoglycaemia have been associated with endothelial injury and increased inflammation, as well as increased coronary artery calcium scores.[7-9] Dysglycaemia has also been shown to lead to autonomic neuropathy, which predicts cardiovascular mortality in type 1 diabetes.[10,11]

Optimising glycaemic control is therefore key to reducing cardiovascular risk in people with type 1 diabetes. Targets for glycated haemoglobin (HbA_{1c}) levels are usually less than 7%, however, they should be individualised. Time in range (3.9 to 10 mmol/L) is increasingly used as an alternative measure if continuous glucose monitoring is available, which is now subsidised under the National Diabetes Services Scheme for all people with type 1 diabetes.[12] Other factors, such as psychosocial issues, comorbidity and frailty, should also be considered in setting glycaemic targets for an individual.[13,14]

Insulin pump therapy may assist in improving overall glycaemia and reducing glycaemic variability. A large Swedish observational study showed that use of insulin pump therapy was associated with improved cardiovascular mortality when compared with multiple daily insulin injections.[15]

Insulin resistance

Insulin resistance, more commonly associated with type 2 diabetes, is underrecognised as a driver of cardiovascular disease in type 1 diabetes. It is partially induced by the necessity of subcutaneous insulin delivery for treatment, bypassing hepatic insulin clearance and leading to peripheral hyperinsulinaemia.[16] Intensive insulin therapy can lead to a vicious cycle of weight gain, increased insulin resistance and higher doses of insulin. The term 'double diabetes' has been coined to signify the occurrence of insulin resistance in people with type 1 diabetes and is estimated to occur in 30% of adults with type 1 diabetes.[17]

Currently, there are limited therapeutic interventions with evidence for directly decreasing insulin resistance. Lifestyle measures to manage weight and increase physical activity are likely to be of benefit. Optimising insulin therapy, including consideration of use of diabetes technologies (e.g. insulin pumps), to minimise overtreatment is also important.

Dyslipidaemia

The lipid profile in type 1 diabetes is altered, and the alteration is likely caused by portal insulin deficiency. HDL-cholesterol levels are often normal or even elevated, and triglyceride and LDL-cholesterol levels are at normal levels. Standard lipid testing can therefore be falsely reassuring in some cases, as increases in intermediate-density lipoprotein and small-dense LDL levels lead to an overall increase in atherogenesis.[18] In addition, elevated cardiovascular risk occurs at younger ages than screening and treatment would normally be considered.

Global lipid management recommendations vary for people with type 1 diabetes and no established cardiovascular disease (primary prevention); however, overall, statin therapy is recommended for all people with type 1 diabetes over 40 years of age, regardless of other cardiovascular risk factors. Statin therapy should also be considered in those under 40 years of age if additional cardiovascular risk factors are

present. In a randomised controlled trial in people aged 40 to 80 years with type 1 or type 2 diabetes, statin therapy improved cardiovascular outcomes, including in those without elevated HDL-cholesterol levels or known cardiovascular disease at baseline. Overall, the result was not significant for the type 1 diabetes subgroup although the trend was similar to those with type 2 diabetes.[19] Lipid management recommendations from major international guidelines are summarised in the Table.[20-23] Statins should be avoided in pregnant or breastfeeding women.

For people with type 1 diabetes and established cardiovascular disease (secondary prevention), recommendations for lipid-lowering therapy are the same as for the general population. Therapy consists of high-intensity statin therapy as first line, with ezetimibe and a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor as needed to reach LDL-cholesterol targets. Options include monoclonal antibodies (evolocumab and alirocumab) or inclisiran, a small interfering ribonucleic acid PCSK9 inhibitor. In Australia, the accepted LDL-cholesterol target for secondary prevention is 1.8 mmol/L, although US guidelines suggest a lower target of 1.4 mmol/L.[20]

Hypertension

Hypertension is common in people with type 1 diabetes.[24] Major guidelines advocate for blood pressure targets in line with other high-risk groups. The American Diabetes Association notes the lack of specific evidence to inform blood pressure targets in people with type 1 diabetes, however, suggests a target of less than 130/80 mmHg (Table).[20-23]

Individualisation of blood pressure targets is important. Autonomic neuropathy in people with type 1 diabetes can lead to postural hypotension, supine hypertension or loss of circadian blood pressure rhythm. This may mean the 130/80 mmHg target is unable to be achieved. In others, a more aggressive target may be achievable and potentially lead to better cardiovascular outcomes. If blood pressure exceeds 120/80 mmHg, lifestyle interventions, including weight loss, increased physical activity, reduced sodium intake, increased potassium intake, limited alcohol intake, smoking cessation and increased physical activity, should be encouraged. For those with established cardiovascular disease or diabetic nephropathy with albuminuria, first-line hypertension treatment should be an ACE inhibitor or angiotensin receptor blocker, although these medications should be avoided in pregnant women. Blockade of the renin-angiotensin-aldosterone system offers additional benefits in reducing albuminuria and cardiovascular risk. Furthermore, microalbuminuria in type 1 diabetes is clearly linked with increased cardiovascular risk.[25] If beta-blocker therapy is indicated, clinicians should caution patients that its use may reduce perception of hypoglycaemia symptoms.

Excess weight

The prevalence of overweight and obesity is increasing in the type 1 diabetes population, and may now exceed general population trends.[26] However, the issue is compounded in people with type 1 diabetes with the necessity of subcutaneous insulin treatment, leading to insulin resistance and weight gain. This creates a difficult balance between managing glycaemia and limiting total daily insulin dose. Excessive weight gain during the DCCT/EDIC trial was associated with an increase in cardiovascular events, which partially offset the benefit derived from intensive glycaemic control.[27]

Although lifestyle interventions, such healthy eating, physical activity and behavioural and psychological support, are the basis of any weight loss intervention, these pose additional challenges in the context of type 1 diabetes. Changes in diet and levels of physical activity require insulin dose adjustment, and during development of new habits this can be an additional barrier to change. A recent Australian study found a prevalence of disordered eating of 31% in a cohort of people with type 1 diabetes attending a metropolitan hospital clinic.[28] Insulin omission is often employed for weight loss, leading to safety concerns.[29]

Limited medication options are approved by the TGA for obesity treatment in Australia.[30] Phentermine, which reduces appetite by stimulating neurotransmitter release, is contraindicated in people with coronary artery disease. Orlistat inhibits lipases and therefore fat absorption, and can be used in type 1 diabetes; however, it is poorly tolerated due to side effects and cases of diabetic ketoacidosis have been reported.[31] A naltrexone and bupropion combination medication may be useful in regulating appetite and reward circuits in the brain, although, typically, weight loss is modest. Adjunctive therapies have been trialled in people with type 1 diabetes to reduce insulin requirements. These include glucagon-like peptide-1 (GLP-1) receptor agonists (liraglutide, semaglutide) and the dual GLP-1/gastric inhibitory polypeptide receptor agonist (tirzepatide). Liraglutide is approved by the TGA for a weight loss indication in Australia, as is 2.4 mg weekly semaglutide (although currently this dose is not available in Australia). Neither are approved by the TGA for use in type 1 diabetes. The potential use of adjunctive therapies in type 1 diabetes is discussed in more detail below.

Cardiovascular risk assessment

The Australian Chronic Disease Prevention Alliance recently updated the Australian cardiovascular disease risk guidelines. These guidelines include the Australian cardiovascular disease risk calculator, which uses a comprehensive equation to account for diabetes-specific risk factors, such as time since diagnosis, HbA_{1c} level, estimated glomerular filtration rate, urinary albumin:creatinine ratio, body mass index and insulin use.[32] However, although these risk factors have all been shown to contribute to cardiovascular risk in type 1 diabetes, the calculator is not validated for this group. Risk calculators specifically developed for type 1 diabetes include the

Steno T1 Risk Engine, derived from studies performed in Denmark, and a risk calculator based on Scottish and Swedish registries.[33-35] It is unclear whether the data may be extrapolated to the Australian population.

Newer imaging techniques, such as coronary artery calcium scores and CT coronary angiography for risk stratification, have been explored in type 1 diabetes. Coronary artery calcium scores have demonstrated validity in type 1 diabetes

TABLE. BLOOD PRESSURE AND LIPID MANAGEMENT RECOMMENDATIONS FOR TYPE 1 DIABETES[20-23]

	American Diabetes Association 2023[20]	United Kingdom National Institute for Health and Care Excellence (NICE) 2022–23[21,22]	European Society for Cardiology 2023[23]
Blood pressure	• If elevated blood pressure (systolic blood pressure 120 to 129 mmHg and diastolic <80 mmHg) suggest lifestyle intervention: – weight loss – reduced dietary sodium and increased dietary potassium – address excess alcohol – smoking cessation – increased physical activity • If blood pressure >130/80 mmHg add: – ACE inhibitor or angiotensin receptor blocker as first-line therapy • Target blood pressure <130/80 mmHg – individualise as appropriate if comorbidities (e.g. autonomic neuropathy and orthostatic hypotension, advanced age) – lower targets may be appropriate if tolerated, particularly in younger patients	• If urinary albumin:creatinine ratio is <70 mg/mmol, aim for blood pressure <140/90 mmHg • If urinary albumin:creatinine ratio is >70 mg/mmol, aim for blood pressure <130/80 mmHg • If age >80 years, target blood pressure <150/90 mmHg regardless of urinary albumin:creatinine ratio • Start a trial of a renin-angiotensin system blocking drug as first-line therapy	• Consider lower blood pressure targets (120/80 mmHg) in young adults with childhood-onset type 1 diabetes
Lipid management	**Primary prevention** • One or more cardiovascular risk factors: use high-intensity statin therapy to reduce LDL-cholesterol by ≥50% of baseline and to target an LDL-cholesterol goal of <1.8 mmol/L • Age 20 to 39 years: consider statin therapy in addition to lifestyle modification • Age 40 to 75 years: moderate-intensity statin therapy in addition to lifestyle modification (weight loss if indicated, Mediterranean or DASH eating pattern, reduce saturated and trans fat, increase dietary n-3 fatty acids, viscous fibre and plant stanol/sterol intake and increase physical activity) • Age 40 to 75 years and higher cardiovascular risk (multiple risk factors, LDL-cholesterol >1.8 mmol/L): consider adding ezetimibe or PCSK9 inhibitor to maximum tolerated statin therapy • Age >75 years: if already on statin therapy, continue, or initiate after risk–benefit discussion **Secondary prevention** • Use high-intensity statin therapy to target LDL reduction ≥50% from baseline and LDL-cholesterol <1.4 mmol/L • Add ezetimibe or PCSK9 inhibitor if goal is not achieved on maximum tolerated statin therapy	**Primary prevention** • Offer statin treatment if: – aged >40 years – diabetes duration >10 years – established nephropathy – other cardiovascular risk factors • Consider statin treatment if aged 18 to 40 years **Secondary prevention** • Target LDL-cholesterol <2.0 mmol/L or non-HDL cholesterol <2.6 mmol/L	**Primary prevention** • Consider statin treatment if aged >40 years • Consider statin treatment if aged 18 to 40 years and with other cardiovascular risk factors, microvascular end-organ damage or 10-year cardiovascular disease risk of >10%

Abbreviations: DASH = Dietary Approaches to Stop Hypertension; PCSK9 = proprotein convertase subtilisin/kexin type 9.

but there is insufficient evidence to recommend they be used for routine screening.[36,37]

Role of adjunctive agents in reducing cardiovascular risk

With the increasing availability of multiple agents shown to improve cardiovascular outcomes in type 2 diabetes, interest in repurposing these medications to improve outcomes in type 1 diabetes is increasing. The 2024 American Diabetes Association guidelines recommend treatment with a sodium-glucose cotransporter-2 (SGLT-2) inhibitor and/or GLP-1 receptor agonist for people with type 2 diabetes and high cardiovascular risk or heart failure.[20] However, at this stage there are no noninsulin medications approved by the TGA for type 1 diabetes, although many are used off label in this context.[38]

Metformin

Evidence for cardiovascular protection with use of metformin is mixed in the general population, in those with type 2 diabetes, and in small trials with surrogate cardiovascular endpoints in type 1 diabetes.[39] A meta-analysis of trials in type 1 diabetes found that use of metformin reduces insulin dose requirements.[40]

The Reducing With Metformin Vascular Adverse Lesions (REMOVAL) study in adults with type 1 diabetes and more than three cardiovascular risk factors followed progression of common carotid intima-media thickness (cIMT) as a surrogate measure of cardiovascular risk for three years. Progression of mean cIMT was not significantly reduced with use of metformin but maximal cIMT, a tertiary endpoint, was significantly reduced.[39] A subgroup analysis by smoking status found that progression of mean cIMT (per year) was reduced by use of metformin versus placebo in never-smokers.[41]

Overall, evidence does not support use of metformin for cardiovascular risk reduction; however, it is relatively safe and may be useful for insulin dose reduction on a case-by-case basis.

SGLT-2 inhibitors

Although originally developed for their glycaemic effects in people with type 2 diabetes, SGLT-2 inhibitors are now approved by the TGA and listed on the PBS for both heart failure and chronic kidney disease, independent of diabetes status. Trials in people with type 1 diabetes have shown a glycaemic benefit with reduced HbA_{1c}, increased time in range, reduced glycaemic variability, weight loss and decreased blood pressure with use of SGLT-2 inhibitors, all of which theoretically translate into reduced cardiovascular risk.[42] However, these trials also demonstrated an increased risk of diabetic ketoacidosis. Trials of SGLT-2 inhibitors at lower than standard therapeutic dose did not show an increased risk of ketoacidosis or hypoglycaemia, although did show benefit for glycaemia and weight.[43] It is unclear whether cardioprotective benefit is maintained at this dose and it should also be noted that people with type 1 diabetes were excluded from trials showing cardiovascular benefit.

If SGLT-2 inhibitors are used in people with type 1 diabetes, careful attention to individual risk of ketoacidosis, education regarding symptoms and potential precipitants, and availability of ketone strips for testing are all crucial and likely require input from an endocrinologist.

GLP-1 and GLP-1/GIP receptor agonists

Large clinical trials in type 2 diabetes have demonstrated a reduction in major adverse cardiovascular events with incretin-based medications, and more recently in obese individuals without diabetes.[44] Liraglutide, semaglutide and tirzepatide have all been shown to lead to weight loss and, in addition to effects on the gut, are thought to cause direct suppression of appetite.[45]

The incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are secreted by the neuroendocrine cells in the intestinal epithelium, and promote insulin release in response to food intake, known as the 'incretin effect'. The effects of GLP-1 or GIP agonism differ in type 1 diabetes because of impaired or absent insulin secretion. However, GLP-1 and GIP modulate glucagon as well as insulin release. Glucagon dysregulation in type 1 diabetes results in inappropriate postprandial glucose release (which raises blood glucose levels) and an inadequate response to hypoglycaemia. GLP-1 has been shown to reduce glucagon levels and increase insulin sensitivity in those with type 1 diabetes, may reduce postprandial hyperglycaemia and reduce insulin dose, in addition to any weight loss or direct cardiovascular effect.[46,47]

At this stage, use of incretin-based medications, such as semaglutide and tirzepatide, remain off label for use in type 1 diabetes; however, real-world use has shown promise and prospective clinical trials are needed and planned.[48,49]

Conclusion

Cardiovascular disease is the greatest contributor to the gap in mortality between people with type 1 diabetes and the general population. This risk can be reduced by optimising glycaemia and addressing traditional risk factors, such as hypertension, dyslipidaemia, smoking and excess weight. Much of the evidence for intervention to reduce cardiovascular risk in type 1 diabetes is extrapolated from studies performed in the general population or in people with type 2 diabetes. It is important to recognise that usual assessment tools have limitations in assessing risk in type 1 diabetes, and a high degree of vigilance is needed to prevent cardiovascular events in this high-risk group. 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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Type 1 diabetes
Reducing cardiovascular risk

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Transgender health
Managing cardiovascular risk in adults who use gender-affirming hormone therapy

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Cardiovascular risk appears to be higher in transgender individuals who are receiving gender-affirming hormone therapy; however, it remains unclear how much of this specifically relates to hormone therapy. Understanding the impact of gender-affirming hormone therapy on specific factors, including venous thromboembolic risk, changes in body composition, insulin resistance, lipid levels and blood pressure, can help mitigate potential cardiovascular risk in the transgender population.

Transgender individuals experience incongruence between the sex assigned to them at birth and their deeply held sense of gender identity. Many transgender individuals use gender-affirming hormone therapy to align their body with their gender identity. Use of masculinising hormone therapy (testosterone) in transgender men and feminising hormone therapy (estradiol and antiandrogen agents) in transgender women are both associated with improvements in psychological outcomes and quality of life.[1]

Gender-affirming hormone therapy is usually continued lifelong and understanding any potential adverse effects is important to try to mitigate any potential risks. Monitoring and longer-term management of the use of gender-affirming hormone therapy largely takes place in the general practice setting and a practical approach to monitoring and optimising cardiovascular risk in transgender adults is needed. An individual considered to be at high risk should be referred for more specialised cardiovascular assessment.

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KEY POINTS

- Transgender adults who are using gender-affirming therapy have an almost twofold higher mortality rate compared with the general population.
- Transgender women are more likely to die from cardiovascular disease and have higher rates of venous thromboembolic disease and stroke compared with the general population.
- Risk of mortality from cardiovascular disease in transgender men is inconclusive, with different studies showing contrasting results.
- Modern gender-affirming hormone therapy formulations may confer a lower risk of cardiovascular disease than the regimens historically studied.
- Ethinylestradiol and conjugated estrogens are not recommended for transgender women. Transdermal, rather than oral, estradiol is preferred for transgender women at higher cardiovascular risk.
- Smoking cessation, regular exercise, dietary interventions and maintaining a healthy weight range are recommended.
- Monitoring blood pressure, weight, body mass index, lipid profile and blood glucose level are recommended annually.

Overall cardiovascular risk

Cardiovascular risk is influenced by genetic and environmental factors. Sex hormone exposure is known to play a significant role, as it influences body composition, insulin resistance and lipid profile. The relations between sex hormones and cardiovascular risk is complex, and it is currently unclear exactly how much of this sex hormone-related risk is assumed or mitigated while taking gender-affirming hormone therapy. In addition, transgender individuals experience significant minority stress and higher socioeconomic disadvantage. As a community, they face higher rates of discrimination, and have significant barriers when accessing healthcare, which are all likely to negatively impact cardiovascular risk.

Trans health research is an emerging field and, as such, our understanding of cardiovascular risk in transgender populations is limited. Ongoing studies typically include a heterogeneity of participants often taking varying hormone formulations, and much of the published data comes from retrospective cohort studies that include participants on hormone therapy regimens no longer used nor recommended.

In 2021, a large Dutch retrospective cohort study found that transgender adults using gender-affirming hormone therapy had an approximate twofold higher mortality rate than the general population. Transgender women had a higher risk of death compared with both general population men and women due to cardiovascular disease, HIV-related disease, lung cancer and suicide.[2] Transgender women were also 2.6 times more likely to die from cardiovascular disease compared with general population women (95% confidence interval [CI], 1.9–3.4) and 1.4 times more likely compared with general population men (95% CI, 1.0–1.8). Death from myocardial infarction was similar compared with general population men but 2.6 times higher (95% CI, 1.7–4.5) compared with general population women.[2]

A large 2019 retrospective cohort study (using data collected between 1972 and 2015) showed that transgender women had a higher rate of venous thromboembolic disease and stroke.[3] A major limitation of the study was the inclusion of data from participants on hormone therapy regimens that are no longer recommended, such as ethinylestradiol and conjugated estrogen.

The previously mentioned 2021 Dutch study found no significant increase in mortality from cardiovascular disease, including myocardial infarction, in transgender men compared with either general population men or women; however, transgender men had a higher risk of death from non-natural causes compared with general population women.[2] By comparison, a large 2019 retrospective cohort study showed that transgender men had similar rates of myocardial infarction to general population men, but higher rates than general population women.[3]

Venous thromboembolic risk

Studies evaluating risks associated with gender-affirming hormone treatment showed that transgender women taking traditionally used formulations, such as ethinylestradiol 100 mcg daily and cyproterone acetate 100 mg daily, had an extremely high venous thromboembolic risk (6.3%).[4] Conjugated equine estrogens have also been associated with a high risk of venous thromboembolism (VTE) and are no longer recommended.[5] In contrast, modern gender-affirming hormone therapy regimens involving oral or transdermal estradiol have a lower risk of VTE, with recent observational data suggesting the risk is between 0 and 2%.[6] Transdermal estradiol may confer the lowest risk of VTE, based on studies in menopausal women using hormone therapy.[7] It is unclear if antiandrogen agents have an independent effect on cardiovascular risk.

Transgender men using intramuscular testosterone had a higher rate of polycythaemia than those taking transdermal preparations, which may contribute to thromboembolic risk.

Body composition and insulin resistance

A potential explanation for higher cardiovascular risk in transgender adults is the large body composition changes that occur during gender-affirming hormone therapy. Although an individual's overall weight may change only by a few kilograms, there are large fluctuations in lean and fat mass. Body composition studies in transgender women show higher overall fat mass (median, +9.8 kg), higher gynoid distribution of fat (hip and thigh) and lower lean mass (median, –6.9 kg). These changes were associated with higher levels of markers of insulin resistance. Although transgender women had more gynoid fat, the central android fat mass was not actually lower, which, along with the lower lean mass, likely explained the insulin resistance in this group.[8]

Transgender men had significantly higher lean mass (median, +7.8 kg) as well as a higher android to gynoid fat ratio; however, no significant differences in insulin resistance were observed. This may be because there was no overall increase in fat mass compared with control women (who were not taking gender-affirming hormone therapy), with the increase in lean mass conferring some protection.[8]

Lipids

In transgender women taking feminising hormone therapy, a meta-analysis of 29 studies (n=323) showed no significant differences in total, LDL or HDL cholesterol levels. Triglyceride levels, however, were higher than baseline after 24 months using hormone therapy.[9] Two large cohort studies and one prospective study of participants taking masculinising hormone therapy observed higher total LDL cholesterol and triglyceride levels, as well as lower protective HDL cholesterol.[10-12]

Blood pressure

Studies of feminising and masculinising hormone therapy regimens show conflicting results regarding blood pressure, with some studies showing an increase and others showing no increase in blood pressure in people taking these hormone therapies.[10,11,13,14] Therefore, overall blood pressure is not thought to be significantly affected by gender-affirming hormone therapy regimens. Nonetheless, hypertension is common in all populations and a standard approach to prevention and management is important.

Other factors

Other factors, such as smoking, diet and exercise, may also affect cardiovascular risk, but these factors have not yet been extensively studied in transgender populations. Minority stress, such as gender-based discrimination, violence and structural stressors, may also contribute to social determinants of health.

Monitoring cardiovascular risk

Before a person commences gender-affirming hormone therapy, performing a full set of baseline blood tests is recommended, including full blood examination, liver function tests and electrolyte, fasting lipid and glucose levels, as well as estradiol and total testosterone levels.[15] In addition, blood pressure and weight should be checked at baseline and rechecked at least annually.[15] More frequent blood testing is usually performed during the first year

of gender-affirming hormone therapy but longer term, monitoring fasting glucose and lipid levels at least once every 12 months is recommended.[15]

When monitoring biochemistry results in transgender patients, using the reference range of the affirmed gender is generally recommended (for example, the male reference range should be used when interpreting blood tests in a transgender man). An exception is high-sensitivity cardiac troponin testing, as it appears that little cardiac remodelling or change in cardiac size occurs, even with high-dose testosterone concentrations. Therefore, reference range that correlates to presumed sex at birth should instead be used when interpreting high-sensitive cardiac troponin levels (i.e. the female reference range should be used in a transgender man), and taking serial measurements can be helpful.[16]

A practical approach to cardiovascular risk prevention

It is prudent to encourage smoking cessation, an active lifestyle and a healthy diet in all patients. Blood pressure should be checked routinely, and weight and body mass index monitored at least annually.

In transgender women, transdermal preparations of estradiol are generally preferred, particularly in those aged over 45 years or with any additional risk factor for VTE such as smoking, diabetes or obesity.[15] For those at very high risk of VTE (such as a prior pulmonary embolus), anticoagulation therapy may be appropriate. Serum estradiol should be monitored to prevent supratherapeutic levels, and ethinylestradiol and conjugated estrogens should not be used.

In transgender men taking testosterone, haematocrit level should be monitored and ideally remain below 0.5 L/L. If polycythaemia is present, lowering the dose of testosterone or swapping from an intramuscular to a transdermal testosterone preparation can be useful in addition to smoking cessation.

Conclusion

With the limited data available to date, transgender individuals appear to have a higher cardiovascular risk than the general population. Modern formulations may confer a lower risk of cardiovascular disease than the regimens historically studied. Monitoring cardiovascular risk is performed through baseline and annual blood tests, as well as physical examination (blood pressure, weight, body mass index). Individuals should be counselled on what is known about cardiovascular risk and the contributing factors to that primary prevention strategies can be implemented. Smoking cessation, regular exercise and a healthy diet are recommended. Insulin resistance, lipid profile and blood pressure should be optimised. When investigating high sensitivity troponin levels, using the reference range relating to sex presumed at birth is recommended. To accurately understand cardiovascular risk in transgender adults, additional research that evaluates modern hormone therapy regimens while also controlling for potential confounding factors (such as smoking and minority stress) are needed. MT

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