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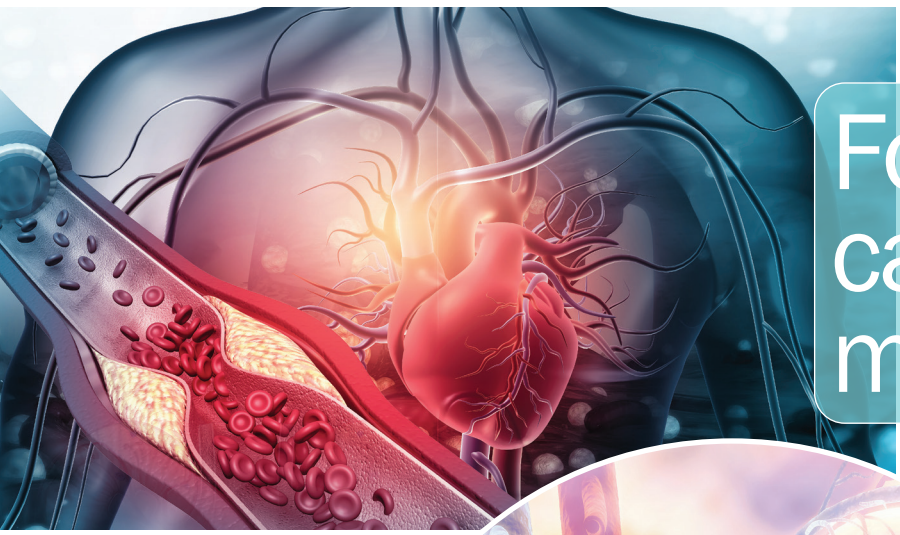
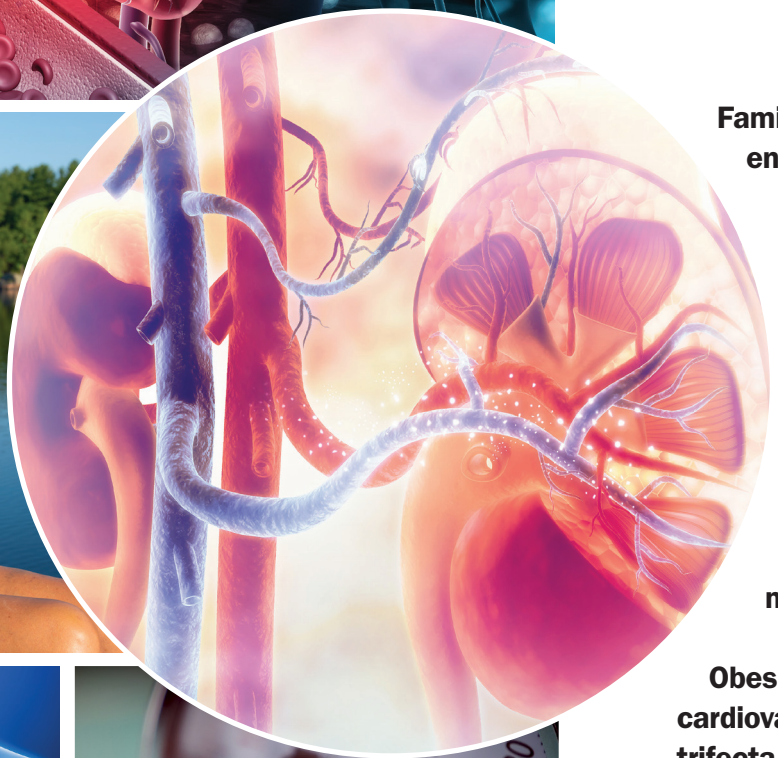
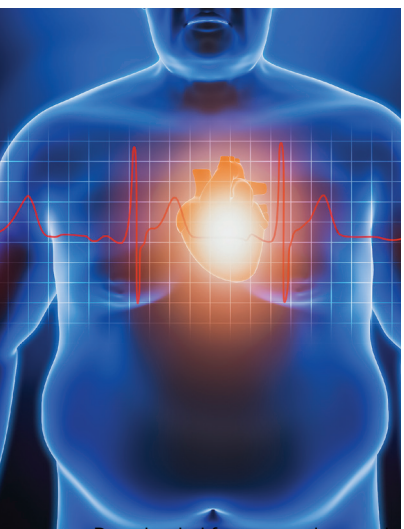


August 2023

Focus on cardiometabolic matters





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SYDNEY OFFICE
Suite 210, 40 Yeo Street,
Neutral Bay NSW 2089

POSTAL ADDRESS
PO Box 1473,
Neutral Bay NSW 2089

TELEPHONE (02) 9908 8577
FACSIMILE (02) 9908 7488

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FOREWORD FROM THE SUPPLEMENT EDITORS

FEATURE ARTICLES PEER REVIEWED

CARDIOMETABOLISM CLINIC PEER REVIEWED

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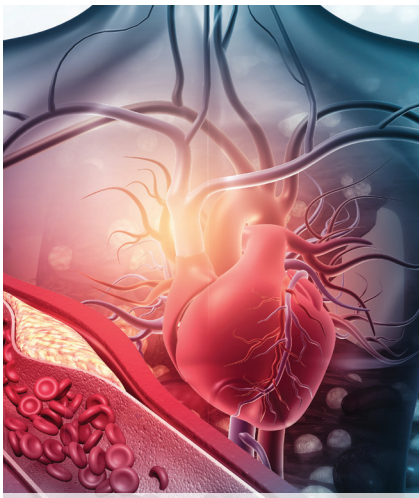

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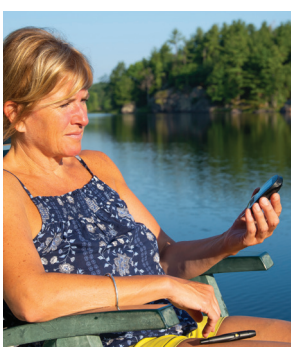

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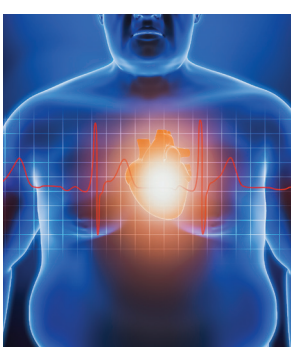

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Foreword
from the Supplement Editors

Cardiometabolic challenges

Cardiometabolic disease describes a spectrum of common but often preventable conditions that pose a significant health and economic burden. Advances in screening and investigation to identify predisposing and contributing risk factors pave the way for preventive management in patients. Furthermore, the emergence of new therapies and approaches in diabetes, hypertension, hypercholesterolaemia and kidney disease will result in an enhanced toolkit in our fight against cardiometabolic disease.

This supplement contains five articles that explore approaches to the diagnosis, management and treatment of a range of conditions that increase an individual's cardiovascular risk, including hypertension, type 2 diabetes, hypercholesterolaemia, kidney disease and obesity.

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

PROFESSOR GEMMA FIGTREE

PROFESSOR LOUISE BURRELL

Professor Gemma Figtree MBBS, DPhil (Oxon), FRACP, FCSANZ, FAHA

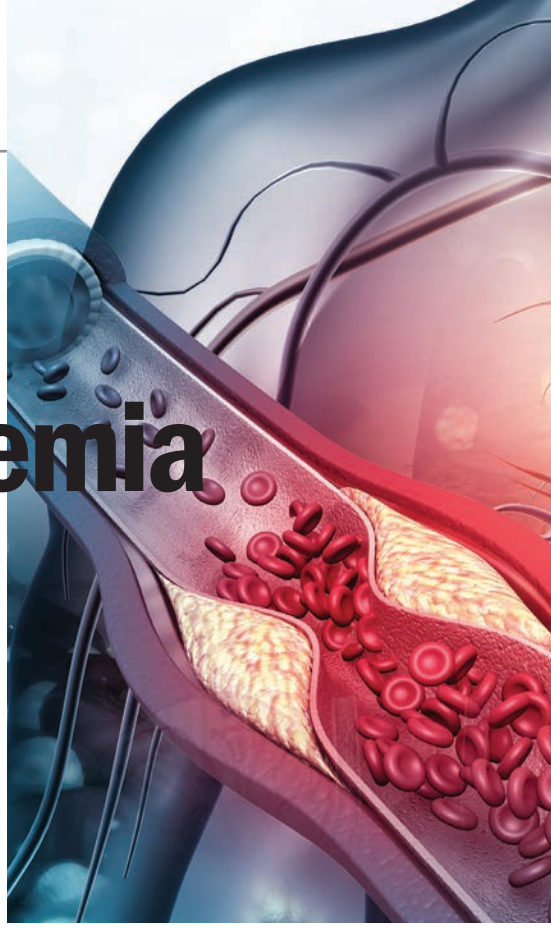
Professor in Medicine at The University of Sydney; and Professor of Medicine Northern Clinical School at Kolling Institute of Medical Research, Sydney, NSW.

Professor Figtree co-leads the Cardiovascular Theme for Sydney Health Partners, an NHMRC Advanced Health Research and Translation Centre, and is the Chair of The University of Sydney's multidisciplinary Cardiovascular Initiative. She is also President of the Australian Cardiovascular Alliance and Chair of the Mission for the Medical Research Future Fund Cardiovascular Health Expert Advisory Panel.

Professor Louise Burrell MBChB, MRCP, MD, FRACP, FAHA

Professor of Medicine at the University of Melbourne; and Head of Medical Unit 4 and Director of Research in General Medicine at the Austin Hospital in Melbourne Vic; and a Board Member of the Institute of Breathing and Sleep.

At the University of Melbourne, she heads the Cardiovascular Research Group, a multidisciplinary team of scientists, physicians and PhD students. She has held major roles with the International Society of Hypertension, including Vice President, Treasurer and Chair of the International Forum and Regional Advisory Groups.



Familial hypercholesterolaemia

Enhancing the care of patients and families

NICK S.R. LAN MB BS(Hons), MClinUS, MClinRes(Dist); **JING PANG** PhD
GERALD F. WATTS DSc, PhD, MD, FRCP, FRACP

Familial hypercholesterolaemia (FH) is a common genetic disorder of LDL-cholesterol, that, if untreated, leads to premature atherosclerotic cardiovascular disease (ASCVD). With early diagnosis and initiation of cholesterol-lowering treatment, the risk of ASCVD can be substantially reduced. Yet, many people with FH remain undiagnosed and undertreated. GPs can play an important role in the care of patients and families with FH.

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Dr Lan is a Cardiology Advanced Trainee in the Departments of Internal Medicine and Cardiology, Royal Perth Hospital; and a Clinical Senior Lecturer in the School of Medicine, University of Western Australia, Perth. Dr Pang is a Research Fellow in the School of Medicine, University of Western Australia, Perth. Professor Watts is Senior Consultant Physician in the Departments of Internal Medicine and Cardiology, Royal Perth Hospital, Perth; and Winthorp Professor of Cardiometabolic and Internal Medicine at the University of Western Australia, Perth, WA.

Familial hypercholesterolaemia (FH) is an autosomal dominant and highly penetrant genetic disorder affecting the LDL receptor pathway. FH is characterised by lifelong elevated plasma LDL-cholesterol (LDL-C) levels due to impaired hepatic clearance, and by an increased risk of atherosclerotic cardiovascular disease (ASCVD), particularly coronary artery disease.[1] Heterozygous FH is one of the most common monogenic conditions, with an estimated prevalence of one in 250 people worldwide.[2] Some ethnic groups may have a higher frequency of FH due to gene founder effects, including the Afrikaans, Christian Lebanese and French Canadian populations. In Australia, there are about 100,000 people living with FH.[3] Compared with the general population, the risk of coronary artery disease may be over 10-fold higher in patients with heterozygous FH.[4,5] Homozygous or compound heterozygous FH has an estimated prevalence of one in 160,000 to 300,000 people and manifests as very elevated levels of LDL-C (typically >10 mmol/L), with severe ASCVD and aortic valve sclerosis often present by the late teenage years, or earlier if untreated.[6]

The major driver of ASCVD risk in people with FH is the cumulative exposure to elevated plasma LDL-C levels from birth (Figure 1).[7] Early initiation of lifestyle measures and medications to reduce LDL-C levels in people with FH can effectively reduce the risk of ASCVD.[8] However, most people with FH remain undiagnosed and undertreated, representing a missed opportunity for ASCVD prevention and a major public health problem.[9] GPs request more than 90% of LDL-C measurements and 88% of Australians present to GPs annually.[10,11] A survey of Australian GPs showed that most considered they were the most effective health practitioners for managing FH.[12]

KEY POINTS

- Familial hypercholesterolaemia (FH) is a common genetic disorder of the LDL receptor pathway, with the heterozygous form affecting one in 250 individuals.
- A diagnosis of FH should be suspected in people with an elevated LDL-cholesterol (LDL-C) level (>5 mmol/L), especially if there is a personal or family history of premature coronary artery disease.
- The Dutch Lipid Clinic Network Criteria can be used to make a phenotypic diagnosis of FH; however, it should not be used in children.
- Genetic testing plays a role in confirming the diagnosis (MBS item 73352), atherosclerotic cardiovascular disease risk stratification and cascade testing (MBS item 73353).
- Because FH is an autosomal dominant condition, cascade testing is important to identify undiagnosed relatives of index cases.
- High-intensity statins remain the cornerstone of therapy; however, the addition of ezetimibe and monoclonal antibodies targeting PCSK9 may be required to attain LDL-C goals.
- A multidisciplinary approach and integration of services are required to implement optimal care of patients and families with FH.

GPs are ideally placed to enhance the care of patients and families with FH.[11] The purpose of this article is to provide a contemporary overview of the diagnosis and management of FH.

Screening

FH meets all criteria for screening for a condition. Several strategies for universal, targeted, systematic and opportunistic screening have been proposed to detect probands (i.e. the first person diagnosed with FH in a kindred).[13] Examples of FH screening strategies (Table 1) include universal screening of children at the time of immunisations coupled with 'reverse' cascade testing of parents if the child is found to have the condition, targeted screening of patients with premature ASCVD in coronary care units or rehabilitation programs, application of electronic tools to systematically search GP patient databases, and interpretative comments and alerts on lipid profile results issued by pathology laboratories.[13,14]

Opportunistic screening of adults, such as during a health check, should be employed in primary care to detect FH, based on an LDL-C level above 5 mmol/L.[3] Owing to practical advantages, nonfasting samples can be considered for FH screening but should be used with caution in patients with hypertriglyceridaemia

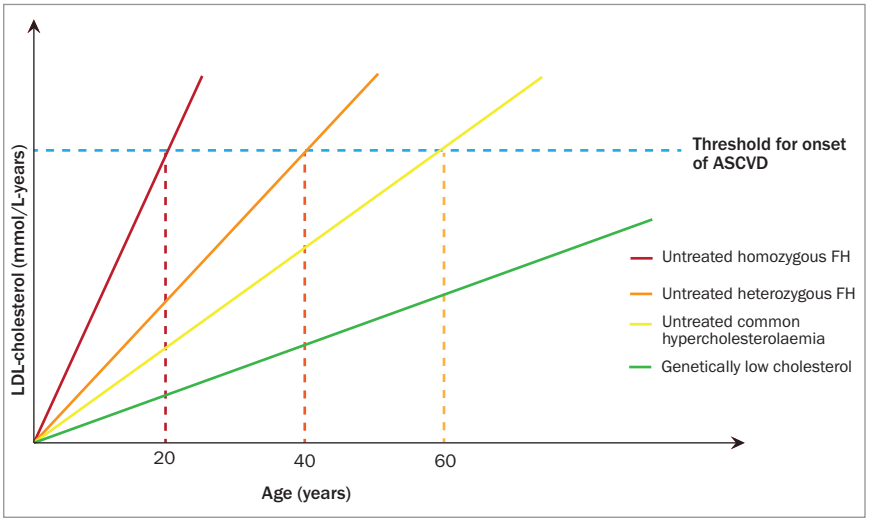


Figure 1. Time course for the onset of ASCVD. The solid lines represent different plots of cumulative LDL-C with age in individuals with varying risk of ASCVD, with the threshold for onset represented by the dashed horizontal line. Patients with untreated homozygous FH have the steepest slope of LDL-C versus age (red line) and experience earlier onset of ASCVD compared with those with untreated heterozygous FH (orange line) or untreated common hypercholesterolaemia (yellow line). Individuals with genetically low cholesterol from birth have a markedly reduced risk of developing ASCVD (green line).

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol.

Adapted from Shapiro MD, Bhatt DL. J Am Coll Cardiol 2020; 29: 1517-1520.[7]

TABLE 1. SCREENING STRATEGIES FOR FAMILIAL HYPERCHOLESTEROLAEMIA

Screening strategy	Features
Opportunistic screening for family history and lipid profile	• Patients with a positive family history have their plasma lipid profile measured and are examined for clinical features of FH • Patients with high LDL-C levels (>4.9 mmol/L for adults and >4.0 mmol/L for children) are reviewed for family history and clinical features of FH
Opportunistic alerts and interpretative comments on pathology reports	Flagging of LDL-C higher than 5.0 mmol/L on pathology reports to alert GPs and suggest referral to a specialist for assessment
Targeted screening of high-risk coronary patients in secondary and tertiary centres	Targeted screening in: • patients younger than 60 years of age presenting to coronary care, stroke, cardiothoracic and vascular units • patients attending cardiac rehabilitation programs
Systematic searching of medical records	Search of electronic records and systematic selection of medical notes to identify potential index cases
Universal screening of newborns	Integrating FH testing into the newborn screening programs
Universal screening of children	Universal screening of children, where all children at a certain age have their lipid levels measured; for example, at time of immunisation
Population screening of young adults	Offer DNA testing to all young adults for a range of preventable conditions
Cascade screening (or testing) of family members	• Systematic screening of blood relatives of index cases with a definite diagnosis of FH. This usually starts after identification of an adult with FH • 'Reverse cascade screening' is when a child is first identified, and family members are subsequently tested

Abbreviations: FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol.

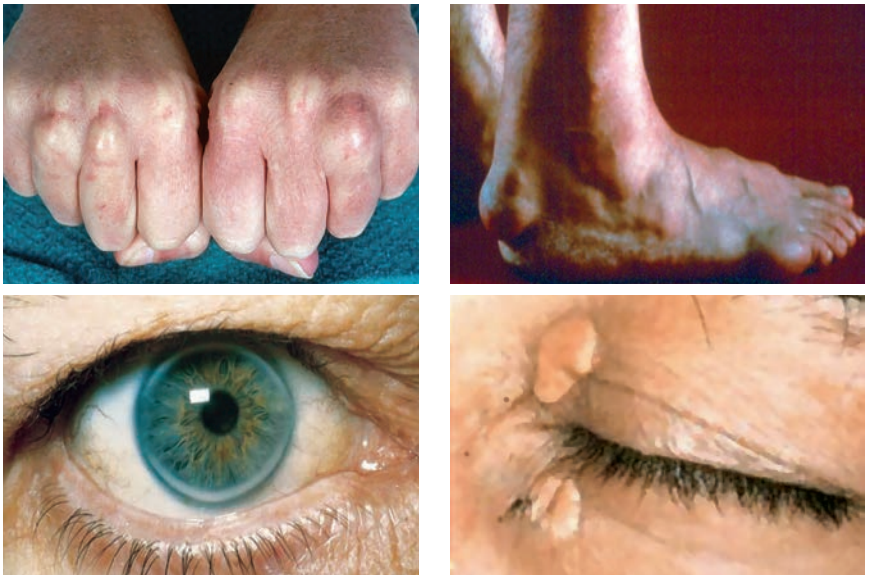


Figure 2. Florid examples of physical signs of familial hypercholesterolaemia. Tendon xanthomata (white or yellow lumps of cholesterol deposits) around the knuckles (a, top left) and Achilles tendon (b, top right); corneal arcus (a circular deposit of cholesterol at the edge of the cornea; c, bottom left); and xanthelasma (a yellow deposit of cholesterol around the eyelid or medial canthus area; d, bottom right).

Reproduced with permission from The Royal Australian College of General Practitioners from: Brett T, Arnold-Reed DE. Familial hypercholesterolaemia: a guide for general practice. Aust J Gen Pract 2019; 48: 650-652. Available online at: www1.racgp.org.au/ajgp/2019/september/familial-hypercholesterolaemia.

(triglyceride level >4.5 mmol/L), who should have fasting samples tested.[3] It has also been advocated that FH be considered part of the newborn bloodspot screening program in Australia; however, such a strategy needs further development.[15] Recommended ages for screening children for FH are as early as possible (no later than 2 years) for suspected homozygotes and from the age of 5 years (no later than 10 years) for suspected heterozygotes.

Providing educational resources and national programs to raise awareness among the public and health professionals about the health impacts of high cholesterol, and FH specifically, are also important.[16] The FH Australasia Network provides online resources on FH (https://www.athero.org.au/fh/).

Phenotypic diagnosis

FH can be diagnosed using criteria combining personal and family history of hypercholesterolaemia and premature

ASCVD, LDL-C levels and physical signs of cholesterol deposition, such as tendon xanthoma, arcus cornealis and xanthelasma (Figure 2).[17-20] Physical stigmata can be subtle and are less prevalent due to statin therapy. Thus, their absence does not exclude the diagnosis of FH.[21] Although several diagnostic tools are available, the Dutch Lipid Clinic Network Criteria score (DLCNC) (Table 2) is the preferred tool in Australia for adults.[3,22] The DLCNC tool assigns a score to each diagnostic criterion and the total score is used to categorise the likelihood of FH as 'definite', 'probable', 'possible' or 'unlikely'. In patients taking a statin or ezetimibe, the pretreatment LDL-C level can be estimated using a correction factor.[23]

In children, the clinical diagnosis of FH relies on LDL-C levels and family history. Testing for suspected heterozygous FH using a phenotypic and/or a genotypic strategy should be considered in children between the ages of 5 and 10 years.[3] The DLCNC tool is not suitable for children.[21] A probable diagnosis of FH should be considered in children with an LDL-C level higher than:[21,24]

- 5.0 mmol/L in the absence of parental history of hypercholesterolaemia or premature ASCVD
- 4.0 mmol/L with parental history of hypercholesterolaemia or premature ASCVD
- 3.5 mmol/L with a parent with a pathogenic or likely pathogenic gene variant.

If FH is suspected, a fasting plasma or serum lipid profile should be performed, ideally on two occasions, in both adults and children, and secondary causes of hypercholesterolaemia, such as hypothyroidism, nephrotic syndrome, cholestatic liver disease and medication use (e.g. steroids, isoretinoids), excluded.[3] After a diagnosis is made, patients with FH should be referred to, or discussed with, a specialist with expertise in lipidology.[3]

TABLE 2. DUTCH LIPID CLINIC NETWORK CRITERIA[22]*

Criteria	Score†
Family history	
• First-degree relative with known premature coronary or vascular disease;‡ or • First-degree relative with known LDL-C above the 95th percentile for age and sex	1
• First-degree relative with tendinous xanthomata or arcus cornealis; or • Children younger than 18 years with an LDL-C level above the 95th percentile for age and sex	2
Clinical history	
Patients with premature coronary artery disease‡	2
Patients with premature cerebral or peripheral vascular disease‡	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis before 45 years of age	4
Untreated LDL-C (mmol/L)	
LDL-C ≥8.5	8
LDL-C 6.5–8.4	5
LDL-C 5.0–6.4	3
LDL-C 4.0–4.9	1
Score: definite FH: ≥8; probable FH: 6–8; possible FH: 3–5; unlikely FH: <3	

Abbreviations: FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol.
* The Dutch Lipid Clinical Network Criteria calculator can be accessed online (https://www.athero.org.au/fh/calculator/).
† Only the highest score in each section is chosen to add up to the total score, to a maximum of 18.
‡ Men younger than 55 years and women younger than 60 years.

Genetic testing

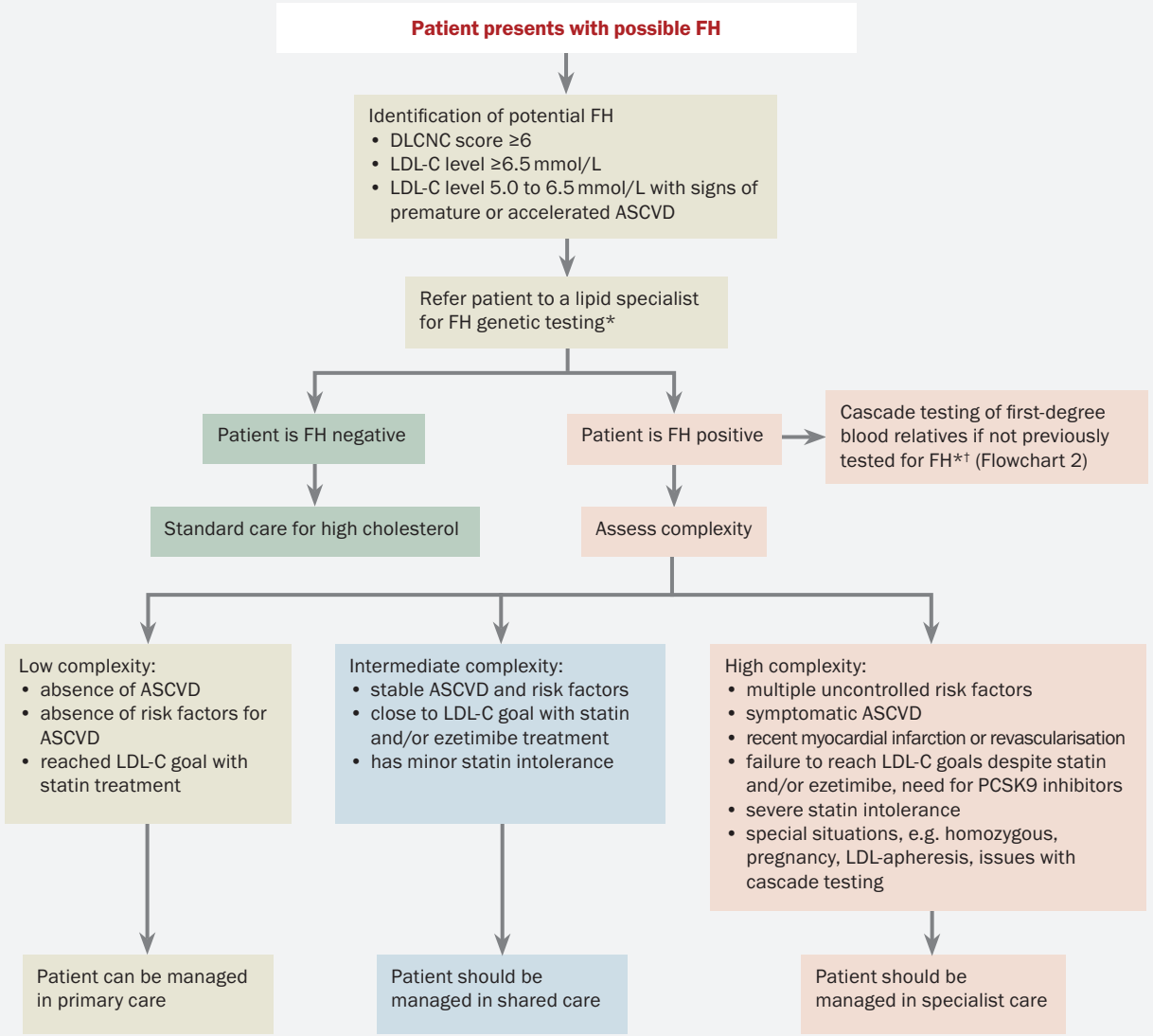
Genetic testing is the gold standard for diagnosing FH and should be offered when available.[3] However, the absence of a causative variant does not exclude the diagnosis, especially when the phenotypic expression is strong.[25] Pathogenic gene variants are detected in 60 to 80% of those with 'definite' FH and in 20 to 40% with 'probable' FH.[25] Variants in the LDL receptor (*LDLR*), apolipoprotein B (*APOB*) and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes contribute to more than 95% of genetically confirmed cases. There is also a very rare form of autosomal recessive FH due to variants in the LDL receptor adaptor protein 1 (*LDLRAP1*) gene.[26,27] Patients with phenotypic FH, but without a detectable FH-causing variant, may have an unidentified genetic variant or polygenic hypercholesterolaemia.[25]

Genetic testing remains underutilised, despite its value in:[25,28]

- increasing the specificity of diagnosis
- enabling more efficient genetic counselling
- improving the accuracy of risk stratification
- improving adherence to treatment
- enabling access to special therapies.

Genetic testing should ideally be offered to adult index cases with a definite or probable diagnosis of FH by the DLCNC and be performed using accredited methods in certified laboratories.[3] The MBS has introduced new pathology services to facilitate genetic testing for FH-causing variants in index cases (MBS item 73352), which requires non-GP specialist authorisation.[11,29]

1. GENETIC TESTING AND MANAGEMENT OF PATIENTS WITH FAMILIAL HYPERCHOLESTEROLAEMIA



Abbreviations: ASCVD = atherosclerotic cardiovascular disease; DLCNC = Dutch Lipid Clinic Network Criteria; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; MBS = Medicare Benefits Schedule; PCSK9 = proprotein convertase subtilisin/kexin type 9.

* The MBS offers genetic testing for FH-causing variants for index cases (MBS item 73352) and cascade testing for first- and second-degree relatives (MBS item 73353).

† Genetic cascade testing may be undertaken by a specialist lipid clinic in collaboration with a GP.

Adapted from Vickery AW, et al. Heart Lung Circ 2014; 23: 1158-1164.[29]

One of the major benefits of genetic testing for FH is to enable cascade testing of at-risk family members. If an index case has a pathogenic FH-causing variant, cascade genetic testing of first- or second-degree relatives should be offered, and GPs can request this (MBS item 73353).[11]

Pre- and post-test counselling is an integral part of the process for FH genetic testing and should be delivered by a healthcare professional with skills in genetic counselling.[25] Information for GPs on genetic counselling is available through the WA HealthPathways (https://wa.communityhealthpathways.org/981755.htm). A shared-care approach between GP and non-GP specialists can facilitate genetic testing of index cases and cascade testing.[29] An algorithm for genetic testing and management of patients with FH is presented in Flowchart 1.

Cascade testing

Cascade testing is the systematic testing of blood relatives of an index case with the condition.[30] Since FH is a monogenic autosomal dominant genetic disorder with high penetrance, 50% of first-degree relatives of index cases will have the condition (Figure 3).[14,25,31] After FH is diagnosed in an index case, cascade testing of first- and second-degree relatives should be offered using phenotypic (i.e. LDL-C levels) and genotypic (MBS item 73353) approaches where feasible. An approach to cascade testing of biological relatives of a patient with confirmed FH is summarised in Flowchart 2.[3,31] Genetic testing should be offered to diagnose FH in children after a pathogenic or likely pathogenic gene variant has been identified in a parent or first-degree relative.[3,21] Cascade genetic testing also identifies relatives who do not inherit the genetic variant, which gives reassurance that they do not have FH.[25]

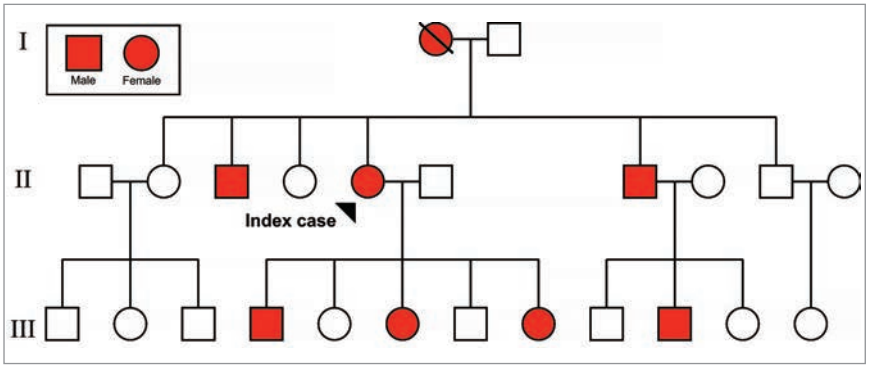
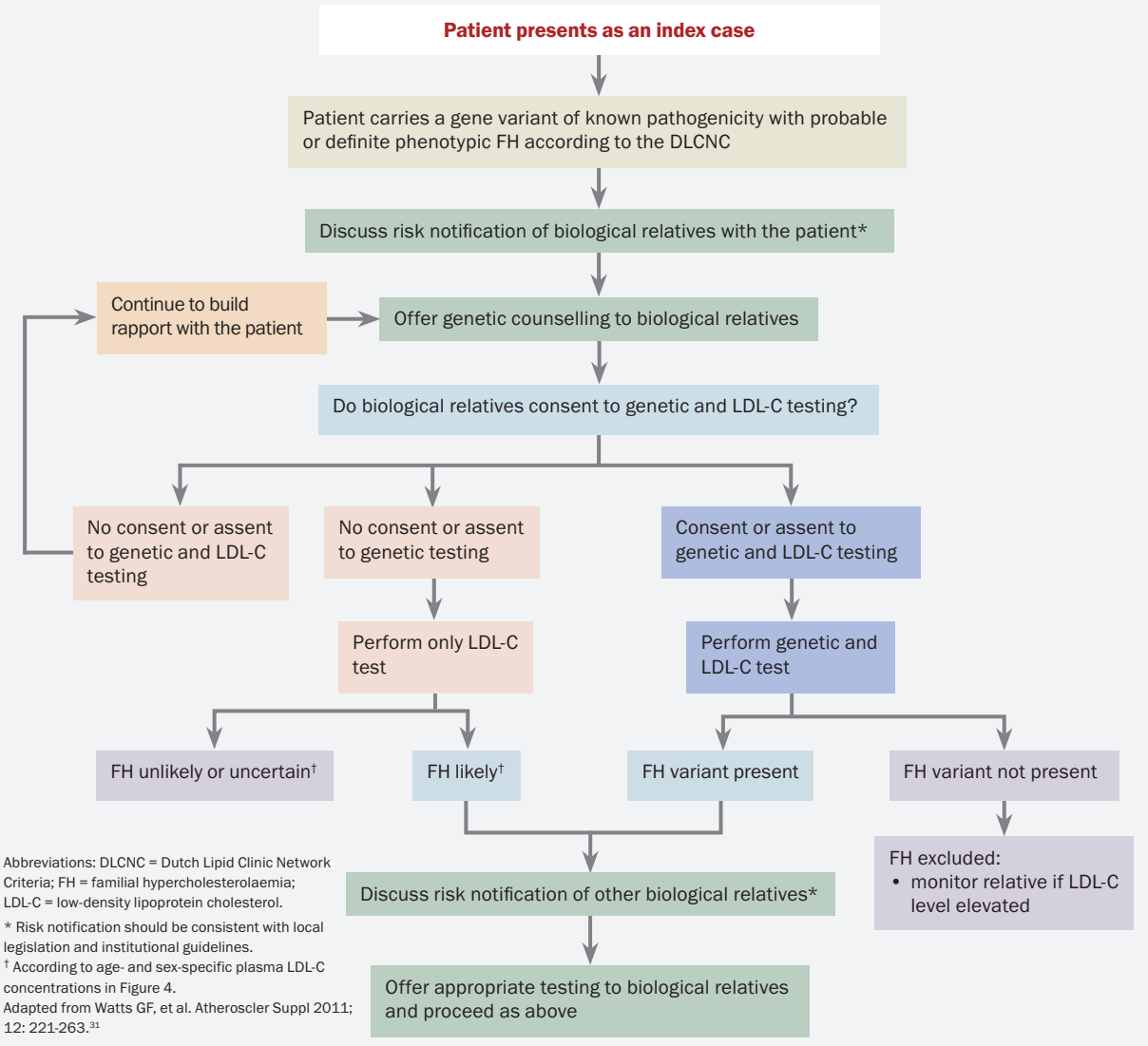


Figure 3. An example family pedigree depicting the autosomal dominant inheritance of familial hypercholesterolaemia.[31]

Cascade screening programs that use variant-specific genetic testing have been shown to be feasible and cost-effective.[32] However, cascade testing should ideally be co-ordinated by a well-resourced centre that can also enable testing via GPs.[3] Risk notification of family members should be performed according to local legislation and institutional guidelines.[3] As with genetic testing of index cases, pre- and post-test counselling for genetic cascade screening should be delivered by a healthcare professional with skills in genetic counselling.[25] In the absence of genetic testing, cascade testing of relatives of index cases may be carried out using measurement of fasting

2. CASCADE TESTING OF BIOLOGICAL RELATIVES OF A PATIENT WITH CONFIRMED FAMILIAL HYPERCHOLESTEROLAEMIA



Abbreviations: DLCNC = Dutch Lipid Clinic Network Criteria; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol.

* Risk notification should be consistent with local legislation and institutional guidelines.

† According to age- and sex-specific plasma LDL-C concentrations in Figure 4.

Adapted from Watts GF, et al. Atheroscler Suppl 2011; 12: 221-263.[31]

LDL-C, with age-and gender-specific levels (Figure 4); the DLCNC should not be used to make the diagnosis of FH in relatives.[3,25,33]

ASCVD risk stratification

After FH is diagnosed, a comprehensive ASCVD risk assessment should be conducted to develop a personalised treatment plan and guide management.[34] Traditional ASCVD risk factors remain significant predictors of ASCVD in patients with FH, highlighting the importance of a multifactorial approach to risk reduction.[35,36] In women, female-specific ASCVD risk factors, such as hypertension or toxaemia in pregnancy, gestational diabetes and premature menopause, should be considered. Tendon xanthomata reflect cumulative exposure to elevated plasma LDL-C levels and are associated with higher ASCVD risk.[37] Furthermore, lipoprotein(a) [Lp(a)] is a genetically determined LDL-like particle bound to apolipoprotein(a) that is a causal risk factor for ASCVD and calcific aortic valve stenosis.[38] In patients with FH, an elevated Lp(a) level is common and is a potent risk factor for coronary artery disease; it may also mimic the FH phenotype diagnostically, especially when markedly elevated or if coexisting with common hypercholesterolaemia.[38,39] Measurement of Lp(a) should be considered as part of routine evaluation, noting that an MBS item is not yet available and that

out of pocket costs may be incurred. However, Lp(a) measurement is a one-off test, as Lp(a) levels are considered stable throughout a person's lifetime.[40] Genetic testing provides information on ASCVD risk, as the presence of a pathogenic gene variant is associated with a higher cumulative exposure to LDL-C and is predictive of ASCVD.[41]

Primary prevention ASCVD risk calculators for the general population (such as the Australian CVD Check or the Framingham Risk Score) should not be used in patients with FH, as lifelong exposure to elevated LDL-C levels are not considered, thus risk will be underestimated.[42] FH-specific equations for absolute ASCVD risk have been developed for people with genetically confirmed FH. For instance, the Spanish Familial Hypercholesterolemia Cohort Study risk equation (SAFEHEART-RE) takes into account age, sex, previous ASCVD, hypertension, obesity, smoking, LDL-C levels and Lp(a) levels; however, requires further validation in an Australian population.[43]

Noninvasive imaging for atherosclerosis, such as carotid ultrasonography, coronary artery calcium scoring and CT coronary angiography, can facilitate personalised risk assessment; it enables the identification of patients with atherosclerotic disease who may require more intensive treatment, including referral for further cardiac evaluation.[42] Patients with symptoms of ASCVD should be referred to a cardiologist for further investigation and management.

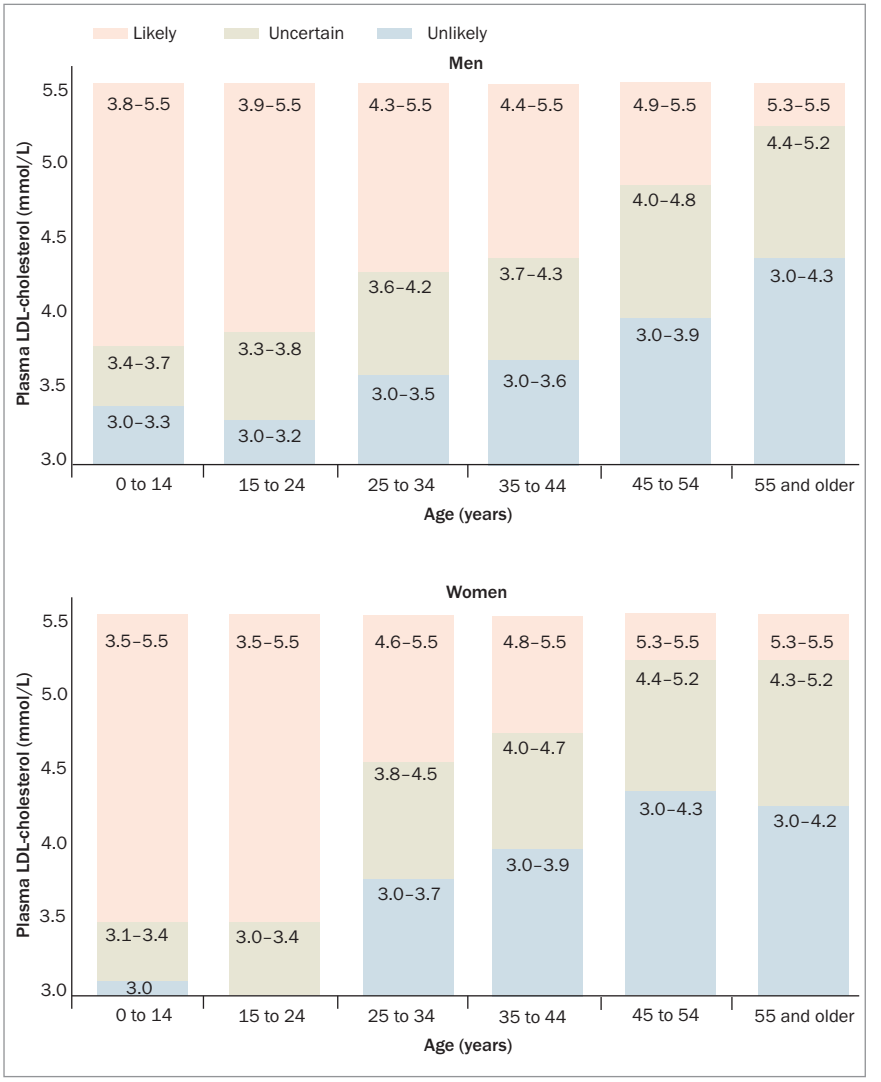


Figure 4. Age- and sex-specific thresholds for making a phenotypic diagnosis of familial hypercholesterolaemia (FH) during cascade testing. When genetic testing is not feasible, the diagnosis of FH in close relatives during cascade testing should be made phenotypically using age- and sex-specific LDL-C levels. The Dutch Lipid Clinic Network Criteria should not be used.
Adapted from Starr B, et al. Clin Chem Lab Med 2008; 46: 791-803.[33]

Lifestyle modifications and management of non-cholesterol risk factors

Modifications targeting a heart-healthy diet, smoking cessation, regular exercise, weight loss, moderation in alcohol consumption and mitigation of psychological stress are emphasised by all guidelines for the prevention of ASCVD and are recommended for all patients with FH.[3] Hypertension, diabetes and obesity should be managed according to relevant guidelines. The recommended cardioprotective diet for patients with FH is one that is low in saturated fat and cholesterol, coupled with the preference for unsaturated fat, particularly within the context of the Mediterranean-style or DASH-style (Dietary Approaches to Stop Hypertension) dietary patterns.[44] Referral to a dietitian for specialised advice is recommended.[3,45] However, a heart-healthy diet alone does not usually provide adequate reduction of LDL-C levels in patients with FH. Nutraceutical regimens, including plant sterols, red yeast rice, soluble fibre and berberine, may be useful adjunctive therapies in certain patients.[3,46,47]

Pharmacotherapy for lowering LDL-cholesterol

Based on extensive clinical trial, registry and genetic data, cholesterol lowering with statins remains the mainstay therapy for

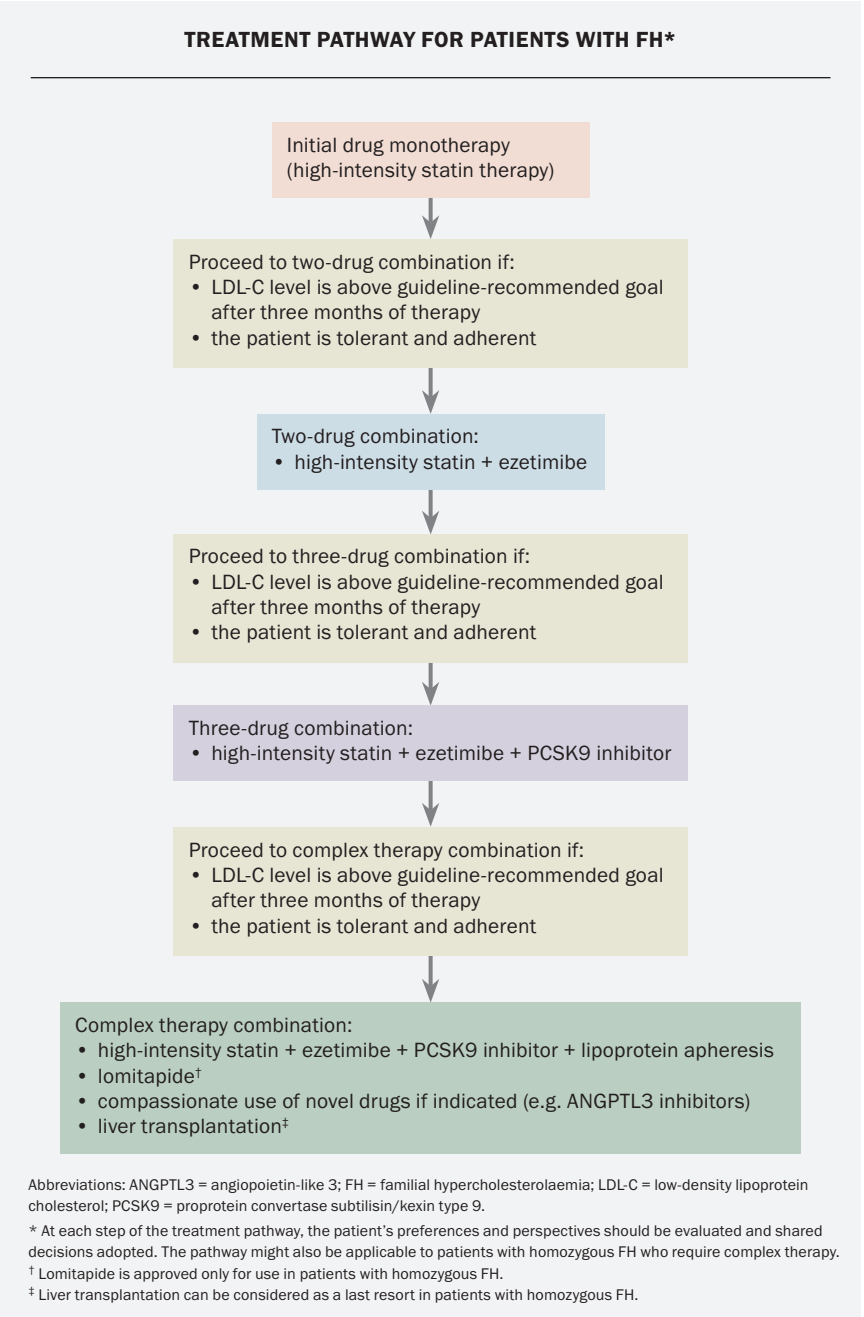


Figure 5. Treatment pathway for patients with familial hypercholesterolaemia.
Adapted from Watts GF, et al. Nat Rev Cardiol 2020; 17: 360-377.[34]

reducing the cumulative burden to elevated LDL-C levels and to prevent ASCVD.[48]

Adults with heterozygous FH

In adults with heterozygous FH, high-potency statins (such as high-dose atorvastatin or rosuvastatin) should be initiated as soon as possible after the diagnosis, with shared decision making to improve adherence. According to the FH Australasia Network guidelines, the LDL-C goal for adults with FH is a greater than 50% reduction in LDL-C levels and either an LDL-C level below:[3]

- 2.5 mmol/L in the absence of ASCVD or other major ASCVD risk factors
- 1.8 mmol/L if there is imaging evidence of ASCVD or if other major ASCVD risk factors are present
- 1.4 mmol/L if there is clinical ASCVD.

However, statins alone are often insufficient to attain LDL-C goals in most patients and sequential addition of other therapies is needed (Figure 5).[34,49] The addition of ezetimibe (a cholesterol absorption inhibitor) can further reduce LDL-C levels by up to 20%. It is recommended as add-on therapy, or as monotherapy in those who are statin-intolerant, with good safety and efficacy and low cost.[50,52] Bile acid sequestrants modestly reduce LDL-C levels but are seldom used, owing to gastrointestinal adverse effects.[52] Bempedoic acid (an adenosine triphosphate citrate lyase inhibitor) is well tolerated and can be considered in patients who are statin-intolerant; however, it is not yet available in Australia.[53] Statin intolerance is an important issue and should be managed according to established guidelines.[54]

Therapies targeting PCSK9 (a protein that binds to the LDL receptor resulting in degradation of the receptor) are also available.[55] Inhibition of PCSK9 leads to upregulation of LDL receptor activity, thereby lowering plasma LDL-C levels. The PCSK9 inhibitors alirocumab and evolocumab are fully human monoclonal antibodies that are usually administered subcutaneously every two weeks. They lower LDL-C levels by 50 to 60% and reduce CVD events when added to statin therapy.[56,57] These agents are safe and efficacious in patients with FH, with injection site reactions being the main adverse effect.[58-62] Accordingly, these agents are recommended as third-line therapy after statins and ezetimibe.[3] Monoclonal antibodies targeting PCSK9 are reimbursed on the PBS for patients with FH and can be initiated by GPs in consultation with a specialist.[3]

Pregnancy and FH

Women of child bearing age should be offered individualised prepregnancy counselling and contraception advice, as statins are associated with risk of teratogenesis.[3] Safe and reliable forms of contraception should be recommended during statin treatment. Statins and other systemically absorbed cholesterol-lowering medications should be ceased three months prior to planned conception and during pregnancy and breastfeeding.[3] However, prolonged periods off cholesterol-lowering treatment due to conception planning, pregnancy and breastfeeding may increase ASCVD risk.[63] In pregnant women with FH, the severity of hypercholesterolaemia, presence of ASCVD and risks and benefits of cholesterol-lowering therapies need to be considered.[64] Bile acid sequestrants are safe to use in pregnancy but can affect absorption of fat-soluble vitamins, such as vitamin K.[64] Additionally, lipoprotein apheresis can be performed safely during pregnancy, and may be required for patients with homozygous FH or severe heterozygous FH, depending on ASCVD risk.[65] A multidisciplinary approach involving experienced lipidologists, obstetricians and cardiologists should be followed.[3]

Children with heterozygous FH

In children with FH, modest and sustained reductions in LDL-C levels have a major impact in preventing ASCVD.[21,24] Statins licensed for this age group (pravastatin, fluvastatin and simvastatin) should be initiated after age 8 to 10 years.[3] An LDL-C goal below 3.5 mmol/L or a 50% reduction in LDL-C levels can be considered for children older than 10 years with FH.[3,21] Studies have shown that statins are safe and efficacious in children with FH, with 20-year observational follow-up data showing a reduction in ASCVD events and death from ASCVD.[66,67] Ezetimibe and monoclonal antibodies targeting PCSK9 are approved for patients older than 10 years with FH, with recent studies showing their safety and efficacy.[68-71] Weight, growth, physical and sexual development, and wellbeing should be monitored in children receiving cholesterol-lowering therapies.[3,21] Children with FH should preferably be reviewed by a paediatrician with expertise in lipidology.[3,21] A multidisciplinary approach founded on shared decision making with the parents and an all-inclusive approach should be undertaken, addressing barriers and enablers to treatment. Transition clinics from childhood to adulthood are recommended, and should be planned well in advance.[3,21]

Children and adults with homozygous FH

Patients with homozygous FH should be referred to specialist centres as management is substantially more difficult.[3] In children and adults with homozygous FH, statins should be initiated as soon as possible after the diagnosis.[3] Ezetimibe and monoclonal antibodies targeting PCSK9 can be used; however, response to treatment may be reduced in patients carrying LDLR-negative variants who have minimal or no residual LDL-receptor function.[62] Lipoprotein apheresis may therefore be required to attain adequate reduction in LDL-C levels and has been performed safely in children.[65] Apheresis is performed weekly or every two weeks, with adequate vascular access and appropriately trained staff being essential.[65] Barriers include lack of availability, high cost, expertise required, patient inconvenience and adverse effects. Other therapies for patients with homozygous FH include lomitapide (a microsomal triglyceride transfer protein inhibitor) and evinacumab (a monoclonal antibody targeting angiopoietin-like 3 protein); both work independently of LDL-C receptor function but require specialist consultation as they are obtained via special access or compassionate use schemes.[72,73] Liver transplantation may be considered as a very last resort for patients with homozygous FH; however, it has rarely been performed in Australia.[74]

On the horizon

Inclisiran is a double-stranded small interfering ribonucleic acid therapy that inhibits hepatic synthesis of PCSK9. Inclisiran is administered subcutaneously every six months and can reduce LDL-C levels by 40 to 50% in patients with heterozygous FH, with the main adverse effects being injection site reactions and nasopharyngitis.[75,76] Bempedoic acid may also play a role in the management of FH, as it has been shown to lower LDL-C levels by about 20% and reduce ASCVD events in patients with statin intolerance and ASCVD or ASCVD risk factors.[53] Several novel cholesterol-lowering agents are also in clinical development.[77]

Conclusion

FH is a common genetic disorder that GPs will encounter in their practice. GPs can play a central role in the continuity of care of patients with FH, spanning screening, diagnosis, cascade testing, ASCVD risk stratification and lipid management. Earlier diagnosis and initiation of effective cholesterol-lowering treatments is required to reduce the burden of ASCVD in patients and their families with FH. Advances in cholesterol-lowering therapies have provided strategies that allow more patients with FH to approach recommended treatment goals. Effective implementation of FH care requires an integrated health system approach, with shared care between GPs and other specialities. MT

References

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Familial hypercholesterolaemia

Enhancing the care of patients and families

NICK S.R. LAN MBBS(Hons), MClinUS, MClinRes(Dist); **JING PANG** PhD
GERALD F. WATTS DSc, PhD, MD, FRCP, FRACP

References

1. Goldstein JL, Brown MS. The LDL receptor. Arterioscler Thromb Vasc Biol 2009; 29: 431-438.
2. Akioyamen LE, Genest J, Shan SD, et al. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. BMJ Open 2017; 7: e016461.
3. Watts GF, Sullivan DR, Hare DL, et al. Integrated guidance for enhancing the care of familial hypercholesterolaemia in Australia. Heart Lung Circ 2021; 30: 324-349.
4. Wong B, Kruse G, Kutikova L, Ray KK, Mata P, Bruckert E. Cardiovascular disease risk associated with familial hypercholesterolemia: a systematic review of the literature. Clin Ther 2016; 38: 1696-1709.
5. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab 2012; 97: 3956-3964.
6. Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J 2014; 35: 2146-2157.
7. Shapiro MD, Bhatt DL. "Cholesterol-Years" for ASCVD risk prediction and treatment. J Am Coll Cardiol 2020; 76: 1517-1520.
8. Besseling J, Hovingh GK, Huijgen R, Kastelein JJP, Hutten BA. Statins in familial hypercholesterolemia: consequences for coronary artery disease and all-cause mortality. J Am Coll Cardiol 2016; 68: 252-260.
9. Wilemon KA, Patel J, Aguilar-Salinas C, et al. Reducing the clinical and public health burden of familial hypercholesterolemia: a global call to action. JAMA Cardiol 2020; 5: 217-229.
10. Bell DA, Hooper AJ, Bender R, et al. Opportunistic screening for familial hypercholesterolaemia via a community laboratory. Ann Clin Biochem 2012; 49(Pt 6): 534-537.
11. Brett T, Radford J, Heal C, et al. Implications of new clinical practice guidance on familial hypercholesterolaemia for Australian general practitioners. Aust J Gen Pract 2021; 50: 616-621.
12. Bell DA, Garton-Smith J, Vickery A, et al. Familial hypercholesterolaemia in primary care: knowledge and practices among general practitioners in Western Australia. Heart Lung Circ 2014; 23: 309-313.
13. Lan NSR, Martin AC, Brett T, Watts GF, Bell DA. Improving the detection of familial hypercholesterolaemia. Pathology 2019; 51: 213-221.
14. Pang J, Vickery AW, Watts GF. Familial hypercholesterolemia: bridging and minding the gap in healthcare. Advances in dyslipidemia. Future Medicine Ltd; UK, 2013. p. 18-41.
15. Brett T. Universal screening for familial hypercholesterolaemia in newborns: time for general practice to contribute. Aust J Gen Pract 2023; 52: 246-248.
16. Bulsara C, Brett T, Radford J, et al. Awareness of familial hypercholesterolaemia in Australian primary care: a qualitative descriptive study. Aust J Gen Pract 2021; 50: 634-640.
17. Umans-Eckenhausen MA, Defesche JC, Sijbrands EJ, Scheerder RL, Kastelein JJ. Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands. Lancet 2001; 357: 165-168.
18. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. BMJ 1991; 303(6807): 893-896.
19. Williams RR, Hunt SC, Schumacher MC, et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. Am J Cardiol 1993; 72: 171-176.
20. Harada-Shiba M, Arai H, Ishigaki Y, et al; Working Group by Japan Atherosclerosis Society for Making Guidance of Familial Hypercholesterolemia. Guidelines for diagnosis and treatment of familial hypercholesterolemia 2017. J Atheroscler Thromb 2018; 25: 751-770.
21. Horton AE, Martin AC, Srinivasan S, et al. Integrated guidance to enhance the care of children and adolescents with familial hypercholesterolaemia: practical advice for the community clinician. J Paediatr Child Health 2022; 58: 1297-1312.
22. World Health Organization (WHO). Human Genetics Programme. Familial Hypercholesterolemia: report of a Second WHO Consultation. Document number: WHO/HGN/FH/Cons/99.2. WHO; Geneva, 1999. Available online at: https://apps.who.int/iris/handle/10665/66346 (accessed May 2023).
23. Haralambos K, Whatley SD, Edwards R, et al. Clinical experience of scoring criteria for familial hypercholesterolaemia (FH) genetic testing in Wales. Atherosclerosis 2015; 240: 190-196.
24. Wiegman A, Gidding SS, Watts GF, et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J 2015; 36: 2425-2437.
25. Sturm AC, Knowles JW, Gidding SS, et al. Clinical genetic testing for familial hypercholesterolemia: JACC Scientific Expert Panel. J Am Coll Cardiol 2018; 72: 662-680.

26. Berberich AJ, Hegele RA. The complex molecular genetics of familial hypercholesterolaemia. Nat Rev Cardiol 2019; 16: 9-20.
27. Usifo E, Leigh SE, Whittall RA, et al. Low-density lipoprotein receptor gene familial hypercholesterolemia variant database: update and pathological assessment. Ann Hum Genet 2012; 76: 387-401.
28. Watts GF, Gidding SS, Hegele RA, et al. International Atherosclerosis Society guidance for implementing best practice in the care of familial hypercholesterolaemia. Nat Rev Cardiol Accepted; In Press.
29. Vickery AW, Bell D, Garton-Smith J, Kirke AB, Pang J, Watts GF. Optimising the detection and management of familial hypercholesterolaemia: central role of primary care and its integration with specialist services. Heart Lung Circ 2014; 23: 1158-1164.
30. Defesche JC, Gidding SS, Harada-Shiba M, Hegele RA, Santos RD, Wierzbicki AS. Familial hypercholesterolaemia. Nat Rev Dis Primers 2017; 3: 17093.
31. Watts GF, Sullivan DR, Poplawski N, et al. Familial hypercholesterolaemia: a model of care for Australasia. Atheroscler Suppl 2011; 12: 221-263.
32. Ademi Z, Watts GF, Pang J, et al. Cascade screening based on genetic testing is cost-effective: evidence for the implementation of models of care for familial hypercholesterolemia. J Clin Lipidol 2014; 8: 390-400.
33. Starr B, Hadfield SG, Hutten BA, et al. Development of sensitive and specific age- and gender-specific low-density lipoprotein cholesterol cutoffs for diagnosis of first-degree relatives with familial hypercholesterolaemia in cascade testing. Clin Chem Lab Med 2008; 46: 791-803.
34. Watts GF, Gidding SS, Mata P, et al. Familial hypercholesterolaemia: evolving knowledge for designing adaptive models of care. Nat Rev Cardiol 2020; 17: 360-377.
35. Besseling J, Kindt I, Hof M, Kastelein JJ, Hutten BA, Hovingh GK. Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: a study of a cohort of 14,000 mutation carriers. Atherosclerosis 2014; 233: 219-223.
36. Akioyamen LE, Genest J, Chu A, Inibhunu H, Ko DT, Tu JV. Risk factors for cardiovascular disease in heterozygous familial hypercholesterolemia: a systematic review and meta-analysis. J Clin Lipidol 2019; 13: 15-30.
37. Tada H, Kawashiri MA, Nohara A, Inazu A, Mabuchi H, Yamagishi M. Impact of clinical signs and genetic diagnosis of familial hypercholesterolaemia on the prevalence of coronary artery disease in patients with severe hypercholesterolaemia. Eur Heart J 2017; 38: 1573-1579.
38. Kronenberg F, Mora S, Stroes ESG, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J 2022; 43: 3925-3946.
39. Ellis KL, Pang J, Chan DC, et al. Familial combined hyperlipidemia and hyperlipoprotein(a) as phenotypic mimics of familial hypercholesterolemia: frequencies, associations and predictions. J Clin Lipidol 2016; 10: 1329-1337.e3.
40. Trinder M, Paruchuri K, Haidermota S, et al. Repeat measures of lipoprotein(a) molar concentration and cardiovascular risk. J Am Coll Cardiol 2022; 79: 617-628.
41. Khera AV, Won HH, Peloso GM, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. J Am Coll Cardiol 2016; 67: 2578-2589.
42. Mata P, Alonso R, Pérez de Isla L. Atherosclerotic cardiovascular disease risk assessment in familial hypercholesterolemia: does one size fit all? Curr Opin Lipidol 2018; 29: 445-452.
43. Perez de Isla L, Alonso R, Mata N, et al. Predicting cardiovascular events in familial hypercholesterolemia: the SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort Study). Circulation 2017; 135: 2133-2144.
44. Sacks FM, Lichtenstein AH, Wu JHY, et al. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. Circulation 2017; 136: e1-e23.
45. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020; 41: 111-188.
46. Cicero AFG, Fogacci F, Zambon A. Red yeast rice for hypercholesterolemia: JACC focus seminar. J Am Coll Cardiol 2021; 77: 620-628.
47. Barkas F, Nomikos T, Liberopoulos E, Panagiotakos D. Diet and cardiovascular disease risk among individuals with familial hypercholesterolemia: systematic review and meta-analysis. Nutrients 2020; 12: 2436.
48. Fulcher J, O'Connell R, Voysey M, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet 2015; 385: 1397-1405.
49. Perez de Isla L, Alonso R, Watts GF, et al. Attainment of LDL-cholesterol treatment goals in patients with familial hypercholesterolemia: 5-Year SAFEHEART Registry follow-up. J Am Coll Cardiol 2016; 67: 1278-1285.
50. Kastelein JJ, Akdim F, Stroes ES, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med 2008; 358: 1431-1443.
51. Gagné C, Gaudet D, Bruckert E. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation 2002; 105: 2469-2475.
52. Huijgen R, Abbink EJ, Bruckert E, et al. Colesevelam added to combination therapy with a statin and ezetimibe in patients with familial hypercholesterolemia: a 12-week, multicenter, randomized, double-blind, controlled trial. Clin Ther 2010; 32: 615-625.
53. Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. N Engl J Med 2023; 388: 1353-1364.
54. Newman CB, Preiss D, Tobert JA, et al. Statin safety and associated adverse events: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol 2019; 39: e38-e81.
55. Tavori H, Fan D, Blakemore JL, et al. Serum proprotein convertase subtilisin/kexin type 9 and cell surface low-density lipoprotein receptor: evidence for a reciprocal regulation. Circulation 2013; 127: 2403-2413.
56. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018; 379: 2097-2107.
57. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017; 376: 1713-1722.
58. Hovingh GK, Raal FJ, Dent R, et al. Long-term safety, tolerability, and efficacy of evolocumab in patients with heterozygous familial hypercholesterolemia. J Clin Lipidol 2017; 11: 1448-1457.
59. Farnier M, Hovingh GK, Langslet G, et al. Long-term safety and efficacy of alirocumab in patients with heterozygous familial hypercholesterolemia: an open-label extension of the ODYSSEY program. Atherosclerosis 2018; 278: 307-314.
60. Santos RD, Stein EA, Hovingh GK, et al. Long-term evolocumab in patients with familial hypercholesterolemia. J Am Coll Cardiol 2020; 75: 565-574.
61. Dufour R, Hovingh GK, Guyton JR, et al. Individualized low-density lipoprotein cholesterol reduction with alirocumab titration strategy in heterozygous familial hypercholesterolemia: results from an open-label extension of the ODYSSEY LONG TERM trial. J Clin Lipidol 2019; 13: 138-147.
62. Raal FJ, Hovingh GK, Blom D, et al. Long-term treatment with evolocumab added to conventional drug therapy, with or without apheresis, in patients with homozygous familial hypercholesterolaemia: an interim subset analysis of the open-label TAUSSIG study. Lancet Diabetes Endocrinol 2017; 5: 280-290.
63. Klevmoen M, Bogsrud MP, Retterstøl K, et al. Loss of statin treatment years during pregnancy and breastfeeding periods in women with familial hypercholesterolemia. Atherosclerosis 2021; 335: 8-15.
64. Graham DF, Raal FJ. Management of familial hypercholesterolemia in pregnancy. Curr Opin Lipidol 2021; 32: 370-377.
65. Padmanabhan A, Connelly-Smith L, Aqui N, et al. Guidelines on the use of

therapeutic apheresis in clinical practice - evidence-based approach from the Writing Committee of the American Society for Apheresis: the eighth special issue. J Clin Apher 2019; 34: 171-354.
66. Luirink IK, Wiegman A, Kusters DM, et al. 20-year follow-up of statins in children with familial hypercholesterolemia. N Engl J Med 2019; 381: 1547-1556.
67. Vuorio A, Kuoppala J, Kovanen PT, et al. Statins for children with familial hypercholesterolemia. Cochrane Database Syst Rev 2019; 2019(11): CD006401.
68. Kusters DM, Caceres M, Coll M, et al. Efficacy and safety of ezetimibe monotherapy in children with heterozygous familial or nonfamilial hypercholesterolemia. J Pediatr 2015; 166: 1377-1384.e1-3.
69. Santos RD, Ruzza A, Hovingh GK, et al. Evolocumab in pediatric heterozygous familial hypercholesterolemia. N Engl J Med 2020; 383: 1317-1327.
70. Santos RD, Ruzza A, Hovingh GK, et al. Paediatric patients with heterozygous familial hypercholesterolaemia treated with evolocumab for 80 weeks (HAUSER-OLE): a single-arm, multicentre, open-label extension of HAUSER-RCT. Lancet Diabetes Endocrinol 2022; 10: 732-740.
71. Daniels S, Caprio S, Chaudhari U, et al. PCSK9 inhibition with alirocumab in pediatric patients with heterozygous familial hypercholesterolemia: The ODYSSEY KIDS study. J Clin Lipidol 2020; 14: 322-330.e5.
72. Blom DJ, Averna MR, Meagher EA, et al. Long-term efficacy and safety of the microsomal triglyceride transfer protein inhibitor lomitapide in patients with homozygous familial hypercholesterolemia. Circulation 2017; 136: 332-335.
73. Raal FJ, Rosenson RS, Reeskamp LF, et al. Evinacumab for homozygous familial hypercholesterolemia. N Engl J Med 2020; 383: 711-720.
74. Ishigaki Y, Kawagishi N, Hasegawa Y, et al. Liver transplantation for homozygous familial hypercholesterolemia. J Atheroscler Thromb 2019; 26: 121-127.
75. Raal FJ, Kallend D, Ray KK, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N Engl J Med 2020; 382: 1520-1530.
76. Ray KK, Troquay RPT, Visseren FLJ, et al. Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial. Lancet Diabetes Endocrinol 2023; 11: 109-119.
77. Tokgözoğlu L, Libby P. The dawn of a new era of targeted lipid-lowering therapies. Eur Heart J 2022; 43: 3198-3208.

Preventing diabetic kidney disease progression

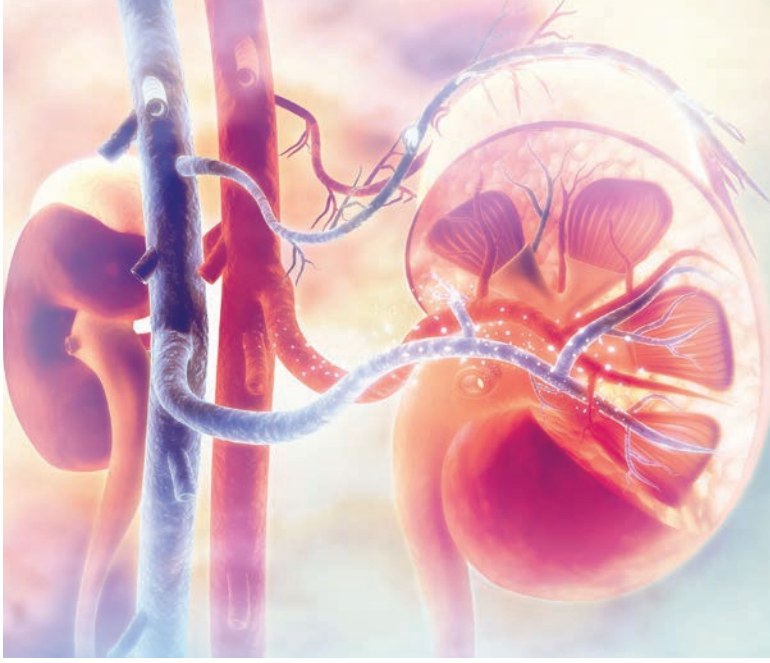
An update

JEAN C. LU MB BS, BMedSci, FRACP; **ELIF EKINCI** MB BS, FRACP, PhD
DAVID O'NEAL MD, FRACP, FRCP
RICHARD J. MACISAAC BSc(Hons), PhD, MB BS, FRACP

It is important to implement treatments to delay and prevent diabetic kidney disease progression by aiming for tight metabolic and blood pressure control and simultaneously addressing cardiovascular risk factors aggressively. Using pharmacological agents with cardiovascular and renal benefits, including renin–angiotensin system inhibitors and sodium-glucose cotransporter-2 inhibitors, is paramount. Glucagon-like peptide-1 receptor agonists may also be renoprotective.

KEY POINTS

- In patients with type 2 diabetes, screen for diabetic kidney disease (DKD) by measuring the albumin to creatinine ratio in an early-morning spot urine sample and measuring the serum creatinine level to calculate the estimated glomerular filtration rate (eGFR).
- A diagnosis of DKD should be made if repeat testing confirms an elevated albumin to creatinine ratio (greater than 2.5 mg/mmol in men or greater than 3.5 mg/mmol in women) or an eGFR less than 60 mL/min/1.73 m^2.
- Delay the progression of DKD by aiming for glycaemic (general HbA_{1c} target: less than 53 mmol/mol) and blood pressure (general target: less than 130/80 mmHg) control.
- Use single-agent renin–angiotensin system inhibitors at maximally tolerated doses and, when appropriate, sodium-glucose cotransporter-2 inhibitors and finerenone to slow the progression of DKD.
- Treat cardiovascular risk factors aggressively in patients with DKD.



The incidence of diabetes is increasing worldwide, secondary to the marked increase in the incidence of type 2 diabetes. Diabetes is also an established and major risk factor for the development and progression of chronic kidney disease (CKD). As a result, diabetes is now the leading cause of end-stage kidney disease in Western countries. Traditionally, diabetic kidney disease (DKD) has been referred to as 'diabetic nephropathy', but this is a term that should be reserved for people with progressive albuminuria. There is now growing appreciation that renal impairment can develop in people with diabetes in the absence of increasing albuminuria and in the presence of other nondiabetes-related causes of CKD. Therefore, the term DKD is now preferred to describe CKD in people with diabetes.[1]

DKD occurs in 25 to 40% of people with type 1 or type 2 diabetes who also have risk factors, including hyperglycaemia, hypertension, a history or current habit of smoking, poor plasma lipid control and a genetic predisposition.[2] People who have DKD have increased rates of morbidity and mortality, mainly

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Dr Lu is a Consultant Endocrinologist and PhD candidate at St Vincent's Hospital Melbourne and the University of Melbourne. Professor Ekinci is the Director of Diabetes at Austin Health; Professor of Medicine; Weary Dunlop Medical Research Foundation Professorial Fellow; and Director of the Australian Centre for Accelerating Diabetes Innovations (ACADI), School of Medicine, University of Melbourne. Professor O'Neal is a Professorial Fellow and Deputy Director of ACADI, School of Medicine, University of Melbourne. Professor MacIsaac is the Director of Endocrinology & Diabetes at St Vincent's Hospital Melbourne; Professorial Fellow; and co-Leader of the diabetic kidney disease stream at ACADI, School of Medicine, University of Melbourne, Melbourne, Vic.

TABLE 1. MANAGEMENT STRATEGIES FOR CKD IN PEOPLE WITH DIABETES ACCORDING TO THE eGFR AND ALBUMIN LEVELS[5]

Albumin level (mg/mmol)	eGFR (mL/min/1.73 m²)*					
	90 and greater (normal to high)	60 to 89 (mild reduction)	45 to 59 (mild to moderate reduction)	30 to 44 (moderate to severe reduction)	15 to 29 (severe reduction)	Less than 15 (kidney failure)
Less than 3 (normal to mild increase)	Screen 1	Screen 1	Treat 1	Treat 2	Treat and refer 3	Treat and refer 4†
3 to 29 (moderate increase)	Treat 1	Treat 1	Treat 2	Treat and refer 3	Treat and refer 3	Treat and refer 4†
30 and greater (severe increase)	Treat and refer 3	Treat and refer 3	Treat and refer 3	Treat and refer 3	Treat and refer 4†	Treat and refer 4†

Abbreviations: CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate.
* Numbers in the boxes are a guide to the frequency of clinical visits (number of times per year).
† Or more.

because of the high risk of cardiovascular (CV) events.[3,4] In parallel, renal failure also predisposes to poorer glycaemic control (both hyper- and hypoglycaemia) because of an altered renal physiology, which disrupts normal glucose and insulin metabolism. Therefore, in people with diabetes, the early identification of DKD and implementation of effective treatments are imperative to minimise the progression of CKD and its associated comorbidities.

However, the good news is that novel effective treatments to help prevent the progression of DKD in people with type 2 diabetes have been developed over the past decade. Ample evidence indicates that optimising metabolic health and using renin-angiotensin system inhibitors and sodium-glucose cotransporter-2 (SGLT-2) inhibitors can delay the progression of DKD. The novel mineralocorticoid receptor antagonist finerenone is also emerging as a promising approach to slowing loss of renal function in people with type 2 diabetes. This article focuses primarily on DKD management in people with type 2 diabetes.

Screening for diabetic kidney disease

Early-stage DKD is usually a silent disease, with minimal clinical manifestations until the patient has progressed to an advanced stage of kidney disease. Therefore, it is essential to screen for markers of kidney disease in people with diabetes as part of routine clinical care (Table 1).[5]

A spot urine sample should be collected annually to measure the albumin to creatinine ratio. A diagnosis of DKD should only be made if repeat testing confirms an elevation in this ratio (greater than 2.5 mg/mmol in men or greater than 3.5 mg/mmol in women). The urine albumin to creatinine ratio fluctuates by 30 to 40% on the basis of several factors, such as the presence of a fever, dehydration, vigorous physical activity or urinary tract infection. Therefore, if an abnormal albumin to creatinine ratio is found, perform one to two more tests over the subsequent three months to ensure persistent albuminuria.

Serum creatinine levels should be measured to calculate the estimated glomerular filtration rate (eGFR). A persistent eGFR less than 60 mL/min/1.73 m² indicates possible DKD, even in the absence of albuminuria if nondiabetes-related causes of CKD are excluded.

In type 2 diabetes, the timing of onset is often difficult to determine; therefore, screening should begin at the time of diagnosis. In type 1 diabetes, the general approach is to start screening for DKD five years after diagnosis.[6] However, earlier screening is suggested in people with poor metabolic control or other risk factors.

Screening for nondiabetic kidney disease

Careful consideration should be given to nondiabetic causes of CKD, particularly in patients with rapidly increasing albuminuria or decreasing eGFR. Factors that should alert clinicians to possible nondiabetic aetiologies include an absence of retinopathy, duration of diabetes less than five years, acute renal injury pattern of renal dysfunction rather than gradual progression, presence of haematuria or other systemic disease and presence of nephrotic syndrome (albuminuria greater than 3 g/day, low serum albumin level, oedema and symptoms such as frothy urine). The absence of retinopathy and a short duration of diabetes are the strongest predictors of nondiabetes-related kidney disease, although DKD may still occur in some people without retinopathy.

A rapidly decreasing eGFR or rapidly increasing albuminuria should prompt referral of the patient to a nephrologist. A general cut-off of the eGFR of less than 30 mL/min/1.73 m² can also be used as a guide for referral, but ideally, the severity

TABLE 2. SELECTING GLUCOSE-LOWERING AGENTS IN PEOPLE WITH DKD[5]

Glucose-lowering agent	Glucose-lowering effect	Risk of CKD progression	Risk of atherosclerotic CV disease	Risk of heart failure	Risk of hypoglycaemia	Body weight
Metformin	High	No effect	Reduction*	Reduction*	Reduction	No effect
SGLT-2 inhibitors	Intermediate	Reduction	Reduction	Reduction	Reduction	Reduction
GLP-1 receptor agonists	High	Reduction*	Reduction	Reduction*	Reduction	Reduction
DPP-4 inhibitors	Intermediate	No effect	No effect	Increase*	Reduction	No effect
Insulin	Very high	No effect	No effect	No effect	Increase	Increase
Sulfonylureas	High	No effect	No effect	No effect	Increase	Increase
Thiazolidinediones	High	No effect	Reduction*	Increase	Reduction	Increase
α-Glucosidase inhibitors	Intermediate	No effect	No effect	No effect	Reduction	No effect

Abbreviations: CKD = chronic kidney disease; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide 1; SGLT-2 = sodium-glucose cotransporter-2.
* Potential effect.

of albuminuria should also be taken into account, which may warrant the involvement of a nephrologist before arriving at this eGFR cut-off.[5] Referral of the patient to a nephrologist is important, as complications such as volume overload, anaemia, electrolyte imbalances and CKD-related mineral and bone disorders can become prominent management issues when the eGFR declines to below the cut-off. Timely initiation of iron replacement, epoetin and phosphate-binding treatments are important considerations. Furthermore, early preparation for pre-emptive kidney or possible combined kidney and pancreas transplantation for type 1 diabetes is beneficial, as is early preparation for kidney replacement therapy.

Preventing the progression of diabetic kidney disease

Multimorbidity is common in people with DKD and, therefore, there is an increasing emphasis on comprehensive, holistic medical care to improve overall patient outcomes.[5] This approach incorporates treatment directed to optimise lifestyle factors, targeted pharmacological therapy to preserve end-organ function and additional therapies to address risk factors such as glycaemia, hypertension and dyslipidaemia.

Management of lifestyle factors

The newest guidelines from the American Diabetes Association and Kidney Disease Improving Global Outcomes (KDIGO) highlight the role of patient education in nutritional management from dietitians for optimal diabetes management. The recommendation is for patients to consume balanced diets high in vegetables, fruits and whole grains but low in refined carbohydrates and sugar-containing sweetened beverages.[7,8]

Although there is some evidence that low protein diets can slow the progression of DKD, this approach is rarely used in clinical practice. People with advanced-stage kidney disease on maintenance dialysis are advised to have a higher protein intake, considering that this population is often malnourished or in a catabolic state. Moderate to intense physical activity for more than 150 min/week and the avoidance of sedentary activity is also recommended.[7,8] Tobacco should not be consumed by any person with diabetes. Alcohol consumption should be limited.[6]

Glycaemia management

Intensive glycaemic management (glycated haemoglobin [HbA_{1c}] less than 53 mmol/mol) delays the development and progression of albuminuria and slows the rate of eGFR decline and progression to end-stage kidney disease. Early initiation of metformin treatment plus an SGLT-2 inhibitor is recommended in most people with type 2 diabetes, followed by the addition of glucose-lowering agents as needed to achieve individualised glycaemic targets (Table 2).[5] Dose adjustment and medication choice based on the eGFR (Table 3) is important to take into consideration.[5]

Diabetes technologies, including continuous glucose monitors, are increasingly becoming a part of routine clinical management, particularly for type 1 diabetes, for which they are subsidised under the National Diabetes Services Scheme. Continuous glucose monitoring technology is a powerful tool to identify and correct glycaemic derangements, prevent hypoglycaemia, direct medication management and guide medical nutritional therapy and physical activity recommendations. Continuous glucose monitoring technology with and without insulin pump therapy is an emerging attractive

TABLE 3. DOSE ADJUSTMENTS OF GLUCOSE-LOWERING AGENTS IN PEOPLE WITH A LOW eGFR[5]

Glucose-lowering agent	eGFR range (mL/min/1.73 m^2)		
	30 to 44	15 to 29	Less than 15
Insulin	Start and titrate with caution to avoid hypoglycaemia		
Metformin	Reduce dose to 1000 mg/day	Do not use	
SGLT-2 inhibitors			
Dapagliflozin	Use 10 mg daily (if eGFR is between 25 and 44 mL/min/1.73 m^2)	Do not start if eGFR <25 mL/min/1.73 m^2; may continue using 10 mg daily if tolerated until dialysis	
Empagliflozin	Use 10 mg daily (do not start for glycaemic control if eGFR is <30 mL/min/1.73 m^2 or for heart failure if eGFR is <20 mL/min/1.73 m^2)		Do not start if eGFR <20 mL/min/1.73 m^2; may continue using 10 mg daily if tolerated until dialysis
Ertugliflozin	Do not use		
GLP-1 receptor agonists			
Dulaglutide	No dose adjustment required		
Liraglutide	No dose adjustment required		
Semaglutide	No dose adjustment required		
DPP-4 inhibitors			
Alogliptin	Use maximum 12.5 mg daily	Use maximum 6.25 mg daily	
Linagliptin	No dose adjustment required		
Saxagliptin	Use maximum 2.5 mg daily		
Sitagliptin	Use maximum 50 mg daily	Use maximum 25 mg daily	
Sulfonylureas (second generation)			
Gliclazide	Start at 30 mg daily with caution	Do not use	
Glimepiride	Start at 1 mg daily with caution; titrate slowly to avoid hypoglycaemia		
Glipizide	Start at 2.5 mg daily with caution; titrate slowly to avoid hypoglycaemia		
Glibenclamide	Do not use		
Thiazolidinediones			
Pioglitazone	No dose adjustment required		
α-Glucosidase inhibitors			
Acarbose	No dose adjustment required	Do not use	

Abbreviations: DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide 1; SGLT-2 = sodium-glucose cotransporter-2.

approach to help insulin-treated people with DKD optimise their glycaemic control.

Recent recommendations from the Joint British Diabetes Societies suggest the use of continuous glucose monitors, where available, in patients on dialysis as the best way to monitor glucose control (Figure).[9,10] When continuous glucose monitoring technology can be used, there is an emphasis on looking at the time in range, with the range defined as 3.9 to 10.0 mmol/L, rather than using an HbA_{1c} target. The target time in range is greater than 70% for most people with diabetes. This should be achieved while minimising the time in range for hypoglycaemia, aiming for less than 4% in a range of less

than 3.9 mmol/L.[9] At the time of writing, there are no specific targets for people with DKD.

Blood pressure management

A crucial goal for the prevention of CKD progression, CV disease and heart failure is managing blood pressure. For people with diabetes, hypertension and a high risk of atherosclerotic CV disease (10-year risk greater than 15%), a blood pressure target of less than 130/80 mmHg is suggested. Previously, for those with diabetes, hypertension and a low risk of atherosclerotic CV disease (10-year risk less than 15%), a blood pressure target of less than 140/90 mmHg was the recommendation.[8] The general blood pressure target for people with diabetes has now been revised to 130/80 mmHg by the American Diabetes Association, and the systolic blood pressure target recommended by KDIGO for patients with CKD not on dialysis is less than 120 mmHg.[11] Therefore, lowering systolic blood pressure levels to less than 130 mmHg in most people with DKD and to less than 120 mmHg in high-risk patients may be a reasonable approach. The blood pressure targets should be individualised and account for possible adverse outcomes, such as postural hypotension, which is particularly relevant in people with concurrent autonomic neuropathy.

Renin–angiotensin system inhibitors are the preferred initial pharmacological antihypertensive agents. It is important that these medications are titrated to maximally tolerated approved doses. They have been shown to decrease the risk of CKD, as well as slowing the progression to end-stage kidney disease in people with a reduced eGFR and macroalbuminuria. Calcium channel blockers are suggested as a second- line agent, followed by a diuretic as a third-line antihypertensive agent. General advice to patients to reduce salt intake by substituting with nonsalt-containing food flavourings (e.g. pepper, garlic, lemon and ginger) are also helpful lifestyle measures to lower blood pressure.

A new nonsteroidal, mineralocorticoid receptor agonist, finerenone, is available in Australia. Although its blood pressure-lowering effects appear to be less than spironalactone and eplerenone (both steroidal mineralocorticoid receptor antagonists), this drug has impressive benefits in the setting of DKD.

Management of lipid levels

Lipid-lowering agents, particularly statins, are the cornerstone of both primary and secondary prevention of atherosclerotic CV disease, which has a markedly high risk of developing in people with DKD. There are no specific lipid targets for patients with diabetes and CKD, but it is recommended to initiate statin therapy in most of these patients who are not on dialysis.[12,13] By virtue of having both diabetes and CKD, this population is considered to be at high risk for CV disease. Therefore, the following targets are recommended:[14]

- LDL-cholesterol less than 2.0 mmol/L (or less than 1.8 mmol/L if CV disease is established)
- HDL-cholesterol greater than 1.0 mmol/L
- triglycerides: less than 2.0 mmol/L.

Proprotein convertase subtilisin/kexin type 9 inhibitors can also lower LDL-cholesterol levels and improve CV outcomes when added to statin therapy for secondary prevention.[15,16] Some evidence indicates that fenofibrate, which is effective in treating hypertriglyceridaemia, attenuates albuminuria and eGFR decline in type 2 diabetes.[17]

Recent advances in pharmacological treatments

Sodium-glucose cotransporter-2 inhibitors

SGLT-2 inhibitors (empagliflozin and dapagliflozin) are recommended in most people with type 2 diabetes and CKD, given the strong evidence that SGLT-2 inhibitors reduce CKD progression, heart failure and the risk of atherosclerotic CV disease in people with type 2 diabetes and CKD. These effects are independent of

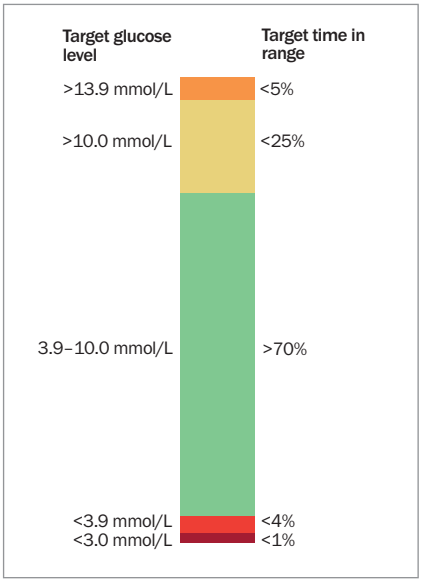

Figure. Continuous glucose monitoring-based targets for nonfrail people with diabetes.[9]

HbA_{1c} levels or the need for additional glucose lowering.[5,18]

Empagliflozin is not recommended for use in patients with an eGFR of less than 20 mL/min/1.73 m^2 and dapagliflozin is not recommended for patients with an eGFR of less than 25 mL/min/1.73 m^2. Although the renoprotective effects of SGLT-2 inhibitors are maintained at these eGFRs, the glucose-lowering effects of SGLT-2 inhibitors are significantly impaired at low eGFRs. The addition of other glucose-lowering therapies may therefore be required in people with low eGFRs.

Dapagliflozin is PBS listed for CKD and for heart failure with reduced ejection fraction (HFrEF), independent of diabetes status. Empagliflozin is also PBS listed for HFrEF, independent of diabetes status but is not currently TGA approved for CKD. Both medications are TGA approved for the treatment of heart failure with preserved ejection fraction (HFpEF), but at the time of writing, neither is PBS subsidised for this indication (refer to the PBS schedule and TGA website for full details). Although the atherosclerotic CV disease risk reduction and CKD progression benefits of SGLT-2 inhibitors may be found to be a class effect in future, the

SICK DAY MEDICATION LIST (SAD MANS) FOR PEOPLE WITH TYPE 2 DIABETES AND KIDNEY DISEASE

S – Sulfonylureas

A – ACE inhibitors

D – Diuretics

M – Metformin

A – Angiotensin receptor blockers

N – NSAIDs

S – Sodium-glucose cotransporter-2 inhibitors

evidence for ertugliflozin (a third SGLT-2 inhibitor recently deleted from the market in Australia) is less robust with further studies ongoing.

Importantly, despite the evidence for use of SGLT-2 inhibitors for DKD treatment, they should not be used in patients with type 1 diabetes because of the risk of euglycaemic diabetic ketoacidosis. SGLT-2 inhibitors can be associated with diabetic ketoacidosis in patients with type 2 diabetes, particularly during times of fasting or illness. Therefore, guidelines have been developed to address appropriate SGLT-2 inhibitor withdrawal for these cases.[19]

Glucagon-like peptide-1 receptor agonists

Many of the large-scale CV outcome trials of glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes have included kidney disease outcomes as secondary outcomes. These studies have indicated a reduction in albuminuria or lower risk of new or worsening nephropathy and slowing of the expected eGFR decline.[20-22] However, a reduction in the progression to end-stage kidney disease is yet to be demonstrated.

An ongoing trial of the GLP-1 receptor agonist semaglutide for type 2 diabetes and CKD is ongoing (clinical trial registration no. NCT03819153). In people with type 2 diabetes and advanced-stage CKD who have obesity and exceed body mass index limits required for kidney transplantation, the use of GLP-1 receptor agonists has been suggested to aid with weight loss, which may then facilitate eligibility for transplantation.

Furthermore, the TGA-approved dual glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonist tirzepatide has some evidence of renal benefit, based on a post-hoc analysis of the SURPASS-4 trial findings.[23] Dedicated renal outcome trials of tirzepatide are warranted.

Nonsteroidal mineralocorticoid receptor antagonist

Finerenone has recently been investigated in people with DKD (defined as an albumin to creatinine ratio of at least 3 mg/mmol and eGFR of 25 to 75 mL/min/1.73 m^2) who were treated with renin–angiotensin system inhibitors. This medication was shown to reduce the risk of CKD progression and renal failure, as well as dialysis initiation, in the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease trial, which involved participants with type 2 diabetes who had albuminuria and advanced CKD.[24] Furthermore, the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease trial, which involved participants with stage 2 to 4 CKD and moderately elevated albuminuria or stage 1 or 2 CKD and severely increased albuminuria, showed a reduction in CV morbidity, most prominently through a reduction in heart failure-related hospitalisations, with finerenone therapy.[25] A pooled analysis of the findings of these two trials further showed the safety and efficacy of finerenone in a large cohort of patients with type 2 diabetes and CKD to reduce important renal and CV outcomes.[26] Hyperkalaemia was an adverse effect in a small proportion of participants; regular monitoring of potassium levels is recommended when using this medication. Finerenone is TGA approved to delay progressive decline of kidney function in adults with CKD associated with type 2 diabetes (with albuminuria). It is also listed on the PBS for patients who fulfill the following key clinical criteria:

- an eGFR of 25 mL/min/1.73 m^2 or greater
- an ACR of 22.6 mg/mmol or greater
- must be on a stable dose of either an ACE inhibitor or ARB
- must not have established heart failure with reduced ejection fraction
- must be on an SGLT-2 inhibitor unless medically contraindicated or intolerant (please refer to the full PBS clinical criteria at: https://www.pbs.gov.au/pbs/home).

Combination therapy

Some evidence suggests that combination therapy with SGLT-2 inhibitors and mineralocorticoid receptor antagonists in patients with type 2 diabetes and CKD reduces the risk of CV events and the mineralocorticoid receptor antagonist-associated risk of hyperkalaemia without a significant interaction between the two drugs.[27] However, dedicated trials involving both SGLT-2 inhibitors and mineralocorticoid receptor antagonists are required to demonstrate the true benefits of combining these two classes of medications.

Of note, even before the introduction of the newer classes of medications, multifactorial, target-driven therapies addressing glycaemic, blood pressure and lipid control that incorporated renin–angiotensin system blockade, the use of statins and attention to lifestyle factors significantly reduced the progression to end-stage kidney disease by about 50% in people with type 2 diabetes, hypertension and microalbuminuria.[28]

Sick day management

GPs can play an important role in reinforcing the principles of sick day management, especially those related to medication use, in people with DKD. The acronym 'SAD MANS' is a useful mnemonic to remember medications that may have reduced clearance and an increased risk of adverse effects in people with CKD

(Box). Some medications need dose adjustments or withdrawing, especially in the setting of acute illness that can result in dehydration and acute renal failure.

Most guidelines support the use of metformin in people with an eGFR of 30 mL/min/1.73 m^2 or greater (although not at maximum recommended doses) and that there is a growing appreciation of temporarily withholding SGLT-2 inhibitors when patients are unwell or need to fast for a prolonged period of time to prevent the development of euglycaemic diabetic ketoacidosis.

Conclusion

Screening people with diabetes for early markers of DKD and initiating measures to slow the progression of kidney disease are part of routine clinical practice. In addition, it is necessary to measure, assess and manage CV risk factors aggressively. Attention to glycaemic, blood pressure and lipid control, as well as improving lifestyle factors (e.g. consuming a healthy diet, avoiding weight gain and undertaking regular physical activity) remain the cornerstone of management in people with DKD. The use of renin–angiotensin system inhibitors, SGLT-2 inhibitors and novel agents, such as finerenone, have also been shown to slow the progression of DKD to end-stage kidney disease and provide CV protection. There is emerging evidence for GLP-1 receptor agonists as renoprotective agents, but their role in slowing progression to end-stage kidney disease is yet to be established. Consideration of sick day management, patient education, the adjustment of glucose-lowering medications as the eGFR declines and screening for other microvascular diabetes-related complications (e.g. retinopathy and foot disease), together with a timely referral to a nephrology service, are important considerations in the optimal care of people with DKD. MT

References

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

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Preventing diabetic kidney disease progression

An update

JEAN C. LU MB BS, BMedSci, FRACP; **ELIF EKINCI** MB BS, FRACP, PhD
DAVID O'NEAL MD, FRACP, FRCP; **RICHARD J. MACISAAC** BSc(Hons), PhD, MB BS, FRACP

References

1. MacIsaac RJ, Ekinci EI, Jerums G. Markers of and risk factors for the development and progression of diabetic kidney disease. Am J Kidney Dis 2014; 63: S39-S62.
2. Hall PM. Prevention of progression in diabetic nephropathy. Diabetes Spectrum 2006; 19: 18-24.
3. Barkoudah E, Skali H, Uno H, Solomon SD, Pfeffer MA. Mortality rates in trials of subjects with type 2 diabetes. J Am Heart Assoc 2012; 1: 8-15.
4. Groop P-H, Thomas MC, Moran JL, et al. The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. Diabetes 2009; 58: 1651-1658.
5. de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care 2022; 45: 3075-3090.
6. Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes Care 2005; 28: 164-176.
7. American Diabetes Association. Introduction: standards of medical care in diabetes—2022. Diabetes Care 2022; 45: S1-S2.
8. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int, 2022; 102: S1-S127.
9. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care 2019; 42: 1593-1603.
10. Frankel AH, Wahba M, Ashworth V, et al. Management of adults with diabetes on dialysis: Summary of recommendations of the Joint British Diabetes Societies guidelines 2022. Diabet Med 2023; 40: e15027.
11. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int 2021; 99: S1-S87.
12. Wanner C, Tonelli M; Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. KDIGO clinical practice guideline for lipid management in CKD: summary of recommendation statements and clinical approach to the patient. Kidney Int 2014; 85: 1303-1309.
13. Sharp Collaborative Group. Study of Heart and Renal Protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. Am Heart J 2010; 160: 785-794.e10.
14. Royal Australian College of General Practitioners. Management of type 2 diabetes: a handbook for general practice. East Melbourne: Victoria; 2020.
15. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018; 379: 2097-2107.
16. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017; 376: 1713-1722.
17. Keech A, Drury P, Davis TM, et al. Protection against nephropathy with fenofibrate in type 2 diabetes mellitus: the FIELD study. Am Heart Assoc 2009; 120: S419-S420.
18. American Diabetes Association Professional Practice Committee. 11. Chronic kidney disease and risk management: standards of medical care in diabetes-2022. Diabetes Care 2022; 45: S175-S184.
19. Periprocedural diabetic ketoacidosis (DKA) with SGLT2 inhibitor use in people with diabetes. Sydney: Australian Diabetes Society; 2022. Available online at: https://www.diabetessociety.com.au/guideline/periprocedural-diabetic-ketoacidosis-dka-with-sglt2-inhibitor-use-in-people-with-diabetes-july-2022/ (accessed June 2023).
20. Marso SP, Holst AG, Vilsbøll T. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2017; 376: 891-892.
21. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019; 394: 121-130.
22. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375: 311-322.
23. Heerspink HJL, Sattar N, Pavo I, et al. Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial. Lancet Diabetes Endocrinol 2022; 10: 774-785.
24. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med 2020; 383: 2219-2229.
25. Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med 2021; 385: 2252-2263.
26. Agarwal R, Filippatos G, Pitt B, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J 2022; 43: 474-484.
27. Tsukamoto S, Morita R, Yamada T, et al. Cardiovascular and kidney outcomes of combination therapy with sodium-glucose cotransporter-2 inhibitors and mineralocorticoid receptor antagonists in patients with type 2 diabetes and chronic kidney disease: A systematic review and network meta-analysis. Diabetes Res Clin Pract 2022; 194: 110161.
28. Oellgaard J, Gæde P, Rossing P, Persson F, Parving HH, Pedersen O. Intensified multifactorial intervention in type 2 diabetics with microalbuminuria leads to long-term renal benefits. Kidney Int 2017; 91: 982-988. Erratum in: Kidney Int 2017; 91: 1257.

Resistant hypertension

An approach to management

SAYEH HEIDARI NEJAD MD, MPH
OMAR AZZAM MB ChB, MRCP (UK), FRACP
MARKUS P. SCHLAICH MD, FESC, FAHA, ISHF

Resistant hypertension (RH) is a prevalent and significant cause of morbidity and mortality. Adverse health outcomes, including cardiovascular disease, hypertension-mediated organ damage and chronic kidney disease, can be significant. This article describes the means for GPs to identify predisposing and contributing factors to RH and recommends an evidence-based approach to diagnosis and management.

Hypertension affects nearly one billion individuals worldwide and is a common presentation in general practice. It is one of the most significant modifiable risk factors for disability and death worldwide.[1] The global prevalence of resistant hypertension (RH) is 5 to 30%; this wide range is due to variability in the definition and the analysed population among different studies. The prevalence is estimated to be about 10 to 15% in the treated population based on the latest RH definitions (excluding apparent causes).[2]

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KEY POINTS

- Resistant hypertension (RH) affects about 10 to 15% of treated patients diagnosed with hypertension and is associated with an increased risk of adverse cardiovascular outcomes and hypertension-mediated organ damage (HMOD).
- True RH must be confirmed by adequate in-office and out-of-office blood pressure (BP) measurements (home or ambulatory). Common causes of apparent RH include white-coat hypertension, nonadherence with prescribed antihypertensive therapy, inadequate antihypertensive combination therapy and the use of interfering concomitant medications.
- Obesity, obstructive sleep apnoea and renal parenchymal disease are among the most common contributing features of RH; affected patients should be screened for secondary causes of hypertension (especially primary aldosteronism) regardless of their age.
- Management of RH relies on lifestyle measures (maintaining a healthy weight through regular physical activity and a healthy diet, salt restriction, limiting alcohol intake and smoking cessation), pharmacotherapy and interventional approaches, where required.
- Pharmacotherapy includes a combination of a renin-angiotensin-system blocker, a long-acting calcium channel blocker and a diuretic at maximally tolerated doses, ideally as a single pill combination.
- Spironolactone is currently recommended as the preferred fourth-line therapy, with alpha blockers, beta blockers, centrally acting sympatholytic agents, or vasodilators as alternatives.
- If BP control cannot be achieved with the above strategies, interventional approaches such as renal denervation and novel therapeutic agents (once available) should be considered.

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Dr Heidari Nejad is a Medical Registrar at the Dobney Hypertension Centre, Royal Perth Hospital, Perth. Dr Azzam is a Consultant Nephrologist and General Medicine Physician at the Dobney Hypertension Centre, Royal Perth Hospital, Perth. Professor Schlaich is the Chair in Clinical Research at the Dobney Hypertension Centre, Royal Perth Hospital; Professor at the Medical School at the University of Western Australia; and a Consultant Nephrologist and Hypertension Specialist at the Royal Perth Hospital, Perth, WA.

Defining resistant hypertension

The European Society of Cardiology/European Society of Hypertension (ESC/ESH) 2018 guidelines defined RH as a diagnosis given to patients who are above the target blood pressure (BP) despite being on maximally tolerated doses of three antihypertensive drug classes, including a diuretic, and preferably a long-acting calcium channel blocker and a renin-angiotensin system blocker (i.e. ACE inhibitor or angiotensin receptor blocker

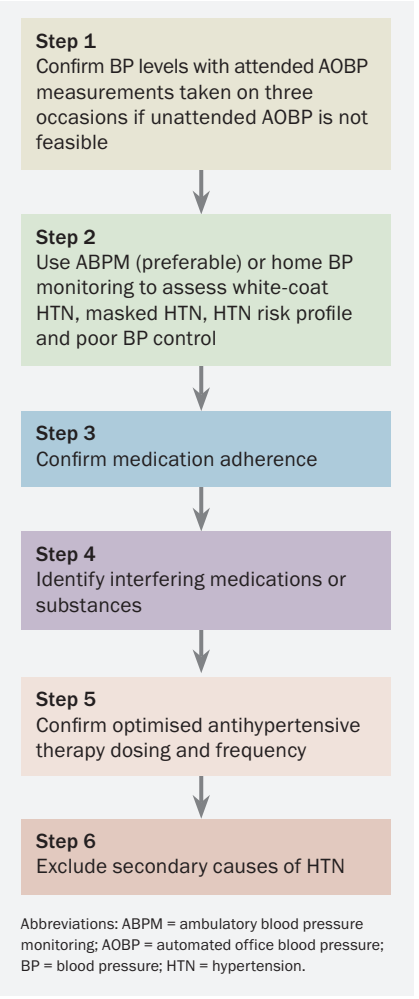

Figure 1. Steps for diagnosis of true resistant hypertension.

[ARB]).[3] Patients who require treatment with four or more classes of antihypertensive medication are also considered to have RH, regardless of their BP.[4]

The American College of Cardiology/American Heart Association 2018 hypertension guidelines adopt a lower office BP threshold of 130/80 mmHg or higher for the definition of hypertension, compared with most other guidelines (including those for Australia), which propose an office BP threshold of 140/90 mmHg or higher.[4]

RH is associated with a higher incidence of adverse cardiovascular outcomes, including myocardial infarction, cerebrovascular events and congestive heart failure.[5] It is also associated with a higher incidence of hypertension-mediated organ damage (HMOD), chronic kidney disease (CKD) and all-cause mortality.[6] Hence, it is crucial to identify and treat RH aggressively to improve outcomes.

Risk factors and pathophysiology

Predictive risk factors for difficult-to-control hypertension include:[7]

- higher baseline BP (especially systolic)
- older age
- obesity
- African-American heritage
- male sex
- presence of left ventricular hypertrophy
- CKD
- diabetes.

The underlying pathophysiology of RH is a combination of volume and sodium retention, aldosterone excess and sustained increased activity of the sympathetic nervous system and the renin-angiotensin-aldosterone system.[8-11] The endothelin-1 pathway is another important contributor to the pathophysiology of RH; blockade of this pathway has recently demonstrated promising outcomes in the management of RH.[12]

Clinical assessment

The patient should be asked about potential contributing lifestyle and dietary factors, including their salt and alcohol intake, weight and height, level of physical activity and sleep patterns. Details of personal and family history of hypertension and presence of cardiovascular risk factors should be obtained.

On physical examination, the signs of secondary hypertension as well as evidence of HMOD, including hypertensive retinopathy, left ventricular hypertrophy, microalbuminuria and CKD, should be sought. The basic and extended screening tests for HMOD are detailed in Box 1.

Diagnosis

RH can be true or apparent. Diagnosis of true RH requires the exclusion of undetected secondary causes of hypertension and pseudoresistant hypertension, which is defined as seemingly treatment-resistant hypertension that is primarily due to interfering factors in BP measurement or treatment.[3]

The ESC/ESH 2018 guidelines list five of the most common causes of pseudoresistant hypertension to be excluded in confirming the diagnosis of true RH. These include poor adherence to antihypertensive therapy, poor office BP measurement techniques, suboptimal antihypertensive therapy, white-coat phenomenon, and severe brachial artery calcification.[3] Figure 1 summarises the proposed steps in diagnosing true RH.

Diagnostic steps

Step 1. Measure BP accurately

Office BP measurement remains the basis of diagnosing and managing hypertension. Automated office BP (AOBP), with the attending clinician absent from the room, is the most reliable method of office BP measurement, and was used in The Systolic BP Intervention Trial (SPRINT) and other studies.[13,14] However, the triplicate standardised attended AOBP is the most feasible method in primary care. If attended AOBP is performed on three or more occasions under standardised conditions, the result is comparable in reliability to unattended AOBP.[15] Figure 2 displays the international consensus on standardised AOBP.[16]

Step 2. Exclude white-coat hypertension, masked hypertension and poor BP control

White-coat hypertension is defined as elevated office BP, but normal out-of-office BP. It is estimated that white-coat hypertension might be present in 28 to 39% of individuals with apparent RH.[2] The white-coat phenomenon can be significantly reduced or eliminated by AOBP that is unattended.[17] However, relying solely on office BP measurements can result in missed diagnoses of

RH in patients with masked hypertension; such patients may have BP exceeding the recommended targets during ambulatory blood pressure monitoring (ABPM), but not during office BP measurement. Additionally, the initial reason for a patient's clinic visit, such as pain or other medical issues, could influence the office BP readings.[18]

Patients whose RH was confirmed by ABPM have a higher prevalence of HMOD and cardiovascular disease.[19] ABPM recordings provide additional relevant indices, such as 24-hour BP variability, morning BP surge, and ambulatory arterial stiffness index, which have some predictive value. Overall, there is clear evidence that office BP measurements alone are inadequate in identifying RH. ABPM with or without home BP monitoring must be used to confirm the diagnosis.[3]

Step 3. Confirm adherence to medication

Partial medication adherence and complete nonadherence occurs in 17 to 46% and 9 to 35% of patients with RH, respectively.[19] The high prevalence of nonadherence in this patient group is in part attributable to polypharmacy, complex medication regimens, high incidence of medication intolerance and adverse effects and poor patient–clinician relationship.[13] Some of the practical methods to assess medication adherence include direct questioning about adherence in a nonjudgemental manner, medication adherence questionnaires, pill counts, and electronic pill boxes. The less feasible (but more reliable) methods of assessing adherence include biochemical assay of medications or their metabolites in blood or urine, as well as observed pill intake when patients' medication is administered in the clinic with their BP measured before and several hours after medication consumption.[19]

Step 4. Identify interfering substances or medications

Concurrent use of a variety of medications (e.g. over-the-counter medications, substances and homeopathic medications) can raise BP or interfere with the effects of antihypertensives by increasing sympathetic activity, increasing intravascular volume or decreasing sodium excretion.[2] NSAIDs are possibly the most common drugs to raise BP or interfere with effects of antihypertensives.[3] Some of the other common agents that affect BP include homeopathic medications, decongestants, stimulants used for weight loss (e.g. phentermine), oral contraceptives, recreational drugs (e.g. cocaine, anabolic steroids), ciclosporin and corticosteroids, through volume retention.[2]

Step 5. Confirm optimised antihypertensive therapy dosing and frequency

Failure of treatment intensification is a common cause of high BP.[20,21] It is crucial to optimise the dose of all three recommended antihypertensive medications in RH to the maximum tolerated dose.

Step 6. Exclude secondary causes of hypertension

The prevalence of secondary causes of hypertension is approximately 10% in adult populations.[22] Obstructive sleep apnoea, primary aldosteronism and renovascular and renal parenchymal diseases are among the most prevalent secondary causes of hypertension. It is important to remember that secondary causes of hypertension can also occur in the elderly.[22,23]

RH is a common indication for secondary hypertension screening, in addition to grade 3 hypertension, grade 2 hypertension in adults younger than 40 years of age, acute worsening in previously well-controlled cases of hypertension, evidence of extensive HMOD, clinical or biochemical signs of secondary causes and hypertension in children and adolescents.[3] A list of secondary causes of hypertension and the initial screening is outlined in the Table.

Interpreting some initial screening tests for RH (e.g. aldosterone-renin ratio to exclude primary hyperaldosteronism) may pose challenges if patients are taking antihypertensive medications that could interfere with the accuracy of these tests.[24] GPs should seek the opinion of relevant specialists, particularly if the initial screening tests yield results that are inconclusive or suggestive of secondary causes.

1. WORKUP FOR HYPERTENSION-MEDIATED ORGAN DAMAGE

Basic screening

- ECG to screen for LVH and ischaemia; document cardiac rhythm and heart rate
- eGFR and electrolytes to screen for renal disease
- Urine ACR to screen for renal disease
- Fundoscopic examination[3] to detect retinopathy

Extended screening, if indicated

- Transthoracic echocardiography
- Carotid ultrasonography
- Abdominal and doppler studies, CT angiography or MR angiography
- Pulse wave velocity
- Brain imaging
- Cognitive function testing

Risk factors for further prognostication

- HbA_{1c}, fasting BGL or OGTT to screen for diabetes
- Fasting lipid profile to screen for dyslipidaemia
- 24-hour urinary sodium, creatinine and protein levels to assess salt intake

Abbreviations: ACR = albumin: creatinine ratio; BGL = blood glucose level; CT = computed tomography; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycated haemoglobin; LVH = left ventricular hypertrophy; MR = magnetic resonance; OGTT = oral glucose tolerance test.

Management

The general principles of treatment for RH are the same as those for milder forms of hypertension, including:

- the modification of contributory lifestyle factors
- the cessation of interfering substances/medications, where possible

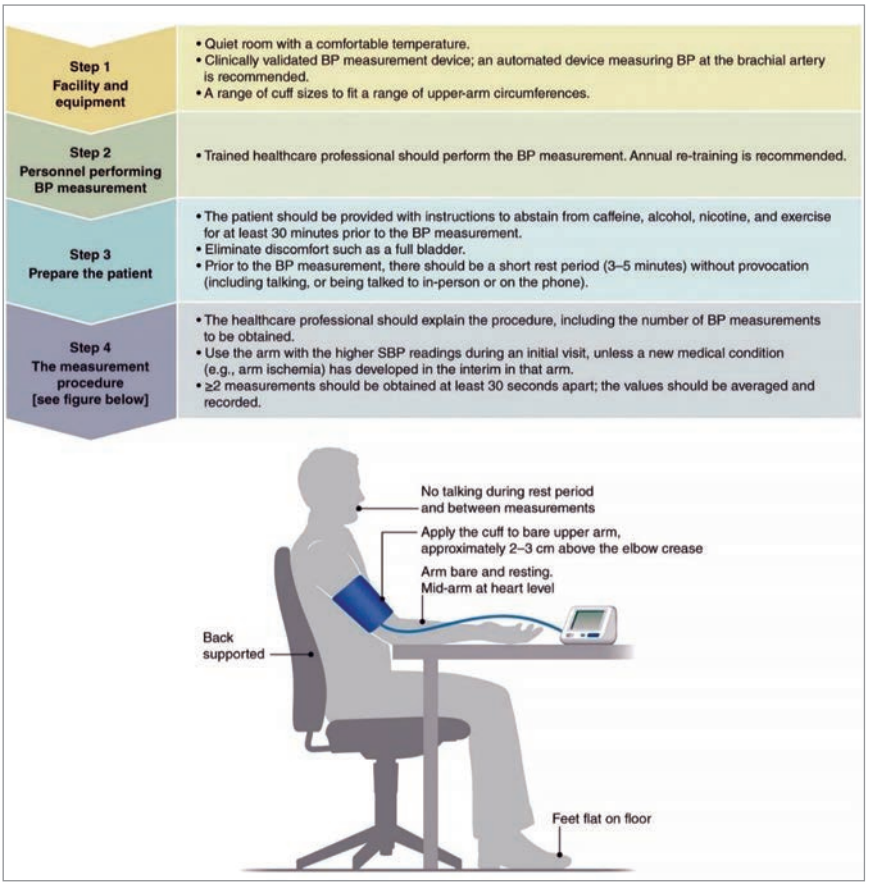

Figure 2. Steps for implementing standardised office blood pressure measurement.[16]
Abbreviation: SBP = systolic blood pressure.

- the sequential addition of guideline-recommended antihypertensive agents with different modes of action, ideally in the form of single pill combinations to improve adherence
- using the full armamentarium of antihypertensive drugs, where required.

Promising novel drugs for RH, such as the dual endothelin antagonist, aprocitentan, and the aldosterone synthase inhibitor, baxdrostat, are in the advanced stages of clinical development and may facilitate improved BP control in RH when they become available.[12,25] Interventional approaches, such as renal denervation, should be considered a safe and effective means of achieving sustained BP reduction at various stages of the patient's management.[26]

Lifestyle modification

Patients with RH are more likely to be non-adherent to lifestyle and dietary measures, such as limiting alcohol intake, reducing sodium intake, maintaining a healthy weight and performing regular physical activity.[3]

Regular light to moderate physical activity (including long-term aerobic exercise and heated pool exercise) showed favourable outcomes as a successful BP lowering intervention.[27,28]

Smoking cessation and minimal alcohol intake should be recommended in individuals with RH, as with all other patients diagnosed with hypertension.[29]

Overweight and obese individuals with RH should aim for a 6 to 8% decrease in body weight to achieve a 5 and 4 mmHg reduction in systolic and diastolic BP, respectively.[29]

High dietary sodium intake significantly contributes to RH and is a well-known factor in antihypertensive medication resistance. A reduced sodium intake of less than 1500 mg daily decreases office systolic and diastolic BP readings by 22.7 and 9.1 mmHg, respectively.[30] The BP-lowering effect of sodium restriction is similarly profound in patients with CKD and RH.[31] Diets, such as the DASH and Mediterranean diets, can help with BP control, but have not been well studied in the management of RH (Box 2).

Pharmacotherapy

The antihypertensive regimen for the management of RH is usually based on comorbidities, underlying secondary causes, previous medication intolerances and financial constraints.

A common and effective combination includes an ACE inhibitor or ARB, a long-acting calcium channel blocker and a thiazide or thiazide-like diuretic. This combination should be prescribed at maximally tolerated doses at an appropriate frequency, with reference to the half-life of the medications involved.

Maximised diuretic therapy is essential for the treatment of RH, as volume retention and sodium excess are common causes of RH, even though obvious signs of hypervolaemia (such as lower limb oedema) may be absent.[30-32] An important consideration for the management of ongoing residual hypertension is the switching of thiazide therapy to a more potent diuretic (e.g. indapamide or chlorthalidone) if the estimated glomerular filtration rate (eGFR) is 30 mL/min/1.73 m^2 or greater. Chlorthalidone is frequently used in the USA, but rarely prescribed in Australia, despite being a more potent diuretic with a longer half-life than hydrochlorothiazide.[35]

The recently published results from the Diuretic Comparison Project suggested no significant difference in cardiovascular outcomes and noncancer-related deaths between chlorthalidone and hydrochlorothiazide, but found more frequent hypokalaemia with the use of

TABLE. INVESTIGATING SECONDARY CAUSES OF HYPERTENSION

Secondary cause	Suggestive symptoms and signs	Screening investigations
Obstructive sleep apnoea	Snoring; obesity (but can be present in nonobese); morning headache; daytime somnolence	Epworth score and home-based ambulatory polygraphy
Renal parenchymal disease	Mostly asymptomatic; diabetes; haematuria, proteinuria, nocturia; anaemia, renal mass in adult polycystic CKD	Plasma creatinine and electrolyte levels, eGFR; urine dipstick for blood and protein, urinary albumin: creatinine ratio; renal ultrasound
Atherosclerotic renovascular disease	Older patients; widespread atherosclerosis (especially PAD); diabetes; smoking; recurrent flash pulmonary oedema; abdominal bruit	Duplex renal artery Doppler ultrasound, CT angiography or MR angiography
Fibromuscular dysplasia	Younger patients; more common in women; abdominal bruit	
Primary aldosteronism	Mostly asymptomatic; muscle weakness (rare)	Baseline plasma aldosterone, renin and potassium levels; aldosterone: renin ratio
Phaeochromocytoma	Episodic symptoms (the 5 'Ps'): paroxysmal hypertension, pounding headache, perspiration, palpitations and pallor; labile BP; BP surges precipitated by use of medications (e.g. beta blockers, metoclopramide, sympathomimetics, opioids and TCA)	Plasma or 24-hour urinary fractionated metanephrines
Cushing's syndrome	Moon face, central obesity, skin atrophy, striae and bruising; diabetes; chronic steroid use	24-hour urinary free cortisol (two measurements) or midnight salivary cortisol (two measurements) or 1 mg dexamethasone suppression test
Thyroid disease (hyperthyroidism or hypothyroidism)	Changes in weight, heart rate, skin, eyes, thoughts, emotions or energy	Thyroid function tests
Hyperparathyroidism	Hypercalcaemia, hypophosphataemia	Parathyroid hormone, serum calcium
Coarctation of the aorta	Usually detected in children or adolescents; different BP (≥20/10 mmHg) between upper and lower extremities or between right and left arm and delayed radial to femoral artery pulsation; low ABI; interscapular ejection murmur; rib notching on chest x-ray	Echocardiography

Abbreviations: ABI = ankle brachial index; BP = blood pressure; CKD = chronic kidney disease; CT = computed tomography; eGFR = estimated glomerular filtration rate; MR = magnetic resonance; PAD = peripheral arterial disease; TCA = tricyclic antidepressants.

Adapted with permission from Cheung AK, et al. Am J Med 2023; 136: 438-445.[16]

chlorthalidone.[36] Given that single pill combinations are associated with improved adherence, hydrochlorothiazide and indapamide are likely to remain the preferred choices, as, unlike chlorthalidone, they are both available in combination with renin-angiotensin system blockers as single pill combinations. If a patient's eGFR is 30 mL/min/1.73 m^2 or lower, the benefit of thiazide-like therapy is less, and loop diuretics (e.g. frusemide or bumetanide) can be added to the regimen or used as a substitute.[3]

The mineralocorticoid receptor antagonist (MRA) spironolactone is currently considered the preferred fourth-line agent, to be used in addition to previously maximised combination therapy.[8,37] If spironolactone is not tolerated, eplerenone can be used as an alternative.[38] The potassium-sparing diuretic amiloride is no longer available in Australia. Common adverse effects of MRAs include hyperkalaemia and reduction in eGFR, which require close monitoring. With particular reference to spironolactone, high doses of MRAs can cause gynaecomastia and erectile dysfunction and preferably should not be prescribed at doses greater than 50 mg daily in people with primary RH. Such adverse effects are minimal with eplerenone, which is less potent and requires twice daily dosing due to its shorter half-life.

There are limited data to guide the choice of a fifth-line antihypertensive agent, if uncontrolled hypertension persists despite the recommended regimens. A reasonable approach is to add further agents based on comorbidities and the patient's preference.

Patients with a baseline heart rate above 70 beats per minute and those with a diagnosis of coronary artery disease or heart failure would benefit from the addition of beta blockers. Labetalol, carvedilol and

2. DIETS TO HELP WITH BLOOD PRESSURE CONTROL[32-34]

The Dietary Approaches to Stop Hypertension (DASH) diet

- High consumption of whole nutrient-dense foods, such as fruits, vegetables, whole grains, lean protein sources and low fat dairy products
- Limited consumption of high-calorie, high-fat and high-sugar foods, with a reduction in sodium intake to typically less than 2300 mg per day (lower targets for people with high blood pressure)

The Mediterranean diet

- High consumption of fruits, vegetables, whole grains, legumes, nuts, fish and olive oil
- Limited consumption of red and processed meat, sweets and refined grains

nebivolol have vasodilatory effects and are more effective in lowering BP compared with other commonly used beta blockers.[39]

Centrally acting agents (e.g. methyldopa or clonidine) can be used to suppress sympathetic nervous activity, which is usually elevated in RH. In the Resistant Hypertension Optimal Treatment (ReHOT) trial, clonidine was shown to have similar efficacy to spironolactone in lowering BP; however, common adverse effects of clonidine include somnolence, dry mouth sensation and rebound phenomena.[40] More advanced and better tolerated centrally acting sympatholytic agents, such as the selective imidazoline receptor agonist moxonidine, are a useful alternative.

Other available medications for RH management include alpha blockers (e.g. prazosin) or direct vasodilators (e.g. hydralazine or minoxidil). The latter group should generally be used with a loop diuretic to address the common adverse effect of hypervolaemia and lower limb oedema.[3]

Promising novel drugs

New classes of medications with substantial BP-lowering efficacy are under investigation. Baxdrostat, an aldosterone synthase inhibitor, resulted in reduced office systolic BP readings over 12 weeks of 20.3, 17.5 and 12.1 mmHg at 2 mg, 1 mg and 0.5 mg doses, respectively, confirming the significant dose-related BP-lowering effect when added to stable doses of three antihypertensive medications in the management of RH.[25] Aprocitentan, a dual endothelin antagonist, was recently shown to have a significant dose-dependent reduction in office and 24-hour ABPM after four weeks of therapy in individuals with RH on three background antihypertensive medications. The greatest BP-lowering effect was evident in elderly patients and those with macroalbuminuria and stage 3 to 4 CKD.[12]

Interventional therapies

Interventional approaches (e.g. renal denervation) have been shown in multiple sham-controlled trials to exert substantial BP-lowering effects in various forms of hypertension, including RH. The catheter-based procedure has a favourable safety profile with long-term BP-lowering efficacy demonstrated to nine years postprocedure.[41,42] This method aims to inhibit renal sympathetic efferent nerve activity, which contributes to reduced renal blood flow, decreased urinary salt, reduced water excretion and high renin release in the kidneys.[43] The ESH recently issued a position paper on renal denervation, summarising the available evidence and providing recommendations for its use in routine clinical practice (Box 3).[44] A position paper on the use of renal denervation in an Australian context is in preparation.

3. RECOMMENDATIONS REGARDING RENAL DENERVATION[44]

The European Society for Hypertension 2018 guidelines include a consensus on the following:

- Renal denervation can be used to treat hypertension, in addition to lifestyle changes and blood pressure-lowering drugs, based on consistent results of several sham-controlled clinical trials
- Renal denervation therefore expands therapeutic options to address the first objective of hypertension treatment, which is to effectively reduce elevated blood pressure and achieve blood pressure targets
- Renal denervation is considered a safe endovascular procedure without significant short-term or long-term adverse effects based on data available for up to three years
- Renal denervation is an alternative or additive, not a competitive treatment strategy
- A structured pathway for the clinical use of renal denervation in daily practice is recommended
- Patients' perspective and preference, as well as patients' stage of hypertensive disease, including comorbidities, should lead to an individualised treatment strategy in a shared decision-making process, which carefully includes the various options of treatment, including renal denervation

Conclusion

RH remains challenging to manage and is a modifiable risk factor for adverse health outcomes. Recommended management of RH includes: excluding pseudoresistant hypertension; identifying relevant contributing factors, focusing on lifestyle modification; using simple medication regimens (ideally, in the form of single pill combinations of guideline-recommended drugs with different modes of action), adding further drug classes as required (based on comorbidities); and considering renal denervation as an evidence-based option to safely and effectively lower BP. Appropriate management of RH results in improved cardiovascular outcomes for this high-risk patient cohort. MT

References

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

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Resistant hypertension

An approach to management

SAYEH HEIDARI NEJAD MD, MPH; **OMAR AZZAM** MB ChB, MRCP (UK), FRACP
MARKUS P SCHLAICH MD, FESH, FAHA, ISHF

References

1. Collaborators GBDRF. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017; 390: 1345-1422.
2. Doumas M, Imprialos KP, Kallistratos MS, Manolis AJ. Recent advances in understanding and managing resistant/refractory hypertension. F1000Res 2020; 9.
3. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). G Ital Cardiol 2018; 19 (11 Suppl 1) :3S-73S.
4. Carey RM, Calhoun DA, Bakris GL, et al. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association. Hypertens 2018; 72: e53-e90.
5. Daugherty SL, Powers JD, Magid DJ, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. Circ 2012; 125: 1635-2112.
6. Sim JJ, Bhandari SK, Shi J, et al. Comparative risk of renal, cardiovascular, and mortality outcomes in controlled, uncontrolled resistant, and nonresistant hypertension. Kidney Int 2015; 88: 622-632.
7. Chia R, Pandey A, Vongpatanasin W. Resistant hypertension-defining the scope of the problem. Prog Cardiovasc Dis 2020; 63: 46-50.
8. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 2015; 386: 2059-2068.
9. Gaddam KK, Nishizaka MK, Pratt-Ubunama MN, et al. Characterization of resistant hypertension - Association between resistant hypertension, aldosterone, and persistent intravascular volume expansion. Arch Intern Med 2008; 168: 1159-1164.
10. Wilson AL, Gandhi J, Suh YJ, Joshi G, Smith NL, Khan SA. Renal innervation in resistant hypertension: a review of pathophysiology and renal denervation as potential treatment. Curr Hypertens Rev 2020; 16: 115-127.
11. Hwang AY, Dietrich E, Pepine CJ, Smith SM. Resistant hypertension: mechanisms and treatment. Curr Hypertens Rep 2017; 19: 56.
12. Schlaich MP, Bellet M, Weber MA, et al. Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial. Lancet 2022; 400: 1927-1937.
13. Johnson KC, Whelton PK, Cushman WC, et al. Blood pressure measurement in SPRINT (Systolic Blood Pressure Intervention Trial). Hypertension 2018; 71: 848-857.
14. Stergiou G, Kollias A, Parati G, O'Brien E. Office blood pressure measurement the weak cornerstone of hypertension diagnosis. Hypertension 2018; 71: 813-815.
15. Stergiou GS, Kyriakoulis KG, Kollias A. Office blood pressure measurement types: different methodology-different clinical conclusions. J Clin Hypertens 2018; 20: 1683-1685.
16. Cheung AK, Whelton PK, Muntner P, et al. International Consensus on Standardized Clinic Blood Pressure Measurement - A Call to Action. Am J Med 2023; 136: 438-445.
17. Myers MG, Valdivieso M, Kiss A. Use of automated office blood pressure measurement to reduce the white coat response. J Hypertens 2009; 27: 280-286.
18. Tang O, Juraschek SP, Appel LJ, et al. Comparison of automated clinical and research blood pressure measurements: Implications for clinical practice and trial design. J Clin Hypertens 2018; 20: 1676-1682.
19. Lamirault G, Artifoni M, Daniel M, Barber-Chamoux N, Nantes University Hospital Working Group On Resistant Hypertension: Novel Insights. Curr Hypertens Rev 2020; 16: 61-72.
20. Egan BM, Zhao Y, Li J, Brzezinski WA, et al. Prevalence of optimal treatment regimens in patients with apparent treatment-resistant hypertension based on office blood pressure in a community-based practice network. Hypertension 2013; 62: 691-697.
21. Acelajado MC, Hughes ZH, Oparil S, Calhoun DA. Treatment of resistant and refractory hypertension. Circ Res 2019; 124: 1061-1070.
22. Siru R, Conradie JH, Gillett MJ, Page MM. Approach to the diagnosis of secondary hypertension in adults. Aust Prescr 2021; 44: 165-169.
23. Charles L, Triscott J, Dobbs B. Secondary hypertension: discovering the underlying cause. Am Fam Physician 2017; 96: 453-461.
24. Reincke M, Bancos I, Mulatero P, Scholl UI, Stowasser M, Williams TA. Diagnosis and treatment of primary aldosteronism. Lancet Diabetes Endo 2021; 9: 876-892.
25. Freeman MW, Halvorsen YD, Marshall W, et al. Phase 2 trial of baxdrostat for treatment-resistant hypertension. N Engl J Med 2022; 388: 395-405.
26. Weber MA, Mahfoud F, Schmieder RE, et al. Renal denervation for treating hypertension current scientific and clinical evidence. JACC-Cardiovasc Interv 2019; 12: 1095-1105.
27. Santos LP, Moraes RS, Vieira PJC, et al. Effects of aerobic exercise intensity on ambulatory blood pressure and vascular responses in resistant hypertension: a crossover trial. J Hypertens 2016; 34: 1317-1324.
28. Guimaraes GV, Cruz LGD, Fernandes-Silva MM, Dorea EL, Bocchi EA. Heated water-based exercise training reduces 24-hour ambulatory blood pressure levels in resistant hypertensive patients: A randomized controlled trial (HEx trial). Int J Cardiol 2014; 172: 434-441.
29. Weiss EP, Albert SG, Reeds DN, et al. Effects of matched weight loss from calorie restriction, exercise, or both on cardiovascular disease risk factors: a randomized intervention trial. Am J Clin Nutr 2016; 104: 576-586.
30. Pimenta E, Gaddam KK, Oparil S, et al. Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension results from a randomized trial. Hypertension 2009; 54: 475-481.
31. McMahon EJ, Bauer JD, Hawley CM, et al. A randomized trial of dietary sodium restriction in CKD. J Am Soc Nephrol 2013; 24: 2096-2103.
32. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. N Engl J Med 2001; 344: 3-10.
33. Teres S, Barcelo-Coblijn G, Benet M, et al. Oleic acid content is responsible for the reduction in blood pressure induced by olive oil. Proc Natl Acad Sci USA 2008; 105: 13811-13816.
34. Guasch-Ferre M, Willett WC. The Mediterranean diet and health: a

comprehensive overview. J Intern Med 2021; 290: 549-566.
35. Ingelfinger JR. Thiazide-like versus Thiazide Diuretics - Finally, an Answer? N Engl J Med 2022; 387: 2462-2463.
36. Ishani A, Cushman WC, Leatherman SM, et al. Chlorthalidone vs. hydrochlorothiazide for hypertension-cardiovascular events. N Engl J Med 2022; 387: 2401-2410.
37. Oparil S, Schmieder RE. New Approaches in the Treatment of Hypertension. Circ Res 2015; 116: 1074-1095.
38. Bazoukis G, Thomopoulos C, Tsioufis C. Effect of mineralocorticoid antagonists on blood pressure lowering: overview and meta-analysis of randomized controlled trials in hypertension. J Hypertens 2018; 36: 987-994.
39. Aronow WS. approaches for the management of resistant hypertension in 2020. Curr Hypertens Rep 2020; 22: 3.
40. Krieger EM, Drager LF, Giorgi DMA, et al. Spironolactone versus clonidine as a fourth-drug therapy for resistant hypertension: The ReHOT Randomized Study (Resistant Hypertension Optimal Treatment). Hypertension 2018; 71: 681-690.
41. Townsend RR, Mahfoud F, Kandzari DE, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet 2017; 390: 2160-2170.
42. Kandzari DE, Bohm M, Mahfoud F, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet 2018; 391: 2346-2355.
43. Osborn JW, Foss JD. Renal nerves and long-term control of arterial pressure. Compr Physiol 2017; 7: 263-320.
44. Schmieder RE, Mahfoud F, Mancia G, et al. Members of the ESH Working Group on Device-Based Treatment of Hypertension. European Society of Hypertension position paper on renal denervation 2021. J Hypertens 2021; 39: 1733-1741.

PEER REVIEWED FEATURE

Type 2 diabetes

Advances in investigation and management

ROSE LIN BBMed, MD
RICHARD J. MACISAAC BSc(Hons), PhD, MB BS, FRACP
ELIF EKINCI MB BS, FRACP, PhD

Major advances have occurred in the investigations and management of type 2 diabetes, ranging from detection and complications screening to pharmacotherapy, which offers cardiovascular and kidney protection.

KEY POINTS

- Type 2 diabetes is becoming increasingly prevalent and is associated with a high risk of developing cardiovascular and kidney diseases.
- Measurement of glycated haemoglobin remains the gold standard for assessing glycaemic control, with a general target of less than 7% (53 mmol/mol), although this should be individualised to the person with type 2 diabetes.
- Type 2 diabetes is increasingly associated with complications such as heart failure, cognitive impairment and depression, malignancy and fatty liver disease.
- A multifactorial approach targeting glycaemic, blood pressure, lipid and weight control, as well as modifying lifestyle factors, are required for the optimal management of type 2 diabetes.
- Sodium-glucose cotransporter-2 inhibitors should be used in people with type 2 diabetes who have established cardiovascular disease (or who are at high risk of cardiovascular disease), heart failure or chronic kidney disease.
- Finerenone, which has been recently PBS listed, offers renoprotection and should be used in conjunction with SGLT-2 inhibitors.
- The introduction of tirzepatide to Australia as an agent to further manage type 2 diabetes and its associated metabolic abnormalities is eagerly anticipated.
- Type 2 diabetes remission can be achieved with significant weight loss in people who are overweight or obese, including from lifestyle changes and/or bariatric surgery.

The prevalence of type 2 diabetes is increasing. The number of people living with diabetes in Australia has increased by almost 2.8-fold between 2000 and 2020, from 460,000 to 1.3 million people.[1] People with type 2 diabetes are at an increased risk of developing diabetes-associated complications. Although there is evidence that the rate of complications is declining, disease burden remains high due to increasing diabetes prevalence and greater longevity. Fortunately, there have been major advancements in the management of type 2 diabetes and diabetes-associated complications. This article outlines these recent advances in the investigation and management of type 2 diabetes, with a focus on cardio-kidney health.

Investigations

Measurement of glycated haemoglobin (HbA_{1c}) and blood glucose levels (BGL) is key to diagnosing type 2 diabetes and assessing glycaemic control. In asymptomatic patients, repeated testing with the following results are diagnostic of diabetes (Table 1):

- HbA_{1c} level 6.5% or more (48 mmol/mol)
- fasting BGL 7 mmol/L or more
- random or two-hour oral glucose tolerance test BGL 11.1 mmol/L or more.

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Dr Lin is an Advanced Trainee in the Endocrinology Department at Austin Health and Northern Health in Melbourne.
Professor MacIsaac is Director and Professor of Endocrinology at St Vincent's Hospital Melbourne and the University of Melbourne and co-stream lead for Diabetic Kidney Disease at the Australian Centre for Accelerating Diabetes Innovations.
Professor Ekinci is Director of Diabetes at Austin Health in Melbourne and Director of Australian Centre for Accelerating Diabetes Innovations, and the Sir Edward Dunlop Medical Research Foundation Principal Research Fellow in Metabolic Medicine at the University of Melbourne, Vic.

TABLE 1. SUMMARY OF INVESTIGATIONS TO STRATIFY GLYCAEMIC STATUS

Investigation	Normal levels	Pre-diabetes	Diabetes
HbA_{1c}	<6.0% (<42 mmol/mol)	6.0–6.4% (42–46 mmol/mol)	≥6.5% (≥48 mmol/mol)
Fasting BGL	≤6.0 mmol/L	6.1–6.9 mmol/L	≥7 mmol/L
Random BGL	<7.8 mmol/L	7.8–11 mmol/L	≥11.1 mmol/L
2-hour OGTT	<7.8 mmol/L	7.8–11 mmol/L	≥11.1 mmol/L

Abbreviations: BGL = blood glucose level; HbA_{1c} = glycated haemoglobin; OGTT = oral glucose tolerance test.

For patients with type 2 diabetes, general management targets are:

- HbA_{1c} level 7% or less (53 mmol/mol)
- fasting/preprandial BGL 4.0 to 7.0 mmol/L
- postprandial BGL 5.0 to 10.0 mmol/L.

However, individualisation is required for some patients. This could include tighter targets for people with a shorter duration of type 2 diabetes taking metformin only, or less stringent targets for people with a long duration of diabetes and high complications burden who are taking insulin or have recurrent hypoglycaemia.

Complications screening

It is imperative that patients with type 2 diabetes undergo regular screening for diabetes-associated complications (Table 2). Microvascular complications of type 2 diabetes include nephropathy, retinopathy and neuropathy. Macrovascular complications include stroke, myocardial infarction and peripheral vascular disease. Regular monitoring of glycaemia, blood pressure, lipid profiles, kidney function and urine albumin-creatinine ratio (ACR), as well as eye checks and feet examination, play a central role in preventing the development and progression of diabetes-related complications.

Routine screening for coronary artery disease is not recommended in asymptomatic people, although a low threshold for investigation is recommended for patients with atypical cardiac symptoms or resting electrocardiogram abnormalities. Coronary calcium score or CT coronary angiography can be used to assess the risk of future cardiovascular events in people with type 2 diabetes. Heart failure is increasingly recognised as a complication of type 2 diabetes. Routine screening with echocardiography in asymptomatic people is not considered cost effective and therefore is not used in clinical practice. The American Diabetes Association consensus guidelines promotes measurements of B-type natriuretic peptide or high-sensitivity cardiac troponin levels in symptomatic people with diabetes to help identify those at high risk of heart failure who need to proceed to echocardiography.[2]

Type 2 diabetes is associated with various other complications. Intracerebral microvascular damage from type 2 diabetes has been linked with increased risk of ischaemic and haemorrhagic stroke, cognitive dysfunction and depression.[3] Type 2 diabetes and obesity increase the risk of cancer, particularly endometrial, liver, breast, pancreatic and colorectal cancers,[4] although cancer screening guidelines currently remain the same in people with or without diabetes. Type 2 diabetes is also associated with nonalcoholic fatty liver disease, progression to nonalcoholic steatohepatitis and advanced fibrosis, and hepatocellular carcinoma. International guidelines suggest screening for nonalcoholic fatty liver disease with liver ultrasound, irrespective of liver enzyme levels, in patients with type 2 diabetes.[5]

Glycaemic management

A summary of the action, potential benefits and place in management of the major classes of glucose-lowering medications is presented in the Flowchart. Please also refer to the Australian Type 2 Diabetes Glycaemic Management algorithm (https://www.diabetessociety.com.au/guideline/australian- type-2-diabetes-glycaemic-management-algorithm-august-2022/).

Metformin

Metformin, together with lifestyle changes, is the backbone of management of type 2 diabetes and is typically continued lifelong. Metformin reduces HbA_{1c} levels by 0.5 to 1.0% (5.5 to 10 mmol/mol) and is weight neutral. The landmark United Kingdom Prospective Diabetes Study and its 10-year follow-up study showed that metformin was associated with reduced cardiovascular and all-cause mortality.[6,7] Metformin may also reduce the incidence of cancer and dementia, and is beneficial in patients with polycystic ovary syndrome, fatty liver disease and inflammatory bowel disease.[8] Side effects associated with metformin use include gastrointestinal upset and, rarely, lactic acidosis. Metformin is generally not recommended if the estimated glomerular filtration rate (eGFR) is less than 30 mL/min/1.73 m^2.[9]

SGLT-2 inhibitors

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, empagliflozin and dapagliflozin, have gained popularity owing to multiple trials demonstrating their cardio-kidney benefits (Table 3). SGLT-2 inhibitors increase urinary glucose excretion (Figure 1), with an HbA_{1c} reduction of 0.4 to 0.8% (4.5 to 9 mmol/mol) when used with metformin. Significantly greater HbA_{1c} reductions are seen when baseline glycaemic control is poor. SGLT-2 inhibitors reduce weight and blood pressure and confer a low risk of hypoglycaemia. Side effects of include polyuria, thirst, fungal genitourinary infections and euglycaemic ketoacidosis.

SGLT-2 inhibitors improve cardiovascular outcomes, particularly in people with cardiovascular disease (or at high risk of cardiovascular disease) or heart failure. Use of SGLT-2 inhibitors in patients with type 2 diabetes who have cardiovascular disease or who are at high risk of cardiovascular events has been shown to reduce cardiovascular and all-cause mortality and heart failure hospitalisation.[10] In people with heart failure with mildly reduced or preserved (left

TABLE 2. RECOMMENDED SCREENING FOR PATIENTS WITH TYPE 2 DIABETES-RELATED COMPLICATIONS

Screening/complications	Assessment frequency
Lifestyle factors: • diet, exercise, smoking cessation	Assess every 3 to 4 months
Glycaemic profile: • HbA_{1c} level • hypoglycaemia, including awareness • BGLs on skin prick testing	Assess every 3 to 4 months: • HbA_{1c} target ≤7% (53 mmol/mol) • fasting BGL target 4 to 7 mmol/L
Physical profile: • weight • injection sites for lipohypertrophy • fingers for damage from skin-prick BGL checks	Assess every 3 to 4 months: • weight loss target 5 to 10%
Blood pressure	Assess every 3 to 4 months: • in people with increased cardiovascular risk, existing cardiovascular disease or albuminuria, blood pressure target ≤130/80 mmHg
Lipid profile	Assess every 12 months: • total cholesterol target <4.0 mmol/L • LDL-cholesterol target <2.0 mmol/L* • triglyceride target <2.0 mmol/L • HDL-cholesterol target ≥1.0 mmol/L
Retinopathy	• Assess every 12 months in Aboriginal and Torres Strait Islander people and people with known retinopathy, long duration of diabetes or high HbA_{1c} level • Assess every 2 years in all other patients if previous eye examination was normal
Nephropathy: • eGFR • albuminuria	Assess every 3 to 6 months: • microalbuminuria: urine ACR 3 to 29 mg/mmol • macroalbuminuria: urine ACR ≥30 mg/mmol
Neuropathy, vasculopathy, diabetic foot ulcers: • foot examination • lower limb neurological examination	• Assess every 3 to 4 months in patients at intermediate or high risk of complications, especially if known foot abnormality • Assess every 12 months in patients at low risk of complications
Other	• Consider liver ultrasound to screen for nonalcoholic fatty liver disease • Consider measurement of BNP or troponin levels ± transthoracic echocardiography to screen for heart failure • Consider CTCA to assess coronary calcium score to screen for ischaemic heart disease

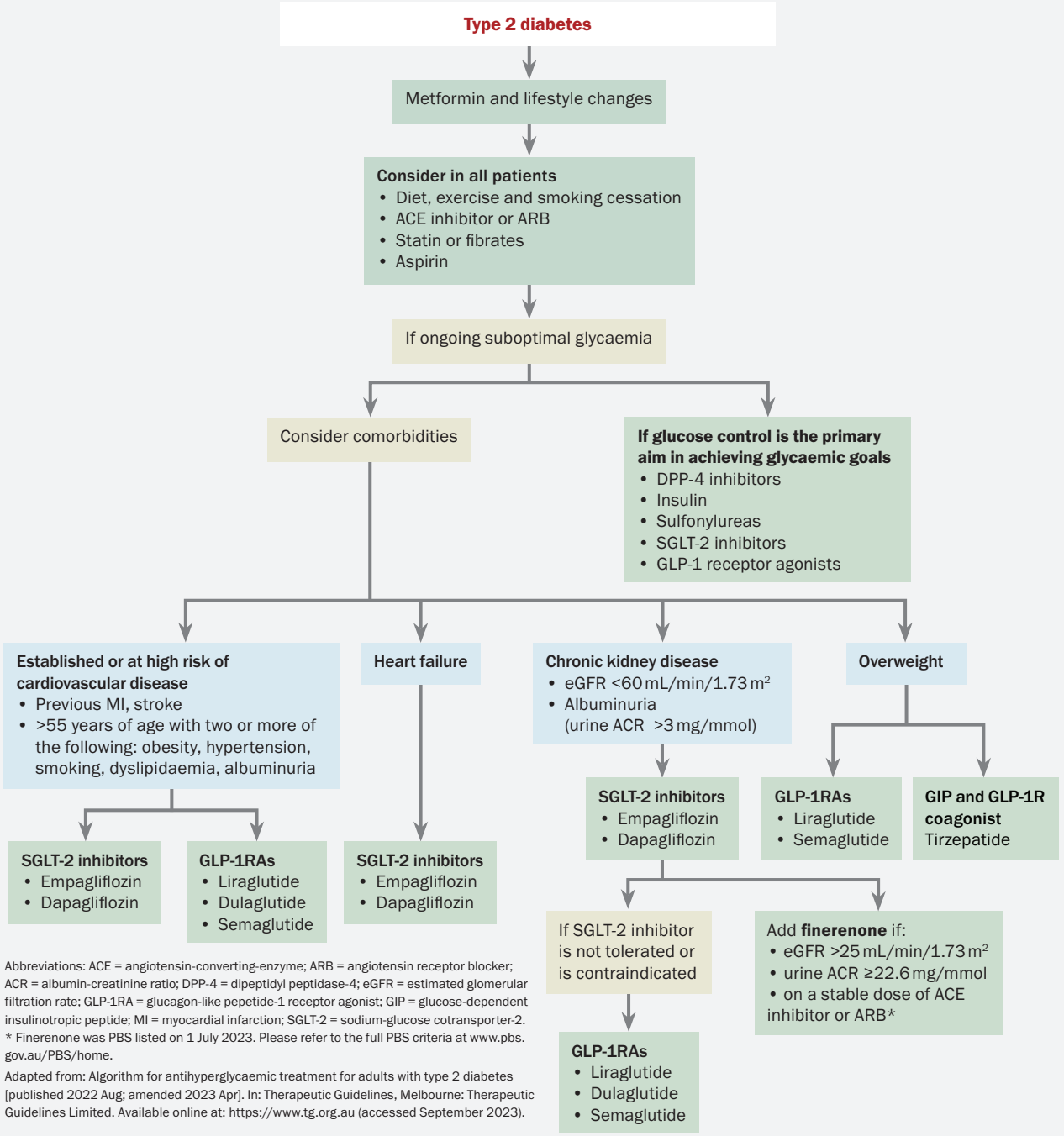
Abbreviations: ACR = albumin-creatinine ratio; BGL = blood glucose level; BNP = B-type natriuretic peptide; CTCA = computed tomography coronary angiography; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycated haemoglobin.
* Target of at least <1.8 mmol/L in very high-risk patients.

ventricular ejection fraction [LVEF] ≥40%) and reduced (LVEF <40%) ejection fraction, SGLT-2 inhibitors have also been shown to reduce heart failure exacerbations, hospitalisation and cardiovascular death.[11,12]

Use of SGLT-2 inhibitors improves kidney outcomes, particularly in people with kidney impairment and albuminuria (macroalbuminuria: urine ACR ≥30 mg/mmol). In patients with chronic kidney disease (CKD), the risk of progression of kidney disease, end-stage kidney failure or death from renal or cardiovascular causes were significantly lower with use of SGLT-2 inhibitors than with placebo.[13-15]

The cardio-kidney protection achieved with use of SGLT-2 inhibitors is likely to be independent of glycaemia. Mediation analyses within outcome trials have demonstrated that the results were independent of the magnitude of HbA_{1c} decline, and similar effects are also seen in people without diabetes. Current international consensus guidelines suggest that patients with type 2 diabetes and cardiovascular disease (or who are at high risk of cardiovascular disease), heart failure or CKD (eGFR <60 mL/min/1.73 m^2) or albuminuria (urine ACR ≥3 mg/mmol) should receive an SGLT-2 inhibitor, in addition to metformin, irrespective of baseline HbA_{1c} levels.[16] Dapagliflozin is PBS listed for a diagnosis of CKD in patients with an eGFR 25 to 75 mL/min/1.73 m^2 and urine ACR 22.6 to 565 mg/mmol that has been stable with use of an ACE inhibitor.[17] The

PHARMACOLOGICAL MANAGEMENT OF TYPE 2 DIABETES[16]



Abbreviations: ACE = angiotensin-converting-enzyme; ARB = angiotensin receptor blocker; ACR = albumin-creatinine ratio; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like pepetide-1 receptor agonist; GIP = glucose-dependent insulinotropic peptide; MI = myocardial infarction; SGLT-2 = sodium-glucose cotransporter-2.
* Finerenone was PBS listed on 1 July 2023. Please refer to the full PBS criteria at www.pbs.gov.au/PBS/home.

Adapted from: Algorithm for antihyperglycaemic treatment for adults with type 2 diabetes [published 2022 Aug; amended 2023 Apr]. In: Therapeutic Guidelines, Melbourne: Therapeutic Guidelines Limited. Available online at: https://www.tg.org.au (accessed September 2023).

glucose-lowering effect of SGLT-2 inhibitors can be reduced with kidney impairment; therefore, additional glucose-lowering therapies may be required, although the cardio-kidney protective effects are maintained.

GLP-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists, including semaglutide, liraglutide and dulaglutide, stimulate glucose-dependent insulin secretion from the pancreas, but also slow gastric emptying to minimise postprandial hyperglycaemia and promote satiety via centrally-mediated effects (Figure 2). GLP-1 receptor agonists reduce HbA_{1c} by 0.6 to 1.5% (6.5 to 16.5 mmol/mol) when used with metformin and are administered subcutaneously (oral semaglutide

TABLE 3. SUMMARY OF SGLT-2 INHIBITORS WITH CARDIO-KIDNEY BENEFITS

SGLT-2 inhibitor	Administration	Cardiovascular benefits	Kidney benefits	Kidney impairment
Empagliflozin	10 or 25 mg once daily*	Yes	Yes	• Glucose-lowering effect reduced if eGFR <30 mL/min/1.73 m^2 • Not recommended if eGFR <20 mL/min/1.73 m^2
Dapagliflozin	10 mg once daily	Yes	Yes	• Glucose-lowering effect reduced if eGFR <45 mL/min/1.73 m^2 • Not recommended if eGFR <25 mL/min/1.73 m^2

Abbreviations: eGFR = estimated glomerular filtration rate; SGLT-2 = sodium glucose cotransporter-2.

* Although empagliflozin is approved at a higher dose of 25 mg, there are minimal additional glycaemic or nonglycaemic benefits of the higher dose compared with the lower dose, so there may be no clinical benefit from increasing the dose.

is not yet available in Australia). GLP-1 receptor agonists also reduce weight and blood pressure and have a modest effect on improving lipid profiles. They can cause gastrointestinal upset, but this generally dissipates with continued treatment.

GLP-1 receptor agonists offer cardiovascular benefit (Table 4). Multiple cardiovascular outcomes trials involving people with cardiovascular disease or at high risk of cardiovascular disease have variably reported a reduced incidence of myocardial infarction, stroke and cardiovascular and all-cause mortality with use of GLP-1 receptor agonists.[18-21] However, unlike SGLT-2 inhibitors, GLP-1 receptor agonists, to date, have not been shown to be beneficial in preventing heart failure exacerbations or hospitalisation for heart failure.

Cardiovascular outcomes trials in patients with relatively preserved kidney function suggest that GLP-1 receptor agonist use reduces macroalbuminuria and potentially eGFR decline, with benefits being most pronounced in participants with pre-existing CKD and/or albuminuria. To date, no trial has shown that GLP-1 receptor agonists slow progression to end-stage CKD. The Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease (FLOW) trial is the first specific kidney outcome trial involving GLP-1RAs, which is expected to finish in 2024.

GLP-1RAs cause weight loss. In the Effect and Safety of Semaglutide 2.4 mg Once-Weekly in Subjects with Overweight or Obesity (STEP 1) trial, involving people with obesity or overweight (body mass index [BMI] >30 kg/m^2 or >27 kg/m^2 in people with weight-related conditions), high-dose semaglutide (2.4 mg per week) in people without diabetes resulted in 12.4% more weight reduction compared with placebo.[22] In contrast, the STEP-2 trial showed that high-dose semaglutide resulted in only 6.2% more weight loss compared with placebo in adults with diabetes and BMI of 27 kg/m^2 or more, and HbA_{1c} level 7 to 10% (53 to 86 mmol/mol).[23] This trial also showed that high-dose semaglutide use was associated with an absolute drop in HbA_{1c} of 1.2% compared with placebo. Furthermore, although high-dose semaglutide resulted in 2.7% greater weight loss than semaglutide 1.0 mg per week, HbA_{1c} differences between the two doses of semaglutide were of marginal significance (absolute difference 0.2%).

Current guidelines suggest that an SGLT-2 inhibitor or GLP-1 receptor agonists should be used in people with type 2 diabetes and cardiovascular disease or in those at high risk of cardiovascular disease, regardless of HbA_{1c} levels. Of note, the current PBS listings for semaglutide and dulaglutide require a patient with type 2 diabetes to have an HBA_{1c} measurement greater than 7% before initiation of a GLP-1 receptor agonist. It is anticipated that further PBS restrictions for prescribing GLP-1 receptor agonists will be introduced in late 2023. A GLP-1 receptor

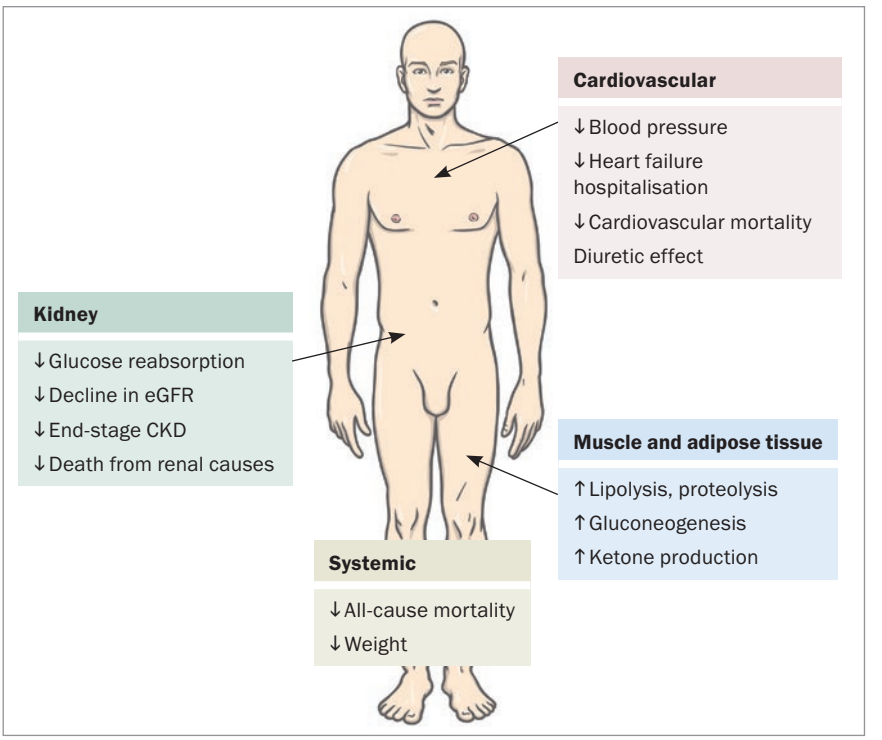


Figure 1. Effects of sodium-glucose cotransporter-2 receptor inhibitors.
Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

TABLE 4. SUMMARY OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

GLP-1RA	Administration	Cardiovascular benefits	Indicated for weight loss	Kidney impairment
Liraglutide	Subcutaneous daily	Yes	Yes	Nil contraindications – GI effects can worsen in kidney impairment
Semaglutide	Subcutaneous weekly Oral daily*	Yes	Yes	Limited data for eGFR <30 mL/min/1.73 m²†
Dulaglutide	Subcutaneous weekly	Yes	No	Limited data for eGFR <20 mL/min/1.73 m²†

Abbreviations: eGFR = estimated glomerular filtration rate; GI = gastrointestinal; GLP-1RA = glucagon-like peptide-1 receptor agonist.
* Oral semaglutide is not yet available in Australia.
† Semaglutide and dulaglutide need to be dose adjusted in people with kidney impairment (not required with liraglutide).

agonist should be used if SGLT-2 inhibitors are contraindicated or not tolerated.[16] Unfortunately, there is currently a global shortage of dulaglutide and semaglutide, which is not expected to improve until mid-2023, so intensification of lifestyle measures and alternative medications, such as liraglutide, SGLT-2 inhibitors, DPP-4 inhibitors or even short-term insulin therapy, should be used in the interim.

Tirzepatide

Tirzepatide is a glucose-dependent insulinotropic peptide and GLP-1 receptor coagonist, which was recently TGA approved to treat hyperglycaemia in people with type 2 diabetes, and will likely be available in Australia in late 2023. Tirzepatide is administered subcutaneously as a once-weekly injection. Studies have reported HbA_{1c} reductions of 1.6 to 2.6% (20 to 28 mmol/mol).[24-28] Tirzepatide is associated with low risk of hypoglycaemia, weight loss (greater than the effect of semaglutide in one study),[25] improved lipid profile and reduced blood pressure. However, it is not yet approved for weight loss. Side effects include gastrointestinal upset, especially nausea.

Tirzepatide is potentially associated with cardio-kidney benefits. Trials to date have demonstrated cardiovascular safety[26-28] and it is expected that further trials involving tirzepatide will also show cardiovascular protective effects and, possibly, favourable outcomes related to kidney health. A recent study has shown that tirzepatide reduced progression of albuminuria and kidney function decline (especially in participants with eGFR <60 mL/min/1.73 m²).[29] Trials are underway to definitively demonstrate the cardiovascular and kidney benefits of this medication.

Other glucose-lowering therapies

Dipeptidyl peptidase-4 (DPP-4) inhibitors, including alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin, prevent the enzymatic breakdown of endogenous GLP-1, producing a HbA_{1c} reduction of 0.5 to 0.6% (5.5 to 6.5 mmol/mol) when used with metformin. DPP-4 inhibitors are weight neutral with minimal risk of hypoglycaemia; however, they do not offer any specific cardio-kidney benefits. In fact, one trial demonstrated an increased risk of hospitalisation for heart failure with saxagliptin use.[30] Some trials have suggested a reduction in albuminuria,[31] but the independence of this effect from glucose lowering has yet to be established. Linagliptin is the only DPP-4 inhibitor that does not require dose reduction at an eGFR of less than 50 mL/min/1.73 m².

Sulfonylureas including glimepiride and modified-release gliclazide promote insulin secretion, offering an HbA_{1c} reduction of 0.5 to 0.7% (5.5 to 7.5 mmol/mol) when used with metformin. Although effective for glucose lowering, sulfonylureas can cause hypoglycaemia (especially in people with kidney impairment) and weight gain. Studies have demonstrated cardiovascular safety for glimepiride and modified-release gliclazide, but these medications do not offer any additional cardio-kidney benefits independent of glucose lowering.

Pioglitazone is the only thiazolidinedione still approved in Australia. Its use is limited by concerns regarding precipitation of heart failure, and increased risk of postmenopausal fractures, bladder cancer and macular oedema. Pioglitazone sensitises the effects of insulin, so it can be used in people with severe insulin resistance; however, other medications are now generally favoured. Rosiglitazone was withdrawn in 2010 following concerns regarding increased cardiovascular risk.

Acarbose inhibits alpha-glucosidase to delay carbohydrate digestion and glucose absorption to reduce postprandial glucose peaks, but it must be taken with the first few mouthfuls of food to be effective. Acarbose has been shown to reduce cardiovascular events, especially myocardial infarction and hypertension in people with impaired glucose tolerance,[32] although these effects are not as pronounced as with metformin in people with type 2 diabetes.[33] The use of acarbose may be limited by gastrointestinal adverse effects, including flatulence, bloating and diarrhoea.

Insulin therapy

Subcutaneous insulin is used to supplement endogenous insulin production and has a dose-dependent glucose-lowering effect. Many people with type 2 diabetes will eventually require insulin due to progressive insulin resistance and pancreatic beta-cell failure. However, insulin can cause weight gain and hypoglycaemia,

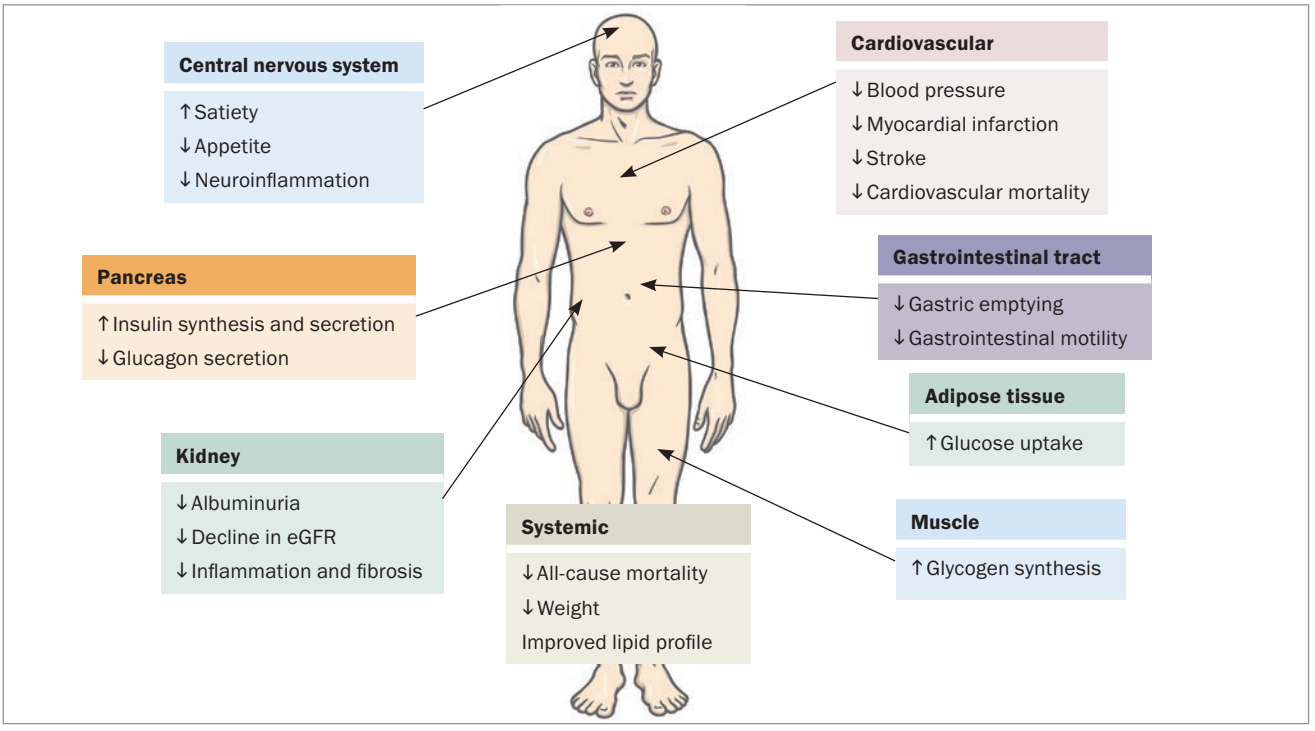


Figure 2. Mechanisms of action of glucagon-like peptide-1 agonists.
Abbreviation: eGFR = estimated glomerular filtration rate.

and its efficacy is dependent on patient education and engagement. When insulin is started in patients with type 2 diabetes, an initial dose of 0.1 to 0.2 units/kg of long- or intermediate-acting insulin (alone or combined with short-acting insulin) is recommended. A timely insulin dose titration schedule is vital for all patients starting insulin therapy. If hyperglycaemia continues, short-acting insulin can be added, or the regimen changed to twice-daily mixed insulin.

Nonglucose-lowering adjunctive therapies

Finerenone

Finerenone is a nonsteroidal mineralocorticoid receptor antagonist that has no glucose-lowering effects but offers kidney benefits. Finerenone was recently approved by the TGA to delay the progressive decline of kidney function in adults with type 2 diabetes-associated CKD with albuminuria. In people with type 2 diabetes and albuminuric CKD, finerenone has been shown to significantly reduce the risk of kidney failure (kidney death or decrease eGFR by 57% or more). Finerenone also demonstrated cardiovascular safety, and reduced heart failure hospitalisation and, potentially, cardiovascular death and myocardial infarction.[34] Finerenone does not cause off-target effects such as gynaecomastia. However, it can cause hyperkalaemia, although at lower rates than the steroidal mineralocorticoid receptor agonists spironolactone or eplerenone, so potassium levels should be monitored, and only offers very modest blood pressure-lowering effects compared with spironolactone or eplerenone.

Finerenone was listed on the PBS on 1 July 2023 for patients with CKD and type 2 diabetes who:

- have an eGFR of 25 mL/min/1.73 m^2 or greater
- have an ACR of 22.6 mg/mmol or greater
- are on a stable dose of either an ACE inhibitor or ARB
- do not have established heart failure with reduced ejection fraction
- are on an SGLT-2 inhibitor unless medically contraindicated or intolerant (please refer to the full PBS clinical criteria at www.pbs.gov.au/pbs/home).

Other multifactorial interventions

People with type 2 diabetes have a two to six times increased risk of cardiovascular death compared with people without diabetes. Multifactorial, target-driven interventions remain the cornerstone of primary and secondary cardiovascular protection in people with diabetes. This includes blood pressure and hyperlipidaemia management with the use of ACE inhibitors or angiotensin receptor blockers and statins, respectively, in addition to glycaemic management and attention to lifestyle factors. The Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria (Steno-2) study showed that intensive, multifactorial risk-factor modification in people with type 2 diabetes, hypertension and microalbuminuria resulted in significantly reduced microvascular complications (except peripheral neuropathy), cardiovascular events, heart failure hospitalisation, progression to end-stage CKD

and all-cause mortality, with all outcomes being reduced by more than 50%.[35] A contemporary approach would also involve prescribing cardiovascular protective medications, such as SGLT-2 inhibitors or GLP-1 receptor agonists, for people with type 2 diabetes.

Current guidelines recommend multifactorial risk-factor modification in people with type 2 diabetes aged over 60 years with microalbuminuria or moderate-severe CKD (eGFR <45 mL/min/1.73 m^2). Lifestyle interventions, including smoking cessation, exercise and weight control, are paramount in reducing the risk of development and progression of type 2 diabetes-associated complications. Increased physical activity is an essential component of lifestyle advice for people with diabetes. Glycaemic targets for people with type 2 diabetes include HbA_{1c} less than 7% (53 mmol/mol), with individualisation if required. Blood pressure targets are 140/90 mmHg or less in general, or 130/80 mmHg or less in people with albuminuria or at high cardiovascular risk, although the American Diabetes Association has recently lowered its general blood pressure target to less than 130/80 mmHg. General lipid targets include total cholesterol level of less than 4.0 mmol/L, HDL level of 1 mmol/L or more, LDL level of less than 2.0 mmol/L (and at least <1.8 mmol/L in people with cardiovascular disease), and triglyceride levels of less than 2.0 mmol/L. Statins may be indicated for people with cardiovascular disease or those at high cardiovascular risk regardless of lipid profile. Urine ACR should be less than 3.5 mg/mmol in women and less than 2.5 mg/mmol in men.

Weight loss and type 2 diabetes remission

Type 2 diabetes remission can be achieved with substantial weight reduction from dietary changes or bariatric surgery in people who are overweight or obese, and is more likely within the first few years of diagnosis. Type 2 diabetes remission is defined as an HbA_{1c} level less than 6.5% (48 mmol/mol) sustained for three months without using glucose-lowering medication. Dietary changes include very low energy diets of 3300 kJ/day or less, or ketogenic diets high in fat and protein and low in carbohydrates. Metabolic surgery includes gastric band, gastric sleeve or gastric bypass, and resulted in 23 kg more weight loss and 1.3% (15 mmol/mol) greater reduction in HbA_{1c} compared with GLP-1 receptor agonists in a meta-analysis.[36]

Metabolic surgery should be considered for people with type 2 diabetes and a BMI of 30 kg/m^2 or more, in whom diet, exercise and pharmacotherapy have been unsuccessful.[37] In one study, metabolic surgery resulted in type 2 diabetes remission in 37.5% of participants, which was sustained over the 10-year follow-up period. People who

relapsed after metabolic surgery maintained better glycaemia (mean HbA_{1c} level 6.7% [50 mmol/mol]) compared with medical therapy. Metabolic surgery also significantly reduced the incidence of diabetes-related complications compared with medical therapy (5.0% *vs* 72.2%),[38] a finding also seen in other observational studies. However, until more evidence becomes available, patients in remission should continue to receive regular screening for diabetes complications.

Conclusion

Type 2 diabetes is a prevalent condition associated with many established and emerging complications. Strategies for detecting and managing type 2 diabetes and associated complications continue to improve. The use of HbA_{1c} to stratify glycaemic status and hence diagnose diabetes is now routine in clinical practice. Regular monitoring of HbA_{1c} supplemented by BGL measurements remain the gold standard for assessing glycaemia in people with type 2 diabetes. Routine screening for coronary artery disease is still not recommended, although assessing coronary calcium score can be a useful cardiovascular risk stratification approach. Heart failure is an emerging complication of type 2 diabetes with some international guidelines recommending annual screening.

Over the past decade there have been major advances in the pharmacological management of type 2 diabetes, with the introduction of medications that improve glycaemia (and have a low risk of hypoglycaemia), promote weight loss and provide cardio-kidney protection. The introduction of tirzepatide to Australia to further manage type 2 diabetes and its associated metabolic abnormalities and complications is eagerly anticipated. In addition, attention to lifestyle factors and use of a multifactorial, target-driven approach to the management of glycaemia, blood pressure and lipid control remain cornerstones of type 2 diabetes management. MT

References

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

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Type 2 diabetes
Advances in investigation and management

ROSE LIN BBMed, MD; **RICHARD J. MACISAAC** BSc(Hons), PhD, MB BS, FRACP; **ELIF EKINCI** MB BS, FRACP, PhD

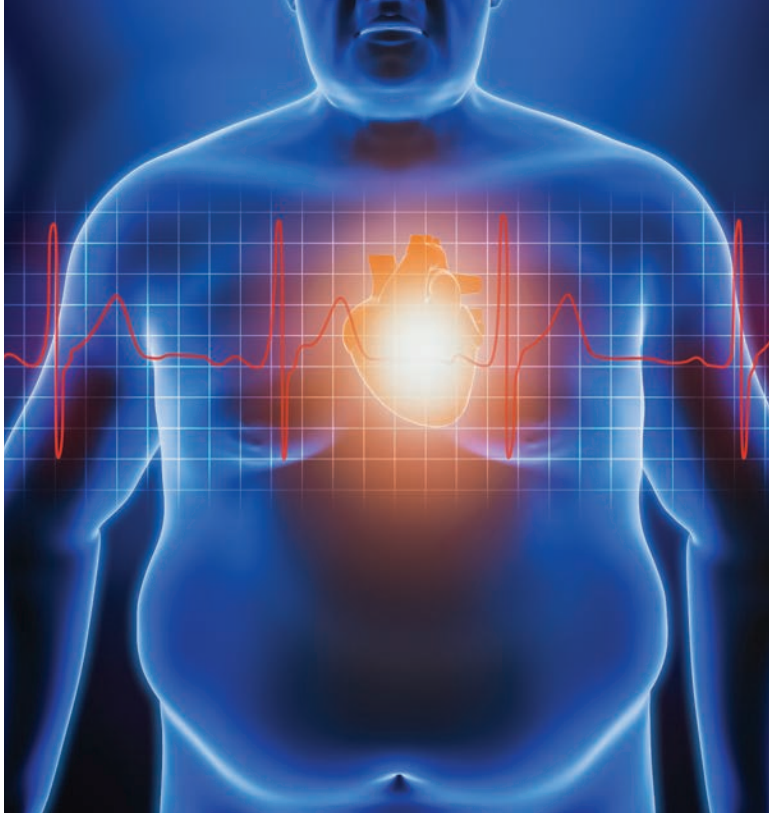
References

1. Australian Institute of Health and Welfare. Diabetes: Australian facts 2020. Available online at: https://www.aihw.gov.au/reports/diabetes/diabetes/contents/how-common-is-diabetes/all-diabetes (accessed September 2023).
2. Pop-Busui R, Januzzi JL, Bruemmer D, et al. heart failure: an underappreciated complication of diabetes. a consensus report of the American Diabetes Association. Diabetes Care 2022; 45: 1670-1690.
3. van Sloten TT, Sedaghat S, Carnethon MR, Launer LJ, Stehouwer CDA. Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression. Lancet Diabetes Endocrinol 2020; 8: 325-336.
4. Bonagiri PR, Shubrook JH. Review of associations between type 2 diabetes and cancer. Clin Diabetes 2020; 38: 256-265.
5. European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016; 64: 1388-1402.
6. King P, Peacock I, Donnelly R. The UK prospective diabetes study (UKPDS): clinical and therapeutic implications for type 2 diabetes. Br J Clin Pharmacol 1999; 48: 643-648.
7. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359: 1577-1589.
8. Top WMC, Kooy A, Stehouwer CDA. Metformin: a narrative review of its potential benefits for cardiovascular disease, cancer and dementia. Pharmaceuticals 2022; 15: 04.
9. Tanner C, Wang G, Liu N, Andrikopoulos S, Zajac JD, Ekinci EI. Metformin: time to review its role and safety in chronic kidney disease. Med J Aust 2019; 211: 37-42.
10. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373: 2117-2128.
11. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019; 381: 1995-2008.
12. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med 2022; 387: 1089-1098.
13. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019; 380: 2295-2306.
14. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020; 383: 1436-1446.
15. Herrington W, Staplin N, Wanner C, et al. Empagliflozin in patients with chronic kidney disease. N Engl J Med 2022; 388: 117-127.
16. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2022; 45: 2753-2786.
17. NPS Medicine Wise. Dapagliflozin for chronic kidney disease 2022. Available online at: https://www.nps.org.au/radar/articles/dapagliflozin-for-chronic-kidney-disease (accessed September 2023).
18. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016; 375: 1834-1844.
19. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375: 311-322.
20. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019; 381: 841-851.
21. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019; 394: 121-130.
22. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 2021; 384: 989-1002.
23. Davies M, Faerch L, Jeppesen OK, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet 2021; 397: 971-984.
24. Rosenstock J, Wysham C, Frias JP, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. Lancet 2021; 398: 143-155.
25. Frias JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med 2021; 385: 503-515.
26. Ludvik B, Giorgino F, Jodar E, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. Lancet 2021; 398: 583-598.
27. Del Prato S, Kahn SE, Pavo I, et al. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. Lancet 2021; 398: 1811-1824.
28. Dahl D, Onishi Y, Norwood P, et al. Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial. JAMA 2022; 327: 534-545.
29. Heerspink HJL, Sattar N, Pavo I, et al. Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial. Lancet Diabetes Endocrinol 2022; 10: 774-785.
30. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. N Engl J Med 2013; 369: 1317-1326.
31. Perkovic V, Toto R, Cooper ME, et al. Effects of linagliptin on cardiovascular and kidney outcomes in people with normal and reduced kidney function: secondary analysis of the CARMELINA Randomized Trial. Diabetes Care 2020; 43: 1803-1812.
32. Chiasson J-L, Josse RG, Gomis R, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance The STOP-NIDDM Trial. JAMA 2003; 290: 486-494.
33. Chang C-H, Chang Y-C, Lin J-W, Chen S-T, Chuang L-M, Lai M-S. Cardiovascular risk associated with acarbose versus metformin as the first-line treatment in patients with type 2 diabetes: a nationwide cohort study. J Clin Endocrinol Metab 2015; 100: 1121-1129.
34. Agarwal R, Filippatos G, Pitt B, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J 2021; 43: 474-484.
35. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003; 348: 383-393.
36. Sarma S, Palcu P. Weight loss between glucagon-like peptide-1 receptor agonists and bariatric surgery in adults with obesity: a systematic review and meta-analysis. Obesity 2022; 30: 2111-2121.
37. Australian Diabetes Society. The Australian obesity management algorithm 2016. Available online at: https://diabetessociety.com.au/documents/ObesityManagementAlgorithm18.10.2016FINAL (accessed September 2023)
38. Mingrone G, Panunzi S, De Gaetano A, et al. Metabolic surgery versus conventional medical therapy in patients with type 2 diabetes: 10-year follow-up of an open-label, single-centre, randomised controlled trial. Lancet 2021; 397: 293-304.

Obesity, atrial fibrillation and cardiovascular risk

A classic trifecta

PARAG BARWAD MB BS
JONATHAN KALMAN AO, MB BS, PhD, FRACP, FAAHMS



Obesity is widely established to play a causal role in the development of atrial fibrillation (AF) through the augmentation of cardiovascular risk factors, such as hypertension, type 2 diabetes and obstructive sleep apnoea. The classic combination of obesity and AF is being increasingly recognised among patients and requires a patient-centred and evidence-based approach for management.

Obesity is a global epidemic with a prevalence that has been increasing progressively since 1980.[1] According to the WHO, 39% of all adults were overweight and 13% had obesity in 2016.[1] By 2025, the prevalence of obesity is projected to reach 18% among men and 21% among women.[2-9] GPs and specialists may encounter patients with cardiovascular (CV) conditions, such as atrial fibrillation (AF), in the presence of obesity. Management in these cases requires a patient-tailored and evidence-based approach.[10] This article describes a clinical case of newly diagnosed AF in a woman who copresents with severe obesity and hypertension. Management of her AF requires a careful consideration of her comorbidities and risk factors.

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Dr Barwad is a Fellow in Electrophysiology and Pacing at Royal Melbourne Hospital. Professor Kalman is a Professor of Medicine in the Department of Medicine at the University of Melbourne; and Director of Heart Rhythm Services in the Department of Cardiology at Royal Melbourne Hospital, Melbourne, Vic.

Case scenario

A 38-year-old woman attends your general practice clinic regularly. She has class 3 obesity, with a body mass index (BMI) of 44 kg/m^2. Her comorbidities include hypertension, for which you have prescribed perindopril 5 mg daily, as well as newly diagnosed AF with rapid ventricular response, which is causing symptoms of palpitations and lightheadedness. Her CHA_2DS_2-VASc score is 1, and a decision was made to commence her on a non-vitamin K antagonist oral anticoagulant. You have prescribed metoprolol 25 mg twice daily. You are considering a referral to a cardiologist for AF ablation (pulmonary vein isolation).

What is the significance of the patient's class 3 obesity in terms of elevating her CV risk?

The mortality associated with CV disease (CVD) may be reduced with primary prevention approaches to care, which particularly include the management of key risk factors such as obesity.[3,11] Obesity accelerates the process of atherosclerosis via several mechanisms including insulin resistance and inflammation. It is often associated with other CV risk factors, such as hypertension, dyslipidaemia and elevated blood glucose levels, which collectively increase the risk of accelerated atherosclerosis and early onset of CVD.[2-5]

A large meta-analysis has shown that BMIs 25 kg/m^2 and greater are strongly associated with an elevated CV risk.[4-6] The BMI is the standard measure to quantify obesity (Table); however, the total cumulative exposure to excessive adiposity, as expressed in BMI-years or waist circumference-years, may be an even stronger predictor of CV risk.[5-7] A relationship between the BMI and all-cause mortality has been consistently reported worldwide and is independent of sex.[3] In particular, BMIs 40 kg/m^2 or greater are associated with a reduction in life expectancy by about 10 years, and BMIs 30 to 34.9 kg/m^2 are associated with a reduction in life

expectancy by about three years compared with BMIs 18.5 to 24.9 kg/m^2.[7-11] BMIs greater than 25 kg/m^2 are positively associated with an increased risk of mortality due to coronary artery disease and stroke.[6] Evidence points to a direct causal link between obesity and CVD.[12]

What are the associations among the patient's class 3 obesity, hypertension and obstructive sleep apnoea?

Similar to obesity, hypertension has a profound impact on global health. The excessive accumulation of adipose tissue initiates a cascade of events that give rise to elevated blood pressure; as such, obesity-induced hypertension is commonly recognised. Increased sympathetic activity, elevated adipokines and insulin levels in individuals with obesity are proposed to cause new-onset hypertension or may accelerate pre-existing hypertension. Renal function, sodium excretion, salt sensitivity and renin–angiotensin–aldosterone system activity are also significantly altered in the presence of obesity, which promotes the development of hypertension.[13] Long-term follow-up data indicate that CVD-related mortality is exponentially increased in the presence of both hypertension and obesity.[14] The prevalence of obstructive sleep apnoea (OSA) also increases significantly in patients with an elevated BMI and has also been shown to predict hypertension and adverse CV outcomes, such as the development of AF.[15]

Can weight loss reverse the patient's CV risk profile and alleviate her current comorbidities?

Weight management is of central importance in managing CV risk in patients with obesity. Weight loss beneficially affects traditional CV risk factors, such as hypertension, type 2 diabetes and dyslipidaemia, and may reverse OSA. In a randomised controlled trial of patients with type 2 diabetes, lifestyle interventions that led to at least a 10% reduction in body weight in the first year of the study resulted in a 21% lower risk of CVD related mortality.[16] This study suggests that achieving a threshold of weight loss may be necessary before a mortality benefit is gained.

TABLE. BODY WEIGHT CATEGORIES ACCORDING TO THE BMI

BMI (kg/m^2)	Body weight category
Less than 18.5	Underweight
18.5 to 24.9	Healthy
25.0 to 29.9	Overweight
30.0 to 34.9	Class 1 obesity
35.0 to 39.9	Class 2 obesity
40.0 and greater	Class 3 (severe) obesity

Abbreviation: BMI = body mass index.

What options are available to help with weight loss?

Recommended weight loss interventions include lifestyle, behavioural, pharmacological and surgical options. Dietary modifications (e.g. consuming a Mediterranean diet) have been shown to be beneficial in the primary prevention of CVD, which is predominantly related to the consequent weight loss. Consuming a ketogenic diet might lead to greater weight loss and a positive effect on blood sugars and dyslipidaemia.[17]

... CVD-related mortality is exponentially increased in the presence of both hypertension and obesity

Traditional pharmacological treatments for weight reduction, such as phentermine and bupropion with naltrexone, have varying degrees of efficacy and are restricted by cost and safety concerns. Until recently, they have not been widely adopted.[18-21] Phase 3 studies of the glucagon-like peptide 1 receptor agonist drug semaglutide (STEP trials 1 to 4) showed an average weight loss of about 15% together with improvements in CV risk factors.[22] Ongoing CV outcome studies are evaluating oral semaglutide in patients with obesity and established CVD. Trials in patients with AF are planned.

Bariatric surgical procedures, such as gastric sleeve or bypass surgery, have been shown to result in notable weight loss in patients with class 3 obesity. In observational studies, this weight reduction has resulted in reduced incidence rates of type 2 diabetes, CVD related death, myocardial infarction and stroke over a 15-year follow-up period.[23] Although surgery is highly effective for achieving significant weight loss, the proportion of people able to access bariatric surgery is low compared with the number of people living with obesity; this discrepancy is attributed to limited availability with prolonged waiting times, cost and surgical morbidity. Bariatric surgery will continue to be an important option for selected patients with severe obesity but is not broadly applicable among patients with obesity.

What is the association between the patient's class 3 obesity and AF?

A wide array of epidemiological data and randomised studies have confirmed the strong causative relationship between obesity and incident AF. Obesity has been suggested as one of the major factors responsible for the rising epidemic of AF.[10,24-26] The mechanisms by which obesity results in AF are multifactorial and include the promotion of hypertension, type 2

diabetes and OSA. In addition, the accumulation of excess epicardial adiposity has both direct and indirect effects on the atrial myocardium.

Both pharmacological and interventional catheter ablation treatment options have been shown to be significantly less effective in patients with obesity than in patients who do not have obesity. In particular, late recurrence after an apparently effective ablation procedure is a well-recognised complication in patients with obesity. The complication rates of catheter ablation procedures may also be higher in patients who have obesity. Randomised controlled trials have shown that comprehensive risk factor management centred around weight loss and increasing physical exercise, either as a primary strategy or in association with catheter ablation, can significantly reduce the AF burden and symptom recurrence.[27,28] Optimal effects are seen in patients who achieve a greater than 10% reduction in body weight, but benefits have also been reported in those with a 3% to 9% weight reduction.[27] The REVERSE-AF trial showed that weight reduction achieved through physician-led risk factor management frequently resulted in a significant reduction in AF burden and reversal of persistent AF to paroxysmal AF.[27] Patients achieving 10% or greater reductions in body weight showed a high prevalence of AF freedom.[28] Bariatric surgery in patients with severe obesity and AF has also been associated with significant reduction in AF burden and reduced incidence of new AF.[29]

What are some considerations before planning AF ablation in this patient?

The ARREST-AF cohort study showed significantly improved outcomes of catheter ablation in patients who lost weight with comprehensive risk factor management from a dedicated clinic.[28] Long-term follow up of these patients indicated that persistent weight loss is associated with excellent long-term outcomes of catheter ablation. Similarly, observational studies of bariatric surgery in patients with severe obesity and AF have indicated that it is possible to achieve ablation outcomes comparable with those in patients who do not have obesity.[30] In these studies, weight loss was accompanied by improvements in both blood pressure management and glycaemic control and reductions in sleep apnoea incidence and severity. There is a higher incidence of both minor and major complications in patients with obesity undergoing AF ablation, although this has not been universally reported and does not seem prohibitive.[31,32] The National Health Service in the UK has proposed that ablation should not be offered to patients with BMIs greater than 40 kg/m^2, and patients with BMIs between 35 and 40 kg/m^2 will need to demonstrate weight reductions of at least 10% of their body weight to become eligible for this treatment.[33] In Australia, a patient-centred approach has been adopted, wherein the timing of ablation is discussed in relation to lifestyle modifications and other weight loss strategies without specifying particular BMI cutoffs.

... weight loss and increasing physical exercise, either as a primary strategy or in association with catheter ablation, can significantly reduce the AF burden and symptom recurrence

Although clinical trials have not yet evaluated the impact of glucagon-like peptide 1 receptor agonists on weight loss and AF outcomes in patients with AF, a number of trials are ongoing. These drugs have the potential to greatly improve AF outcomes in patients with obesity, but to date, definitive data are lacking.

Case management

Based on the patient's young age, you refer her to a specialist cardiologist or electrophysiologist. Her initial investigations should include routine blood tests (including thyroid function, renal function and fasting glucose level), 12-lead ECG (which may provide evidence of left ventricular hypertrophy or other structural abnormality) and an echocardiogram (to evaluate left ventricular function and left atrial size and to exclude valvular pathology). You also consider a simple home screening study for OSA.

At present, her CHA_2DS_2-VASc score is 1 (assuming normal left ventricular function and the absence of type 2 diabetes), and guidelines suggest that this is a grey zone for anticoagulation indications. However, you prescribe her a non-vitamin K antagonist oral anticoagulant. It is unclear how long she has had AF, and you attempt to restore her sinus rhythm. As the patient is young, an antiarrhythmic agent (e.g. sotalol) should be initiated rather than a simple rate control agent, along with a discussion of the potential side effects and risks. You then plan a cardioversion with a preceding transoesophageal echocardiogram to exclude left atrial appendage thrombus, as you are uncertain of her AF duration.

The long-term strategy is directed towards weight loss with appropriate referral to a specialist weight loss clinic where weight reduction options are considered. You also focus on achieving adequate blood pressure control.

Conclusion

Patients are increasingly presenting with concurrent obesity and AF. In young patients who have severe obesity and recurrent and difficult-to-control AF despite pharmacotherapy, GPs should discuss with them the advantages and disadvantages, and risks and benefits, of AF ablation as a treatment option. MT

References

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

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PARAG BARWAD MB BS; **JONATHAN KALMAN** AO, MB BS, PhD, FRACP, FAAHMS

References

1. World Health Organization (WHO). Obesity and overweight. Geneva: WHO; 2021. Available online at: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed Jun 2023).
2. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. Lancet 2016; 387: 1377-1396.
3. Aune D, Sen A, Prasad M, et al. BMI and all-cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. BMJ 2016; 353: i2156.
4. Berenson GS, Srinivasan SR, Bao WH, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. N Engl J Med 1998; 338: 1650-1656.
5. McGill HC Jr, McMahan CA, Malcom GT, et al. Relation of glycohemoglobin and adiposity to atherosclerosis in youth. Arterioscler Throm Vasc Biol 1995; 15: 431-440.
6. Bogers RP, Bemelmans WJ, Hoogenveen RT, et al.; BMI-CHD Collaboration Investigators. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. Arch Intern Med 2007; 167: 1720-1728.
7. Reis JP, Allen N, Gunderson EP, et al. Excess body mass index- and waist circumference-years and incident cardiovascular disease: the CARDIA study. Obesity (Silver Spring) 2015; 23: 879-885.
8. di Angelantonio E, Bhupathiraju S, Wormser D, et al.; Global BMI Mortality Collaboration. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet 2016; 388: 776-786.
9. Peto R, Whitlock G, Jha P. Effects of obesity and smoking on U.S. life expectancy. N Engl J Med 2010; 362: 855-857.
10. Lavie CJ, Pandey A, Lau DH, Alpert MA, Sanders P. Obesity and atrial fibrillation prevalence, pathogenesis, and prognosis: effects of weight loss and exercise. J Am Coll Cardiol 2017; 70: 2022-2035.
11. Grover SA, Kaouache M, Rempel P, et al. Years of life lost and healthy life-years lost from diabetes and cardiovascular disease in overweight and obese people: a modelling study. Lancet Diabetes Endocrinol 2015; 3: 114-122.
12. The Emerging Risk Factors Collaboration. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet 2011; 377: 1085-1095.
13. Leggio M, Lombardi M, Caldarone E, et al. The relationship between obesity and hypertension: an updated comprehensive overview on vicious twins. Hypertens Res 2017; 40: 947-963.
14. Stamler J, Dyer AR, Shekelle RB, Neaton J, Stamler R. Relationship of baseline major risk factors to coronary and all-cause mortality, and to longevity: findings from long-term follow-up of Chicago cohorts. Cardiology 1993; 82: 191-222.
15. Lau DH, Nattel S, Kalman JM, Sanders P. Modifiable risk factors and atrial fibrillation. Circulation 2017; 136: 583-596.
16. Gregg EW, Jakicic JM, Blackburn G, Bloomquist P, Bray GA, Clark JM, Coday M, Curtis JM, Egan C, Evans M, Foreyt J, Foster G, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jeffery RW, Johnson KC, Kitabchi AE, Knowler WC, Kriska A, Lang W, Lewis CE, Montez MG, Nathan DM, Neiberg RH, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Redmon B, Regensteiner J, Rejeski J, Ribisl PM, Safford M, Stewart K, Trence D, Wadden TA, Wing RR, Yanovski SZ; Look AHEAD Research Group. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol 2016; 4: 913-921.
17. Zhou C, Wang M, Liang J, He G, Chen N. Ketogenic diet benefits to weight loss, glycemic control, and lipid profiles in overweight patients with type 2 diabetes mellitus: a meta-analysis of randomized controlled trails. Int J Environ Res Public Health 2022; 19: 10429.
18. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ ACC/ TOS guideline for the management of overweight and obesity in adults. J Am Coll Cardiol 2014; 63: 2985-3023.
19. Bessesen DH, van Gaal LF. Progress and challenges in anti-obesity pharmacotherapy. Lancet Diabetes Endocrinol 2018; 6: 237-248.
20. Electronic Medicines Compendium (EMC). Saxenda 6 mg/mL solution for injection in pre-filled pen. Sussex: Novo Nordisk Limited; 2022. Available online at: https://www.medicines.org.uk/emc/product/2313/smpc (accessed Jun 2023).
21. Markovic TP, Proietto J, Dixon JB, et al. The Australian Obesity Management Algorithm: a simple tool to guide the management of obesity in primary care. Obes Res Clin Pract 2022; 16: 353-363.
22. Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet 2021; 397: 971-984.
23. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ ACC/TOS guideline for the management of overweight and obesity in adults. J Am Coll Cardiol 2014; 63: 2985-3023.
24. Lau DH, Nattel S, Kalman JM, Sanders P. Modifiable risk factors and atrial fibrillation. Circulation 2017; 136: 583-596.
25. Mahajan R, Lau DH, Brooks AG, et al. Atrial fibrillation and obesity: reverse remodeling of atrial substrate with weight reduction. JACC Clin Electrophysiol 2021; 7: 630-641.
26. Javed S, Gupta D, Lip GYH. Obesity and atrial fibrillation: making inroads through fat. Eur Heart J Cardiovasc Pharmacother 2021; 7: 59-67.
27. Middeldorp ME, Pathak RK, Meredith M, et al. PREVEntion and regReSsive effect of weight-loss and risk factor modification on atrial fibrillation: the REVERSE-AF study. EP Europace 2018; 20: 1929-1935.
28. Abed HS, Wittert GA, Leong DP, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. JAMA 2013; 310: 2050-2060.
29. Jamaly S, Carlsson L, Peltonen M, Jacobson P, Sjöström L, Karason K. Bariatric surgery and the risk of new-onset atrial fibrillation in Swedish obese subjects. J Am Coll Cardiol 2016; 68: 2497-2504.
30. Donnellan E, Wazni O, Kanj M, et al. Outcomes of atrial fibrillation ablation in morbidly obese patients following bariatric surgery compared with a nonobese cohort. Circ Arrhythm Electrophysiol 2019; 12: e007598. Erratum in: Circ Arrhythm Electrophysiol 2020; 13: e000047.
31. Javed S, Gupta D, Lip GYH. Atrial fibrillation in obesity: weighing up the evidence for catheter ablation. Clin Cardiol 2020; 43: 1064-1066.
32. Winkle RA, Mead RH, Engel G, et al. Impact of obesity on atrial fibrillation ablation: patient characteristics, long-term outcomes, and complications. Heart Rhythm 2017; 14: 819-827.
33. National Health Service (NHS) England. Clinical Commissioning Policy: Catheter ablation for paroxysmal and persistent atrial fibrillation 1903. Redditch: NHS England; 2020. Available online at: https://www.engage.england.nhs.uk/consultation/catheter-ablation/ (accessed Jun 2023).