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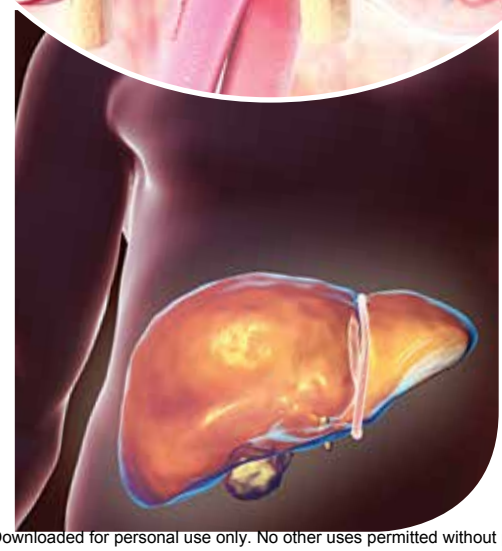
Focus on cardiometabolic matters



Dyslipidaemia in type 2 diabetes: cardiovascular risk assessment and management

Diabetic kidney disease and CVD

Nonalcoholic fatty liver disease

Reducing cardiovascular risk in type 2 diabetes

Aspirin therapy in diabetes: current recommendations

Formerly **MODERN MEDICINE**

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THE PEER REVIEWED JOURNAL OF CLINICAL PRACTICE

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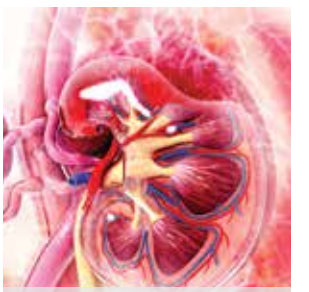
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Foreword
from the Supplement Editors

Cardiometabolic challenges

New developments in metabolic syndrome and diabetes are particularly impactful regarding cardiovascular complications and are hugely relevant to the burden of disease faced in primary care. The advent of sodium-glucose cotransporter-2 inhibitors is providing us with an enhanced toolkit. These agents can not only improve glycaemic control, but also have benefits on hard cardiovascular endpoints.

GPs have a major role to play in ensuring all people in Australia with diabetes and metabolic syndrome have access to the best care, thus preventing, in particular, the development of heart failure – one of the biggest causes of morbidity and mortality among these patients.

This supplement brings together five articles that provide an up-to-date guide to state-of-the-art approaches in areas including cardiovascular risk assessment and management in patients with type 2 diabetes, the relationship between kidney disease and the heart, and nonalcoholic fatty liver disease. A particular highlight is the update on aspirin therapy in diabetes, an area in which Australian researchers have led the world in a substantial shift in recommendations.

We hope that this supplement, which brings together diverse expert authors, will provide a clinically relevant overview of these important topics that will help GPs around Australia improve the cardiovascular health of their patients with diabetes.


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Dyslipidaemia in type 2 diabetes

Cardiovascular risk assessment and management

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GPs play a crucial role in reducing the burden of atherosclerotic cardiovascular disease (ASCVD) in high-risk patients with type 2 diabetes, using a multifactorial approach to risk-factor modification. This article provides an optimal approach to ASCVD risk assessment, setting of lipid targets and use of statin and nonstatin therapies in patients with type 2 diabetes and dyslipidaemia.

Macrovascular disease – atherosclerotic coronary, cerebrovascular and peripheral large artery diseases – is a major complication of type 2 diabetes.[1] The pathogenesis of macrovascular disease in diabetes entails a wide spectrum of risk factors, principal amongst which is dyslipidaemia. Dyslipidaemia is common in type 2 diabetes, and may be seen in up to one in three people with the condition.[2]

This article reviews the pathophysiology, assessment and treatment of dyslipidaemia in people with type 2 diabetes, with a personal perspective based on recent evidence, including international clinical practice guidelines.[3-5]

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How does dyslipidaemia in type 2 diabetes occur?

The pathophysiology of dyslipidaemia in type 2 diabetes involves the impact of insulin resistance on peripheral adipose tissue and the liver (Figure).[6,7] Insulin resistance is closely related to obesity, present in the vast majority of patients with type 2 diabetes. Insulin resistance results in the increased delivery of free fatty acids from adipose tissue to the liver and upregulation of the hepatic proteins, microsomal transfer protein and apolipoprotein C3, which collectively increase hepatic lipogenesis, leading to increased production and secretion of triglyceride-rich very low-density lipoproteins (VLDL) into the circulation.[2,7] This in turn results in

KEY POINTS

- Dyslipidaemia is common in type 2 diabetes and is primarily due to insulin resistance.
- The typical lipid profile of dyslipidaemia in type 2 diabetes is an increase in triglyceride and apolipoprotein B levels, and a reduction in HDL-cholesterol levels.
- Fasting is not routinely required for measuring the lipid profile, unless triglyceride levels are more than 5 mmol/L in the nonfasting state or a change in therapy is planned.
- Remnant lipoproteins are highly atherogenic triglyceride-rich particles and should be quantitated by calculating non-HDL-cholesterol from the standard lipid profile report; measurement of apolipoprotein B levels is also useful but is not currently Medicare rebatable.
- Glycaemic control, lifestyle factors, obesity, secondary causes of dyslipidaemia and other cardiovascular risk factors should be addressed.
- Risk-enhancing factors may be used to improve cardiovascular risk stratification beyond traditional risk factors.
- Patients with dyslipidaemia and diabetes should be treated with a moderate- or high-intensity statin as first-line therapy to reduce LDL-cholesterol levels.
- Ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors should be added to statin therapy if lipid targets are not reached in high-risk patients.
- Fenofibrate should be added to statin and ezetimibe therapy in high-risk patients with optimal LDL-cholesterol levels who remain hypertriglyceridaemic.

increased production of small dense LDL and decreased HDL particles in a process enabled by cholesteryl ester transfer protein.[2,7] Insulin resistance also results in an increased production of chylomicron particles in the postprandial state and reduced clearance of triglyceride-rich lipoproteins by the liver.[2,7] The atherogenicity of this dyslipidaemia is a consequence of the generation of small dense LDL particles and the accumulation of triglyceride-rich lipoprotein particles in plasma in both the fasting and postprandial state.[7]

The plasma lipid profile reflects these changes as an increase in triglyceride and apolipoprotein B (ApoB) levels (reflecting the number of atherogenic lipid particles), as well as by a reduction in HDL-cholesterol (HDL-C) levels (Box 1). An increase in both small dense LDL particles (reflected by an increased ApoB concentration) and triglyceride-rich lipoproteins (reflected by calculated remnant cholesterol or non-HDL-C) are especially atherogenic owing to increased chemical modification in the subendothelial space, uptake by macrophages and retention in the artery wall.[7] The toxicity of these lipoproteins is enhanced in diabetes by a coexistent inflammatory, dysglycaemic, hyperoxidative and prothrombotic state. Beyond insulin resistance, dyslipidaemia may be exacerbated by poor glycaemic control, obesity, diet, albuminuria and chronic kidney disease, as well as by medications that disturb lipid and lipoprotein metabolism.

How to assess?

The plasma lipid profile

The National Vascular Disease Prevention Alliance (NVDPA) 2012 *Guidelines for the Management of Absolute Cardiovascular Disease Risk* and the RACGP and Diabetes Australia 2016-18 guidelines on *General Practice Management of Type 2 Diabetes* recommend basing treatment decisions on fasting lipid profiles.[8,9] However, elevated nonfasting triglyceride levels are associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD), independent of traditional risk factors.[10,11] Recent international guidelines state that fasting is not routinely required for lipid profile measurement, because nonfasting does not lead to a clinically significant difference in total cholesterol, LDL-cholesterol (LDL-C), triglyceride or HDL-C levels compared with a fasting lipid profile in the population.[12] However, if triglyceride levels are more than 5.0 mmol/L on a nonfasting lipid profile, these patients should have a repeat sample in a fasting state. In addition, a fasting lipid profile should be performed to assess changes in treatment. When stable, nonfasting lipid profile can be used to monitor treatment over time.

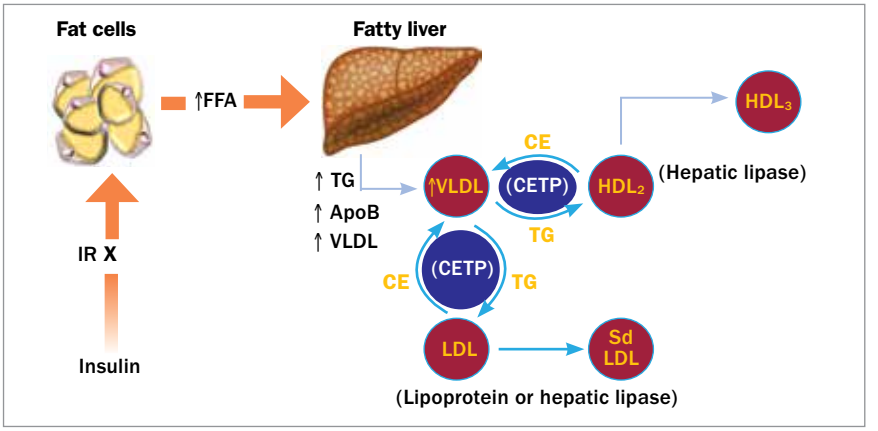


Figure. Mechanisms associating insulin resistance, diabetes and atherogenic dyslipidaemia. Insulin resistance results in increased delivery of free fatty acids to the liver, which increases hepatic lipogenesis and secretion of triglyceride-rich VLDL into the circulation. This leads to increased production of small dense LDL particles and decreased HDL particles in a process enabled by CETP. The imbalance between hepatic lipid import and export leads to hepatocyte lipid accumulation (nonalcoholic fatty liver disease). Dyslipidaemia in diabetes may be further exacerbated by other factors such as chronic kidney disease and genetics (not shown here).
Adapted from Ginsberg J. Clin Invest 2000; 106: 453-458.[6]

Abbreviations: ApoB = apolipoprotein B; CE = cholesteryl ester; CETP = cholesteryl ester transfer protein; HDL = high-density lipoprotein; FFA = free fatty acids; IR = insulin resistance; LDL = low-density lipoprotein; TG = triglycerides; sdLDL = small dense low-density lipoprotein; VLDL = very low-density lipoprotein.

Elevated triglyceride-rich or remnant lipoproteins are more prevalent in patients with type 2 diabetes and are highly atherogenic.[11] Measurement of the lipid profile in the nonfasting state also allows the calculation of nonfasting remnant lipoproteins (total cholesterol – HDL-C – LDL-C).[12] A nonfasting 1 mmol/L increase of remnant cholesterol is associated with a 2.8-fold increase in the risk of ischaemic heart disease independent of HDL-C.[13] Furthermore, the atherogenic risk of remnant lipoproteins can be considered by calculating the remnant lipoproteins, using non-HDL-C (total cholesterol – HDL-C) or by measuring ApoB levels.[12] Measurement of ApoB levels has been shown to be the best marker of ASCVD risk, as both LDL-C and triglyceride concentrations become non-significant when ApoB was included in a multivariate analysis of the association of LDL-C, triglycerides and ApoB.[14] However, although ApoB measurement is available in Australia, it is not currently Medicare reimbursed. Therefore, calculated non-HDL-C may be an appropriate alternative measure for use in general practice.

Cardiovascular risk stratification

People with type 2 diabetes are considered to be at high risk of ASCVD if they are over the age of 60 years, have microalbuminuria (urine albumin:creatinine ratio >2.5 mg/mmol for men and >3.5 mg/mmol for women), moderate chronic kidney disease (persistent proteinuria or estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m^2) or hypertension, according to the NVDPA 2012 guideline.[9] In addition, Aboriginal and Torres Strait Islander peoples are considered to be at higher risk.[8]

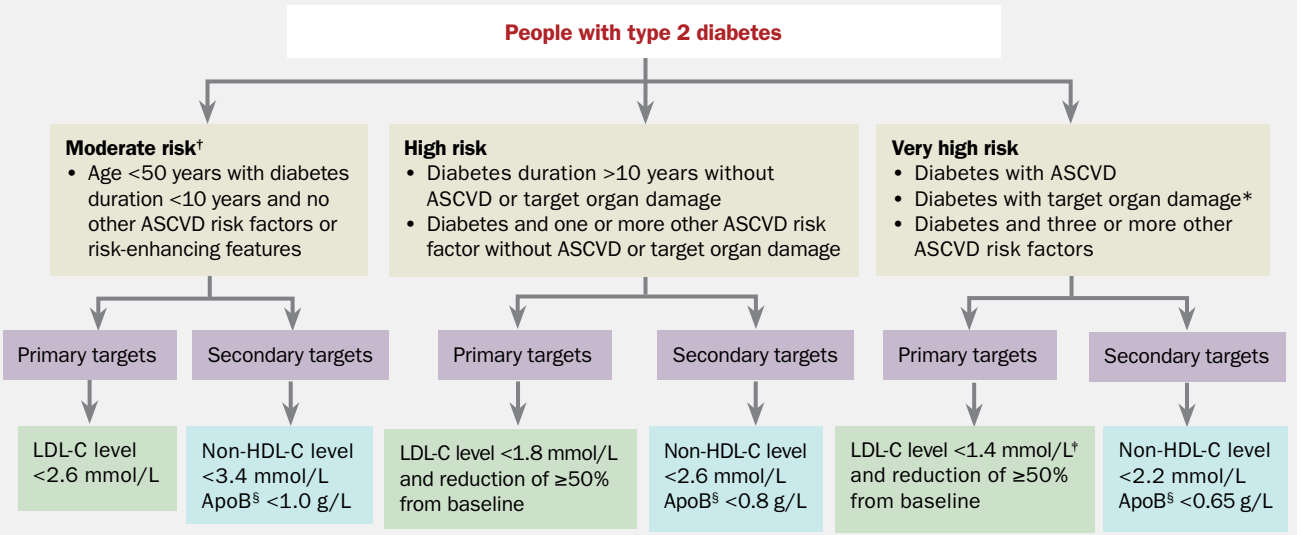
The RACGP 2016-18 guideline recommends assessment of ASCVD risk on initial presentation of a patient with type 2 diabetes without established ASCVD, and then assessment and management based on their absolute five-year ASCVD risk (low [<10%], moderate [10 to 15%] or high [>15%]) as assessed by the Australian absolute cardiovascular disease risk calculator (www.cvdcheck.org.au).[8] This calculator is based on the Framingham Heart Study and uses total cholesterol and HDL-C as lipid parameters. However, it does not take into account diabetes duration and type, glycaemic control, family history of premature ASCVD or presence of microvascular complications (i.e. albuminuria), all of which affect ASCVD risk. Performing absolute ASCVD risk assessment may also uncover individuals who require specialist assessment for severe or inherited lipid disorders, including those with familial hypercholesterolaemia (who could qualify for Medicare rebated genetic confirmation and treatments), severe hypertriglyceridaemia and chylomicronaemia.

However, international guidelines offer different strategies to cardiovascular risk stratification. The American Heart Association and American College of Cardiology (AHA/ACC) 2018 guideline uses an ASCVD risk calculator called the pooled cohort equation (http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/) for patients without established ASCVD.[5] This risk calculator is not applicable in Australia, as it is not based on studies within the Australian population and it estimates 10-year rather than five-year ASCVD risk. The European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) 2019 guideline offers an alternative method of risk stratification, in which patients with diabetes are either moderate-, high- or very high-risk depending on the presence of ASCVD, target organ damage, additional risk factors, age and duration of diabetes. The ESC/EAS 2019 guideline uses the Systematic Coronary Risk Evaluation (SCORE) calculator to estimate

1. KEY FEATURES OF DYSLIPIDAEMIA IN TYPE 2 DIABETES

- Increased triglyceride levels
- Reduced HDL-cholesterol levels
- Accumulation of small dense LDL particles
- Increased apolipoprotein B levels
- Increased triglyceride-rich lipoprotein remnants
- Postprandial hypertriglyceridaemia

1. RECOMMENDATIONS FROM ESC/EAS FOR ASCVD RISK STRATIFICATION AND LIPID/LIPOPROTEIN TARGETS IN PEOPLE WITH TYPE 2 DIABETES[4]



Abbreviations: ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; ESC = European Society of Cardiology; EAS = European Atherosclerosis Society; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

* Target organ damage defined as nephropathy (microalbuminuria), retinopathy or neuropathy.
† In selected moderate-risk people, measurement of coronary artery calcium score or lipoprotein(a) can also be considered as a risk modifier, but these tests are not reimbursed by Medicare.
‡ LDL-C goal of <1.0 mmol/L may be considered in people who experience a second cardiovascular event within two years while taking maximally tolerated statin.
§ ApoB measurement is not reimbursed by Medicare.

ASCVD mortality; however, the calculator is not recommended in patients with diabetes.[4] Using this guideline, no patient with type 2 diabetes is considered to be low risk.[4] This approach to risk stratification is simple, includes updated lipid targets and is our preferred approach (see Flowchart 1).

Additional methods of risk stratification

Several risk enhancers may improve ASCVD risk stratification beyond traditional methods. The presence of a risk-enhancing factor according to the AHA/ACC 2018 guideline in patients at low or moderate/intermediate risk favours the initiation of lipid-lowering therapy as these factors can assign patients to a higher risk category (Box 2).[5]

Briefly, lipoprotein(a) [Lp(a)] is an LDL-like particle that has an apolipoprotein(a) bound to LDL and is largely genetically determined. Elevated plasma concentrations of Lp(a) predicts ASCVD, peripheral arterial disease and calcific aortic valve stenosis in patients with and without diabetes, independent of other ASCVD risk factors.[15-18]

In addition, increased coronary artery calcium (CAC) score predicts ASCVD, is superior to risk stratification using traditional risk factors, and can be obtained noninvasively using electrocardiogram-gated noncontrast computed tomography scan.[19,20] CAC scoring can be used to identify lower- and higher-risk patients. A CAC score of zero reclassifies patients to a lower-risk group who do not benefit from statin therapy, whereas a score of 100 Agatston units or more, or 75th centile or more for age and sex, is considered higher risk, and statin therapy is recommended.[4,5] In patients with type 2 diabetes, evaluation of subclinical atherosclerosis with CAC scoring predicts 10-year coronary heart disease events beyond the Framingham Risk Score and the American pooled cohort equation.[20]

2. RISK-ENHANCING FACTORS FOR ASCVD ASSESSMENT IN TYPE 2 DIABETES

- Long duration of diabetes (10 years or more)
- Albuminuria (micro or macro)
- Estimated glomerular filtration rate <60 mL/min/1.73 m^2
- Retinopathy
- Neuropathy
- Ankle-brachial index <0.9
- Family history of premature ASCVD (in men aged <55 years, women aged <65 years)
- High-risk race/ethnicity
- High-sensitivity C-reactive protein >2.0 mg/L
- Apolipoprotein B level >1.3 g/L
- Lipoprotein(a) level >0.5 g/L
- Coronary artery calcium score ≥100 Agatston unit or ≥75th percentile

Abbreviation: ASCVD = atherosclerotic cardiovascular disease.

TABLE 1. INTENSITY AND FORMULATIONS OF STATINS LISTED ON THE PBS*

Intensity	Statin formulation
High-intensity statin (reduces LDL-C levels by ≥50%)	Atorvastatin 40–80 mg Rosuvastatin 20–40 mg
Moderate-intensity statin (reduces LDL-C levels by 30–49%)	Atorvastatin 10–20 mg Rosuvastatin 5–10 mg Simvastatin 20–40 mg Pravastatin 40–80 mg Fluvastatin 80 mg modified release
Low-intensity statin (reduces LDL-C levels by <30%)	Simvastatin 10 mg Pravastatin 10–20 mg

* Adapted from the American Diabetes Association 2020 Guideline and the American Heart Association and American College of Cardiology 2019 Guideline.

Measurement of Lp(a) or CAC score may be considered in patients in whom the decision to initiate a statin is uncertain (i.e. low or moderate/intermediate risk); however, these tests are not currently Medicare reimbursed.[18] Guidance on these risk stratification methods has been provided elsewhere.[18,21]

Whom to treat?

Lowering plasma LDL-C levels using 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) decreases ASCVD events in the primary and secondary prevention setting in patients with diabetes.[22] Patients with diabetes should be treated with a moderate- or high-intensity statin as first-line therapy rather than a low-intensity statin (Table 1). However, it is important to balance the benefits and potential adverse effects in patients over the age of 75 years.[5]

Secondary prevention

Cholesterol-lowering with high-intensity statin therapy is indicated for patients with diabetes and established ASCVD, irrespective of their lipid levels, acknowledging their significantly increased risk of recurrent events.[3,5,23]

Primary prevention

According to the RACGP 2016-18 guideline, lipid-lowering therapy is indicated for high-risk patients with type 2 diabetes.[8] Lipid-lowering therapy is not routinely recommended unless three to six months of lifestyle intervention has not reduced the risk for patients with type 2 diabetes at moderate (10 to 15%) or low (<10%) five-year ASCVD risk.[8] However, if a low- or moderate-risk patient has a risk-enhancing factor based on the AHA/ACC 2018 guideline (Box 2), or is an Aboriginal and Torres Strait Islander patient (RACGP 2016-18 guideline), then lipid-lowering therapy should be considered.[5,8]

Briefly, the American Diabetes Association (ADA) 2020 guideline and the AHA/ACC 2018 guideline provide different recommendations regarding initiation and intensification of statin therapy based on treatment thresholds (Table 2).[3,5] For primary prevention, statin therapy is

TABLE 2. RECOMMENDATIONS FROM ADA AND AHA/ACC FOR THE USE OF LIPID-REGULATING THERAPIES IN PEOPLE WITH DIABETES ACCORDING TO RISK CATEGORY AND TREATMENT THRESHOLDS OF LDL-C LEVELS

Risk category	Recommendations
Diabetes with ASCVD	• High-intensity statin • Consider adding ezetimibe (preferred second line) or PCSK9 inhibitor* if LDL-C level is >1.8 mmol/L and very high risk†
Diabetes and LDL-C >4.9 mmol/L	• High-intensity statin • Consider adding ezetimibe if LDL-C level is >2.6 mmol/L
Diabetes and aged 40 to 75 years	• Moderate-intensity statin • High-intensity statin if aged 50 to 70 years or other ASCVD risk factors present or 10-year ASCVD risk >20% • Consider adding ezetimibe to high-intensity statin if 10-year ASCVD risk >20%
Diabetes and aged <40 years with a risk-enhancing factor (see Box 2)	• Consider moderate-intensity statin‡

Abbreviations: ADA = American Diabetes Association; AHA/ACC = American Heart Association and American College of Cardiology; ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.

* In Australia, evolocumab was subsidised on the PBS from the 1st May 2020 for patients with diabetes and symptomatic ASCVD with an LDL-C >2.6 mmol/L on maximum tolerated statin, ezetimibe and lifestyle therapy, if they are aged >60 years, have microalbuminuria, or are Aboriginal or Torres Straits Islanders, after specialist review.
† Very high risk is defined as a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.
‡ Statins are contraindicated in pregnancy and lactation, and should be stopped three months before conception.

TABLE 3. SECONDARY CAUSES OF DYSLIPIDAEMIA

Cause	Hypercholesterolaemia	Hypertriglyceridaemia
Dietary		
Positive energy balance	+	+
High saturated or trans fat	+	–
High glycaemic load	–	+
Excess alcohol	–	+
Anorexia nervosa	+	–
Disease states		
Chronic kidney disease	+	+
Nephrotic syndrome	+	+
Cholestatic liver disease	+	–
Diabetes mellitus	–	+
Weight gain/obesity	+	+
Hypothyroidism	+	+
Polycystic ovary syndrome	+	+
Menopause transition	+	+
Drugs		
Progestins	+	–
Oral oestrogens	+	+
Tamoxifen	+	+
Anabolic steroids	+	–
Glucocorticoids	+	+
Retinoids	+	+
Cyclosporin	+	+
Sirolimus	–	+
Thiazide diuretics	+	+
Fibrates	+	–
Bile acid sequestrants	–	+
Beta blockers	–	+
Protease inhibitors	–	+
Atypical antipsychotics	–	+

Key: + = increase; – = no change.

recommended in people with diabetes over the age of 40 years or who have LDL-C level of 4.9 mmol/L or above (which may suggest familial hypercholesterolaemia).[3,5] There is a paucity of data indicating the age at which statin therapy should be initiated, as relatively few patients with type 2 diabetes under the age of 40 years were enrolled in statin trials.[22,24] Given the significantly increased life-time risk of developing ASCVD, younger patients with diabetes are likely to benefit from early statin therapy, especially if a risk-enhancing factor is present (Box 2).[5,24-26] Statins are contraindicated in women during pregnancy and lactation; they should also be avoided in women planning pregnancy.

Although aggressive treatment of dyslipidaemia in patients with type 2 diabetes is generally advocated, the large number of guidelines with differing approaches can be confusing.[3-5] Our preferred approach is to assess ASCVD risk and use plasma lipid and lipoprotein targets (Flowchart 1) to determine which patient with type 2 diabetes should be initiated on lipid-lowering therapy. This strategy may also guide statin dose titration or use of additional lipid-lowering therapies when targets are not met, enable patient–doctor communication, and facilitate adherence to therapy.[4] The NVDPA 2012 guideline also specifies lipid targets, but the targets differ to the ESC/EAS 2019 guideline.[4,9] A target driven approach will be further discussed in the next section.

How to treat?

Lifestyle modifications

Patients with diabetes should have individually tailored lifestyle interventions aimed at reducing body weight (by at least 5 to 10%), modifying dietary intake (ideally supported by a dietitian), reducing alcohol intake (≤2 standard drinks per day), increasing physical activity (at least 30 minutes of moderate-intensity physical activity on most, if not all, days) and smoking cessation.[8] The Mediterranean diet or the Dietary Approaches to Stop Hypertension (DASH) diet are recommended.[27,28]

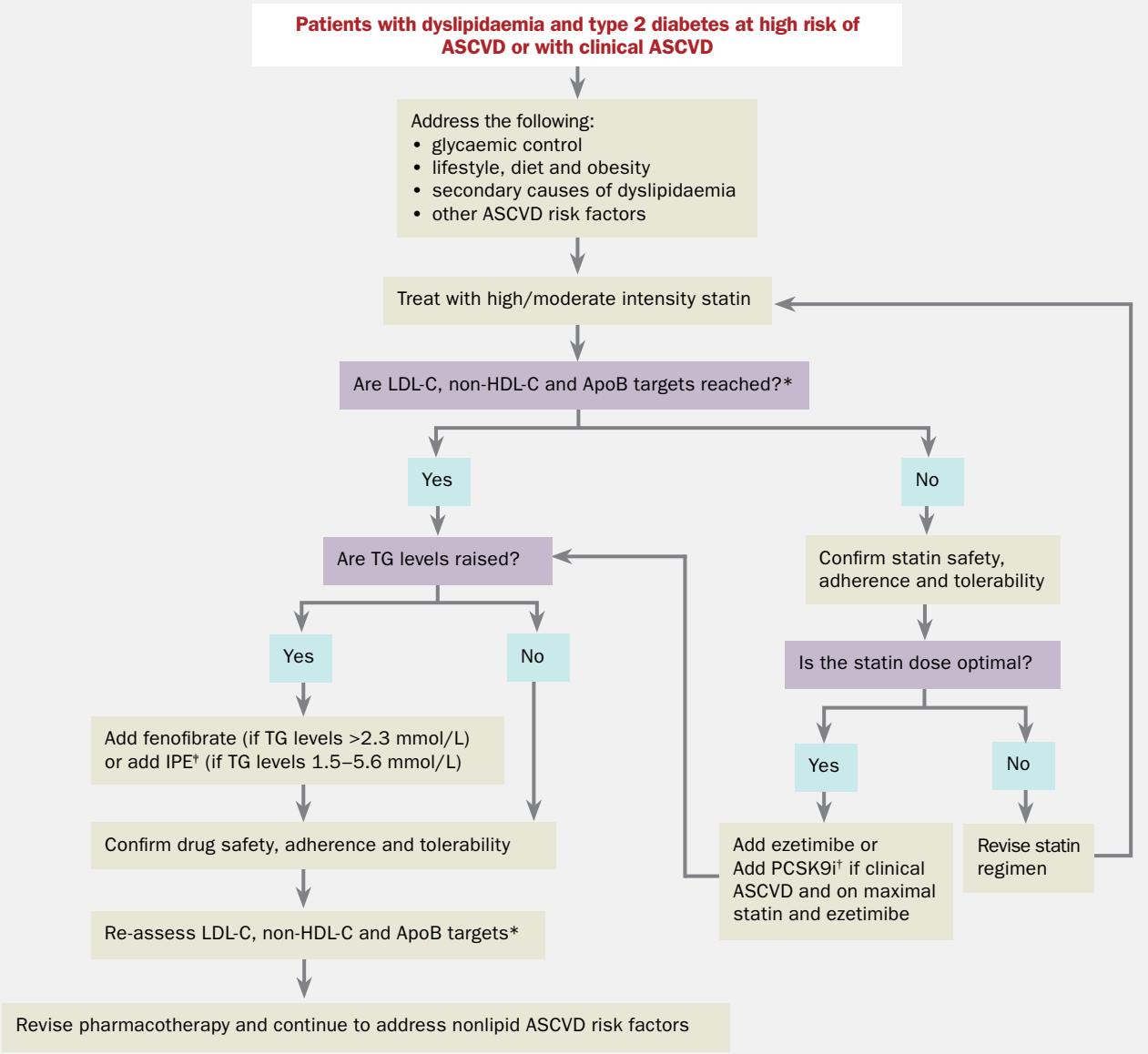
Exclude other causes of dyslipidaemia

Secondary (Table 3) and genetic (primary) causes of the dyslipidaemia (such as familial hypercholesterolaemia, polygenic hypercholesterolaemia, familial combined hyperlipidaemia, familial hypertriglyceridaemia, dysbetalipoproteinaemia and familial chylomicronaemia) should first be identified and treated.[29] Optimising glycaemic control and implementing lifestyle modifications can effectively improve dyslipidaemia in type 2 diabetes.

Reduce LDL-C levels with statin therapy

The first step in managing dyslipidaemia in patients with diabetes is to lower LDL-C levels; therefore, statins are the cornerstone of therapy. The LDL-C targets recommended by the recent ESC/EAS 2019 guideline are presented in Flowchart 1.[4] These LDL-C targets are lower than those recommended by previous guidelines, indicating a more intensive approach in modern management.[30] High-intensity statins may need to be prescribed at the maximally tolerated dose to achieve these LDL-C targets. The new European

2. TREATMENT PATHWAY FOR PEOPLE WITH DYSLIPIDAEMIA AND TYPE 2 DIABETES[4]



Abbreviations: ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; IPE = icosapent ethyl; LDL-C = low-density lipoprotein cholesterol; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; TG = triglycerides.

* Re-assess lipid profile three months after changes to therapy. ApoB measurement is not reimbursed by Medicare.

† Evolocumab was subsidised on the PBS from the 1st May 2020 for people with diabetes and symptomatic CVD with an LDL-C level >2.6 mmol/L on maximum tolerated statin, ezetimibe and lifestyle therapy, if they are aged >60 years, have microalbuminuria, or are Aboriginal or Torres Straits Islanders, after specialist review.

‡ Icosapent ethyl is not currently registered for use in Australia.

guideline also provides ApoB and non-HDL-C secondary targets (Flowchart 1), which are particularly important in patients with type 2 diabetes and hypertriglyceridaemia.[4]

Reduce LDL-C levels with nonstatin therapies

Nonstatin agents are used when LDL-C targets are not attained despite lifestyle modifications and use of maximally tolerated statins, or as monotherapy in statin-intolerant patients. If LDL-C target is not reached, it is important to assess adherence to statin therapy. The addition of ezetimibe to statin therapy has been

shown to reduce LDL-C levels by a further 15 to 30% and lower ASCVD risk, especially in patients with type 2 diabetes and established ASCVD.[23,31,32] Furthermore, the addition of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, such as evolocumab or alirocumab (both given as subcutaneous injections), to statin therapy has been shown to reduce LDL-C levels by a further 50 to 60% and can lower ASCVD risk, especially in patients with type 2 diabetes and established ASCVD.[23,33-36] Ezetimibe is recommended as the second-line agent for lowering LDL-C due to its lower cost. Evolocumab is now subsidised by the PBS after an initial review by a specialist for patients with diabetes and symptomatic ASCVD with an LDL-C of more than 2.6 mmol/L on maximum tolerated statin, ezetimibe and lifestyle therapy, aged over 60 years, have microalbuminuria, or are Aboriginal or Torres Straits Islanders. Trial evidence consistently shows that PCSK9 inhibitors reduce ASCVD risk in high-risk secondary prevention.[23,33-36]

Bile acid sequestrants, such as cholestyramine, can reduce LDL-C levels, although there is a lack of evidence for reduction in ASCVD outcomes. Additionally, the therapy is often poorly tolerated due to gastrointestinal side effects, decreases the absorption of many drugs, and can be associated with an increase in triglyceride levels.[5]

Lowering elevated triglyceride levels

Due to the increased ASCVD risk associated with hypertriglyceridaemia, statin therapy should be initiated or intensified to achieve LDL-C and non-HDL-C targets, and lower risk.[4] Additional therapies may be required in patients with hypertriglyericidaemia because statins reduce triglyceride levels by only 10 to 20%.[4] Although there are no specific triglyceride or HDL-C treatment targets in the ESC/EAS 2019 guideline, this guideline did specify non-HDL-C and ApoB targets (Flowchart 1),[4] which are particularly applicable to patients with diabetes.

In the overall group of patients enrolled in clinical endpoint trials, the combination of statin plus a fibrate has not been shown to reduce ASCVD risk.[37,38] Accordingly, this combination is not recommended by the ADA 2020 guideline or ACC/AHA 2018 guideline.[3,5] However, the ESC/EAS 2019 guideline recommends consideration of combination therapy when LDL-C is at target but triglyceride level is 2.3 mmol/L or above (Flowchart 2), as prespecified subgroup analyses and meta-analyses have shown ASCVD benefit with fibrates in moderate hypertriglyceridaemia.[4,39,40] Fenofibrate is preferred over gemfibrozil, owing to the lower risk of myopathy when used in combination with statin therapy.[5] Fenofibrate can also reduce the progression of retinopathy in patients with type 2 diabetes and pre-existing retinopathy, irrespective of baseline lipid levels, and is approved for this indication in Australia.[38,41] In patients with severe hypertriglyceridaemia (fasting triglyceride levels of 5.6 mmol/L or more), fibrate or fish oils should be considered to reduce the risk of acute pancreatitis.[3,5]

Statin plus niacin combination therapy has also not been shown to reduce ASCVD risk, and is associated with increased adverse effects.[38,42] This combination is also not routinely recommended for reducing ASCVD risk.[3-5]

Icosapent ethyl, a highly purified ethyl ester of eicosapentaenoic acid, at 4 g/day, has been shown to reduce ASCVD risk in high-risk patients with fasting triglyceride levels between 1.5 and 5.6 mmol/L who are on statin therapy.[43] At present, icosapent ethyl is not registered for use in Australia, and the results of the icosapent ethyl trial should strictly not be extrapolated to other omega-3 fatty acid products. In the US, icosapent ethyl is branded as Vascepa, which has recently come off-patent, therefore, generic formulations may potentially become available in Australia in the near future.

Statin-associated side effects

Statins are generally well tolerated and side effects were rare in trials. However, there is a general public perception that statin use results in side effects, fuelling the nocebo effect.[44] Adequately addressing the benefits and risks of statins may improve adherence. Strategies including rechallenging with a lower dose, alternate-day dosing or trialling an alternative statin should be considered for patients who do not tolerate the intended dose of a statin. Evaluation of other causes of muscle symptoms or factors predisposing to statin side effects must be undertaken.[5] If statin-associated muscle symptoms are severe, rhabdomyolysis should be considered and creatinine kinase level measured. The management of statin intolerance has been reviewed elsewhere in detail.[45]

Conclusion

Dyslipidaemia in type 2 diabetes is characterised by a cluster of lipid and lipoprotein abnormalities that are primarily secondary to insulin resistance and result in accelerated macrovascular disease.

Informed by recent major international guidelines that have a common base, we have provided our opinion on the optimal approach to ASCVD risk assessment, setting of lipid targets and use of statin and nonstatin therapies for dyslipidaemia in patients with diabetes. GPs encounter many high-risk patients with type 2 diabetes and play a crucial role in reducing the burden of ASCVD based on a multifactorial approach to risk-factor modification.[46] MT

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

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Dyslipidaemia in type 2 diabetes

Cardiovascular risk assessment and management

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Diabetic kidney disease and CVD

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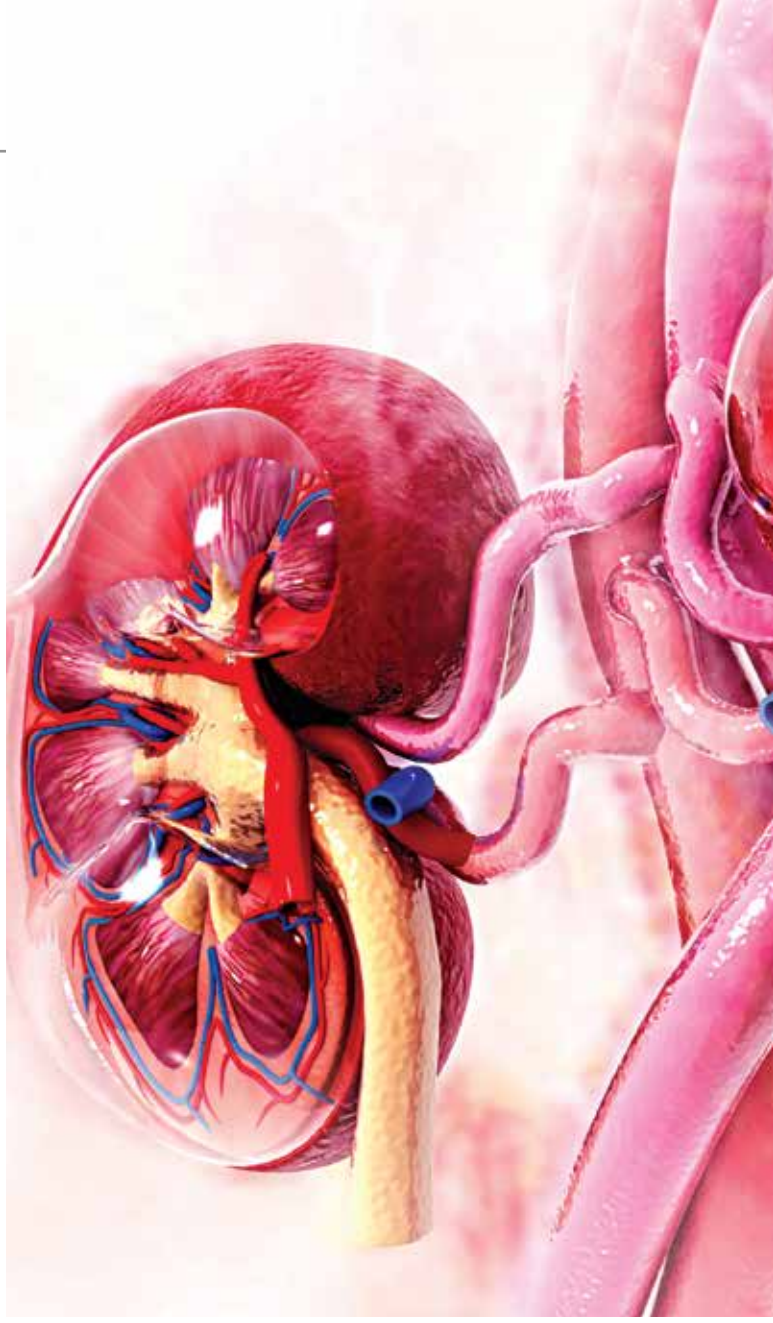
Diabetic kidney disease is a common complication in both type 1 and type 2 diabetes. Appropriate surveillance of kidney function and timely intervention are key to mitigate the severity and burden of this disease. This article summarises the current recommendations for monitoring and treating diabetic kidney disease in general practice as well as emphasising its link to the risk of cardiovascular disease.



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Diabetic kidney disease is a chronic complication of both type 1 and type 2 diabetes. About 30% of individuals with diabetes develop diabetic kidney disease, also known as diabetic nephropathy, despite increasing efforts to modify risk factors, including blood pressure and glycaemic control.[1] Furthermore, in Australia as well as in other western countries, diabetes remains the most common cause of end-stage renal disease requiring either kidney transplantation or dialysis.[2]

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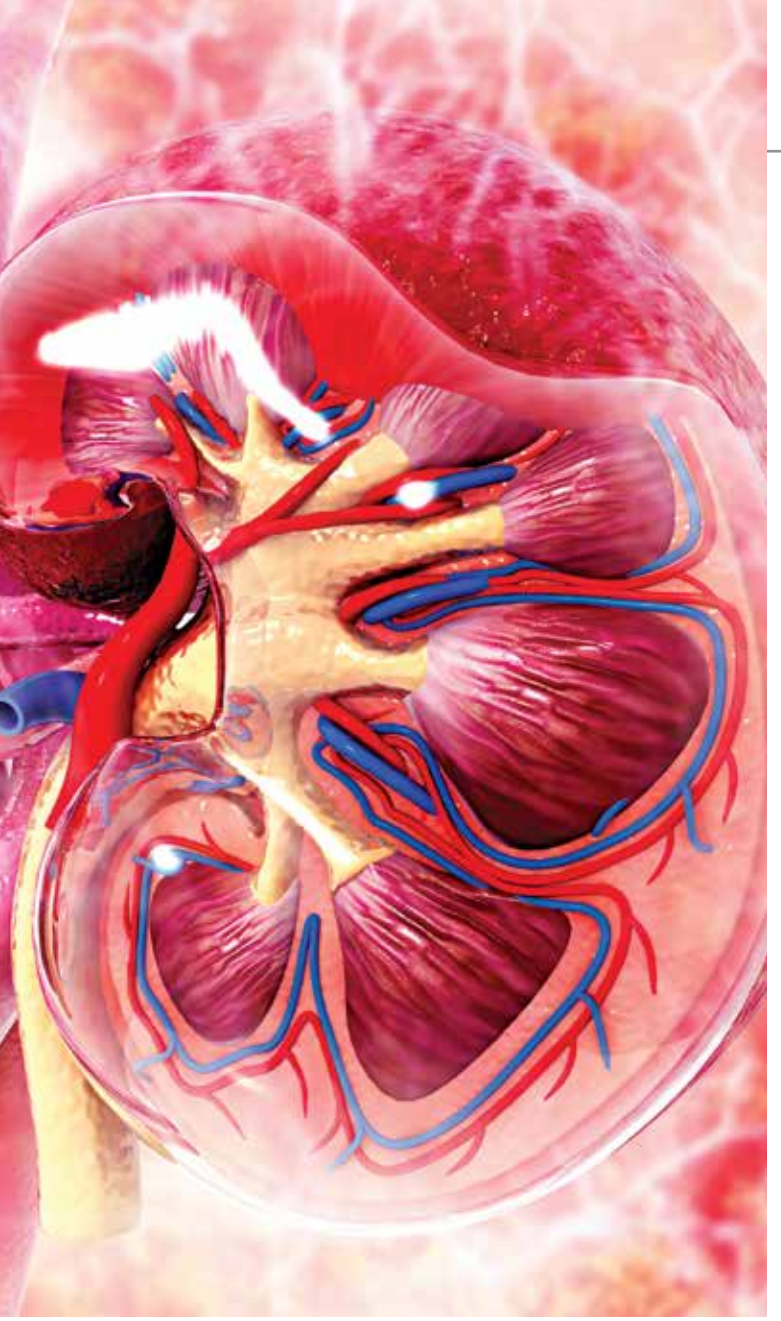
As diabetic kidney disease is a progressive disease, which can be halted, reversed or slowed at an early stage, it is essential to identify this specific complication of diabetes, so that it can be monitored and treated in an optimal manner. The risk of cardiovascular disease (CVD) is significantly increased in patients with diabetic kidney disease; therefore, it is crucial to identify symptoms and signs of heart and macrovascular disease, which can be difficult to detect early. Furthermore, it is important to commence strategies directed at protecting both the kidney and the cardiovascular system as soon as possible.

Diagnosis and monitoring

Diabetic kidney disease is diagnosed based on evidence of renal injury as reflected by an abnormal urinary albumin excretion and/or a reduced estimated glomerular filtration rate (eGFR) in the context of diabetes. As a late complication, diabetic kidney disease is classically observed after 10 years of type 1 diabetes



KEY POINTS

- Early recognition of diabetic kidney disease is important for early intervention to reverse, halt or slow the progression of the disease.
- Close monitoring of urinary albumin excretion and estimated glomerular filtration rate is required to detect diabetic kidney disease.
- Tight blood pressure and glucose control are cornerstones in the treatment of diabetic kidney disease.
- Sodium glucose transporter 2 inhibitors and glucagon-like peptide 1 receptor agonists are new classes of glucose-lowering drugs that seem to be particularly renoprotective.
- Patients with a urinary albumin-to-creatinine ratio higher than 30 mg/mmol or an estimated glomerular filtration rate of less than 30 mL/min/1.73m^2 should be referred to a nephrologist.

and usually in conjunction with diabetic retinopathy. However, the time course of diabetic kidney disease in type 2 diabetes is less clear, presumably because of the presence of incipient abnormalities in glucose homeostasis before the development of overt diabetes, which may therefore be present at the same time as when diabetes is diagnosed.

It is recommended that the urinary albumin-to-creatinine ratio (ACR) and eGFR should be monitored at least once per year in all patients with type 2 diabetes and in those with type 1 diabetes with a duration of more than five years.[3] ACR and eGFR are traditionally graded by increasing severity as shown in Tables 1 and 2.[4]

The ACR may be falsely elevated during infections, severe hypertension, menstruation and after exercise. eGFR may similarly be affected by exercise or loss of muscle mass.

Diabetic kidney disease is defined as a persistent abnormal ACR and/or reduced eGFR in two out of three measurements in a patient with no other cause of renal impairment. Alternative causes of renal impairment must be considered in certain settings, such as rapid change in eGFR or ACR, concomitant haemoglobinuria, severe hypertension or another systemic disease, which may explain the renal impairment. Furthermore, renal findings after only a short duration of type 1 diabetes may also indicate a nondiabetic cause of kidney injury.

Management

Glucose control

Improving glucose management decreases the risk and the rate of progression of diabetic kidney disease and is therefore a cornerstone in the prevention and treatment of the condition.[5,6] The stage of renal impairment should be considered in patients with type 2 diabetes, as this has an impact on the choice of pharmacological treatment and the suggested algorithm of escalation. Furthermore, evidence of CVD or presence of cardiovascular risk factors, as well as the personalised glycaemic targets, are other considerations when developing a glucose-lowering plan for these patients.

Metformin, sodium glucose transporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists deserve special mention in the context of diabetic kidney disease. Although sulfonylureas remain widely used in patients with diabetes at risk of diabetic kidney disease, these agents have not been shown to be renoprotective independently of their glucose-lowering effect. Nevertheless, in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) study, a significant proportion of patients who were taking the sulfonylurea gliclazide had improved renal outcomes.[7]

TABLE 1. ALBUMINURIA CATERGORIES IN DIABETIC KIDNEY DISEASE

Category	Sex	Urinary ACR (mg/mmol)
Normoalbuminuria	Men	<2.5
	Women	<3.5
Microalbuminuria	Men	2.5–25
	Women	3.5–35
Macroalbuminuria	Men	>25
	Women	>35

Abbreviation: ACR = albumin-to-creatinine ratio.

TABLE 2. GLOMERULAR FILTRATION RATE CATEGORIES IN DIABETIC KIDNEY DISEASE

Category	eGFR
Mild to severely decreased	<60 mL/min/1.73m^2
Severely decreased	<30 mL/min/1.73m^2

Abbreviation: eGFR = estimated glomerular filtration rate.

Metformin

Metformin is still the most often chosen first-line therapy for glucose lowering in people with type 2 diabetes. The dose of metformin should be adjusted if eGFR is less than 45 mL/min/1.73m^2, and is contraindicated if eGFR is less than 30 mL/min/1.73m^2. Metformin itself has not been shown to be renoprotective independent of its glucose-lowering actions.

Sodium glucose transporter 2 inhibitors

Clinical trials have demonstrated the cardiovascular benefits of the addition of SGLT-2 inhibitors to existing antidiabetic treatments in patients with type 2 diabetes who have established CVD. The SGLT-2 inhibitors empagliflozin, dapagliflozin and canagliflozin were all found to have significant protective effects on cardiovascular events in these study populations when added to existing treatments.[8-10]

This drug class is also attracting special attention because of emerging evidence of kidney-protective effects, which presumably are not solely explained by their glucose-lowering effects. Canagliflozin is the drug within this class that is best characterised with respect to the effects on renal function as described in the landmark CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial.[11] In patients with type 2 diabetes and ACR of 300 to 5000 mg/g and eGFR ranging from 30 to 9 mL/min/1.73m^2, canagliflozin reduced the incidence of the primary outcomes including worsening of renal function and mortality from renal or cardiovascular causes as well as additional secondary renal specific outcomes.[11] However, it is important to note that canagliflozin is no longer available on the PBS.

A renally dedicated study, the DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trial, which evaluated the effect of dapagliflozin on renal outcomes and cardiovascular mortality in patients with chronic kidney disease, has been terminated early due to positive results, although the full data set is not yet publicly disclosed. These results are in line with the secondary outcomes reported in the specific cardiovascular outcome trials using empagliflozin, dapagliflozin and canagliflozin.[9,12,13] These benefits are likely to be glucose independent since in patients with a low GFR (<45 mL/min/1.73m^2) no clear cut reduction in glycosylated haemoglobin (HbA_{1c}) levels has been observed in various clinical trials[14] despite this class of drugs conferring renoprotection in a population with low GFR.[11]

Finally, it is important to emphasise that patients included in these trials either had established CVD or were at high risk of CVD and the effects of these drugs in other populations of type 2 diabetes, such as in those without these complications, remain to be determined. Another exciting finding from this class of drug is the identification of a significant reduction in heart failure in people with type 2 diabetes.[9,12,13] Furthermore, this benefit also appears to be unrelated to glucose lowering since in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) study the risk of worsening heart failure or death from cardiovascular causes was lower, even in people without diabetes.[15]

Glucagon-like peptide 1 receptor agonists

Clinical trials have investigated the cardiovascular outcome of the addition of GLP-1 receptor agonists to existing antidiabetic treatments. In these trials it was reported that the addition of the GLP-1 receptor agonists liraglutide, semaglutide and dulaglutide to existing hypoglycaemic agents in patients with type 2 diabetes and established CVD or at high risk of CVD reduced the risk of cardiovascular events.[16-18] Semaglutide and dulaglutude but not liraglutide are

currently available on the PBS. Specific cardiovascular effects among the various trials were not uniform with effects on coronary events and stroke reported in some but not all trials. Furthermore, unlike SGLT-2 inhibitors, no effect on heart failure was observed with this class of drugs.

In addition, the evaluation of secondary outcomes in the cardiovascular outcome trials of GLP-1 receptor agonists indicated that these drugs are kidney protective in addition to their effects on blood glucose, body weight and cardiovascular events when added to existing glucose-lowering therapy.[19-22] This includes studies of lixisenatide, exenatide, liraglutide, semaglutide and dulaglutide.[19-22] In general, these agents do not appear to be as impressive on renal endpoints as SGLT-2 inhibitors. Reduction in albuminuria has generally been observed with these agents, which appears to be, at least in part, glucose independent. Effects on eGFR have not been consistent but the recent REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) trial with dulaglutide reported a reduced incidence of a 40% and 50% decline in eGFR.[23] These intriguing results have stimulated the commencement of dedicated renal trials with this class of drug.

Blood pressure lowering

The importance of blood pressure lowering regarding both mortality, cardiovascular events and new or worsening of albuminuria in patients with type 2 diabetes has been confirmed in a meta-analysis of over 100,000 participants.[24]

Blockade of the renin-angiotensin-system has been shown to have cardiac and renoprotective effects in hypertensive patients with type 2 diabetes and signs of diabetic kidney disease. Therefore, both ACE inhibitors and angiotensin 2 receptor blockers are recommended in this population, but not as dual therapy since this combination approach has been associated with hyperkalaemia and acute decline in renal function. The ACE inhibitor captopril was shown to prevent the deterioration of kidney disease in patients with type 1 diabetes who have increased urinary albumin excretion with or without hypertension.[25] Similar renoprotective effects of angiotensin II receptor blockers were later observed in patients with type 2 diabetes in the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) and the IDNT (Irbesartan Diabetic Nephropathy Trial) trials.[26-28] Subsequent studies also confirmed benefits in patients with type 2 diabetes with earlier disease as reflected by the presence of microalbuminuria.[27] In these studies of patients with microalbuminuria, there was a decreased progression to overt proteinuria and increased regression to normoalbuminuria.

It should be noted that the role of renin-angiotensin-system blockers in the setting of normal blood pressure and normoalbuminuria has not been clearly demonstrated.

Blood pressure targets remain controversial but in the 2020 position statement from the American Diabetes Association, a blood pressure target of less than 140/90 mmHg is recommended to reduce CVD mortality and slow the progression of chronic kidney disease in all people with diabetes. However, it is also suggested to consider setting personalised lower targets (e.g. <130/80 mmHg) on the basis of potential benefits and risks in patients with diabetic kidney disease as they have a high risk of progression, especially in the presence of increased albumin excretion, as well as CVD.[3]

When to refer

Patients with impaired kidney function, such as decreased eGFR or abnormal ACR of unknown cause, should always be considered for referral and review by a kidney specialist (see Box). Furthermore, if the cause of kidney disease is unknown and there are atypical clinical features, such as absence of retinopathy, overt haematuria and clinical features not typical of diabetes, patients should be referred to a nephrologist as renal biopsy may need to be undertaken to confirm the underlying diagnosis.

WHEN TO REFER PATIENTS WITH IMPAIRED KIDNEY FUNCTION

Refer patients to a kidney specialist if you suspect diabetic kidney disease and they have any of the following features:

- ACR of 30 mg/mmol or above
- eGFR less than 30 mL/min/1.73m^2
- rapid decline in eGFR (e.g. faster than 5 mL/min/1.73m^2/year)

Abbreviations: ACR = albumin-to-creatinine ratio; eGFR = estimated glomerular filtration rate.

Conclusion

Annual monitoring of ACR and eGFR is recommended for all patients with type 2 diabetes and in those with type 1 diabetes with a duration of more than five years. Addition of an SGLT2 inhibitor or a GLP-1 receptor agonist to existing glucose-lowering therapy should be considered when metformin is insufficient to maintain glucose control, and end-organ protection (both cardiovascular and renal) is a treatment priority. ACE inhibitors and angiotensin 2 receptor blockers have pleiotropic renoprotective effects in patients with diabetic kidney disease and should be used if possible to slow or reverse disease progression. Patients with signs of severe disease, including those with an ACR of 30 mg/mmol or above and/or eGFR of less than 30 mL/min/1.73m^2, should be referred to a nephrologist. MT

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

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Diabetic kidney disease and CVD

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Nonalcoholic fatty liver disease

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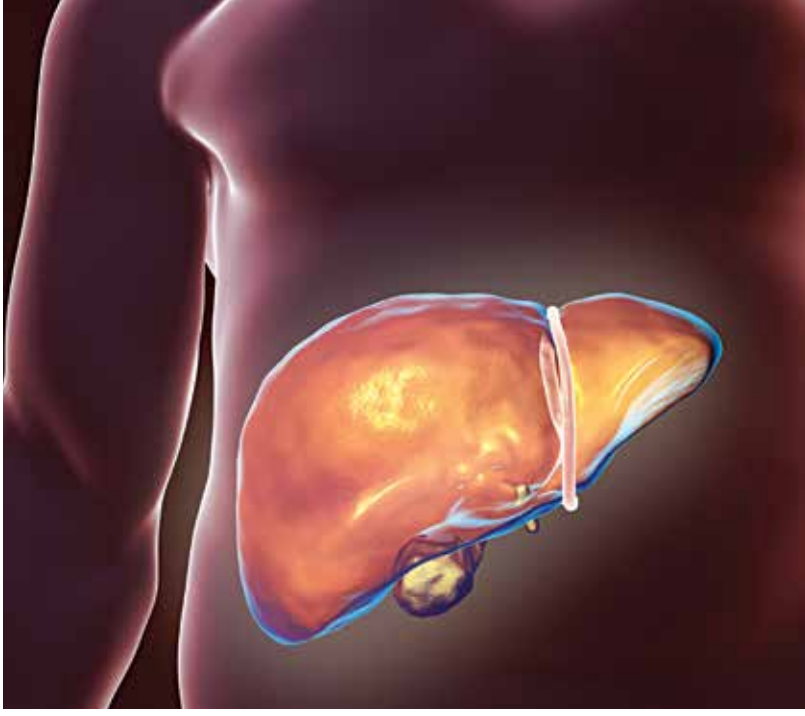

Disease progression in patients with nonalcoholic fatty liver disease (NAFLD) occurs more commonly in patients with other features of the metabolic syndrome. Primary care physicians play an important role in diagnosing NAFLD, managing metabolic risk factors and noninvasive assessment of disease stage.

KEY POINTS

- Nonalcoholic fatty liver disease (NAFLD) affects about a quarter of Australia's population.
- NAFLD encompasses a broad spectrum of clinical disease ranging from benign simple steatosis to end-stage cirrhosis.
- Patients with the metabolic syndrome are more likely to have NAFLD and more likely to have progressive liver disease from NAFLD.
- A noninvasive assessment for fibrosis and cirrhosis should be performed in patients with NAFLD.
- All patients with NAFLD should be counselled about the importance of weight loss and exercise.
- There is currently no approved, disease-modifying therapy for NAFLD and patients who have significant liver disease due to NAFLD should be referred to a gastroenterologist for assessment and consideration of participation in a clinical drug trial.

Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum of clinical disease ranging from benign fat accumulation in the liver (simple steatosis) to severe nonalcoholic steatohepatitis (NASH) causing cirrhosis and hepatocellular carcinoma. NAFLD is the most common cause of deranged liver function test results in Australia, and a recent study has found that its clinical significance is often underappreciated.[1] This article provides practical information for primary care givers on the management of patients with NAFLD and its metabolic disease associations.

What is NAFLD?

NAFLD is defined as the presence of fat in the liver (known as steatosis) in the absence of a secondary cause such as excessive alcohol intake (>20g daily for women and >30g daily for men).[2] Patients with NAFLD are asymptomatic until late stages of the disease and the diagnosis is often made incidentally. The requirements for diagnosis of NAFLD are summarised in Box 1.

Liver function test results do not have to be abnormal to make a diagnosis of NAFLD; however, mild to moderate elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamyltransferase (GGT) levels are common among people with NAFLD in the absence of symptoms. A diagnosis of NAFLD should be suspected in patients who have any of the following:

- elevated liver enzymes (ALT/AST >30IU/L or GGT >60IU/L)
- steatosis on ultrasound or CT imaging
- two or more of the comorbidities from the metabolic syndrome.

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1. NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) DIAGNOSIS

A diagnosis of NAFLD requires:

- presence of steatosis on imaging or histological assessment of liver biopsy

and

- exclusion of secondary cause of steatosis, commonly excessive alcohol consumption, medications (amiodarone, methotrexate, tamoxifen, corticosteroids) and starvation.

In a patient with suspected NAFLD, clinicians should exclude other aetiologies of steatosis or elevated liver enzymes and try to establish whether the patient has fibrosis or cirrhosis.

How common is NAFLD?

There are no published Australian data on the prevalence of NAFLD in adults, although its prevalence is estimated to be 25% from a study of its global burden.[3] The current burden of NAFLD in Australia is estimated to be 5.5 million cases, and is predicted to increase to 7 million by 2030.[4] Although NAFLD is more common among elderly patients, an Australian study found its prevalence to be 15% among a cohort of adolescents.[5,6] A total of 21% of this cohort had a body mass index in the obese range.

The natural history of NAFLD

The clinical spectrum of NAFLD ranges from benign, nonprogressive steatosis to end-stage cirrhosis with liver failure and hepatocellular carcinoma. The three main stages of NAFLD and their risks of progression to end-stage liver disease are shown in Box 2. A range of clinical and biochemical features can suggest the most likely NAFLD stage in an individual patient.

The progression of NAFLD to NASH was previously shown to occur in about 10 to 30% of patients;[7,8] however, more recent data suggest that the true rate of progression may be higher, with one study showing that nearly half of patients with biopsy-proven simple steatosis progressed to NASH over an average 6.6-year period.[6] The Figure illustrates the progression of NAFLD to NASH and cirrhosis.[9] Reversal of liver injury back to NAFL can be achieved in patients with established NASH. The progression of NAFLD to cirrhosis is estimated to occur in up to 20 to 30% of patients, with higher rates of progression reported in studies with longer follow-up periods. Patients with NAFLD who have diabetes or obesity or who consume alcohol heavily are at increased risk of disease progression.[10]

Previous data regarding NAFLD and mortality have been conflicting. The largest meta-analysis to date showed patients with NAFLD had increased all-cause mortality compared with those without NAFLD, and most deaths occurred due to cardiovascular disease.[11]

NAFLD and the metabolic syndrome

The metabolic syndrome is diagnosed in patients with at least three of the following five abnormalities: hypertension, elevated triglyceride level, low HDL cholesterol level, elevated fasting blood glucose level and central obesity.[12] NAFLD and the metabolic syndrome are closely linked. The epidemiology and natural history of NAFLD is altered in patients with comorbidities from the metabolic syndrome. Further, patients with moderate to severe NAFLD are more likely to have the metabolic syndrome than the general population, with one study showing 18% of patients with NAFLD also had the metabolic syndrome.[13] Therefore, NAFLD and the metabolic syndrome are bidirectionally linked and patients with one of these diagnoses should be regularly screened for the other.

NAFLD and type 2 diabetes

Patients with type 2 diabetes are about twice as likely to have concurrent NAFLD as people who do not have type 2 diabetes.

2. STAGES OF NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Once NAFLD diagnosis is established, the stages are defined as follows:

- NAFL or simple steatosis
  - presence of >5% hepatic steatosis without features of inflammation or fibrosis
  - low risk of progressive liver disease
- Nonalcoholic steatohepatitis (NASH)
  - presence of >5% hepatic steatosis with inflammation, with or without fibrosis
  - significant risk of progressive liver disease
- NASH cirrhosis
  - cirrhosis with evidence of current or past NASH
  - risks of liver failure and hepatocellular carcinoma

A recent study showed a 56% prevalence of NAFLD in patients with type 2 diabetes.[14] Rates of progression of NAFLD to NASH with advanced fibrosis are also higher in patients with type 2 diabetes.

NAFLD and obesity

The rising prevalence of NAFLD is associated with the obesity epidemic. The prevalence of NAFLD increases significantly with worsening obesity, and NAFLD is seen in up to 90% of patients who undergo bariatric surgery.[15] Obesity appears to increase both all-cause and liver-specific mortality among patients with NAFLD.[16]

Differential diagnosis

NAFLD is the most common cause of mildly elevated ALT, AST and GGT levels among asymptomatic people in Australia, but primary care physicians play an important role in excluding relevant differential diagnoses. An accurate alcohol history is essential before a diagnosis of NAFLD can be considered. A complete drug history including complementary and alternative medicines should be taken.

We recommend testing all patients with suspected NAFLD for chronic hepatitis B and C infections, haemochromatosis and autoimmune liver diseases. Screening for other, rarer, causes of abnormal liver function test results such as Wilson's disease or alpha-1 antitrypsin deficiency can be guided by the history, particularly by the family history. A summary of relevant investigations can be found in Table 1.

Chronic viral hepatitis

The most commonly missed alternative diagnosis causing mildly to moderately elevated liver function test results is chronic viral hepatitis (hepatitis B or C infection). Hepatitis B infection should be suspected in all patients in remote Aboriginal communities and those born in countries outside Australia where hepatitis B infection is common, such as Asia or Africa. Hepatitis C infection should be suspected in patients who use intravenous drugs or have a past history of intravenous drug use, have undergone a transfusion with blood products before the introduction of hepatitis C screening in 1990, have tattoos or piercings done in nonsterile conditions, as well as those who may have undergone nonsterile medical or dental procedures in countries where hepatitis C is more common.

Iron overload

Genetic haemochromatosis is an important, treatable differential diagnosis in asymptomatic patients with abnormal liver function test results. Presentation with other features of this condition such as diabetes, skin pigmentation or arthritis can increase clinical suspicion. However, patients with NAFLD commonly have hyperferritinaemia in the absence of haemochromatosis, and transferrin saturation levels greater than 45% can help to determine which patients need to have haemochromatosis genotyping performed.

Assessment of fibrosis and cirrhosis in NAFLD

Once a diagnosis of NAFLD is made, it is crucial to assess the fibrosis stage, as patients with advanced fibrosis or cirrhosis require screening for hepatocellular carcinoma and referral to a gastroenterologist. Liver biopsy is the gold standard for determining fibrosis stage but is invasive and not practical to perform in most patients with NAFLD. Well-validated methods can be used by the primary care physician to assess for advanced fibrosis and cirrhosis noninvasively, as outlined below.

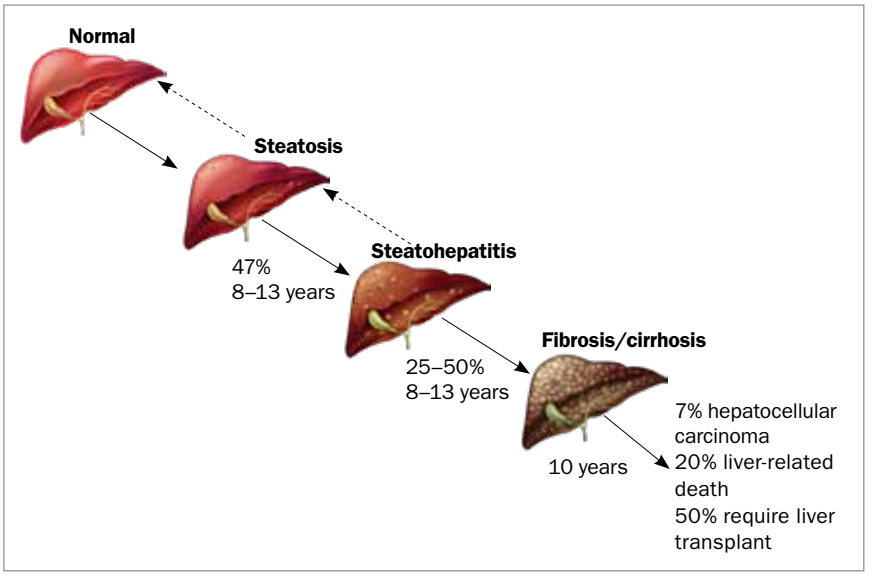


Figure. Progression of nonalcoholic fatty liver disease to nonalcoholic steatohepatitis and cirrhosis.

Adapted with permission from Moore JB. Proc Nutrition Soc 2010; 69: 211-220.[9]

TABLE 1. INVESTIGATIONS IN A PATIENT WITH SUSPECTED NAFLD AND ABNORMAL LIVER FUNCTION TEST RESULTS

Investigation	Rationale for investigation
HBV surface antigen, HBV core antibody and HBV surface antibody	All patients with elevated ALT level should be checked for active HBV, past HBV and evidence of HBV immunity
Hepatitis C antibody	All patients with elevated ALT level should be checked for HCV
Iron studies	Hyperferritinaemia is common in NAFLD; hereditary haemochromatosis is a differential diagnosis
Serum caeruloplasmin	This is a screening test for Wilson's disease. Consider testing in young patients or patients with a family history of liver disease
Anti-smooth muscle antibody, anti-liver kidney microsomal antibody, immunoglobulin G level	Recommended to screen for autoimmune hepatitis in patients with a history of other autoimmune conditions, age <65 years and ALT >100 IU/L
Antimitochondrial antibody	Recommended if ALP level is also elevated

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; HBV = hepatitis B virus; HCV = hepatitis C virus; NAFLD = nonalcoholic fatty liver disease.

TABLE 2. CLINICAL SIGNS TO ASSESS IN A PATIENT WITH SUSPECTED NAFLD

Clinical sign	Clinical interpretation
Spider naevi >3	Suggestive of cirrhosis
Palmar erythema, ascites, pitting oedema	Suggestive of portal hypertension; ascites suggests decompensated cirrhosis
Numerous ecchymoses	Nonspecific sign that may suggest decompensated cirrhosis with coagulopathy
Hepatomegaly	Nonspecific sign seen in NAFLD, alcoholic liver disease, viral hepatitis, Wilson's disease and hereditary haemochromatosis
Consistency of liver	Firm liver or nodular liver edge suggests cirrhosis
Jaundice	Suggestive of decompensated cirrhosis or biliary obstruction

Abbreviation: NAFLD = nonalcoholic fatty liver disease.

Noninvasive fibrosis and cirrhosis assessment

Fibrosis and cirrhosis can be noninvasively assessed for in patients with NAFLD through clinical examination, blood results and imaging of the liver. These results can be used in a number of well-validated scoring systems to differentiate those patients at low risk of liver fibrosis who can be safely managed in the community from those with advanced fibrosis or cirrhosis who need to be referred for further assessment.

Examination

Patients with compensated and decompensated cirrhosis may have several clinical signs that can be elicited at the bedside, although the absence of such signs does not reliably exclude cirrhosis. Common clinical signs and their interpretation are summarised in Table 2.

Noninvasive fibrosis scoring systems

Elevated levels of ALT, AST and GGT are common in patients with and without fibrosis or cirrhosis. No single blood test can assess fibrosis. However, numerous noninvasive scoring systems using bedside and blood tests can be used to assess for the presence of advanced fibrosis in patients with NAFLD. We recommend the use of either the NAFLD fibrosis score (NFS) or the AST to platelet ratio index (APRI) as these scores utilise commonly available variables and can be easily calculated with online calculators. Many patients fall into the 'indeterminate' range of one or both of these scores, and transient elastography can be used to stratify risk.

The NFS was designed and validated for noninvasive fibrosis assessment specifically in NAFLD patients. This score takes into account age, hyperglycaemia, body mass index, platelet count, albumin level and AST/ALT ratio. It can be calculated online at https://nafldscore.com. A score less than -1.455 excludes advanced fibrosis (F3 or F4) and a score greater than 0.676 suggests advanced fibrosis with high accuracy.[17]

Numerous noninvasive scoring systems can be used to assess for the presence of advanced fibrosis in patients with NAFLD

As liver fibrosis progresses to cirrhosis, the platelet count falls owing to portal hypertension and the resulting splenic sequestration of platelets. Hence, the APRI can be used to predict the likelihood of fibrosis or cirrhosis. This is calculated easily by dividing the AST level (as a proportion of the upper limit of normal) by the platelet count (see https://www.hepatitisc.uw.edu/page/clinical-calculators/apri). The closer the APRI is to zero, the less likely it is that a patient has significant fibrosis. The higher the APRI is above 1, the more likely it is that a patient has established cirrhosis.

Transient elastography (Fibroscan)

Transient elastography, or Fibroscan, is an ultrasound-based technology now widely available in Australia. Fibroscan measures patients' liver stiffness in kPA and provides an estimate of fibrosis, with higher values indicating more advanced fibrosis. Fibroscan readings have been validated against liver biopsy as a measure of fibrosis in NAFLD populations.[18] Accurate assessment of fibrosis in primary care can be challenging, and we recommend that all patients with NAFLD undergo transient elastography for fibrosis assessment when the results would change management. Fibroscan readings may not be valid in morbidly obese patients and are not accurate when the standard deviation and interquartile range on the report are high.

Ultrasonography of the liver is useful to detect steatosis but is unreliable in determining the presence of cirrhosis. A coarse and heterogenous appearance of the liver due to fatty infiltration can be difficult to distinguish from architectural change due to cirrhosis. Ultrasound features that are more specific to cirrhosis or portal hypertension are summarised in Box 3. Any patients found to have these features should be referred to a gastroenterologist for further assessment.

Management of patients with NAFLD

An optimal, disease-modifying therapeutic agent for NAFLD would both reduce the level of steatohepatitis and prevent progression of or improve fibrosis. There is currently no approved, disease-modifying therapy for NAFLD. Multiple medications including statins and oral hypoglycaemic agents have been trialled for the treatment of NAFLD. These medications do not specifically improve patients' NAFLD. However, as comorbidities from the metabolic

3. ULTRASOUND FEATURES OF CIRRHOSIS AND PORTAL HYPERTENSION

Ultrasound features of cirrhosis/advanced fibrosis:

- Liver surface nodularity

Ultrasound features of portal hypertension:

- reversal of portal venous flow (hepatopetal is normal, hepatofugal is reversed)
- dilated portal vein >13 mm
- recanalisation of the paraumbilical flow
- portal vein thrombosis or cavernous transformation
- presence of ascites

syndrome worsen NAFLD, we recommend aggressive treatment of comorbidities.

Patients with cirrhosis from NAFLD should be managed in conjunction with a gastroenterologist. We discuss treatments that are of benefit in NAFLD patients below.

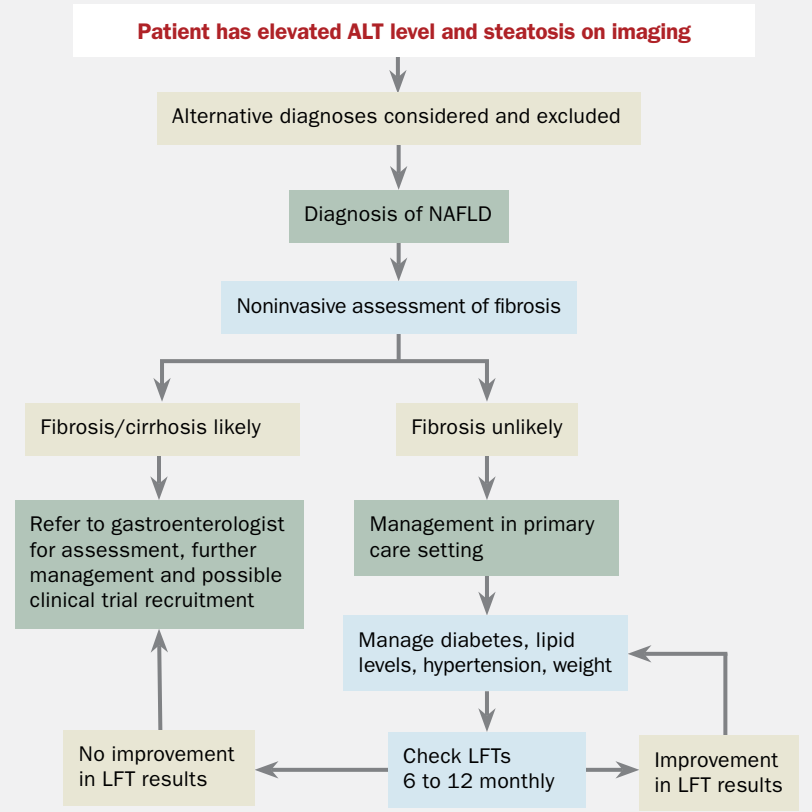
Weight loss

All patients with NAFLD and obesity should be counselled regarding weight loss. Numerous randomised controlled trials assessing the effects of weight loss on NAFLD have consistently shown clinically significant improvements in noninvasive biomarkers of disease severity but have not shown improvement in histological fibrosis.[19] The benefits of weight loss for NAFLD appear after 5 to 10% of body weight loss is achieved. Weight loss through bariatric surgery reverses NAFLD in around two-thirds of patients, although it is not indicated for NAFLD alone.[17]

Exercise

Exercise therapy has been shown in numerous studies to improve noninvasive biomarkers of NAFLD and conditions related to the metabolic syndrome.[20] Regular aerobic exercise of at least moderate intensity is ideal; however, the choice of exercise regimen should be tailored to individual patients based on their preference and physiological reserve.

A SUGGESTED PATHWAY FOR MANAGEMENT OF A PATIENT WITH NAFLD



Abbreviations: ALT = alanine aminotransferase; LFT = liver function test; NAFLD = nonalcoholic fatty liver disease.

Diet and lifestyle measures

Patients with NAFLD should be counselled to eat a balanced diet consisting of low glycaemic-index foods and food low in saturated fats. There is insufficient evidence to recommend a 'best diet' for patients with NAFLD, although the Mediterranean diet has shown promise in cross-sectional studies.[21] It is unknown whether moderate alcohol consumption worsens NAFLD disease progression, but patients with NAFLD should be advised to avoid excessive alcohol consumption. There is evidence of decreased NAFLD risk in coffee drinkers, although there is insufficient evidence to recommend coffee consumption for the prevention of NAFLD.[22]

Diabetes and lipid management

We recommend aggressive diabetes and lipid management in patients with NAFLD. Most medications that are currently used for both type 2 diabetes mellitus and dyslipidaemia treatment have also been studied specifically in patients with NAFLD. These studies have reported improvements in liver biochemistry and steatosis, but no change in fibrosis.[23] At present these medications should not be used specifically for NAFLD disease modification, but only if indicated as therapy for comorbid diabetes or dyslipidaemia.

Pharmacotherapy

A promising medication for NAFLD-treatment is obeticholic acid, which is a farnesoid X receptor agonist. A recent

interim analysis of a phase 3 study showed histological improvement of NAFLD in patients treated with obeticholic acid compared to placebo.[24] Phase 2 and 3 clinical trials are actively recruiting patients with NAFLD. Recruitment is generally limited to patients with elevated liver enzymes and evidence of fibrosis or well-compensated cirrhosis.

When to refer to a gastroenterologist

All patients with NAFLD and cirrhosis should be managed in conjunction with a gastroenterologist. We recommend referral to a gastroenterologist for all patients with NAFLD in whom fibrosis is suspected. A suggested approach to determining location of care is presented in the Flowchart. All patients with NAFLD who are reviewed in tertiary hospital liver clinics are considered for recruitment in NAFLD clinical trials, and patients with cirrhosis or advanced fibrosis are regularly reviewed for complications of their disease.

Conclusion

NAFLD encompasses a wide spectrum of clinical disease and is highly prevalent and under-recognised in Australia. Disease progression to fibrosis and cirrhosis occurs more commonly in patients with other features of the metabolic syndrome, and management of these risk factors forms the mainstay of treatment for NAFLD. For patients with NAFLD and elevated liver enzymes, noninvasive assessment of liver fibrosis is an important aspect of management that identifies patients who require referral to specialist care and those who should be screened for hepatocellular carcinoma. MT

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COMPETING INTERESTS: None

Reducing cardiovascular risk in type 2 diabetes

Emerging therapies

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The increased risk of developing atherosclerotic cardiovascular (CV) diseases in people with type 2 diabetes is well recognised, and a focus on reducing CV risk is just as important as glycaemic control. An individualised multifactorial approach to treating patients with type 2 diabetes is recommended, including lifestyle modification and drug therapy to reduce CV risk and improve renal outcomes, blood pressure control, and lipid and glucose levels.

People with type 2 diabetes mellitus are at higher risk of developing atherosclerotic cardiovascular diseases (ASCVDs) than those without diabetes.[1,2] Optimal management of type 2 diabetes and associated CV risk factors is recommended to address the increased risk of CV and related diseases.[3] Until recently, drug therapy for treating elevated blood glucose levels has had little, if any, impact on reducing ASCVD and its complications in people with type 2 diabetes; however, new glucose-lowering therapies have shown promising results in reducing CV risk. This review will examine the multifactorial approach to reducing CV risk in people with type 2 diabetes, specifically examining the role of the newer glucose-lowering agents that have become available over the past few years.

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Multifactorial CV risk reduction in type 2 diabetes mellitus

In the past, many medical practitioners have had a glucocentric approach to managing type 2 diabetes, focusing primarily on controlling hyperglycaemia and preventing hypoglycaemia, of which the latter is associated with an increased risk of cardiac events.[4] CV disease is prevalent in people with type 2 diabetes and responsible for more morbidity and mortality than the complications of diabetes itself; therefore, slowing and reducing the development of vascular disease and subsequent CV events should be of equal or greater importance to glycaemic control in the management of type 2 diabetes. The Steno-2 study reinforced that a multifactorial approach to modifying risk factors (such as reducing blood pressure and lipid and glucose levels) reduced both macrovascular and microvascular complications in individuals with type 2 diabetes.[5] Both the Hypertension Optimal Treatment Trial and the Heart Protection Study showed significant reductions in CV events in individuals with type 2 diabetes, based on a reduction in diastolic blood pressure and LDL level, respectively.[6,7] Several other studies have also demonstrated positive CV outcomes associated with reduced blood pressure in patients with type 2 diabetes.[8,9] These studies are discussed below and summarised in Table 1.

Blood pressure control

There is no single target blood pressure that should be aimed for in people with diabetes; diabetes management guidelines, including those from the Royal Australian College of General Practitioners and Diabetes Australia, recommend systolic and diastolic targets of below 140 and 90 mmHg, respectively, as a guide to treatment, but below 130/80 mmHg if significant proteinuria exists (timed overnight collection: above 20 mcg/min or spot collection above 20 mg/L).[3,10,11] Therefore, treatment target levels should be individualised for all patients, taking other comorbidities into account.[3]

Renin-angiotensin-aldosterone system blockers, ACE inhibitors or angiotensin-receptor blockers are usually the first choice for treating hypertension in people with type 2 diabetes, especially in the presence of albuminuria, followed by the addition of dihydropyridine calcium channel blockers, a combination that has shown significantly better outcomes than ACE inhibitors in combination with thiazide diuretics.[10-12]

Lipid control

The target LDL cholesterol level should be the same for individuals with type 2 diabetes and those with established CV disease (i.e. below 1.8 mmol/L), as type 2 diabetes is often referred to as a coronary risk equivalent.[3] However, recently published data show that lowering LDL cholesterol level even further (below 1.4 mmol/L) is associated with greater risk reduction, especially in patients with established ASCVD.[13,14]

Glycaemic control

Lowering glycated haemoglobin levels in people with type 2 diabetes has been shown to reduce CV and renal disease, with most of these benefits reducing microvascular events.[15,16] Intensifying glucose-lowering therapy results in a reduction in microvascular complications, both retinal and renal. The UK Prospective Diabetes Study showed reduced risk of retinopathy in patients with newly diagnosed type 2 diabetes assigned therapy with sulfonylureas or insulin compared with those assigned metformin.[17,18] The ADVANCE study showed that more intensive glycaemic control improved renal outcomes, especially with respect to development or progression of nephropathy.[8] Most clinical trials over the past two decades, as well as a meta-analysis, have failed to demonstrate clear benefits of glucose-lowering therapies on various CV endpoints, which is disappointing given ASCVD is the major cause of morbidity and mortality in people with type 2 diabetes.[19-22]

New glucose-lowering therapies and CV risk reduction

Recently, three classes of therapeutic agents have emerged as possible new treatments in reducing the risk of CV events in people with type 2 diabetes: dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists and sodium glucose cotransporter-2 (SGLT-2) inhibitors. The results of key clinical trials are discussed below and summarised in Table 2.

TABLE 1. KEY CLINICAL TRIALS ON MULTIFACTORIAL INTERVENTIONS IN INDIVIDUALS WITH TYPE 2 DIABETES

Study/trial name	Target/end point	Test arm	Outcome
Steno-2[5]	Multifactorial intervention	Conventional treatment *vs* targeted, intensified, multifactorial intervention	Around 50% reduction in risk of cardiovascular (CV) and microvascular events
Hypertension Optimal Treatment Trial[6]	Blood pressure control	Random assignation of target blood pressure	Reduced rate of CV events
Heart Protection Study[7]	LDL control	Simvastatin *vs* placebo	Reduced rate of major vascular events
ADVANCE[8]	Glycaemic control	In addition to current therapy: ACE inhibitor-diuretic combination *vs* placebo	Reduced risk of major vascular events
UK Prospective Diabetes Study[17]	Glycaemic control	Sulfonylurea or insulin *vs* conventional treatment	Reduced risk of microvascular complications, including reduced risk of retinopathy

DPP-4 inhibitors

The DPP-4 inhibitors (saxagliptin, alogliptin, sitagliptin and linagliptin) have been extensively studied in people with type 2 diabetes and high CV risk and were found to be neutral with respect to CV events (myocardial infarction, stroke and CV death).[23-26] There was an increased risk of hospitalisation for heart failure (HF) with saxagliptin and a trend to this with alogliptin, so these agents should be used cautiously in patients with a history of HF. DPP-4 inhibitors have an important role in glycaemic control and are well tolerated with minimal side effects, but have no benefit in reducing CV events in people with type 2 diabetes.

GLP-1 receptor agonists

The GLP-1 receptor agonists have shown mixed results in their effects on reducing CV risk. Lixisenatide has shown neutral CV effects when assessed in people with type 2 diabetes after acute coronary syndrome, whereas liraglutide, semaglutide and dulaglutide significantly improved CV outcomes in people with type 2 diabetes at high CV risk.[27-30] Additionally, the EXSCEL study reported a potential CV benefit of the long-acting, once-weekly GLP-1 analogue, exenatide (extended-release), although the primary endpoint did not reach statistical significance (p=0.06).[31] Interestingly, although there was a significant decrease in all-cause mortality for the overall study group in the EXSCEL trial, post-hoc subgroup analysis showed that patients with peripheral arterial disease had worse outcomes on study medication.[32]

GLP-1 receptor agonists also have a renal protective effect but no effect on development of HF. These injectable agents are often associated with significant weight loss, independent of the nausea they often cause, by promoting earlier satiety, delaying gastric emptying and suppressing appetite. They are injectable, so some patients are not enthusiastic about using them, but once-weekly treatment is generally acceptable.

TABLE 2. KEY CLINICAL TRIALS ON THE EFFECT OF GLUCOSE-LOWERING THERAPIES ON CARDIOVASCULAR (CV) OUTCOME IN INDIVIDUALS WITH TYPE 2 DIABETES

Therapeutic agent	Study/trial name	Test arm	Outcome
DPP-4 inhibitors	CARMELINA[26]	In addition to standard care: linagliptin *vs* placebo	No significant difference in risk of major CV events
GLP-1 receptor agonists	ELIXA[27]	In addition to standard care: lixisenatide *vs* placebo	No significant difference in rate of major CV events or other serious adverse events
	SUSTAIN-6[29]	In addition to standard care: semaglutide *vs* placebo	Reduced rate of CV death, nonfatal myocardial infarction and nonfatal stroke
	REWIND[30]	Dulaglutide *vs* placebo	Reduced rate of nonfatal myocardial infarction, nonfatal stroke or death from CV causes
	EXSCEL[31]	Extended-release exenatide *vs* placebo	No significant difference in major adverse CV events
SGLT-2 inhibitors	EMPA-REG[34]	In addition to standard care: empagliflozin *vs* placebo	Reduced rate of death from CV causes, hospitalisation for heart failure and death from any cause
	DECLARE[35]	Dapagliflozin *vs* placebo	Reduced rate of CV death and hospitalisation for heart failure
	CVD-REAL[37]	Any SGLT-2 inhibitor *vs* other glucose-lowering drugs	Reduced risk of hospitalisation for heart failure and death

SGLT-2 inhibitors

The introduction of the SGLT-2 inhibitors (empagliflozin, dapagliflozin and ertugliflozin) has changed the landscape of type 2 diabetes treatment. Significant CV and renal benefits have been seen in patients with and without pre-existing ASCVD in studies when empagliflozin and dapagliflozin have been compared with placebo.[33-35] The CV and renal benefits of ertugliflozin are consistent with those seen from other SGLT-2 inhibitors.[36] These agents promote glycosuria by blocking the SGLT-2 receptor in the renal tubules, resulting in reduced CV risk factors including blood glucose levels, body weight and blood pressure.[33] In the EMPA-REG study, patients with established ASCVD who were assigned to empagliflozin in addition to standard care had reduced CV events, CV and all-cause mortality and HF, as well as improved renal protection compared with patients assigned to placebo.[34] In the DECLARE study, patients with and without established ASCVD were assigned to either dapagliflozin or placebo. The study showed a reduced rate of hospitalisation for heart failure and increased renal protection in patients treated with SGLT-2 inhibitor compared with the placebo group; however, a reduction in CV events was not shown.[35] Real-world data from a very large observational study (CVD-REAL), conducted in clinical practice in the US and Europe, supported the CV benefits of the SGLT-2 inhibitors reported in these randomised trials.[37]

The effects of SGLT-2 inhibitors on CV event and HF reduction and renal protection in these studies are disproportionate to the changes in glycated haemoglobin level, body weight and blood pressure seen with their use, suggesting that mechanisms independent of these changes are involved in CV and renal outcomes. These mechanisms have not yet been definitively defined but effects on myocardial energy metabolism, renal tubule-glomerular feedback and the use of ketones as a fuel substrate may be involved. There is also emerging evidence that SGLT-2 inhibitors affect the sodium/hydrogen exchanger at a cellular level, which increases mitochondrial ATP and thus energy production.[38]

Given the reduction in CV events and death in patients who have established CV disease with empagliflozin use, and the renal protection and reduction in HF with all SGLT-2 inhibitors in patients with type 2 diabetes with and without established CV disease, SGLT-2 inhibitors should be considered in most patients with type 2 diabetes. Care must be taken, however, as there is an increased risk of fungal genital and urinary tract infection, and, rarely, Fournier's gangrene due to glycosuria. Good genital hygiene is therefore essential if they are used. Additionally, if a patient becomes unwell and cannot maintain their oral fluid intake, or requires fasting for a procedure, it is essential that SGLT-2 inhibitors be transiently discontinued to avoid the risk of euglycaemic diabetic ketoacidosis.

Conclusion

ASCVD is the major cause of morbidity and mortality in people with type 2 diabetes, and CV risk reduction is as important as glycaemic control in the treatment of these patients. Recent studies with newer agents have shown that CV events, mortality, HF and renal protection can be improved with these new therapies, but the choice of therapy still needs to be individualised according to patient characteristics. It remains extremely important to control blood pressure and lipid and blood glucose levels in these patients, and therapeutic agents are now available that have both glycaemic and cardiorenal benefits when used to treat people with type 2 diabetes. MT

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

COMPETING INTERESTS: Associate Professor Amerena has been reimbursed for participation in Advisory Boards for many of the medications mentioned in this article; and has presented paid and unpaid lectures on this topic.

Type 2 diabetes and cardiovascular risk

Emerging therapies

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Aspirin therapy in diabetes

Evidence and current recommendations

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Although aspirin use has become an established therapy for the secondary prevention of cardiovascular disease, newer evidence has influenced recommendations regarding the use of aspirin for primary prevention of cardiovascular disease in high-risk patients.

Diabetes remains an ever-increasing global epidemic with over 422 million people affected worldwide and requiring over $827 billion of global health expenditure annually.[1] In Australia, over 1.7 million people are living with diabetes, including an estimated 500,000 people who are currently undiagnosed.[2,3] Diabetes is associated with a range of acute and chronic complications that contribute to increased morbidity and mortality.[1]

Aspirin has long been recommended for the primary and secondary prevention of ischaemic heart disease, stroke and peripheral vascular disease, the risks of which are increased in patients with diabetes. However, its efficacy and safety for primary prevention of cardiovascular disease (CVD) have been debated over the past decade. In this review, in light of several recently completed large-scale randomised controlled trials, we examine whether aspirin should still be recommended as a regular therapy for patients with diabetes.

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Aspirin – a brief history

Aspirin derivatives, originally extracted from willow bark, have been used for over 3500 years for their analgesic and antipyretic properties. Today's form of aspirin, acetylsalicylic acid, was first manufactured by German scientists in 1897.[4]

Aspirin works by irreversibly inhibiting activity of prostaglandin G/H synthase, also known as cyclo-oxygenase, the enzyme responsible for the first step in the conversion of arachidonic acid to prostaglandin G2. This results in decreased production of prostaglandin H2 and its downstream molecules prostaglandin GI2 (PGI2 – prostacyclin) and thromboxane A2 (TXA2), among others (Figure). PGI2 and TXA2 stimulate platelet aggregation, and their inhibition results in a significant reduction in the platelet response and a prolongation of bleeding time. This antiplatelet/antithrombotic effect reduces formation of blood clots, which is a seminal event in acute CVD.[5]

In 1974 the first randomised controlled clinical trial evaluating aspirin for secondary prevention of CVD reported mortality benefits after myocardial infarction.[6] This was followed by several other trials that firmly established the role of aspirin for secondary prevention of CVD, while also highlighting the potential for adverse bleeding events. Below, we list a summary of the key randomised placebo-controlled clinical trials investigating the use of aspirin in primary and secondary prevention of CVD.

What does the evidence say?

Early key aspirin trial outcomes

- **Early Treatment Diabetic Retinopathy Study (ETDRS) 1991, 1992.** Aspirin use in patients with diabetes did not prevent progression of diabetic retinopathy.[7] Aspirin use in patients with diabetes did not reduce all-cause mortality or fatal or nonfatal myocardial infarction. There was also no evidence of significant harm.[8]
- **International Stroke Trial (IST) 1997.** Aspirin use in the

early stages following an acute ischaemic stroke decreased mortality after adjusting for baseline prognosis and reduced recurrent ischaemic strokes with no increase in haemorrhagic stroke.[9]

- **Chinese Acute Stroke Trial (CAST) 1997.** Aspirin use in the early stages following an acute ischaemic stroke reduced mortality and recurrent ischaemic stroke, with a small increase in haemorrhagic stroke.[10]
- **Hypertension Optimal Treatment (HOT) Trial 1998.** Aspirin use reduced the composite endpoint of major cardiovascular events and the individual secondary endpoint of myocardial infarction but not stroke. Adversely, nonfatal major bleeds almost doubled, although without an increase in fatal bleeds.[11]
- **Thrombosis Prevention Trial (TPT) 1998.** Aspirin use for primary prevention among high-risk men 45 to 69 years of age reduced the composite endpoint of ischaemic heart disease events, mostly due to a reduction in the secondary individual endpoint of nonfatal myocardial infarction.[12]
- **Women's Health Study (WHS) 2005.** Aspirin use for primary prevention among women over 45 years of age did not reduce the composite endpoint of major cardiovascular events. Analysis of secondary individual endpoints showed reduced ischaemic stroke but not myocardial infarction or cardiovascular mortality. Subgroup analysis of those over 65 years of age showed the most consistent benefit with reductions in ischaemic stroke and myocardial infarction but an increase in gastrointestinal bleeding.[13]
- **Prevention of Progression of Arterial Disease and Diabetes (POPADAD) Trial 2008.** Aspirin use among high-risk patients with diabetes and asymptomatic peripheral artery disease did not reduce the composite endpoint of fatal myocardial infarction or stroke, nonfatal myocardial infarction or stroke, or above-ankle amputation due to critical limb ischaemia.[14]
- **Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) 2008.** Aspirin use for primary prevention in patients with diabetes did not reduce the composite endpoint of atherosclerotic events. Secondary individual endpoint analysis showed reduced fatal coronary and cerebrovascular events but not all-cause mortality.[15]

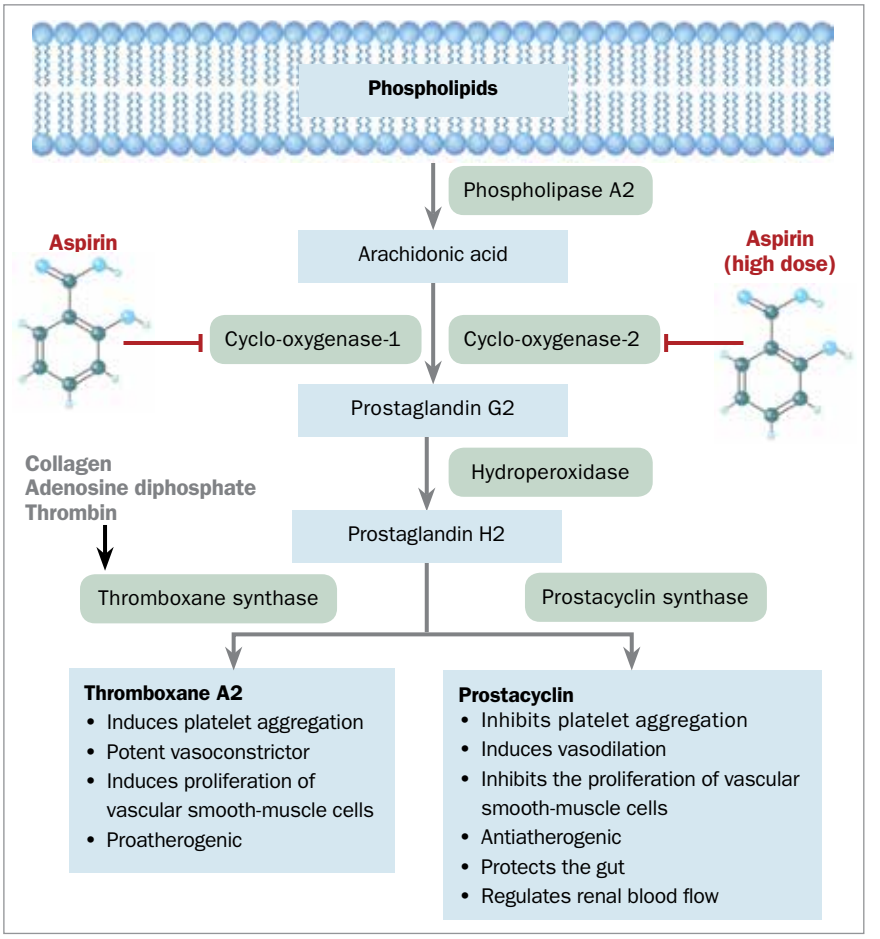

Figure. Mechanism of action of aspirin.

Meta-analyses including the above articles were not conclusive on the effects of aspirin for primary prevention among patients with and without diabetes.[16-19] In response, several large-scale clinical trials were designed and completed, as summarised below.

Recent key aspirin trial outcomes

- **Japanese Primary Prevention Project (JPPP) 2014.** Aspirin use for primary prevention in patients 60 to 85 years of age with multiple atherosclerotic risk factors did not reduce the composite primary outcome of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke. Secondary analysis of individual endpoints demonstrated reduced nonfatal myocardial infarction and transient ischaemic attack, and an increased risk of extracranial haemorrhage.[20]
- **Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) Trial 2018.** Aspirin use for primary prevention in patients with moderate cardiovascular risk (excluding those with diabetes) did not reduce the

CHARACTERISTICS OF PATIENTS WITH HIGH CARDIOVASCULAR RISK[29]

- A Framingham risk evaluation score of >15%
- Diabetes and >60 years of age
- Diabetes and microalbuminuria
- Moderate to severe chronic kidney disease
- Familial hypercholesterolaemia
- A systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg
- A serum total cholesterol >7.5 mmol/L
- Aboriginal or Torres Strait Islander people

composite cardiovascular outcome of time to first myocardial infarction, unstable angina, stroke, transient ischaemic attack or cardiovascular death. However, the overall rate of cardiovascular events was lower than expected in the population studied, making the findings difficult to interpret. Aspirin increased gastrointestinal bleeding.[21]

- **Aspirin in Reducing Events in the Elderly (ASPREE) Trial 2018.** Aspirin use for primary prevention in patients over 70 years of age (including those with diabetes) did not prolong disability-free survival and unexpectedly increased all-cause mortality, primarily due to cancer-related deaths.[22,23] Secondary analysis of cardiovascular endpoints did not demonstrate a reduction in the composite of cardiovascular events, defined as fatal and nonfatal myocardial infarction, fatal and nonfatal stroke or hospitalisation for heart failure. Aspirin increased major haemorrhage, mainly involving upper gastrointestinal and intracranial haemorrhages.[24]
- **A Study of Cardiovascular Events in Diabetes (ASCEND) 2018.** Aspirin use for primary prevention in patients with diabetes reduced the composite endpoint of serious vascular events, defined as myocardial infarction, stroke, transient ischaemic attack or death from any vascular cause excluding intracranial haemorrhage. However, the absolute benefit of aspirin use was counterbalanced by the risk of serious bleeding, mostly due to gastrointestinal bleeding and sight-threatening bleeding events in the eye.[25]

A meta-analysis including pooled data from these recent aspirin trials reported an 11% relative risk reduction and 0.41% absolute risk reduction in composite cardiovascular outcomes in patients without known CVD, without an associated reduction in cardiovascular or all-cause mortality. However, this was accompanied by a 43% relative risk increase and 0.47% absolute risk increase in major bleeding outcomes. This manifested as a number needed to treat of 241, compared with a number needed to harm of 210. Furthermore, a subgroup analysis of patients with diabetes failed to show any significant reduction in cardiovascular events or mortality. This suggests that it would be imperative to consider the potential benefits and risks, in consultation with each individual patient, before the addition of aspirin therapy as primary prevention.[26]

Current guidelines

In response to the new evidence, cardiovascular management guidelines relating to aspirin have been updated. The following recommendations have been summarised from several leading Australian medical authorities, including the Royal Australian College of General Practitioners and the National Vascular Disease Prevention Alliance.

- All adults with type 2 diabetes and known prior CVD should receive long-term antiplatelet therapy unless there is a clear contraindication.[27,28]
- Antiplatelet therapy is not routinely recommended for primary prevention of CVD in high-risk adults (Box), including those with diabetes.[29-31]
- Specific advice and support regarding diet, physical activity and smoking cessation remains the initial approach to cardiovascular risk reduction.[29,30,32]
- Adults with high cardiovascular risk should be simultaneously treated with blood pressure and lipid-lowering agents unless contraindicated or clinically inappropriate.[29,30,32]
- Target blood pressure is ≤130/80 mmHg in patients with diabetes and total cholesterol <4.0 mmol/L, low-density lipoprotein <2.0 mmol/L, high-density lipoprotein ≥1.0 mmol/L and triglycerides <2.0 mmol/L.[29,30,32]
- Response to treatment should be reviewed every six to 12 weeks, and medications adjusted as required, until either sufficient improvement or maximum tolerated dose is achieved.[29]

Removal of aspirin as recommended therapy for primary prevention in patients with diabetes also aids in reducing the burden of polypharmacy and its accompanying potential for adverse events, which can be a common problem for patients with diabetes, who often have multiple comorbidities.

In accordance with recent cardiovascular outcome trials, diabetes management guidelines are now also recommending the addition of either a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon- like peptide-1 (GLP-1) receptor analogue in patients with diabetes who are either at high risk for, or already have, established CVD. This aims to not only improve glycaemic control, but also provide additional cardiovascular and mortality benefits to patients with diabetes.[33]

Conclusion

Aspirin has an established role for secondary prevention of CVD. Updated evidence does not support the routine use of aspirin for primary prevention among patients with diabetes because the risks of serious bleeding appear to counterbalance any modest reductions in cardiovascular events. MT

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

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Aspirin therapy in diabetes

Evidence and current recommendations

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