Reducing the complications of type 2 diabetes

Challenges in individualising care

Individualised complementary lifestyle and pharmacological therapies in people with diabetes increase the challenge of caring for these patients but should reduce complications such as cardiovascular disease, chronic kidney disease, the diabetic foot and retinopathy.

According to the International Diabetes Federation, 382 million people worldwide are now affected by diabetes, with one person dying from diabetes-related complications every six seconds.1 Closer to home, diabetes is no doubt a serious health crisis, and it is estimated that the number of people with type 2 diabetes in Australia will have increased to 3.3 million by 2031.2 Following this trend, typically with a delay of five to 10 years, will be an increase in the prevalence of long-term complications of diabetes.

Despite this, all is not disappointingly bleak, as the application of intensive multifactorial interventions in high-risk patients with type 2 diabetes has been shown to reduce the rate of clinically overt micro- and macrovascular complications.3,4 Indeed, in any one year only a small

Dr Seah is an Endocrinology Advanced Trainee at Austin Health, Melbourne. Dr Yao is a Basic Physician Trainee at Austin & Northern Health, Melbourne. Professor MacIsaac is Director of the Department of Endocrinology and Diabetes, St Vincent’s Hospital, Melbourne, and Professorial Fellow at The University of Melbourne. Dr Ekinci is a Senior Fellow at The University of Melbourne, Head of Diabetes at the Endocrine Centre, Austin Health, Melbourne, and Senior Research Fellow at Menzies School of Health Research, Darwin, NT. Professor Jerums is Professorial Fellow at The University of Melbourne, and Endocrinologist at the Endocrine Centre, Austin Health, Melbourne, Vic.
minority of people with diabetes will develop severe end-organ diabetes complications.6 GPs are directly involved in these intensive interventions and as such are at the forefront of reducing the burden of diabetes at multiple levels, including complications prevention.

The management of patients with type 2 diabetes is emphasised in this article. The positive effects of a multi-interventional approach were demonstrated by the Steno-2 study, where it was shown that intensive treatment of all of hyperglycaemia, dyslipidaemia and hypertension significantly reduced cardiovascular disease (CVD) and microvascular complications of diabetes.6 This emphasises that the management of several individual comorbidities has synergistic effects that exceed the treatment of any single risk factor.

Physicians should also continually encourage smoking cessation as part of a multifactorial intervention, which has an important role in reduction in risks of complications.

This article will consider the following complications of type 2 diabetes:
- cardiovascular events
- diabetic kidney disease
- neuropathy, with a focus on the diabetic foot
- retinopathy, particularly severe retinopathy and maculopathy.

A multidisciplinary approach to preventing and delaying the progression of these micro- and macrovascular complications of diabetes is discussed, with an emphasis on cardiovascular events and kidney disease, including recommendations and strategies for risk stratification of patients.

CARDIOVASCULAR COMPLICATIONS

People with diabetes have more than twice the risk of developing cardiovascular events than people without diabetes. Macrovascular complications (coronary artery disease, peripheral vascular disease and cerebrovascular disease) are the major cause of morbidity and mortality in those with type 2 diabetes.

Identifying high risk patients

It is crucial to identify patients at high risk of developing brain and heart complications so that primary prevention can be instigated, but risk estimation can be cumbersome. There are many cardiovascular risk models available, including the United Kingdom Prospective Diabetes Study (UKPDS) Risk Engine.

The UKPDS Risk Engine is a cardiovascular risk calculator specific for people with type 2 diabetes. It takes into account 10 clinical parameters (age, duration of diabetes, sex, ethnicity, smoking history, presence of atrial fibrillation, glycosylated haemoglobin [HbA1c] level, systolic blood pressure and total cholesterol and HDL cholesterol levels) to calculate the 10-year risk of developing the four different outcomes of non-fatal and fatal coronary heart disease (CHD), fatal CHD, nonfatal and fatal stroke, and fatal stroke. A recent validation of this risk calculator suggested that although there is moderate discrimination on all four outcomes, there is only poor and at most moderate calibration, and hence recommendations for its revision are proposed.7

Studies have shown an increased risk of cardiovascular mortality with increasing nephropathy. As this relationship is increasingly being recognised, albuminuria (measured as the urine albumin-to-creatinine ratio, ACR) has been added as an additional factor in the Diabetes Cohort Study five-year CHD risk equation for people with type 2 diabetes derived from data collected in New Zealand.9

Similarly, the Fremantle Diabetes Study (FDS) risk equation incorporates the ACR for the prediction of a five-year major cardiovascular event for patients with type 2 diabetes.10 This equation can be used for patients with or without pre-existing CVD. The FDS equation is particularly useful for GPs in Australia as it is validated within the Australian population.

Nevertheless, because risk calculation tools can only offer estimations and will invariably always be less than perfect with no two individuals’ risk profiles being exactly the same, the UKPDS Risk Engine remains one of the best tools available to identify people at high risk of macrovascular complications of diabetes.

DIABETIC KIDNEY DISEASE

Diabetes is the leading cause of chronic kidney disease (CKD), and is responsible for 35% of all new end-stage kidney disease (ESKD) in Australia.11 The burden of diabetic kidney disease is also particularly high in Aboriginal and Torres Strait Islander people, given that the prevalence of kidney disease is 10 times higher in these communities than in non-Indigenous people.12

About 70% of patients with diabetic kidney disease have micro- or macroalbuminuria, and about 30% will have normoalbuminuria.13 The development of albuminuria has also been shown to independently predict cardiovascular mortality.14 The presence of micro- or macroalbuminuria is usually but not always specific for CKD.13,15 Regression of albuminuria may not reverse the risk of developing overt diabetic kidney disease characterised by glomerular filtration rate (GFR) decline. Hence, the presence of albuminuria, which has been the main traditional model of assessing diabetic kidney disease, is not the sole prognostic index of diabetic kidney disease.

For the purposes of daily practice, ACR and GFR in combination are the most practical and widely available modalities for diagnosis and management of diabetic kidney disease.

Measurement of ACR and GFR

Considerations and recommendations for testing

- Albuminuria is ideally measured by determining the albumin concentration in an early morning, first-void sample by immunoassay. Although the albumin excretion rate (AER) is the gold standard, ACR is an easier option (Table 1).16
- ACR has an individual coefficient of variation of 30 to 40%. Therefore at least two, and preferably three, measurements should be performed.
before making a diagnosis of microalbuminuria.

- Albuminuria may fluctuate with factors that have no causal relation to the development of nephropathy. This includes concurrent urinary tract infections, exercise, drugs, weight fluctuations, febrile illness and dietary modifications.

- In the Diabetes Control and Complication (DCCT) trial, yearly measurements of change in microalbuminuria in people undergoing intensive blood glucose control led to spontaneous microalbuminuria resolution in 60% of participants over five years. It is therefore important to perform serial measurements to assess AER category as well as intervention efficacy.

- Ageing is associated with an estimated GFR (eGFR) decline of 1 mL/1.73 m² per year after the age of 40 years. With consideration of this, in practice the eGFR trajectory over several years becomes a way of assessing progression of diabetic kidney disease.

- eGFR is not validated for pregnant women or in people younger than 18 years.

### Risk stratification

In the recent Kidney Disease Improving Global Outcome (KDIGO) guideline, the albuminuria categories were renamed from normo-, micro- and macroalbuminuria to normal to mildly increased, moderately increased and severely increased, respectively, and paired with GFR to allow risk stratification. These 2012 guidelines should be followed for risk stratification, and are available online at: www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf.

The proportions of patients alive 10 years following onset of different stages of nephropathy are:

- no nephropathy – 87%
- microalbuminuria – 71%
- macroalbuminuria – 65%
- elevated plasma creatinine (plasma creatinine 175 micromol/L or higher on two consecutive visits) or renal replacement therapy – 9%.

### NEUROPATHY

It has been estimated that 20 to 40% of people with type 2 diabetes have peripheral neuropathy and another 20 to 40% are affected by peripheral vascular disease. Both of these complications contribute to the foot ulceration that affects about 5% of people with diabetes each year, resulting in amputation in about 0.5% of patients a year. Patients with diabetes have a much higher risk (up to 40 times greater) than the general population of needing to undergo amputation.

Peripheral neuropathy affects the peripheral sensory, motor and/or autonomic nerves. Systemic diabetic neuropathy can manifest as diabetic foot, painful femoral amyotrophy, ocular mononeuropathy and pressure palsies. Sensory neuropathy can be either painful (usually described as intolerable night-time burning, pins and needles, or allodynia) or painless. Motor neuropathy contributes to injury susceptibility by reducing muscular control, affecting gait and increasing risk of falls. Autonomic neuropathy causes vasomotor and sudomotor (sweating) abnormalities, resulting in dry cracked skin that is often thinned and atrophied and therefore more susceptible to damage.

Painful peripheral neuropathy in diabetes is common and difficult to treat. It may occur in the absence of reduced sensation so affected individuals may not be at high risk of foot ulceration. This topic is beyond the scope of this article but trials of analgesics may include tricyclic antidepressants, serotonin uptake inhibitors, serotonin and noradrenaline reuptake inhibitors, gabapentin and pregabalin.

The identification of people with diabetes who are at high risk of foot ulcers and their management is discussed in detail later in this article.

### RETINOPATHY

The microvascular complication diabetic retinopathy, along with its associated consequences, is the most common preventable cause of blindness in people with diabetes under the age of 75 years in the developed world. People with diabetes have a 20- to 25-fold increased relative risk of developing significant visual impairment and blindness.

---

**TABLE 1. CATEGORIES OF ALBUMINURIA**

<table>
<thead>
<tr>
<th>Urine albuminuria measurement</th>
<th>Albumin-to-creatinine ratio (ACR), spot urine</th>
<th>Albumin excretion rate (AER), 24-hour collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoalbuminuria (Normal to mildly increased*)</td>
<td>Men &lt; 2.5 mg/mmol Women &lt; 3.5 mg/mmol</td>
<td>&lt; 30 mg/day</td>
</tr>
<tr>
<td>Microalbuminuria (Moderately increased*)</td>
<td>Men 2.5 to 25 mg/mmol Women 3.5 to 35 mg/mmol</td>
<td>30 to 300 mg/day</td>
</tr>
<tr>
<td>Macroalbuminuria (Severely increased*)</td>
<td>Men &gt; 25 mg/mmol Women &gt; 35 mg/mmol</td>
<td>&gt; 300 mg/day</td>
</tr>
</tbody>
</table>

* Kidney Disease and Improving Global Outcome guideline categories.16
include smoking cessation, alcohol modifiable risk factors is essential; these of, and adherence to, therapies to reduce a multifactorial approach. The instigation diabetes is a challenging task, warranting vascular complications in people with type 2 the development of micro- and macrovascular...

**Diabetic retinopathy** typically presents as decreased visual acuity, which often only occurs once the retinopathy has progressed to become irreversible. Nonproliferative diabetic retinopathy occurs in most people with diabetes but will progress in only a minority to vision-threatening diabetic maculopathy or proliferative retinopathy. The identification and management of people with diabetes who are developing these changes are discussed later in this article.

**PREVENTING AND DELAYING PROGRESSION OF DIABETES COMPLICATIONS**

Planning effective management to prevent the development of micro- and macrovascular complications in people with type 2 diabetes is a challenging task, warranting a multifactorial approach. The instigation of, and adherence to, therapies to reduce modifiable risk factors is essential; these include smoking cessation, alcohol reduction and weight reduction where indicated, and control of blood glucose and lipid levels and blood pressure (Table 2).

In general, the importance of therapeutic management of modifiable risk factors is in the order of blood pressure (BP), lipid profile and glycaemic control.

<table>
<thead>
<tr>
<th>Complications/risk factor</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
</tr>
<tr>
<td><strong>Macrovascular (cardiovascular, cerebral and lower limbs)</strong></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>++†</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>+</td>
</tr>
<tr>
<td>Glucose control</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Microvascular (kidney and retinal)</strong></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>+++†</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>+++‡</td>
</tr>
<tr>
<td>Glucose control</td>
<td>++</td>
</tr>
</tbody>
</table>

*Effectiveness based on UKPDS (early intervention) and STENO-2 (late intervention) studies.*

**TABLE 2. EFFECTIVENESS OF EARLY VERSUS LATE INTERVENTIONS IN MANAGING THE COMPLICATIONS OF TYPE 2 DIABETES**

**Blood pressure – 140/80 mmHg or below and RAAS inhibition**

With arterial hypertension having a central role in the development of cardiovascular events and CKD in diabetes, BP control remains an important treatment target. The overall cardiovascular risk profile should also determine aggressiveness of BP control for cardiovascular protection.

There is, however, no ‘one size fits all’ model for BP targets, where aggressive lowering of BP may potentially be at the expense of mortality. In ACCORD, reduction of systolic BP to below 120 mmHg was associated with an incidence of adverse effects three times that of patients with systolic BP above 130 mmHg. This finding should be tempered against the finding that ischaemic stroke was significantly reduced by the lower BP target. As the beneficial effects have been documented with a systolic BP between 130 and 140 mmHg, as a guide, GPs should adopt the new (2013) American Diabetes Association guidelines of maintaining a BP of 140/80 mmHg or below for patients with diabetes regardless of the presence of pre-existing complications.

Drugs inhibiting the renin–angiotensin–aldosterone system (RAAS) should be first-line therapies when initiating BP medications, because they offer renal protection in addition to lowering BP in people with diabetes. In the Irbesartan Diabetic Nephropathy Trial (IDNT), irbesartan significantly reduced the rate of eGFR decline in patients with established diabetic kidney disease compared with amlodipine and placebo, but only partially through reducing BP and proteinuria. Although there was no difference observed in cardiovascular endpoints, it should be noted that the follow up was only for 2.6 years.

As favorable as it is to target the RAAS, particularly with the combination of an angiotensin-converting enzyme (ACE) inhibitor and an angiotensin-receptor blocker (ARB) reducing proteinuria, there is no longer a role for dual therapy, which also raises safety concerns. In the Veterans Affair Nephropathy in Diabetes Study (VA-NPHRON-D), combination ACE inhibitor and ARB therapy significantly increased the risk of hyperkalaemia and acute renal impairment, resulting in early termination of the trial.

Calcium channel blockers, diuretics and beta-blockers are often required in addition to blockade of the RAAS to achieve a target BP of 140/80 mmHg or below. Despite comparable BP levels, in the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACOMPLISH) trial, the combination of an ACE inhibitor with the calcium channel blocker amlodipine was
more effective than the combination with the diuretic hydrochlorothiazide in reducing cardiovascular events in high-risk patients.30

‘Aldosterone escape’ is a phenomenon in which albuminuria continues despite the use of an ACE inhibitor or ARB. In these cases, albuminuria has been shown to respond to spironolactone.31 Although there is a lack of long-term studies on aldosterone antagonists, they are a very useful third- or fourth-line therapy, provided that serum potassium is monitored carefully.

**Lipid profile**

In type 2 diabetes, dyslipidaemia typically consists of elevated triglycerides level, low HDL cholesterol (HDL-C) level and a predominance of small dense low-density lipoprotein particles. As a guide, lipid target levels endorsed by Diabetes Australia based on the National Vascular Disease Prevention Alliance are: total cholesterol below 4.0 mmol/L, HDL-C above 1.0 mmol/L, LDL-C below 2.0 mmol/L and triglycerides below 2.0 mmol/L.32 The gender cardiovascular protective effect normally seen in premenopausal women is lost in those who have diabetes. Lipid profile should be assessed at least annually, and more frequently to review improvement with therapy. However, the overall benefit of lipid-lowering therapy is dependent on the individual’s cardiovascular risk as a whole, rather than lipid levels per se.

Despite the availability of pharmacotherapy, it must not be forgotten that a diet low in both saturated fat (less than 10% total daily energy intake) and cholesterol should be encouraged.33 Improving glycaemic control with insulin may improve the lipid profile, particularly blood triglycerides in patients with moderate to severe hyperglycaemia.

Statins are HMG-CoA reductase agents that lower LDL-C by 20 to 55%. They have been shown to improve cardiovascular outcomes and should be considered as first choice for primary prevention in patients with diabetes. Although well tolerated, the main precautions are myopathy, which occurs in 0.1 to 0.2% of participants in clinical trials and more often (1 to 5%) in the general population.34,35

Ezetimibe, an inhibitor of intestinal cholesterol absorption, has a role not only as monotherapy in statin-intolerant patients but also as an add-on therapy to statins for lowering the LDL-C level (Box). The impact of ezetimibe on cardiovascular outcomes remains unclear, and hopefully the IMPROved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial assessing combined use of ezetimibe and simvastatin with simvastatin alone will improve knowledge in this area.36

Other combination therapies with statins include the addition of fibrates or nicotinic acid (Box). Fibrates may be needed as first-line therapy in patients with severe triglyceridaemia to reduce the risk of pancreatitis. Gemfibrozil and fenofibrate, which have different pharmacokinetic profiles, increase the HDL-C level and reduce LDL-C and triglycerides levels. Fenofibrate has been linked to risk reduction of progression of retinopathy and reduction in need for laser therapy, and could be used in patients with type 2 diabetes who have diabetic retinopathy; however, the retinal protective effects of fenofibrate do not seem to be related to its lipid-lowering effects.37,38

Nicotinic acid is used infrequently as a combination therapy with statins, although it improves all major lipid fractions, with significant increase in HDL-C level. However, it has a poor side effect profile (e.g. flushing, myopathy and gastrointestinal effects). There have been recent concerns of ischaemic stroke with nicotinic acid, but multivariable analysis in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial does not support this association.39

There is limited evidence for the effectiveness of omega-3 fatty acids in improving lipid profiles.

---

**ADD-ON THERAPIES TO STATINS FOR IMPROVING LIPID PROFILES**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe*</td>
<td>First-line combination therapy</td>
</tr>
<tr>
<td>Fibrates</td>
<td>First-line combination therapy if severe hypertriglyceridaemia</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>Combination therapy mainly to increase HDL-C level</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>Limited evidence for use with statin</td>
</tr>
</tbody>
</table>

* Ezetimibe is first-line monotherapy for statin-intolerant patients.

**Glycaemia – HbA₁c 53 mmol/mol (7.0%) or below**

It remains uncertain whether intensive glycaemic control reduces clinical renal outcomes such as doubling of serum creatinine level, end stage renal disease or death from renal disease.40 Evidence for regression of macroalbuminuria is also lacking.

Despite this, it is clear from the DCCT/Epidemiology of Diabetes Intervention and Complications (EDIC) long-term (22 years) follow-up cohort that intensive glycaemic control significantly lowers the long-term risk of developing an impaired eGFR by 50%, which may translate into long-term renal- and cardiovascular protective effects.17 This highlights the concept of ‘metabolic memory’ and achieving good glycaemic control early in the course of diabetes, where intensive therapies have clearly been shown to have a long-term impact.

In addition, once microalbuminuria has occurred, it has been shown that intensive glycaemic control can halt the progression of albuminuria independently, with continued long-term separation in the incidence of micro- and macroalbuminuria.41,42 Furthermore, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, delayed onset of albuminuria was shown in...
the intensive glycaemic control group (HbA1c below 6% [42 mmol/mol]).

It should also be noted that in the DCCT/EDIC studies, intensive glycaemic control was shown to have a relative risk reduction of 57% for major cardiovascular events, with a reduction of microalbuminuria contributing to but not explaining all the difference with respect to cardiovascular disease.

These studies confirm the importance of achieving good glycaemic control, and an HbA1c above 53 mmol/mol (7.0%) should therefore prompt more active treatment, especially if the HbA1c is 5 mmol/mol (0.5%) or more above the target of 59 mmol/mol (7.5%). The 2009 NHMRC guidelines suggest aiming for preprandial blood glucose levels between 6.1 and 8 mmol/L and postprandial levels between 6.0 and 10.0 mmol/L.

### TABLE 3. NEWER GLUCOSE-LOWERING AGENTS FOR PATIENTS WITH TYPE 2 DIABETES (PBS LISTED)

<table>
<thead>
<tr>
<th>Feature</th>
<th>GLP-1 agonists</th>
<th>DDP-4 inhibitors</th>
<th>SGLT-2 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBS-listed agents (March 2014)*</td>
<td>Exenatide (A once-weekly preparation of exenatide is TGA approved but not currently PBS listed)</td>
<td>Sitagliptin Saxagliptin Vildagliptin Linagliptin Alogliptin</td>
<td>Dapagliflozin Canagliflozin</td>
</tr>
<tr>
<td>PBS indications (March 2014; not all requirements listed)</td>
<td>Dual combination with metformin or a sulfonylurea Must have or had a HbA1c &gt; 53 mmol/mol (7.0%) Although not PBS listed for use with insulin, GLP-1 analogues have been approved for use in combination with insulin by the TGA and the US FDA</td>
<td>Dual combination with metformin or a sulfonylurea Must have or had a HbA1c &gt; 53 mmol/mol (7.0%)</td>
<td>Dual combination with metformin or a sulfonylurea Must have or had a HbA1c &gt; 53 mmol/mol (7.0%)</td>
</tr>
<tr>
<td>Mode of administration</td>
<td>Twice-daily injection</td>
<td>Daily, oral</td>
<td>Daily, oral</td>
</tr>
<tr>
<td>Action</td>
<td>Augment insulin secretion and decrease glucagon release</td>
<td>Increase endogenous, active intact GLP-1 and glucose-dependent insulinotropic polypeptide</td>
<td>Induce glycosuria by inhibiting resorption of filtered glucose at the proximal tubule</td>
</tr>
<tr>
<td>HbA1c reduction</td>
<td>8 to 15 mmol/mol (0.8 to 1.5%)</td>
<td>8 to 10 mmol/mol (0.8 to 1.0%)</td>
<td>5 to 10 mmol/mol (0.5 to 1.0%)</td>
</tr>
<tr>
<td>Weight reduction</td>
<td>Modest</td>
<td>Neutral</td>
<td>Modest</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Pancreatitis, gastrointestinal effects, plus others</td>
<td>Gastrointestinal effects, plus others</td>
<td>Symptomatic hypotension with diuretics, RAAS inhibition, hyperkalaemia, and genital urinary mycotic infections</td>
</tr>
<tr>
<td>Use in renal impairment</td>
<td>Contraindicated if eGFR &lt; 30mL/min</td>
<td>Effect dependent on renal function Dose adjustments required except for linagliptin</td>
<td>Effect dependent on renal function Precautions with renal impairment</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS:** eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide 1; DDP-4 = dipeptidyl peptidase-4; FDA = Food and Drug Administration; HbA1c = glycosylated haemoglobin; RAAS = renin–angiotensin–aldosterone system; SGLT-2 = sodium–glucose cotransporter 2; TGA = Therapeutic Goods Administration.

*Not including combination agents.
It is also important to balance tight glycaemic control with the potential risk of hypoglycaemia, as extrapolated from the ACCORD and Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trials. These demonstrated that tight control in high-risk patients with type 2 diabetes and critically unwell patients may be associated with higher mortality.

Metformin, with or without a sulfonylurea, remains the first-line medication for people with type 2 diabetes. For patients who are at risk of hypoglycaemia but require further treatment to achieve glycaemic targets, the newer glucose-lowering agents, which have lower hypoglycaemic risk profiles, may be considered. These are the glucagon-like peptide 1 (GLP-1) agonists, the dipeptidyl peptidase-4 (DPD-4) inhibitors and the emerging sodium–glucose cotransporter 2 (SGLT-2) inhibitors (Table 3). Furthermore, if glycaemic targets are not achieved, insulin should be considered in younger patients with an HbA1c above 59 mmol/mol (7.5%) and in elderly patients with an HbA1c above 64 mmol/mol (8%).

Beyond glucose reduction in particular, the significant blood pressure-lowering effects of SGLT-2 inhibitors and weight-reducing effects of GLP-1 agonists may translate into cardiovascular benefit. With longer term follow up, the cardiovascular and mortality effects of these therapies will become clearer.

**Aspirin**

Best-practice care for patients with a past history of CVD is treatment with aspirin at a dose of 75 to 150 mg daily if not contraindicated. However, the role of aspirin in primary prevention of cardiovascular events in patients with diabetes remains controversial. The benefits of prophylactic aspirin may not be significant on a large scale, but the decision for aspirin therapy should be based on individual risk of cardiovascular events and bleeding.

Generally, there is lack of evidence for patients with low risk to be taking prophylactic aspirin. Indeed, the most recent Australian guidelines do not recommend aspirin in primary prevention, including for those with diabetes. The 2010 recommendation of the American Diabetes Association, American Heart Association and American College of Cardiology, which was based on a meta-analysis, suggests that it may be reasonable to initiate aspirin for high-risk patients, which includes those with an absolute five-year CVD risk of more than 5%. The level of evidence at best, however, is a class IIA recommendation (i.e. weight of evidence is in favour of usefulness/efficacy), and discussions should be carried out with eligible patients.

**DIABETIC FOOT AND NEUROPATHY**

As mentioned earlier, about 5% of patients with diabetes have a foot ulcer each year due to their peripheral neuropathy and peripheral vascular disease, and one in 10 of these will require amputation of the affected foot (Figure 1). Because of this, it is important to identify people with diabetes who are at high risk of foot ulcers and care for them appropriately.

Features of high-risk diabetic foot are the presence of peripheral arterial disease and peripheral neuropathy affecting the peripheral sensory, motor, and/or autonomic nerves. Motor neuropathy contributes to injury susceptibility via alteration of normal foot shape and weight distribution. The vasomotor and sudomotor (sweating) abnormalities caused by autonomic neuropathy result in dry cracked skin that is more susceptible to damage, and sensory neuropathy prevents the person being aware of any injury and taking steps to prevent further injury and treat the damaged skin. The reduced circulation resulting from peripheral arterial disease compromises healing of the damaged skin. Other less robust predictors of ulcer risk are age, gender and concurrent hypertension or dyslipidaemia.

**Surveillance**

A routine basic history and clinical examination is necessary when examining the feet of a person with diabetes. It is important to assess for biomechanical foot abnormalities, impaired sensation to vibration, impaired touch pressure sensation (using a 10 g monofilament) pulses and reflexes, ulcers, infections and hygiene, and also to inspect footwear. People who are judged to be at high risk of diabetic foot ulceration should be counselled and educated about methods to minimise the risk of this complication. This will usually include regular podiatric surveillance and care.

**Diabetic foot ulcers**

The care of people with diabetic foot ulcers requires a multifactorial approach and is well documented in NHRMC evidence-based guidelines. In summary, foot ulcers can be classified into three types:

- neuropathic
- ischaemic
- neuroischaemic.

Neuropathic ulcers commonly arise on the plantar aspect of the foot or toes. One of the most common causes of ulceration is repetitive mechanical friction leading to calluses, resulting in localised tissue necrosis. A foot with such an ulcer is itself often warm with intact pulses. A foot with an ischaemic or neuroischaemic ulcer, however, is often cool and pulseless, with varying degrees of pain. These ulcers are often seen on the margins of the foot (such as tips of toes), the medial surface of the first metatarsophalangeal (MTP) joint or the lateral aspect of the fifth MTP joint.
Diabetic foot ulcers are often complicated by the presence of secondary bacterial infection, which can range in severity from superficial cellulitis to deeper bony involvement. There is no one specific clinical marker to indicate the extent of the infection. Sterile probing of the ulcer can help exclude sinus tracts and detect underlying osteomyelitis. Plain radiography is usually first-line imaging, but the typical bony destruction is often not apparent early on (usually not until at least two weeks after the initial ulcer). Hence MRI and bone scans are frequently required to facilitate the diagnosis.

Management of foot ulcers
Organisms cultured from chronic ulcers are typically a mixture of *Staphylococcus aureus*, Gram-negative bacteria and anaerobes, and occasionally *Streptococcus*. The species present should be the main guide to the antibiotics used.

If ulcers do not heal with the off-loading of pressure on affected areas, antibiotics if indicated, local wound debridement and appropriate dressings, or if a deep infection is suspected, then acute review in a multidisciplinary hospital setting is warranted. This is because revascularisation and more intensive antibiotics may required.

As well as maintaining glycaemic control to help prevent neuropathy and peripheral arterial disease, patients benefit from education. They should be instructed about self-examination of their feet, appropriate foot care and footwear, and advised to avoid walking barefoot and having prolonged exposure to heat (such as close proximity to a heater or contact with a hot water bottle) and to check water temperature before bathing with their hands, not with their feet.

**Disciplinary hospital setting is warranted.**

**Figure 2. Nonproliferative diabetic retinopathy, showing microaneurysms, dot blot haemorrhages, hard exudates and dilation of retinal veins.**

**DIABETIC RETINOPATHY AND MACULOPATHY**

As mentioned earlier, only a small proportion of people with nonproliferative diabetic retinopathy progress to diabetic maculopathy or proliferative retinopathy, both of which threaten vision (Figure 2). It is important to identify the people with diabetes who are developing these changes so that vision can be preserved.

**Surveillance and management**

Diabetic retinopathy screening by an optometrist or ophthalmologist, through measurement of visual acuity, dilated fundoscopy and retinal photography, should be performed annually from the time of diagnosis with type 2 diabetes. More frequent specialist follow up is necessary when an abnormality is detected, or paradoxically, there is rapid improvement in glycaemic control or the individual enters puberty or becomes pregnant, when acceleration of retinopathy may occur.

The DCCT showed that, in type 1 diabetes, intensive glycaemic treatment reduced the risk of development and progression of sustained retinopathy by 76% and 54% in primary and secondary prevention groups respectively. The UKPDS showed a significant reduction (17%) of the risk of progression of retinopathy in patients with type 2 diabetes. The ACCORD Eye study further demonstrated that intensive glycaemic control (HbA₁c below 6% [42 mmol/mol]) prevented and attenuated the progression of nonproliferative diabetic retinopathy, with a risk reduction of 30%. This evidence in combination suggests that primary prevention is paramount in reducing risk of visual loss, whereas secondary prevention has a smaller effect but still remains effective.

Other important contributing variables include intensive management of hypertension and dyslipidaemia, and smoking cessation. Of note, with regards to BP targets, there was no additional benefit in the ACCORD Eye study with intensive treatment (systolic BP below 120 mmHg) compared with standard treatment (systolic BP below 140 mmHg). Fenofibrate, previously mentioned as being often used in combination with a statin to optimise lipid profiles, has recently also been TGA approved for use in reducing the progression of existing diabetic retinopathy in patients with type 2 diabetes.

Laser photocoagulation is the first-line specialist therapy to induce regression of new blood vessel formation and reduction of central macular thickening for established severe, proliferative diabetic retinopathy and maculopathy. Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) drugs such as bevacizumab and ranibizumab are emerging therapies that have been shown to be effective in both diabetic macular oedema and new vessel formation in diabetic retinopathy (ranibizumab is now TGA approved for diabetic macular oedema).

**FINAL CONSIDERATIONS**

Implementing both lifestyle and pharmacological therapies in a complementary manner to promote multifactorial intervention in diabetes is generally ingrained in health practitioners in Australia. The difficulty, however, lies with translating clinical trial evidence into everyday clinical practice to achieve ‘recommended targets’ for individual patients where each patient’s risk, adherence, comorbidities and socioeconomic status are considered. Moreover, psychological aspects – including depression and diabetes distress, each of which are not uncommon – are linked with adverse diabetes outcomes, including lower adherence to lifestyle advice and subsequent complications. This invariably increases the challenge of caring for these patients.
GPs should aim to identify patients at high risk of complications and utilise the multidisciplinary approach as necessary, with strategies including the annual cycle of care. It remains to be verified if the current Australian Model of Chronic Care Management plans have improved communications between patients, GPs and the multidisciplinary specialty team in diabetes care.

Diabetes care is a highly complex area and integrating general practice, specialist and hospital care is the key for diabetes management. If no progress is made in achieving targets for glycaemia, BP and lipid profile in people with type 2 diabetes, referral to a specialist diabetes centre for further support should be considered.

Lastly, although the focus of this article is mainly on type 2 diabetes, most of the complication prevention strategies discussed can be applied to adult patients with type 1 diabetes. However, type 1 diabetes encompasses a wider age group and different baseline risk profiles. As such, although type 2 diabetes is in the province of general practice, type 1 diabetes should be managed primarily in a multidisciplinary specialist setting to ensure the best possible care and best possible opportunities to prevent and delay the progression of complications.

REFERENCES
A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

COMPETING INTERESTS: Dr Seah and Dr Yao: None. Professor MacIsaac has received honoraria for lectures from Eli Lilly, Novo Nordisk, Sanofi-Aventis, AstraZeneca, Merck Sharp & Dohme, Servier, Boehringer Ingelheim and Novartis, and also research grants from Novo Nordisk. Dr Ekinci has received honoraria for lectures from Eli Lilly, Novo Nordisk and AstraZeneca. Professor Jerums: None.

Online CPD Journal Program
Cardiovascular mortality increases with increasing nephropathy. True or false?
Review your knowledge of this topic and earn CPD points by taking part in MedicineToday’s Online CPD Journal Program.
Reducing the complications of type 2 diabetes
Challenges in individualising care

JAS-MINE SEAH MB BS, BMedSci; HENRY YAO MB BS, BMedSci; RICHARD J. MACISAAC BSc(Hons), PhD, MB BS, FRACP; ELIF I. EKINCI MB BS, FRACP, PhD; GEORGE JERUMS MB BS, MD, FRACP

REFERENCES


