

Type 2 diabetes

Tailoring a treatment approach

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The past decade has seen major advances in therapies for type 2 diabetes, leading to a wide array of treatment options. Management should involve a patient-centred approach with individualised glycaemic targets and selection of medications based on comorbidities, cost and patient preference.

KEY POINTS

- Early and optimal glycaemic control in patients with type 2 diabetes is imperative for reducing microvascular and potentially macrovascular complications.
- Glycated haemoglobin (HbA_{1c}) remains the key focus of glycaemic management although targets should be individualised based on age, comorbidities and life expectancy.
- There is a vast array of therapies available and treatment algorithms provided by the Australian Diabetes Society offer guidance on treatment selection.
- Treatment choice should be guided by patient comorbidities, adverse effect profile, acceptability of the method of administration and cost (PBS subsidy).
- Metformin remains first-line treatment unless contraindicated. Insulin may be considered at any stage, particularly where control is poor (HbA_{1c} above 75 mmol/mol [9%]).
- Patients with pre-existing cardiovascular disease can be safely managed with new agents, including some DPP4-inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors, and some therapies may offer cardiovascular mortality benefit.



Type 2 diabetes represents a significant challenge to public health in Australia. With the emergence of the obesity epidemic there has been a steady increase in the prevalence of type 2 diabetes and it has been forecast that between 2000 and 2050 the number of cases in Australia will increase by more than threefold.¹ Furthermore, type 2 diabetes is becoming increasingly common in younger patients, and now accounts for 31% of new diagnoses of diabetes in young adults aged 15 to 19 years.² Research has shown that in 2000, the total estimated annual healthcare cost attributed directly to type 2 diabetes was over \$630 million.¹

The rapid rise in new diagnoses demands clinicians are well educated in the management of this condition. Additionally, potential micro- and macrovascular complications reinforce the need for early control, not only to improve health outcomes for individual patients, but also to mitigate the impact of the disease burden on the Australian economy.

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HbA_{1c} targets and individualising goals

Glycaemic control remains the principal focus of diabetes management, with glycated haemoglobin (HbA_{1c}) targets dictating most treatment decisions. It is well established that control of blood glucose levels is associated with reductions in the rates of microvascular complications and possibly also the macrovascular complications of myocardial infarction (MI), stroke and all-cause mortality.

Several seminal trials have emerged over the past 25 years that have informed clinicians about the ideal targets for HbA_{1c}. It is now accepted that the targets should be individualised based on factors including age, other comorbidities and life expectancy.

Key trials on glycaemic targets

Among the wealth of research in the area of reducing diabetes-related end points through achieving HbA_{1c} targets, four key randomised controlled trials have contributed significantly to the current diabetes management principles. These trials are discussed in Box 1.³⁻⁸

The legacy effect of the glycaemic target trials

Long-term follow up of the four key large clinical trials has shown that tight control in the period following diabetes diagnosis can have a sustained effect for years to come, even if glycaemic control is later relaxed. Results from the UKPDS 10-year follow up found early glycaemic control (HbA_{1c} below 53 mmol/mol [7%])

mitigated long-term risk of any diabetes-related end point and microvascular disease.⁹ The risk of diabetes-related death, MI and death from any cause was also lower in those who received intensive therapy early despite later merging of HbA_{1c} from the two arms (sulfonylurea–insulin group and metformin group).⁹ This concept was termed the ‘legacy effect’, and supports optimal glycaemic control in the early stages of disease.⁸ It emphasises the importance of considering duration of type 2 diabetes when tailoring treatment.

Recommended glycaemic targets

Based on the body of evidence, the Australian Diabetes Society has developed guidelines to assist clinicians in decision-making in this area, the position statement

1. KEY TRIALS ON GLYCAEMIC TARGETS IN PEOPLE WITH DIABETES³⁻⁸

DCCT

The Diabetes Control and Complications Trial (DCCT) was conducted in a population of patients with type 1 diabetes but its findings, published in 1993, have historically been applied to patients with type 2 diabetes also. This study demonstrated that patients with type 1 diabetes and a median HbA_{1c} of 53 mmol/mol (7%) achieved through tight glycaemic control had reduced neuropathy, nephropathy and retinopathy compared with those with higher HbA_{1c} (median 75 mmol/mol, or 9%, with conventional therapy).³ No significant reduction in cardiovascular events was seen, although the cohort was relatively young (mean age, 27 years). Despite improved microvascular outcomes, the incidence of hypoglycaemia was significantly higher in those randomised to intensive therapy.

UKPDS

The UK Prospective Diabetes Study (UKPDS) further explored tightened glycaemic targets in patients with type 2 diabetes, and published its findings in 1998. This trial demonstrated reduced microvascular outcomes, largely due to a reduction in retinopathy, proportional to HbA_{1c} (53 mmol/mol vs 63 mmol/mol [7.0 vs 7.9%]) in intensive [using sulfonylureas or insulin] versus conventional therapy; UKPDS 33).⁴ The population examined in this trial was older (median age, 54 years), and again intensive therapy was associated with a higher risk of hypoglycaemia, as well as weight gain. There was a trend to a reduction in myocardial infarction rates, although overall no significant effect on macrovascular disease or all-cause mortality in the initial randomised phase of the trial.⁴

Overweight patients intensively treated with metformin (UKPDS 34) had greater reductions in complications and less weight gain and hypoglycaemia than patients treated with sulfonylureas or insulin (UKPDS 33).⁵

ADVANCE

More recently (2008), the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial investigated adults (mean age, 66 years) with type 2 diabetes and pre-existing macro- or microvascular disease or at least one other risk factor.⁶ The results showed intensive glycaemic control targeting an HbA_{1c} below 48 mmol/mol (6.5%) improved microvascular outcomes (23% reduction), principally nephropathy.⁶ There was no evidence for reduction in macrovascular event rates and no increased risk of mortality with intensive therapy, although the risk of severe hypoglycaemia and hospitalisation was higher.⁶

ACCORD

The Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD) trial was published around the same time as the ADVANCE trial. This study compared intensive glycaemic control HbA_{1c} (below 42 mmol/mol [6%]) versus standard therapy (HbA_{1c} 53 to 63 mmol/mol [7 to 7.9%]) in patients with pre-existing type 2 diabetes (mean age, 62 years) and either risk factors for or established cardiovascular disease.⁷ The results showed tight glycaemic control was associated with higher all-cause mortality and consequently the trial was prematurely discontinued.⁷ There was also a trend, although not significant, to increased cardiovascular mortality in the intensive therapy arm.⁷ Post hoc analyses showed that in the intensive therapy arm, mortality was higher in those with an HbA_{1c} above 69 mmol/mol (8.5%) at baseline.⁸

These findings created some confusion as the increased mortality seen with tight glycaemic control contrasted with the positive outcomes seen with intensive therapy in the other trials.

Abbreviation: HbA_{1c} = glycated haemoglobin.

Individualisation of Glycated Haemoglobin Targets for Adults with Diabetes Mellitus.¹⁰

These recommendations are endorsed by the Royal Australian College of General Practitioners (RACGP) and are available in their and Diabetes Australia's current guidelines, *General Practice Management of Type 2 Diabetes: 2016–18*.¹¹

It is generally accepted that an HbA_{1c} target of 53 mmol/mol (7%) should be aimed for in most cases, with recommended targets tightened (≤ 48 mmol/mol, or 6.5%) or relaxed (≤ 64 mmol/mol, or 8%) in some individuals (Box 2).^{10,11}

Cardiovascular risk of glucose-lowering agents

The link between type 2 diabetes, cardiovascular disease (CVD) and related mortality is well established. Recently a few major trials have investigated the cardiovascular risk of glucose-lowering agents, because of concerns about a lack of long-term safety data in this area. The results of these trials may assist clinicians in choosing agents for patients with both of these issues. The trials are discussed in Box 3.^{12–17}

2. HbA_{1c} TARGETS IN DIFFERENT PATIENT POPULATIONS^{10,11}

- In most people:
 - ≤ 53 mmol/mol (7%)

However,

- In people without known cardiovascular disease, a long duration of diabetes, severe hypoglycaemia or another contraindication, decrease the target to:
 - ≤ 48 mmol/mol (6.5%)
- In people with reduced hypoglycaemia awareness or major comorbidities, the target may increase to:
 - ≤ 64 mmol/mol (8%)
- In people with limited life expectancy, aim for symptom control:
 - target not necessary
- In women planning a pregnancy, aim for the tightest achievable control without severe hypoglycaemia, preferably:
 - ≤ 42 mmol/mol (6.0%)

3. KEY CARDIOVASCULAR RISK TRIALS IN PEOPLE WITH DIABETES^{12–17}

Trials of DPP-4 inhibitors: TECOS, SAVOR-TIMI-53 and EXAMINE

The cardiovascular safety of dipeptidyl peptidase-4 (DPP-4) inhibitors has been investigated in several recent studies. The trial known as Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) investigated sitagliptin versus placebo, in addition to standard care, and cardiovascular outcomes and mortality in patients with type 2 diabetes and established CV disease.¹² The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 trial (SAVOR-TIMI-53) aimed to evaluate saxagliptin versus placebo in patients with type 2 diabetes and high risk for, or pre-existing CV disease; the primary end point was a composite of CV death, MI or ischaemic stroke.¹³ The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care trial (EXAMINE) investigated alogliptin versus placebo in patients with type 2 diabetes after recent acute coronary syndrome (acute MI or unstable angina) for rates of a composite of CV-related death, nonfatal MI or nonfatal stroke.¹⁴

The patients in these trials were aged 61 to 65 years (mean), overweight/obese (BMI, 28.7 to 31 kg/m²) and had disease duration of 7.2 to 11.6 years. Patients in TECOS had better baseline glycaemic control (HbA_{1c} 55 mmol/mol [7.2%]) than those in SAVOR-TIMI-53 and EXAMINE (HbA_{1c} 64 mmol/mol [8.0%]). Overall these trials found DPP-4 inhibitors were not associated with any improvement in CV outcomes, and in one (SAVOR-TIMI-53) there was a significant increase in hospitalisation due to heart failure. The EXAMINE trial showed a trend (not statistically significant) to increased hospitalisation for heart failure.¹⁴

Sitagliptin may therefore be considered safe in patients with pre-existing CV disease, although saxagliptin, and potentially alogliptin, may need caution until further long-term data are available.

Trials of an SGLT2 inhibitor: EMPA-REG OUTCOME

The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME) evaluated empagliflozin, a sodium–glucose cotransporter-2 (SGLT2) inhibitor, compared with placebo, when added to standard care in a population of adults (mean age, 63 years) with type 2 diabetes (57% having had it for more than 10 years) and established CV disease. The primary outcome was CV mortality, nonfatal MI or nonfatal stroke, with a significant reduction seen in the empagliflozin arm.¹⁵ Subgroup analysis in EMPA-REG OUTCOME looked at specific patient groups in terms of these primary end points and found that the primary outcome only retained significance in certain groups. Specifically, patients aged 65 years and older, and those with HbA_{1c} below 69 mmol/mol (8.5%) showed a significant reduction in mortality, nonfatal MI or nonfatal stroke, suggesting these patients are likely to derive most CV benefit from empagliflozin.¹⁵

Trials of GLP-1 receptor agonists: LEADER and ELIXA

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) and Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trials investigated the cardiovascular effects of the glucagon-like peptide-1 (GLP-1) receptor agonists liraglutide and lixisenatide, respectively.^{16,17}

LEADER looked at liraglutide versus placebo, on a background of standard care, in a similar population to EMPA-REG, i.e. adults with type 2 diabetes and elevated CV risk. Liraglutide was associated with lower rates of first occurrence of CV mortality, nonfatal MI or nonfatal stroke.¹⁶ This population (median age, 64.3 years) was predominantly obese (BMI, 32.5 kg/m²) with long-term diabetes (mean, 12.8 years) and suboptimal control (mean HbA_{1c} 72 mmol/mol [8.7%]). The subgroup analyses showed significance was only retained in patients with established CVD and moderate renal impairment (eGFR below 60 mL/min/1.73 m²).

ELIXA investigated lixisenatide versus placebo, in addition to standard care, in patients with type 2 diabetes and previous MI or recent hospitalisation for heart failure. Lixisenatide was not associated with higher rates of major CV events, including heart failure or mortality, than placebo.¹⁷ Patient characteristics were similar to those in the LEADER trial (mean age, 60 years; BMI, 30.1 kg/m²; and duration of type 2 diabetes 9.3 years) although glycaemic control was better in this cohort (HbA_{1c} 61 mmol/mol [7.7%]). It is important to note, however, that this trial showed noninferiority to placebo, not superiority.

Abbreviation: BMI = body mass index; CV = cardiovascular; HbA_{1c} = glycated haemoglobin; MI = myocardial infarction.

4. CASE 1 – A 63-YEAR-OLD MAN ON MONOTHERAPY WITH POOR GLYCAEMIC CONTROL AND CARDIOVASCULAR DISEASE²⁰⁻²³

Case scenario

A 63-year-old man with an eight-year history of type 2 diabetes presents for review. His last review was more than a year ago. He is overweight (BMI, 28.1 kg/m²) and has a history of hypertension, hyperlipidaemia and previous myocardial infarction requiring cardiovascular stents. His current medications include metformin extended-release 2 g daily, aspirin 100 mg daily, atorvastatin 40 mg daily, metoprolol 50 mg twice daily and perindopril 5 mg daily. He does not exercise regularly.

Examination reveals the man's blood pressure is 145/80 mmHg and he has reduced sensation to monofilament in his feet bilaterally although no evidence of ulceration, infection or Charcot deformity. Cardiovascular, respiratory and abdominal examinations are unremarkable. Investigation results are presented in Table A.

What do the results show?

This patient's HbA_{1c} of 62 mmol/mol (7.8%) is above target, indicating suboptimal glycaemic control. He has stage 3A moderate chronic kidney disease (eGFR, 45 to 59 mL/min) and evidence of albuminuria. A repeat urine ACR test should be performed to confirm this abnormality, with two additional first void specimens collected during the next three months.^{20,21} (Two out of three abnormal ACR results are required to confirm albuminuria, and chronic kidney disease is diagnosed if albuminuria persists for at least three months, with or without decreased GFR.²¹) His fasting lipid levels are within range and his liver function test results are normal.

What will you recommend?

A target for HbA_{1c} needs to be agreed. This patient has evidence of microvascular and macrovascular comorbidity. His renal function is indicative of stage 3A moderate chronic kidney disease with microalbuminuria, and he has signs of peripheral neuropathy. These issues suggest the need for tight glycaemic control, although this should be balanced against his history of cardiovascular disease and risk of hypoglycaemia. Based on Australian Diabetes Society guidelines, an HbA_{1c} of 53 mmol/mol (7%) is recommended. The choice of glucose-lowering agent will depend on his comorbidities (overweight BMI, renal impairment) and his preference.

The importance of following the recommended diet and participating in regular exercise should be reiterated, with a goal of reducing his body weight to 76 kg or lower to achieve a BMI below 25 kg/m². This may be difficult to achieve in the short term, although weight loss should be continually encouraged and achievable goals set to begin with.

The patient is not keen on using injectable agents and would prefer oral therapy. He is already taking metformin as first-line pharmacotherapy but in the setting of renal impairment the dose should be

reduced to 1 g daily. His renal function will need monitoring as further deterioration may warrant metformin cessation.

Given his body weight, a weight-neutral agent is preferable. Potential choices for oral therapy include DPP-4 inhibitors, SGLT2 inhibitors and acarbose. Sulfonyleureas and thiazolidinediones can have an unfavourable effect on weight.²² Thiazolidinediones have been associated with heart failure and hence are not ideal choices for this patient. The use of an SGLT2 inhibitor may be useful with his cardiac history, based on findings from the EMPA-REG OUTCOME trial. A GLP-1 receptor agonist would be useful if suboptimal control persists, particularly given the patient's weight, although he is not ready for an injectable agent yet.

You recommend addition of empagliflozin

10 mg daily to metformin 1 g daily, with a plan for review of HbA_{1c} in three months and escalation of therapy at that time if needed. Renal function should also be monitored as eGFR can decline in the first few weeks following SGLT2 inhibitor commencement.²³ A repeat urine ACR test is arranged and the dose of perindopril is increased to 10 mg daily to improve his blood pressure and also because maximum tolerable doses of ACE inhibitor or angiotensin receptor blocker therapy are recommended for patients with diabetic nephropathy to retard disease progression.

Abbreviations: ACR = albumin to creatinine ratio; BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; HbA_{1c} = glycated haemoglobin; SGLT2 = sodium-glucose cotransporter-2 inhibitor.

TABLE A. INVESTIGATION RESULTS FOR CASES 1, 2 AND 3

Investigation	Reference interval	Case 1	Case 2	Case 3
HbA _{1c} (mmol/mol [%])	<48* (<6.5*)	62 (7.8)	70 (8.6)	44 (6.2)
Hb (g/L)	130 to 180 (M), 120 to 160 (F)	135	125	140
Na ⁺ (mmol/L)	135 to 145	138	139	136
K ⁺ (mmol/L)	3.5 to 5.0	4.9	4.1	4.3
eGFR (mL/min)	>90	50	>90	48
Cholesterol (mmol/L)	<4.0 [†]	3.7	5.0	3.5
LDL cholesterol (mmol/L)	<2.0 [†]	1.5	2.6	1.9
HDL cholesterol (mmol/L)	>1.0 [†]	1.6	1.1	1.0
Triglycerides (mmol/L)	< 2.0 [†]	1.2	2.9	1.2
Urine ACR (mg/mmol)	< 2.5 (M), < 3.5 (F)	13	2.3	1.9

Abbreviations: ACR = albumin to creatinine ratio; eGFR = estimated glomerular filtration rate; F = females; Hb = haemoglobin; HbA_{1c} = glycated haemoglobin; K⁺ = potassium; M = males; Na⁺ = sodium.

* Reference interval for diagnosis of diabetes. Target reference range should be individualised.

[†] Recommended target in patients with diabetes.

Interpreting the key cardiovascular risk trials

To date the evidence from these major cardiovascular risk trials of various glucose-lowering agents suggests the relative safety of DPP-4 inhibitors in type 2 diabetes and CVD, albeit a higher risk of heart failure with saxagliptin and possibly alogliptin. SGLT2 inhibitors, specifically empagliflozin, and GLP-1 receptor agonists, specifically liraglutide, appear to confer a CV benefit patients with established CVD. Several key trials investigating other agents within these classes are currently under way.

The findings from these trials, however, need to be interpreted in the context of the populations in which they were conducted. Important points to consider include the age and sex of the patients, the duration of pre-existing diabetes, the presence of comorbidities including microvascular and cardiovascular disease, the initial HbA_{1c} and the use of concomitant therapies. The risk of hypoglycaemia also needs consideration. Furthermore, the results could possibly apply only to the agent trialled, and not necessarily be a class effect.

Treatment options

The past decade has witnessed major advances in treatment options for type 2 diabetes, leading to a shift in the management paradigm. With the rise in prevalence of this condition, there are still a significant number of patients who do not meet current recommendations for glycaemic targets. Analysis of medical records in primary care in Australia from 2005 to 2013 found that 40% of patients had elevated HbA_{1c}.¹⁸ This is in part due to treatment inertia. Health practitioners now have a range of choices in therapy aimed at regulating blood glucose control with concomitant focus on reducing the incidence of specific comorbidities such as obesity and limiting adverse effects. Inevitably, with disease progression, many patients will require insulin therapy, although in the interim there are many available options for glycaemic control.

Most patients with type 2 diabetes are

5. CASE 2 – A WOMAN WITH SUBOPTIMAL CONTROL DESPITE DUAL THERAPY

Case scenario

A 52-year-old woman presents with a suspected UTI. She has a history of type 2 diabetes diagnosed two years ago, previous UTI, asthma, hypertension, obesity and osteoarthritis. Since her last review, six months ago, she has gained 10 kg in weight (current BMI of 31.6 kg/m²). Her medications have remained unchanged for 18 months and include metformin 1 g twice daily, gliclazide modified release 120 mg daily, amlodipine 5 mg daily, paracetamol 1 g three times daily and salbutamol as required. She finds it difficult to exercise because of knee pain. You suspect her diabetes may be poorly controlled and contributing to recurrent UTIs.

Examination reveals the woman's blood pressure is 125/70 mmHg, her heart rate is 72 beats per minute and her BMI is 31.6 kg/m². There is no evidence of peripheral oedema or foot infection, and pulses and sensation are intact. Cardiovascular, respiratory and abdominal examinations are unremarkable. A bedside urinalysis suggests UTI. Investigation results are presented in Table A.

What do the results show?

This patient's HbA_{1c} of 70 mmol/mol (8.6%) is above target despite her taking two oral glucose-lowering agents. Renal function and serum electrolytes are within range. A fasting lipid profile indicates levels of cholesterol and triglycerides are elevated. There is no evidence of albuminuria.

What will you recommend?

A target HbA_{1c} of 48 mmol/mol (6.5%) is recommended based on Australian Diabetes Society guidelines. There is no current evidence of micro- or macrovascular disease, nor significant risk of hypoglycaemia. Diet and exercise are paramount for both glycaemic control and weight management. A target weight of 67 kg will bring her BMI into the healthy weight range (below 25 kg/m²). A goal of 0.5 kg weight loss per week is suggested and the patient is referred to a dietitian. Although it may take some time for a target weight to be reached, and this may be difficult to achieve, any weight loss should be encouraged and commended.

The patient is already using a maximum dose of metformin, appropriately. Gliclazide is not an ideal agent owing to the association of sulfonylurea use with weight gain. However, this patient has been on this medication for 18 months but her weight has increased over a more recent period. She could either cease gliclazide and substitute another agent or add a third agent in an attempt to achieve glycaemic control and then consider withdrawal of gliclazide. The likelihood of achieving her glycaemic target is higher with triple therapy.

After discussion with the patient, you decide to add exenatide as GLP-1 receptor agonists have a favourable effect on weight. The patient agrees to trialling an injectable agent. The expected HbA_{1c} reduction with the addition of exenatide is

11 to 19 mmol/mol (1 to 1.75%) based on available trials, which is useful in this case. Other possible choices would be a DPP-4 inhibitor or acarbose. SGLT2 inhibitors are probably not a suitable choice in this context as although they are associated with weight loss and have blood pressure-lowering effects and, in patients with pre-existing cardiovascular disease (which this patient does not have), cardiovascular benefits, they have been associated with an increased risk of UTI. Although there are no trials comparing all these agents head to head from a weight perspective, GLP-1 agonists appear to have the greatest effect on weight loss.

Insulin could be considered in this patient, with appropriate counselling surrounding healthy weight targets and methods to achieve this. Insulin has unfavourable effects on weight, but its prescription is not always intended to be permanent and therapy can be withdrawn at any point. Using it in combination with other agents minimises the doses required and thus the potential associated weight gain.

The patient is prescribed exenatide 5 µg twice daily in addition to metformin and gliclazide, with a plan for review in one month. If tolerated, the dose of exenatide may then be increased to 10 µg twice daily. The patient is counselled to be aware of symptoms of hypoglycaemia as the combination of these three agents increases her risk. You plan to review her with a repeat HbA_{1c} at three months and consider withdrawal of gliclazide if glycaemic control has improved. Possible adverse effects of nausea, vomiting and the rare but significant risk of pancreatitis are all discussed. A statin is commenced for hyperlipidaemia.

Abbreviations: BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA_{1c} = glycated haemoglobin; SGLT2 = sodium-glucose cotransporter-2 inhibitor; UTI = urinary tract infection.

managed in the primary care setting with specialist involvement where necessary. The first step in management should be establishing the goals of therapy. An individualised glycaemic target should be identified based on patient age, comorbidities and life expectancy.¹⁹ This target should be regularly reviewed and adjusted, as necessary, to match the patient's specific characteristics and their current health status.

Lifestyle modification with dietary advice and an exercise plan should be the first prescription, with particular attention to weight management. An ideal body weight should be recommended, with a plan to achieve this. Although weight loss to target is recognised as challenging, and is not often achieved in practice, any improvement in body weight should be encouraged. Initial goals may focus on small improvements in weight, with both short- and long-term goals set and reviewed at each appointment. Beyond these recommendations, depending on initial glycaemic control at diagnosis or where glycaemic targets are not met, a proactive approach should be exercised with

escalation of combination therapy as needed.

The case studies in Boxes 4 to 6 illustrate the tailoring of treatment to individuals.²⁰⁻²³

Choice of therapy and specific considerations

With an increasing array of treatment options, decisions in therapy may not be simple. Overall the fundamental principle of management is a patient-centred individualised approach. In recognition of the complexity of such decision-making, the Australian Diabetes Society has published a treatment algorithm to assist medical practitioners in both medicine selection and recommendations for glycaemic targets (Figure; algorithm available online at <http://t2d.diabetessociety.com.au>).^{10,11,19}

Specific drug classes currently available include biguanides (metformin), sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, thiazolidinediones, alpha-glucosidase inhibitors (acarbose) and sodium-glucose cotransporter-2 (SGLT2) inhibitors, as well as different insulins with

various lengths of action. A summary of available treatment options is presented in the Table.²⁴⁻³⁹

First-line therapies

Metformin remains the first-line treatment, unless contraindicated. Its suitability as primary therapy is supported by the UKPDS data showing an association with reduced all-cause mortality.⁵ This finding has been repeated in a recent large meta-analysis.⁴⁰

Second- and third-line therapies

Although the choice of second- and third-line agents is less prescriptive than that of a first-line agent, it should be guided by patient comorbidities, adverse effect profile and acceptability of the method of administration. Government subsidy (PBS) is also an important consideration, as cost plays a significant role, particularly where multiple agents are necessary.

Common choices for second-line therapies include sulfonylureas, DPP-4 inhibitors and SGLT2 inhibitors. GLP-1 receptor agonists can also be used second line, although they may be less favoured by patients because they are administered by injection. Specific comorbidities may influence the choice of agent. For example, where weight is a concern, GLP-1 receptor agonists and SGLT2 inhibitors may have a favourable role. If patients have established CVD, sitagliptin will be safe, although the SGLT2 inhibitor empagliflozin may provide benefit. If the risk of hypoglycaemia is of particular concern, sulfonylureas should be dose-reduced, particularly in combination therapy, or avoided. Unless contraindicated or poorly tolerated, metformin should be continued; it should be noted that many agents are available in combination form with metformin. PBS restrictions may stipulate certain combinations must be trialled before other agents can be introduced.

There are now many approved combinations, containing triple oral or combined oral and injectable agents, for use as third-line therapies. Again, metformin should be continued wherever possible.

Insulin may be considered at any stage in

6. CASE 3 – AN ELDERLY MAN AT RISK OF HYPOGLYCAEMIA

Case scenario

A 78-year old man presents for a routine review. He has a history of type 2 diabetes, hypertension, cataracts and a recent diagnosis of Parkinson's disease. He has had two falls in the past year and currently mobilises with a walking aid. His medications include metformin 1 g twice daily, glibenclamide 5 mg daily, levodopa/benserazide 200/50 mg twice daily and perindopril 5 mg daily.

The man appears frail and mobilises slowly with his walking stick. He has obvious Parkinsonian signs. His blood pressure is 110/70 mmHg sitting and 95/65 mmHg standing, and his BMI is 22.5 kg/m². There is evidence of mild peripheral neuropathy on foot examination although the remainder of the examination is normal. Investigation results are presented in Table A.

What do the results show?

The patient's HbA_{1c} of 44 mmol/mol (6.2%) indicates tight glycaemic control. His renal function is mildly reduced, which is of particular concern with the use of glibenclamide and the current dose of metformin. There is no current evidence of albuminuria and his lipids are within range.

What will you recommend?

Given the patient's age, diagnosis of Parkinson's disease, mobility aid, recent falls and evidence of postural hypotension, hypoglycaemia will pose significant risk. Accordingly, you recommend a more relaxed target for glycaemic control with an HbA_{1c} of 58 to 64 mmol/mol (7.5 to 8%).

Glibenclamide, a sulfonylurea, is associated with hypoglycaemia, particularly in the elderly and in the setting of renal impairment. This patient does have evidence of peripheral neuropathy, and although research suggests that tight glycaemic control may reduce the incidence of this, the risks of hypoglycaemia outweigh this issue in this case.

You cease glibenclamide in this patient and you reduce his metformin dose to 500 mg twice daily, with a plan to review his HbA_{1c} in three months. You also cease perindopril for now, in the setting of postural hypotension and relatively low blood pressure.

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

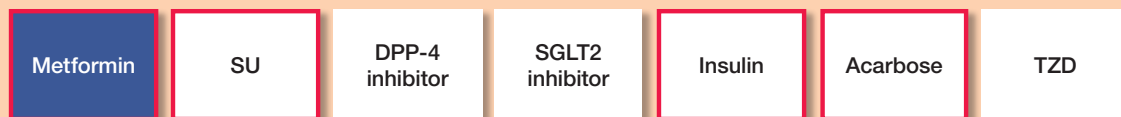
AUSTRALIAN BLOOD GLUCOSE TREATMENT ALGORITHM FOR TYPE 2 DIABETES

All patients should receive education regarding lifestyle measures: healthy diet, physical activity and weight control

Determine the individual's HbA_{1c} target – this will commonly be ≤ 53 mmol/mol (7.0%).

If not at target, or if an HbA_{1c} reduction of ≥ 0.5% is not achieved after 3 months, move down the algorithm.

First line: Metformin is the usual first-line therapy unless contraindicated or not tolerated



If HbA_{1c} target not achieved in 3 months:

- check and review current therapies, stop any that fail to improve glycaemic control
- check patient understanding and self-management
- review use of therapies
- exclude other comorbidities/therapies impacting on glycaemic control
- reinforce lifestyle measures

Second line: If metformin was not used first line, add it now, if not contraindicated

Sulfonylureas (SU) are the usual initial agent to add to metformin. If SU are contraindicated or not tolerated, another agent may be used.



If HbA_{1c} target not achieved in 3 months:

- check and review current therapies, stop any that fail to improve glycaemic control
- check patient understanding and self-management
- review use of therapies
- exclude other comorbidities/therapies impacting on glycaemic control
- reinforce lifestyle measures

Third line: Consider triple oral therapy or addition of GLP-1RA or insulin

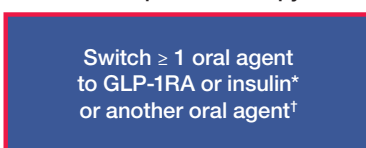


If HbA_{1c} target not achieved in 3 months:

- check and review current therapies, stop any that fail to improve glycaemic control
- check patient understanding and self-management
- review use of therapies
- exclude other comorbidities/therapies impacting on glycaemic control
- reinforce lifestyle measures

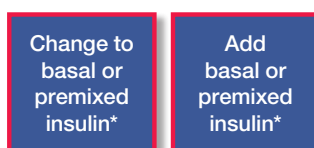
THEN

If on triple oral therapy



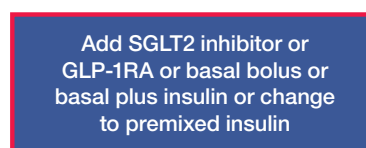
OR

If on GLP-1RA



OR

If on basal insulin*



PBS = Pharmaceutical Benefits Scheme, SU=sulfonylurea, TZD= thiazolidinedione, DPP-4 = dipeptidyl peptidase-4, GLP-1RA= glucagon like peptide 1 receptor agonist, SGLT2 = sodium glucose transporter.

Dark blue boxes indicate usual therapeutic strategy (order is not meant to denote any specific preference) (usual refers to commonly available, evidence based, cost effective therapy). **White boxes** indicate alternate approaches (order is not meant to denote any specific preference). **Red outlines** indicate the classes of glucose lowering agent that include PBS subsidised products.

* Unless metformin is contraindicated, or not tolerated, it is often therapeutically useful to continue it in combination with insulin in people with Type 2 diabetes.

† Switching an oral agent is likely to have the smallest impact on glycaemia.

Figure. The Australian Diabetes Society management algorithm for type 2 diabetes (version v2.4, December 2016; available online at <http://t2d.diabetessociety.com.au>).

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TABLE. TREATMENT OPTIONS FOR TYPE 2 DIABETES²⁴⁻³⁹

Mechanism of action	Use	PBS subsidy restrictions	Effect on HbA _{1c}	Effect on weight	Common adverse effects	Contraindications/precautions
Biguanides (metformin)						
Reduce hepatic glucose output, increase peripheral insulin sensitivity, thus reducing fasting blood glucose	First-line therapy unless contraindicated Start at low dose and titrate up to maximally tolerated dose as needed	Nil	Reduction of approx 12 mmol/mol (1.1%) (monotherapy) ²⁴	Weight neutral	GI upset – patients may require dose reduction or trial of modified release formulation	Reduce dose in renal impairment Contraindicated in severe heart failure, liver or renal impairment (eGFR <30 mL/min)
Sulfonylureas						
Act on pancreatic beta cells to stimulate insulin release in a glucose-dependent manner	Can be used alone as first-line therapy if metformin contraindicated or in combination	Nil	Reduction of approx 17 mmol/mol (1.5%) when used in combination with metformin ²⁵ Systematic review has shown reduction of 17 mmol/mol (1.5%) more than placebo ²⁶	Weight gain	Hypoglycaemia	Caution in elderly, renal impairment or risk of hypoglycaemia
Dipeptidyl peptidase-4 (DPP-4) inhibitors						
Inhibit the breakdown of GLP-1 (an incretin), which inhibits glucagon release, stimulates insulin release and ultimately lowers blood glucose levels Slow gastric emptying	Typically second- or third-line therapy	Must be used in combination with metformin and/or sulfonylurea or with insulin	6 to 7 mmol/mol (0.5 to 0.6%) reduction compared with placebo ^{27,28}	Weight neutral	GI upset, nasopharyngitis, may be self-limiting Some patients experience rash	Rare risk of acute pancreatitis; unclear if this risk is due to DPP-4 inhibitors or to increased background risk in patients with diabetes
Glucagon-like peptide-1 (GLP-1) receptor agonists						
Stimulate the release of insulin, suppress glucagon levels and slow gastric emptying	Typically second- or third-line therapy Useful in overweight/obese patients Injectable agents	Must be part of double or triple therapy with metformin and/or sulfonylurea or triple therapy with metformin and insulin	Reduction of 8 to 12 mmol/mol (0.7 to 1.1%) when added to metformin and/or sulfonylurea ²⁹	Weight loss	Nausea, vomiting, weight loss	Contraindicated in history of pancreatitis or pancreatic cancer Avoid if history of medullary thyroid cancer (only associated in animal studies to date)

(continued on next page)

TABLE. TREATMENT OPTIONS FOR TYPE 2 DIABETES²⁴⁻³⁹ (continued)

Mechanism of action	Use	PBS subsidy restrictions	Effect on HbA _{1c}	Effect on weight	Common adverse effects	Contraindications/precautions
Sodium-glucose cotransporter-2 (SGLT2) inhibitors						
Inhibit SGLT2 (renal) thus facilitating glycosuria and reducing hyperglycaemia Increase urine glucose excretion, facilitating mild osmotic diuresis and loss of calories	May be useful if coexistent CV disease Have mild blood pressure-lowering effects (3 to 5 mmHg systolic)	Must be part of double or triple therapy with metformin, sulfonylurea and/or insulin	Reduction of 6 to 9 mmol/mol (0.5 to 0.8%) compared with placebo ³⁰	Weight loss	Vaginal candidiasis, UTI, dehydration and dizziness	Caution in history of recurrent UTI, female genital mycotic infections Contraindicated if eGFR <45 mL/min (empagliflozin), <60 mL/min (dapagliflozin)
Alpha-glucosidase inhibitors (acarbose)						
Inhibit alpha glucosidase, thus reducing intestinal carbohydrate absorption	Typically used as add on therapy	Nil	Mean reduction of 9 mmol/mol (0.8%) compared with placebo ³¹	Weight neutral	Bloating and flatulence	Should be avoided in patients with inflammatory bowel disease or those prone to intestinal obstruction Also contraindicated in cirrhosis
Thiazolidinediones						
Activate PPAR-γ (peroxisome proliferator-activated receptors) and reduce circulating fatty acid and lipid levels, thereby decreasing insulin resistance and thus lowering blood glucose levels ^{19,32}	Typically third-line therapy in combination May be useful in some patients in combination with metformin and sulfonylurea	Must be used in combination with metformin and/or sulfonylurea	Reduction of 11 to 21 mmol/mol (1.0 to 1.9%) when added to metformin and sulfonylurea ³²⁻³⁶	Weight gain	Weight gain, peripheral oedema	Associated with cardiac morbidity ³⁷ Can worsen cardiac failure and cause weight gain Increased fracture rate in women ³⁸ Increased risk of bladder cancer associated with pioglitazone, although does not appear to be a class effect ³⁹
Insulins						
Supplement endogenous insulin production to lower blood glucose	Can be used at any stage in diabetes management, depending on HbA _{1c} level, patient comorbidities and preference	Nil	HbA _{1c} lowering dose-dependent	Weight gain	Hypoglycaemia	No specific contraindications Hypoglycaemia dose-dependent Caution in renal failure, use lower starting doses

Abbreviations: CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; HbA_{1c} = glycated haemoglobin; SGLT2 = sodium-glucose cotransporter-2; UTI = urinary tract infection.

therapy, particularly where glycaemic control is significantly poor ($\text{HbA}_{1c} > 75 \text{ mmol/mol}$ [9%]). Insulin has often been used in combination therapy with metformin, although more recently has been approved for use in combination with DPP-4 inhibitors, GLP-1 receptor agonists and SGLT2 inhibitors. Weight gain is a recognised side effect of insulin, although this should not necessarily deter its prescription. In combination with other agents, insulin can be used at lower doses, thus minimising weight gain. Additionally it can be withdrawn at any point depending on the individual patient, and thus does not need to be used in an ongoing sense if effects are unfavourable.

Treatment of specific patient groups

Renal failure

The choice of treatment for patients with type 2 diabetes and renal failure is limited because of altered drug metabolism and associated risks of adverse effects, including hypoglycaemia. Such considerations become

more important with advancing chronic kidney disease (CKD), particularly when estimated glomerular filtration rate (eGFR) is below 30 mL/min (stages 4 and 5 CKD), and medications may require dose reduction or cessation if contraindicated.

Metformin is contraindicated if eGFR falls below 30 mL/min because of a risk of lactic acidosis. Sulfonylureas have a higher risk of hypoglycaemia with renal impairment. SGLT2 inhibitors rely on renal function for their mechanism of action and should be avoided if eGFR is below 45 to 60 mL/min, depending on the agent. Within the class of DPP-4 inhibitors, sitagliptin can be used up until stage 4 CKD with dose reduction and linagliptin can be used regardless of eGFR and can be used in patients on dialysis.¹⁹ Insulin is safe to use, but down-titration of dose may be necessary.

Elderly patients

In elderly patients, glycaemic control should be individualised based on life expectancy,

polypharmacy and the risk of hypoglycaemia. In many cases, symptom control should be the sole focus of therapy. A decline in renal function, often seen in this age group, requires caution or dose reduction with multiple therapies.

Conclusion

The key principle in managing type 2 diabetes is individualised treatment. Metformin remains the first-line recommended therapy, unless contraindicated, and insulin may be commenced at any stage in therapy. Beyond these recommendations, clinicians have a wide choice in management options. Targets for HbA_{1c} and treatment choices should be guided by patient comorbidities, life expectancy, acceptability of administration, cost and patient preference. **MT**

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

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Type 2 diabetes

Tailoring a treatment approach

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