

Medical management of glycaemia

Recommendations

Recommendation	Reference	Grade*
Glucose-lowering medication in people newly diagnosed with type 2 diabetes		
A person-centred approach should be used to guide the choice of glucose-lowering medication. Considerations include comorbidities (atherosclerotic cardiovascular disease, heart failure, chronic kidney disease), hypoglycaemia risk, impact on weight, cost, risk for side effects and patient preferences	1 American Diabetes Association, 2019	E†
Healthy behaviour interventions should be initiated at diagnosis	2 Diabetes Canada, 2018	B, level 2
If glycaemic targets are not achieved using healthy behaviour interventions alone within three months, glucose-lowering therapy should be added to reduce the risk of microvascular complications	2 Diabetes Canada, 2018	A, level 1A
Metformin should be chosen over other agents due to its low risk of hypoglycaemia and weight gain	2 Diabetes Canada, 2018	A, level 1A
Individuals with metabolic decompensation (eg marked hyperglycaemia, ketosis or unintentional weight loss) should receive insulin with or without metformin to correct the relative insulin deficiency	2 Diabetes Canada, 2018	D, consensus
All healthcare practitioners who initiate or educate patients on injectable glucose-lowering medications should be familiar with, and follow, the recommended guidelines	RACGP Diabetes Handbook working groups, 2020	Consensus
Advancing treatment		
Dose adjustments to, and/or addition of, glucose-lowering medications should be made in order to attain target glycosylated haemoglobin (HbA1c) within 3–6 months	2 Diabetes Canada, 2018	D, consensus
If glycaemic targets are not achieved, other classes of glucose-lowering agents should be added to improve glycaemic control	2 Diabetes Canada, 2018	B, level 2
*Refer to ' Explanation and source of recommendations ' for explanations of the levels and grades of evidence.		
†E = expert opinion: recommendation in which there is no evidence from clinical trials, in which clinical trials may be impractical, or in which there is conflicting evidence.		

Introduction

In addition to lifestyle modification, most people with type 2 diabetes will eventually require pharmacotherapy to achieve long-term glycaemic control and prevent complications of diabetes. Patients who are symptomatic of hyperglycaemia may need to start medication without delay, in addition to ongoing lifestyle support.

The benefits of management of hyperglycaemia for the prevention of microvascular complications have been demonstrated in randomised clinical trials.³⁻⁵

The choice, order and combination of medications used is based on:

- individualised goals for glycaemia (refer to the section 'Glucose monitoring')
- evidence of improved clinical outcomes
- consideration of potential adverse effects
- patient choice and capacity.

The above should all be taken into consideration when implementing the treatment recommendations in these guidelines.

Note: Hyperglycaemia-related metabolic dysfunction (eg hyperosmolar states or ketosis) constitutes a medical emergency, and may be present at diagnosis in type 2 diabetes. Information about symptoms and emergency management of hyperglycaemia is available on [The Royal Australian College of General Practitioners' \(RACGP's\) website](#).

Clinical context

Glucose-lowering medicines

Many glucose-lowering medicines are available (Table 1). To navigate the many options, the Australian type 2 diabetes management algorithm (Figure 1) was developed by the Australian Diabetes Society in consultation with all key stakeholders, including the RACGP.

Although algorithms are designed to help navigate choice, applying the principles of patient-centred care might mean that choices suggested by algorithm are not always appropriate.

Also note that high-quality clinical trials of the combination therapies that are suggested in current algorithms for glucose treatment in type 2 diabetes may be lacking. Management is also increasingly informed by the outcomes of trials for sodium glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), for which long-term data are emerging with respect to both potential benefits and harms.⁶⁻⁸

Prescribing algorithms for type 2 diabetes suggest multiple ways of combining agents. Always consult the Pharmaceutical Benefits Scheme (PBS) when combining therapy, as restrictions and reimbursements may change.

Table 1 outlines the clinical considerations for choosing glucose-lowering medications. An evidence table summarising properties of these medications is provided with the full Australian type 2 diabetes management algorithm (Figure 1).

Table 1. Clinical considerations when choosing diabetes medications

Clinical outcome	Medication effects on clinical outcomes			
	Metformin	Sulfonylurea (SU)	Dipeptidyl peptidase-4 inhibitor (DPP-4i)	Acarbose
Patients with established or at high risk of CVD (refer to the section 'Type 2 diabetes and cardiovascular risk')	Neutral effect ³	Increased risk when compared with metformin monotherapy (excluding gliclazide), but neutral when used in combination with metformin ⁹	Neutral effect ^{7,10-13} Refer to Note A	Neutral effect ¹⁴
Patients at risk of hypoglycaemia	Lower rates compared to SU ⁹	Higher clinical risks, both as monotherapy and in combination with other agents ⁹ Gliclazide – fewer hypoglycaemia episodes versus other SUs ¹⁵ Glibenclamide – higher rates of hypoglycaemia, especially in older people ¹⁶	Lower rates compared to SU ⁹	Neutral effect
Patients at risk of gastrointestinal conditions (eg IBS, IBD and gastroparesis)	Known intolerance as monotherapy or combination therapy – diarrhoea ^{9,17}	Neutral effect	Neutral effect	Known intolerance – bloating and flatulence [†]
Patients in whom stabilisation of BMI or weight loss is desired	Neutral effect	Neutral effect (gliclazide) ¹⁸ Modest weight gain (other SUs) compared with metformin monotherapy ⁹	Neutral effect	Neutral effect
Patients with renal impairment (eg lowered CrC*)	Reduce dose by 50% with eGFR 30–60 Contraindication with CrC <30 mL/min ¹⁷	Contraindication if CrC <15 mL/min Hypoglycaemia risk increases	Safe with dose reduction but linagliptin can be used in all stages (no dose reduction) Refer to Note B	Contraindication in severe renal impairment [†]
Other class-specific information	Monotherapy or combination with other agents (DPP-4i or SGLT2i) is available to reduce 'pill burden'	The Australian algorithm (Figure 1) suggests SU may be used as monotherapy or combined with other agents	Contraindication – do not use with a GLP-1 RA Increased hospitalisation for heart failure with saxagliptin	

Table 1. Clinical considerations when choosing diabetes medications

Clinical outcome	Medication effects on clinical outcomes			
	Thiazolidinedione (TZD)	Sodium glucose co-transporter 2 inhibitors (SGLT2i)	Glucagon-like peptide-1 receptor agonists (GLP-1 RAs)	Insulin
Patients with established or at high risk of CVD (refer to the section 'Type 2 diabetes and cardiovascular risk')	Contraindication if symptomatic heart disease, including heart failure ^{19§} Pioglitazone is the preferred TZD	Selective benefit, depending on individual drug choice ²⁰	Selective benefit, depending on individual drug choice ²¹	Neutral effect ^{3,4,22}
Patients with risk from hypoglycaemia	Lower rates compared to SU ⁹	Lower rates compared to SU ⁹	Lower rates compared to SU ⁹	Higher clinical risks as monotherapy and in combination with other agents ^{22,23}
Patients at risk of gastrointestinal conditions (eg IBS, IBD and gastroparesis)	Neutral effect	Neutral effect	Known intolerance – nausea and vomiting, diarrhoea ⁹	Neutral effect
Patients in whom stabilisation of BMI or weight loss is desired	Modest gain compared with other dual combination therapies ⁹	Modest weight loss (in monotherapy, plus in combination with metformin versus metformin with alternate dual oral drug combinations) ^{9#}	Weight loss (in monotherapy, plus in combination with metformin versus metformin with alternate dual oral drug combinations) ^{9,24,25***}	Modest gain ^{9,22,23,26}
Patients with renal impairment (eg lowered eGFR)	Neutral effect	Glycaemic-lowering efficacy decreases, thus contraindicated with renal impairment (eGFR ≤45 mL/min) ^{††}	Contraindication eGFR <30 mL/min (dulaglutide <15)	No contraindication, but hypoglycaemia risk increases
Other class-specific information	Increased atypical fractures (relative risk 1.57), ²⁷ with women more at risk than men [§] Pioglitazone is contraindicated in individuals with bladder cancer or un-investigated haematuria [§]	Modest lowering of BP ⁹ Increased genitourinary infections (especially females) Refer to Note C Less common – euglycaemic diabetic ketoacidosis ^{††} (refer also to discussion of surgery in the section 'Managing risks and other impacts of type 2 diabetes')	Once-weekly formulations are available Contraindication – combination with a DPP-4i	Dose required to be titrated to glycaemic goals while mitigating glycaemic variability and hypoglycaemia

BMI, body mass index; BP, blood pressure; CrC, creatinine clearance; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; IBS, irritable bowel syndrome; IBD, inflammatory bowel disease

*The product information of most agents refers to CrC as a measure of kidney function. [Kidney Health Australia](#) offers a conversion to eGFR.

†Acarbose product information is available from the [Therapeutic Goods Administration \(TGA\)](#).

‡CrC <25 mL/min.

§Pioglitazone product information is available on the [TGA](#) website.

||Exenatide product information is available on the [TGA](#) website.

#Dapagliflozin product information: -2.14 kg as an add-on to metformin versus placebo at 104 weeks; empagliflozin: -1.63 kg and -2.03 kg at doses 10 mg and 25 mg respectively as an add-on to metformin at 24 weeks.

**Exenatide -1 kg to 3.9 kg in comparative trials with combinations including metformin and SU and TZD.

††Check renal function and individual medication product information before prescribing.

‡‡The [Australian Diabetes Society](#) has a safety advisory for SGLT2i use and the risk of diabetic ketoacidosis.

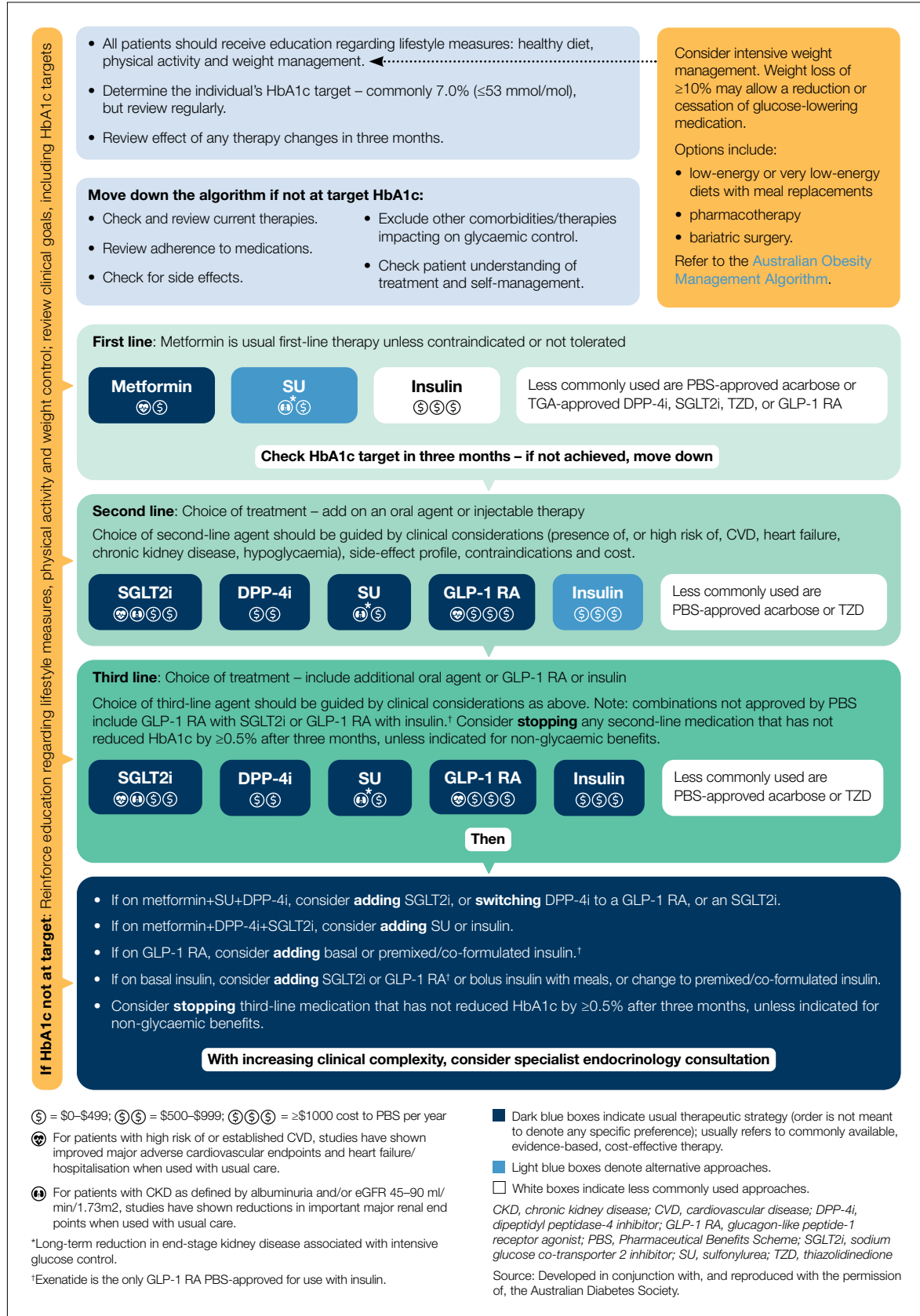
Note A. DPP-4i and heart failure: In the SAVOR-TIMI 53 trial, hospitalisations for heart failure (a secondary outcome) increased with saxagliptin with a non-significant (statistically) trend to increased heart failure with alogliptin. In contrast, cardiovascular outcomes trials of sitagliptin and linagliptin failed to show any heart failure signal.⁷

Note B. DPP-4i: All except linagliptin (no dose reduction) as this is hepatically metabolised.

Note C. All classes: The US Agency for Healthcare Research and Quality (AHRQ) review⁹ determined **no** moderate-to-high levels of evidence for the following adverse events (this does not mean no risk):

- lactic acidosis (metformin)
- urinary tract infections/fractures/volume depletion (SGLT2i)
- pancreatitis (DPP-4i and GLP-1 RA)
- bladder cancer risks (pioglitazone)
- thyroid cancer (GLP-1 RA).

Figure 1. Australian type 2 diabetes management algorithm



In practice

Commencing glucose-lowering therapy

Healthy eating, physical activity and education remain the foundation of all type 2 diabetes treatment programs.

If acute metabolic decompensation appears (sudden weight loss, polydipsia, polyuria, severe fatigue), assess for hyperglycaemic emergencies. If present, or uncertain, seek specialist assistance.

If lifestyle modification is not effective in meeting glycaemic targets within three months, metformin is the first choice unless contraindicated or not tolerated.

Second-line agents (added to existing metformin) may be necessary and should be chosen using an individualised approach, noting that agents work in different ways and should be chosen to work synergistically.

The choice of second-line and subsequent medication choices should be informed by:

- the patient's clinical profile – in particular, renal function status and high-risk, or presence, of CVD
- the likely efficacy of the agent with respect to the magnitude of glycaemic lowering required
- issues that might affect safety, such as hypoglycaemia risk or agent-specific side effects
- tolerability
- cost
- the patient's preferences and abilities to engage in the proposed treatment
- prioritisation of weight-management goals
- emerging and evolving data on new medications and whether medication combinations are available (may assist adherence).

Figure 1 provides options based on consideration of efficacy, non-glycaemic effects (eg effects on cardiovascular and renal outcomes), side effects and cost.

Start with the correct dose of each medication and review on an individual basis at least every 3–6 months, keeping in mind the patient's individual glycosylated haemoglobin (HbA1c) target.^{1,28}

Practice Point: What if medication is not working? The ‘review rule’

The review rule is a call to action. In addition to replacing or intensifying therapies, consideration should also be given to de-prescribing when appropriate.

If, despite optimisation of medication or lifestyle intervention, glycaemic objectives are not being met after three months (six months at the most) **review** and:

- check the patient’s understanding of the medication, its indication and dosing regimen (health literacy)
- assess persistence and adherence to the therapeutic regimen, including lifestyle modification
- exclude potential confounders, such as occult infection (eg urinary), medications that might interfere with glucose control (eg steroids, some antipsychotics) or the presence of unmanaged obesity
- consider alternative diagnoses if not done previously, such as latent autoimmune diabetes of adults (LADA) or maturity-onset diabetes of the young (MODY)
- assess tolerability and safety, particularly hypoglycaemia, and other factors such as planning for pregnancy or adverse effects that might impact patient engagement.

The review rule emphasises that optimisation of the current regimen, including lifestyle modification, should be implemented before advancing through additional glucose-lowering medicines to achieve HbA1c targets within 3–6 months.

Safety

Each class of glucose-lowering medication may have common and uncommon side effects that affect quality of life and require careful clinical reassessment. Examples include hypoglycaemia and weight gain with sulfonylureas and insulin,⁹ and mycotic infections or euglycaemic diabetic ketoacidosis with SGLT2 inhibitors.

Some patient groups (eg older people and those with multiple comorbidities) may not be represented in the published clinical outcome trials of newer diabetes agents, so caution should be exercised when considering choice of agents for these patients.

When used as monotherapy or in combination, metformin, acarbose, glitazones, GLP-1 RA, DPP-4i and SGLT2 inhibitors have a low propensity for causing hypoglycaemia.

Of the sulfonylureas, gliclazide is less likely to cause hypoglycaemia than long-acting sulfonylureas (eg glimepiride) or sulfonylureas with renally excreted metabolites (eg glibenclamide).^{29,30}

Special care needs to be taken with those at increased risk of hypoglycaemia and renal impairment, especially older people.

People with diabetes who drive may need to notify their state motor vehicle licensing authority of their condition, as medications can affect driving performance. For more information, refer to the discussion on driving in the section ‘[Managing risks and other impacts of type 2 diabetes](#)’ or refer to section 3.3.2 of Austroads and National Transport Commission’s [Assessing fitness to drive](#).

Insulin

The use of insulin can improve glycaemic control in most people, but any benefits need to be balanced against increased risks of hypoglycaemia and possible weight gain.²⁶

International and Australian guidelines suggest considering a GLP-1 RA before commencing insulin, unless a person has extreme hyperglycaemic symptoms or an HbA1c of >11%.³¹ GLP-1 RAs are associated with weight loss as well as sparing insulin dose. Limitations to this approach include cost, possible side effects of GLP-1 RAs (nausea), and TGA or PBS restrictions on GLP-1 RA use in combination with other therapy that do not apply to insulin.

Side effects of insulin therapy

Rare adverse events associated with the use of insulin have been reported in observational studies. Such events include congestive heart failure, oedema, lipodystrophy, allergic reactions, reversible transaminitis, reversible nephrotic syndrome and β -cell destruction.³²

Common side effects include hypoglycaemia and weight gain. Risk factors for hypoglycaemia include:

- inappropriate dose
- timing or type of insulin (refer below)
- incorrect injection technique (eg injecting insulin intramuscularly, rather than subcutaneously, can increase absorption rates by 50%)
- missing meals, or meals with no or insufficient carbohydrate
- alcohol intake
- exercise or unplanned physical activity
- weight loss
- treatment with agents potentiating hypoglycaemia (eg sulfonylureas)
- decreased insulin clearance (eg renal failure)
- changes to other medications (eg reducing or ceasing steroids).

Strategies for preventing hypoglycaemia in patients include education about hypoglycaemic symptoms, structured self-monitoring of blood glucose (SMBG), discussing and individualising glycaemic goals, and continued team-based support.³²

Weight gain is variable on initiation of insulin and may accompany initial titration such that weight gain may eventually level off. Slower titration can lead to slower weight gain.

Strategies to address weight include:

- referral to a credentialled diabetes educator (CDE) and/or accredited practising dietitian (APD)
- review of other clinical conditions that may impact glycaemic control, such as depression, occult malignancy, thyroid disease
- review of medications that may contribute to weight gain
- advice on increasing physical activity.

Early insulin intervention

Guidelines outlining the use of insulin in acute hyperglycaemic emergencies (including ketosis-inducing and hyperosmolar crises) are available.^{33,34} The use of insulin in these cases may be life-saving, and reassessment of long-term use can occur on metabolic stabilisation.

Insulin types

Refer to [Appendix 1. Types of insulin available](#).

Insulin delivery options

A range of devices are available to deliver insulin, including insulin pens, syringes and pumps. Choice will depend on patient preference, need and ability to self-manage injections. A CDE or a diabetes nurse practitioner can help provide patient support.

Insulin pens are the most common way of administering insulin, as they make multiple daily injection schedules much easier and allow people to be more flexible in their self-management.

There is mounting evidence of selective beneficial effects of using insulin pumps and insulin patch pumps in people with type 2 diabetes – refer to the section '[Use of technology in type 2 diabetes management](#)'.

The National Diabetes Services Scheme (NDSS) provides subsidised access to insulin pump consumables for people with type 1 diabetes. For people with type 2 diabetes, some health funds cover insulin pumps, but consumables need to be self-funded.

Recommendations for delivery of insulin and non-insulin injectable medications

Using the correct delivery technique to ensure the optimal effect of insulin and GLP-1 RAs is critical to achieving optimal control of diabetes and reducing the risk of some adverse effects of injectable medications.

The following recommendations for insulin delivery are based on the Forum for Injection Technique and Therapy Expert Recommendations (FITTER).³⁵

- Single use of pen needles and syringes is recommended (lipohypertrophy has been associated with reuse of pen needles and syringes).
- Shorter (size 4 mm or shortest available) needles applied to either the abdomen, thigh or buttock are adequate for most adults using insulin pen devices and will lessen the risk of intramuscular injection.
- Lipohypertrophy and lipodystrophy may occur with repeated insulin injections into the same site, and this can affect insulin absorption. This problem is overcome by ensuring rotation of injection sites.

Full recommendations are available on the [Mayo Clinic](#) website.

More information can be found in the *Australian Journal of General Practice (AJGP)* article '[Teaching patients with type 2 diabetes to self-administer insulin](#)'.³⁶

When should patients start insulin?

General practitioners (GPs) should anticipate and proactively address the patient's (and their own) reluctance to start insulin therapy. Early after a diagnosis of diabetes, it is important to discuss with patients that insulin may be used at some point to manage their diabetes.

With the appropriate insulin regimen, insulin therapy can be well managed in general practice, with patients achieving better HbA1c control, fewer hypoglycaemic episodes and less weight gain, thus alleviating many patient concerns.³⁷

Insulin is one of the most effective glucose-lowering agents for type 2 diabetes, and can be titrated to suit the individual patient's requirements. Commencement should not be delayed if hyperglycaemia and symptoms cannot be controlled adequately by a patient's existing treatments. Recent evidence suggests that people who decline treatment with insulin when it is recommended to them can take longer to achieve HbA1c targets.³⁸

Importantly, insulin is not the end of the road for the person with diabetes, nor does it represent therapeutic or patient failure.

Insulin should be initiated in patients with type 2 diabetes who are taking maximal doses of non-insulin glucose-lowering medicines and who have suboptimal glycaemic control (HbA1c or blood glucose above individualised target), whether they are asymptomatic or symptomatic.^{31,39}

Insulin therapy may remain an alternative for older or nursing home patients, even in end-of-life care, with HbA1c >9% (75 mmol/mol), especially if control of symptomatic hyperglycaemia is difficult.

Before starting insulin

Ensure that other possible causes of hyperglycaemia have been addressed (eg lifestyle, non-adherence to non-insulin glucose lowering medicines, other medications or medical conditions).⁴⁰

Discuss with patients the benefits and costs of using insulin for better glycaemic control. Referral is recommended to a CDE and/or APD to provide the necessary support and education to the person with diabetes in the lead-up to insulin initiation.

A GP or CDE can complete the NDSS medication change registration form to allow patients to access syringes or pen needles through the NDSS scheme.

The NDSS has an [information booklet](#) for people with type 2 diabetes who are starting insulin.

Patient education

Initial management planning and education (with both patients and carers) should cover:

- self-management – timing and frequency of SMBG, timing of meals, dose adjustment
- the impact of diet, in particular carbohydrate content (both type and amount)
- the effects of altered eating patterns, such as for religious fasts or weight loss strategies (eg intermittent fasting, 5:2 diets, very-low-calorie diets)
- the impact of physical activity
- hypoglycaemia management
- insulin delivery techniques (Box 1)
- weight management and the mitigation of weight gain with insulin therapy
- sick day management (refer to the section '[Managing risks and other impacts of type 2 diabetes](#)')
- exercise, illness and travel considerations
- identification, roads and maritime services notifications.

This should be followed up regularly with structured education sessions.

Box 1. Insulin delivery

Fundamental information for patients about insulin delivery includes:

- insulin can be stored at room temperature for up to one month
- pre-mix insulin must be resuspended prior to each use
- insulin pen needles should be used only once, as re-use increases the risk of lipohypertrophy⁴¹
- when using a new insulin pen needle, use 1–2 units to expel air prior to dialling up the prescribed dose
- the abdomen is the preferred site for injecting
- insulin needs to be injected only into subcutaneous tissue – injecting into muscle can not only be painful, but can increase the absorption rate of insulin⁴²

Patients should also be educated about:

- how to [safely dispose](#) of used needles
- how to rotate injection sites – patients should be taught and provided with an easy-to-follow injection site rotation plan, reviewed regularly, to reduce risk of lipohypertrophy⁴³
- how to time insulin injections
- the importance of regular inspection of injection sites.

Initiating insulin

All insulins can work effectively.³⁷ Selecting an insulin for initiation will depend on patient as well as disease characteristics. At the selection of the insulin preparation, consider which injecting device is most suitable for the patient.

Set an individualised target (refer to the section '[Glucose monitoring](#)'), following the principle of 'start low, go slow' to gain patient confidence and reduce the risk of hypoglycaemia.⁴⁴

Select one of two insulin schedules:

- basal insulin (eg glargine U100 or U300) once daily, irrespective of meals
- co-formulated insulin (eg degludec–aspart) or premixed (biphasic) insulin (eg lispro–lispro protamine or aspart–protamine insulin) once daily before the largest carbohydrate-containing meal of the day. Premixed insulins have various combinations of intermediate-acting basal insulins and rapid-acting insulins. Common combinations are 25/75, 30/70 and 50/50 (rapid-acting/basal insulins), by percentage.

Basal insulin alone has a slightly lower risk of hypoglycaemia, especially if the fasting glucose is consistently above target.^{31,45}

Premixed or co-formulated insulin may be more appropriate and simpler for a patient where fasting and postprandial glucose are both consistently elevated.

Dosage adjustment can be more complex with premixed and co-formulated insulins, as both insulin components are adjusted simultaneously, possibly increasing the risk of hypoglycaemia and weight gain compared with basal insulin.^{45,46}

Non-insulin glucose-lowering medicines should generally be continued, as:

- cessation of non-insulin glucose-lowering medicines before blood glucose targets are achieved may result in significant hyperglycaemia⁴⁴
- ongoing use can mitigate weight gain (particularly SGLT2i and GLP-1 RAs)³¹
- ongoing use may be insulin-sparing and can reduce the risk of hypoglycaemia as well as hyperglycaemia.⁴⁴

Careful review of use of sulfonylureas should be considered if risks of hypoglycaemia are present (commencing insulin in older people, or up-titration of insulins containing prandial/rapid-acting insulins).

A low starting dose for premixed, co-formulated or basal insulins of 10 units or 0.1–0.2 units/kg in the evening will usually be a safe dose; **however, titration is needed**, as this low dose will be insufficient for achieving glycaemic targets in most people.

[Appendix 2. Guide to insulin initiation and titration](#) provides detailed information about insulin doses, titration and intensification.

Resources

The **Australian Diabetes Educators Association** has produced the [Clinical guiding principles for subcutaneous injection technique](#).

The **National Diabetes Services Scheme** has produced a [fact sheet](#) for people with type 2 diabetes starting on insulin.

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