# Best Practice

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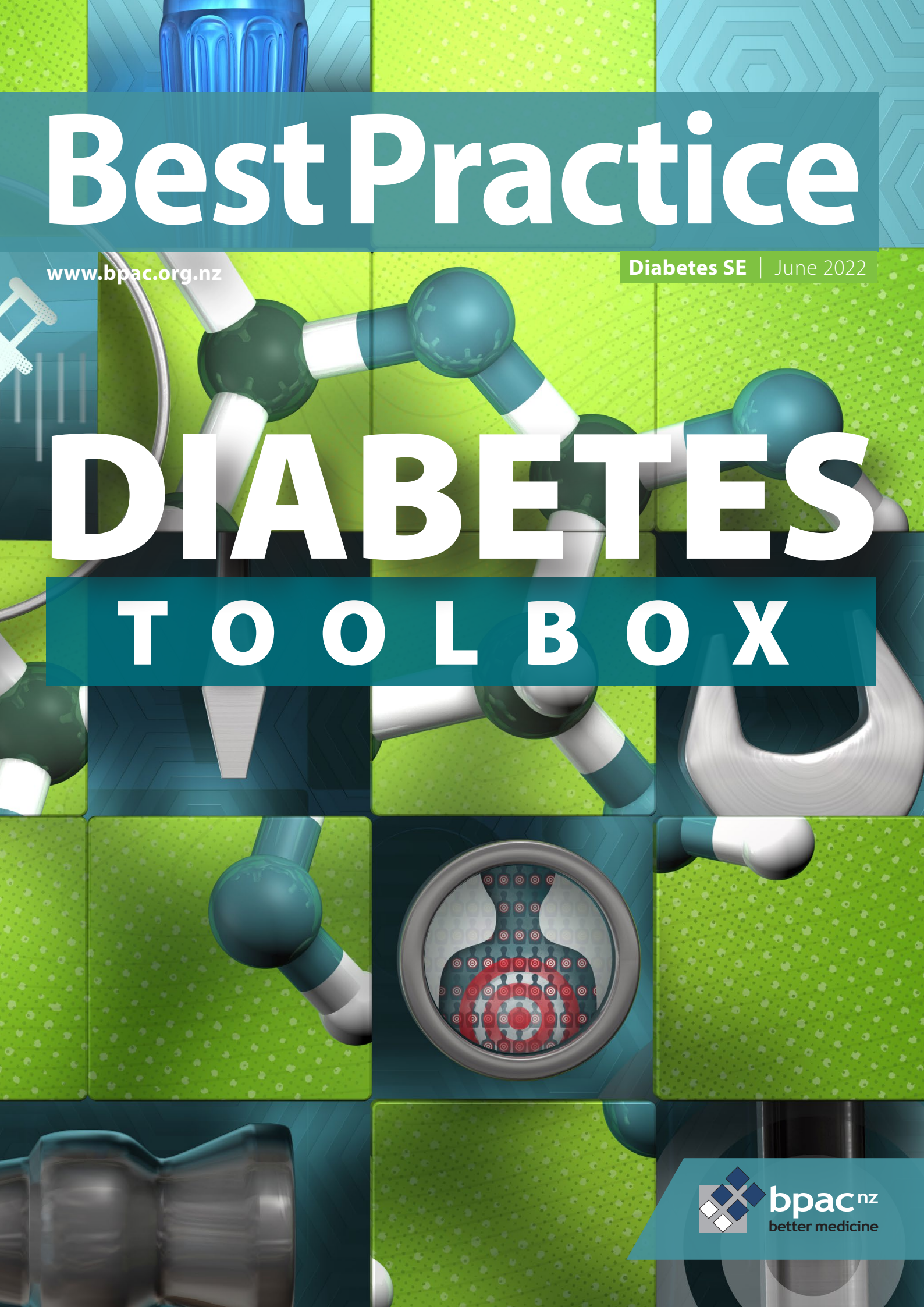
Diabetes SE | June 2022

# DIABETES

## TOOLBOX



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# Best Practice

**Diabetes SE** June 2022




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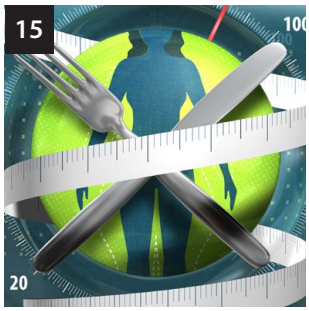


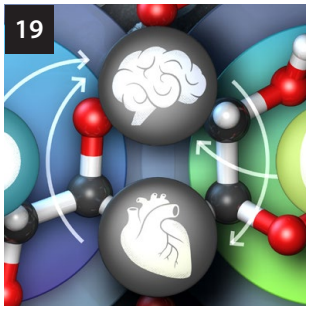


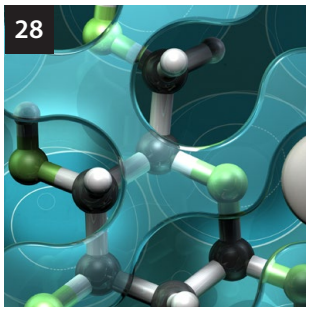


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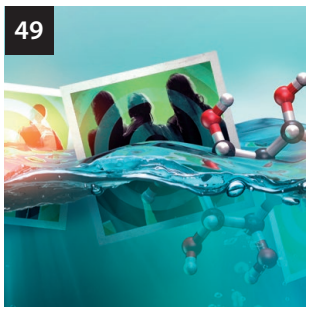





## Clinician's Notepad: type 2 diabetes

**Screening and diagnosis**

- Test $HbA_{1c}$ in people at high risk of type 2 diabetes of any age; the threshold for diagnosis is:
  - $HbA_{1c} \geq 50$ mmol/mol
  - $HbA_{1c}$ 41 – 49 mmol/mol classified as "pre-diabetes"

**Management**

- Select an appropriate glycaemic target based on patient age, co-morbidities, duration of diabetes, history of hypoglycaemia and overall health status:
  - $HbA_{1c} < 48$ mmol/mol, appropriate for younger people, e.g. aged < 40 years
  - $HbA_{1c} < 53$ mmol/mol, appropriate for most people
  - $HbA_{1c}$ 54 – 70 mmol/mol, appropriate if hypoglycaemic risk outweighs benefits of lower target
- Follow a stepwise treatment progression:
  - Step 1: Lifestyle interventions + metformin (initiate at diagnosis)
  - Step 2: Add a second non-insulin glucose-lowering medicine, i.e. empagliflozin, dulaglutide, vildagliptin, a sulfonylurea or pioglitazone; a third medicine can be added instead of stepping up to insulin
  - Step 3: Add insulin (isophane insulin appropriate for most patients)
  - If $HbA_{1c} > 64$ mmol/mol at diagnosis, initiate two glucose-lowering medicines; if $HbA_{1c}$ very high, e.g. 80 – 90 mmol/mol, initiate insulin
- Check adherence to the existing medicine regimen and diet and physical activity approaches before stepping up pharmacological treatment

- Encourage weight loss at any step to induce remission, slow progression, step down treatment intensity or delay treatment escalation
- Encourage consumption of low calorie and low GI foods, increase vegetable intake and minimise dietary fat, sugar and alcohol
- Connect patients to services that can assist with lifestyle changes and provide support
- Consider referral for bariatric surgery if BMI between 35 – 55 kg/m$^2$* to assist with weight loss
- If patients are transitioning from a paediatric service, establish who is responsible for the patient's diabetes care and ensure they are followed up regularly

* Referral criteria may differ; check with your local DHB

**Choosing a Step 2 medicine**

- Consider contraindications, co-morbidities, risk of hypoglycaemia, effects on weight, medicines interactions, adverse effects and eligibility for funding
- Empagliflozin or dulaglutide are preferred for people with established CVD or at high risk (including Māori and Pacific peoples), or with heart failure or diabetic kidney disease
- Vildagliptin is preferred for patients who are not eligible for funded empagliflozin or dulaglutide treatment (and are not self-funding treatment)
- Consider other prescribed medicines and how additional diabetes medicines might affect adherence

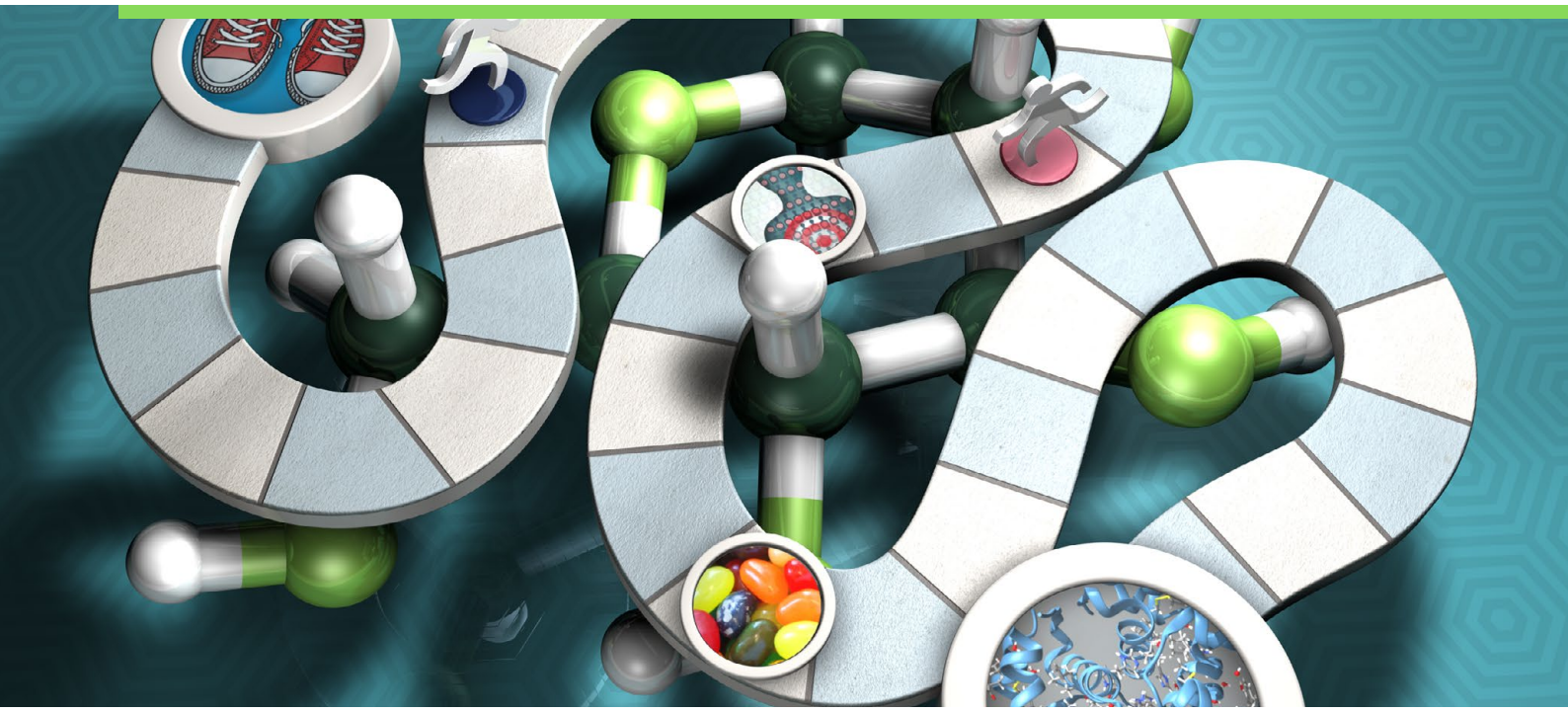
**Initiating insulin**

- Initiate once-daily basal insulin, injected at night; isophane insulin is appropriate for most patients
- Determine initial basal insulin dose using body weight:
  - 0.1 units/kg daily if at least one of: $HbA_{1c}$ < 64 mmol/mol, BMI < 18 kg/m$^2$, older age (e.g. aged > 65 years) or frailty, renal or liver failure
  - 0.2 units/kg daily if $HbA_{1c}$ > 64 mmol/mol and BMI > 18 kg/m$^2$
- Advise patients to begin self-monitoring blood glucose levels once daily before breakfast; goal is blood glucose levels 6 – 8 mmol/L
- Ensure patients understand how to up-titrate the insulin dose based on fasting blood glucose levels + how to manage hypoglycaemia
- If treatment intensification required, add bolus insulin to a basal regimen OR initiate a biphasic (premixed) insulin:
  - If starting basal-bolus regimen, add a rapid-acting insulin before largest meal (start with 4 units); increase by 2 units if blood glucose level increase with the meal is > 3 mmol/L on three occasions

**Annual review**

Standard of care for all people with type 2 diabetes; more frequent review may be indicated.

- Measure weight, waist circumference (optional), blood pressure
- Examine feet (including skin, nails, deformity), teeth and gums
- Request $HbA_{1c}$, urinary ACR, serum creatinine, LFTs, non-fasting lipid studies
- Review:
  - Retinal photoscreening up to date
  - CVD risk
  - Smoking status, alcohol intake and recreational drug use
  - Mental health
  - Contraception
  - Cervical, breast and bowel cancer screening up to date
  - Any other associated complications, e.g. sexual dysfunction, recurrent skin or genitourinary infection



# Type 2 diabetes management toolbox: **from lifestyle to insulin**

The management of type 2 diabetes is multi-faceted, including patient education on management of their condition, lifestyle interventions and pharmacological treatments. Managing $HbA_{1c}$ levels can reduce a patient's risk of microvascular complications associated with diabetes, but treatment regimens and target $HbA_{1c}$ levels need to be tailored to the individual. Lowering $HbA_{1c}$ levels is only one aspect of managing type 2 diabetes; other essential components are managing cardiovascular and renal risk factors and helping patients prioritise dietary and physical interventions.

## KEY PRACTICE POINTS:

- Lifestyle interventions are crucial at all stages of management for patients with type 2 diabetes, reducing the need for pharmacological treatment and inducing remission in some people; help patients by providing regular advice, encouragement and referral to appropriate support programmes
- The overall aim of pharmacological treatment with glucose-lowering medicines is to help reduce $HbA_{1c}$ levels and the risk of complications
- $HbA_{1c}$ targets and the choice of pharmacological treatment should be individualised taking into account overall health status, co-morbidities and risks associated with hypoglycaemia; targets and management may need to change over time
- Check $HbA_{1c}$ levels at least annually, but three- to six-monthly if required
- A recommended approach to initiating glucose-lowering medicines is:
  - Initiate metformin at diagnosis; if $HbA_{1c}$ levels are > 64 mmol/mol, more intensive treatment may be required
  - If treatment with metformin alone does not reduce $HbA_{1c}$ levels to the desired target, add empagliflozin,* dulaglutide,* vildagliptin, a sulfonylurea (glipizide or gliclazide) or pioglitazone
  - If further intensification is required, initiate insulin. Alternatively, combine three oral glucose-lowering medicines or two oral medicines and dulaglutide.
  - Prior to intensifying any pharmacological regimen, check the patient's adherence to their existing medicine regimen and diet and physical activity approaches
- If insulin is required, a basal insulin regimen is the preferred option in most clinical situations. Funded options are isophane insulin (usual first choice) and insulin glargine.

* Special Authority criteria apply.

**This article covers the management of patients with type 2 diabetes. Guidance on the management of patients with type 1 diabetes is available from: https://bpac.org.nz/2019/diabetes-insulin.aspx**

This is a revision of a previously published article. What's new for this update:

- Based on guidance from the NZSSD type 2 diabetes management guideline 2021
- Updated type 2 diabetes management algorithm including the new diabetes medicines, empagliflozin and dulaglutide
- Inclusion of a weight-based approach to determine the initial dose for patients initiating basal insulin

## Diabetes management essentials

Type 2 diabetes continues to be a significant health issue in New Zealand. Overall, 5% of the adult population has been diagnosed with type 2 diabetes, with the highest rates among people of Māori, Pacific and South-Asian ethnicity, people who are socioeconomically disadvantaged and older people (aged > 65 years).[1, 2] The prevalence is also increasing in younger people.

Optimal management, including lifestyle approaches (i.e. a healthy diet and exercise), diabetes education and support, and pharmacological treatments, are key to reducing the risk of long-term diabetes complications and help people with type 2 diabetes to live well.

For further information on diabetes in young people, see: "A rising tide of type 2 diabetes in younger people: what can primary care do?", Page 49

### Management begins with lifestyle

A healthy lifestyle is the foundation of treatment for all people with type 2 diabetes. Cardiovascular disease (CVD) is the greatest cause of early mortality and morbidity in people with type 2 diabetes, and appropriate nutrition and physical activity interventions simultaneously address cardiovascular risk factors and levels of glycaemia.[3]

The first step following diagnosis of type 2 diabetes should be to try to induce remission through lifestyle interventions to achieve weight loss (see below) and metformin treatment (see: "Pharmacological treatment to reduce $HbA_{1c}$ levels").[3, 4] Additional pharmacological treatments may be required to reduce $HbA_{1c}$ levels, but these may be able to be de-escalated or discontinued in some patients who make significant changes to their lifestyle.[4] Weight loss should be encouraged at any stage of type 2 diabetes to induce remission, slow progression, step down treatment intensity or delay the need to escalate treatment.

**Key lifestyle goals** for patients to aim for include:[3]

- At least 150 minutes per week of moderate intensity exercise – this may not be immediately achievable, but patients should have a plan to increase their level of physical activity to reach this goal
- Weight loss (5 – 10% of total body weight) in those who are overweight* – various dietary approaches are available; consider patient preference, tolerance, nutritional requirements, co-morbidities, cultural suitability and cost
- Eating foods with a high fibre content, such as fruits, vegetables and whole grains, and avoiding sugar-sweetened beverages or foods with added sugars

* BMI > 30 kg/m$^2$ or BMI > 25 kg/m$^2$ with waist circumference > 88 cm in females or > 102 cm in males[3]

For further information on weight loss in type 2 diabetes management, see: "Weight loss for the prevention and treatment of type 2 diabetes", Page 15

**Diabetes education and support is a critical aspect of lifestyle management.** The goal is to enable the patient to take an active role in their care without making them feel judged or to blame for having diabetes. Providing patients with an explanation of what goes wrong at a biological level with an increasing duration of type 2 diabetes can help them understand the need for making changes to their lifestyle and the role of medicines in diabetes management.

> *For example, explain to patients that their body is not responding to insulin as well as someone without diabetes, and that in turn the pancreas increases insulin levels in order to decrease blood glucose levels. However, this cannot be maintained long-term and for many people additional oral medicines or injecting dulaglutide or insulin becomes necessary as time goes on. Losing weight, exercising and eating well can improve the body's sensitivity to insulin and therefore this is something that the patient can do to reduce their need for medicines. In some patients, significant sustained lifestyle changes can normalise $HbA_{1c}$ levels and medicines may no longer be required.*

**Connect patients to services that can assist with lifestyle changes and provide support.** This could include referring patients to a dietitian, providing them with a Green Prescription to connect with a Green Prescription support person, or making patients aware of programmes offered by a local PHO, DHB (e.g. DESMOND) or Māori health provider. Diabetes New Zealand has branches throughout the country that provide a variety of services. For further information, see: **www.diabetes.org.nz**

## Pharmacological treatment to reduce $HbA_{1c}$ levels

Prescribing medicines to reduce $HbA_{1c}$ levels in patients with type 2 diabetes is a balancing act, which aims to reduce $HbA_{1c}$ levels as far as possible without causing harm.[5] Hypoglycaemia is the main limiting adverse effect associated with reducing $HbA_{1c}$ levels, and it can carry substantial risks, particularly in patients who are frail. Hypoglycaemia is associated with an increased risk of falls and cognitive impairment, and may increase the risk of mortality.[5]

### Choosing a target: the first step

A $HbA_{1c}$ target should be individualised and determined by factors such as the patient's co-morbidities, potential duration of the patient's exposure to hyperglycaemia, history of hypoglycaemia and overall health status (Table 1).[3,6]

Reaching and maintaining target $HbA_{1c}$ levels can reduce a patient's risk of microvascular complications, e.g. retinopathy, nephropathy, and neuropathy.[3,6] Reducing $HbA_{1c}$ in patients with particularly high levels, e.g. > 80 mmol/mol, to a more moderate level, e.g. < 65 mmol/mol, is thought to offer the greatest reductions in risk of microvascular complications.[6] Aiming for a very low target is not always best if the risks associated with reducing $HbA_{1c}$ levels, e.g. hypoglycaemia, outweigh the benefits.[3,6] Reducing $HbA_{1c}$ is also part of the multi-factorial risk reduction strategy, which includes increasing physical activity, smoking cessation and managing hypertension and dyslipidaemia, to reduce macrovascular complications of diabetes.[7]

For further discussion on adjusting $HbA_{1c}$ treatment targets, see: **bpac.org.nz/2019/diabetes-elderly.aspx**

## Prescribing glucose-lowering medicines: choosing the right tools for the job

The pharmacological management of type 2 diabetes typically follows a stepwise progression with lifestyle interventions, i.e. diet and exercise to induce weight loss, reinforced at each intensification step (Figure 1). The intensity of pharmacological treatments required to reduce and maintain $HbA_{1c}$ at target levels varies greatly between patients and also depends on the extent of lifestyle changes, the length of time they have had diabetes and their particular circumstances and preferences.[5] For patients with high $HbA_{1c}$ levels (> 64 mmol/mol) at diagnosis, initiating two medicines is recommended (e.g. metformin and vildagliptin).[3] For patients with very high $HbA_{1c}$ levels, e.g. > 80 – 90 mmol/mol, or significant symptoms of hyperglycaemia at diagnosis, initiation of insulin (in addition to metformin) is recommended.[3] It is often possible to reduce insulin or remove it from the regimen once $HbA_{1c}$ stabilises.[8]

**Table 1:** Patient characteristics to consider when selecting a $HbA_{1c}$ target[3,5,6]

| Target | < 48 mmol/mol | < 53 mmol/mol | 54 – 70 mmol/mol |
|---|---|---|---|
| Reasons for choosing target | Greatest reduction in risk of microvascular complications. Appropriate if can be achieved without adverse effects. | Reasonable balance between reduction in risk of microvascular complications with risks of treatment | Appropriate if benefits from treating to lower levels are outweighed by risk of hypoglycaemia |
| Characteristics of patients who may benefit from this target | ■ Young, e.g. aged < 40 years<br>■ Are at low risk of hypoglycaemia (i.e. not on insulin or a sulfonylurea)<br>■ Considering pregnancy or are pregnant<br>■ Have microvascular complications (particularly retinopathy and nephropathy) | ■ Most patients | ■ Older patients at risk of falls and fractures<br>■ Frailty<br>■ Cognitive impairment<br>■ Functionally dependent<br>■ Hypoglycaemia experienced at lower targets<br>■ Live alone and are at risk of severe hypoglycaemia<br>■ Short life expectancy<br>■ Already have advanced microvascular or macrovascular diabetes complications<br>■ Require multiple medicines to achieve lower $HbA_{1c}$ targets and have complications caused by polypharmacy |

STEP 1

## Metformin

- **Initiate metformin at or soon after diagnosis** for all patients with type 2 diabetes ($HbA_{1c}$ ≥ 50 mmol/mol)
  - If patients have contraindications to using metformin, initiate an alternative glucose-lowering medicine
  - If patients have high $HbA_{1c}$ levels at diagnosis, e.g. > 64 mmol/mol, consider initiating metformin + another non-insulin medicine; if levels are very high > 80 – 90 mmol/mol, insulin initiation is recommended
- **Consider initiating metformin** in combination with lifestyle advice for patients with "pre-diabetes" ($HbA_{1c}$ 41 – 49 mmol/mol)

STEP 2

## Add a second non-insulin glucose-lowering medicine

See Figure 1 in "New diabetes medicines funded: empagliflozin and dulaglutide" for further guidance on selecting an option.

Initiate any one of the following medicines in combination with metformin:

- Empagliflozin*†
- Dulaglutide†
- Vildagliptin*
- Pioglitazone
- A sulfonylurea: either gliclazide or glipazide
- Acarbose**

## Add a third non-insulin glucose-lowering medicine

An alternative to initiating insulin; the options are:

- Three oral glucose-lowering medicines
- Two oral glucose-lowering medicines + an injectable GLP-1 receptor agonist (i.e. dulaglutide‡)

STEP 3

## Add insulin

- Once daily long-acting insulin is typically used when first initiating insulin; isophane insulin is appropriate for most patients

* Combination formulations with metformin available

† Special Authority criteria apply. For further information see: "New diabetes medicines funded: empagliflozin and dulaglutide"

** May be useful for some patients, however, when added to metformin treatment it is less effective at lowering $HbA_{1c}$ levels than other oral medicines

‡ Dual treatment with dulaglutide and empagliflozin is not currently funded. Some patients may choose to have dual treatment by self-funding one medicine.

## Review management at each step

- Measure $HbA_{1c}$ levels at three to six month intervals
- Discuss diet and physical activity approaches
- Discuss medicine use and adverse effects
- Ask about hypoglycaemia
- Review management of cardiovascular and renal risk factors

**Determine whether changes in treatment are necessary and an appropriate interval for the next review.**

Options could include:

- Continuing with the same plan for treatment
- Increasing dietary or physical activity approaches
- Increasing doses of, or adding, glucose-lowering medicines
- Switching medicines due to adverse effects
- De-escalating treatment

**Figure 1:** Optimising the management of $HbA_{1c}$ levels with glucose-lowering medicines in patients with type 2 diabetes[3, 5]

## Step 1: Metformin is the initial choice of oral medicine for most patients

Metformin is recommended as the initial pharmacological approach for patients with type 2 diabetes, as it reduces $HbA_{1c}$ levels, decreases cardiovascular disease risk independent of glycaemic control, may assist with weight loss and has a low risk of hypoglycaemia (Figure 1 and Table 2).[3] Initiate metformin at a low dose, e.g. 500 mg once daily, and gradually increase the dose over the following weeks to a maximum of 1.5 – 2 g daily, in divided doses, as tolerated.[9] A higher maximum dose of 3 g, daily may be prescribed for patients with creatinine clearance > 120 mL/min.[9]*

* While in many cases eGFR will be sufficient to estimate renal function in patients taking metformin, the NZF recommends using the Cockcroft-Gault equation for a more accurate calculation of creatinine clearance, which may be particularly useful in people with more severe renal impairment.[9] A calculator is available here: **www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation**

## Step 2: Prescribing combination treatment

If patients require intensification of pharmacological management, the recommended next step is to combine metformin with another non-insulin glucose-lowering medicine (or use two of these medicines if metformin is contraindicated or not tolerated). Funded options include:[3, 9]

- A sodium-glucose co-transporter 2 (SGLT-2) inhibitor: **empagliflozin***†
- A glucagon-like peptide (GLP-1) receptor agonist: **dulaglutide**†
- A dipeptidyl-peptidase 4 (DPP-4) inhibitor: **vildagliptin***
- A sulfonylurea: either **gliclazide** or **glipizide****
- A thiazolidinedione: **pioglitazone**

* Available in a single formulation and in combination with metformin

† Special Authority criteria apply. For further information see: "New diabetes medicines funded: empagliflozin and dulaglutide", Page 19.

** Glibenclamide is another subsidised sulfonylurea, however, prescribing glibenclamide is generally not recommended as it is associated with a higher risk of hypoglycaemia than other sulfonylureas[5]

When prescribed in combination with metformin there are no clinically meaningful differences in the extent of $HbA_{1c}$ lowering between the non-insulin glucose-lowering medicines; adding one of these medicines to metformin treatment generally reduces $HbA_{1c}$ by approximately 8 – 11 mmol/mol.[8, 10] There are, however, other reasons for selecting one medicine over another (see: "Which medicine to choose?").

**Acarbose** is another fully funded glucose-lowering medicine which could be added to metformin treatment if other medicines are not tolerated, however, available data suggest it is less effective at lowering $HbA_{1c}$ levels when added to metformin than the medicines above.[11] Adverse effects include bloating, flatulence, diarrhoea and, rarely, deranged liver function tests.[3]

## Which medicine to choose?

Clinicians and patients can jointly decide which of the above options to add to treatment after considering any contraindications, co-morbidities, risk of hypoglycaemia, effects on weight, medicines interactions, adverse effects and eligibility for funding (Table 2).

**Empagliflozin** or **dulaglutide** are preferred for people with established or at high risk of CVD, or with heart failure or diabetic kidney disease, regardless of their $HbA_{1c}$ levels; currently only patients with $HbA_{1c}$ levels > 53 mmol/mol who are at high risk of CVD or renal complications are eligible for funded treatment.[3] A combination metformin + empagliflozin formulation is available fully funded with Special Authority.

For further information on prescribing these medicines, see: "New diabetes medicines funded: empagliflozin and dulaglutide", Page 19

**Vildagliptin** is preferred for patients who are not eligible for funded empagliflozin or dulaglutide treatment.[3] A combination formulation of metformin + vildagliptin is available fully funded without restriction.

Some guidelines favour the addition of vildagliptin or a sulfonylurea instead of pioglitazone due to potential adverse effects associated with pioglitazone.[5] Vildagliptin or pioglitazone may be preferred over a sulfonylurea if patients have problems with hypoglycaemia.

N.B. Prior to initiating vildagliptin, request baseline liver function tests (Table 2).[3]

For further information on prescribing vildagliptin, see: "Prescribing vildagliptin for type 2 diabetes", Page 28

## Escalating beyond dual treatment

Options for treatment intensification for patients who have $HbA_{1c}$ levels above the desired target despite optimal use of two non-insulin medicines and lifestyle approaches are:

- Initiating a third non-insulin medicine (either an oral medicine or an injectable GLP-1 receptor agonist [i.e. dulaglutide])
- Initiating insulin (i.e. Step 3 – see below)

Take into account the patient's other prescribed medicines, which will often include an angiotensin-converting enzyme (ACE) inhibitor, statin, antihypertensives and aspirin, and consider whether triple oral therapy is likely to create difficulties with adherence.

**Table 2:** Funded glucose-lowering medicines and factors to consider when prescribing.[3, 9]

| Medicine | Effects on weight | Risk of hypoglycaemia | Use in patients with renal or hepatic impairment | Other factors and monitoring requirements |
|---|---|---|---|---|
| **Metformin** | Weight loss of approximately 2 – 3 kg over 12 months[12] | Low | ■ Avoid if CrCl < 15 mL/min*<br>■ Reduce doses if CrCl 15 – 59 mL/min*<br>■ Avoid if severe hepatic disease (Child-Pugh grade C) and use with caution if mild hepatic impairment; impaired hepatic function can reduce lactate clearance and increase the risk of lactic acidosis | ■ The preferred oral medicine in patients who are pregnant or breastfeeding<br>■ May cause vitamin B12 deficiency; check levels if patients have symptoms of anaemia or peripheral neuropathy – supplementation may be required[13]<br>■ Up to 20% of patients experience gastrointestinal adverse effects; slow titration and taking metformin with food may help to avoid this[13]<br>■ Consider temporary cessation of metformin in situations that may lead to lactic acidosis, e.g. dehydration due to illness |
| **Empagliflozin** | Weight loss of approximately 2 kg over six months[14] | Low | ■ Maximum dose 10 mg, once daily, in patients with eGFR < 30 mL/min/1.73m$^2$ (however additional glucose lowering treatment should be considered, as needed, as efficacy will likely be reduced)<br>■ Not recommended in patients on dialysis<br>■ No dose adjustment required for people with mild renal impairment | ■ Renal function should be assessed at least annually in patients taking empagliflozin (with or without metformin) and prior to initiating any medicines that may reduce renal function<br>■ May cause diabetic ketoacidosis; treatment should be temporarily stopped during acute illness and prior to elective procedures. Use with caution in patients on a low carbohydrate or ketogenic diet.<br>■ Avoid in patients with a history of severe genitourinary infections |
| **Dulaglutide** | Weight loss of approximately 2 – 3 kg over 12 months[15] | Low | ■ No dose adjustment required | ■ No additional monitoring requirements<br>■ Common, but usually transient, adverse effects include gastrointestinal disturbance and injection site reactions<br>■ Avoid in patients with a history of medullary thyroid cancer; and use with caution in patients with a family history |
| **Vildagliptin** | No change | Low | ■ Reduce dose if eGFR < 50 mL/min/1.73m$^2$ †<br>■ Avoid in patients with hepatic dysfunction, e.g. ALT levels > 2.5 times the upper limit of normal | ■ Avoid use in patients with severe heart failure (New York Heart Association functional class IV)<br>■ Assess liver function prior to initiation, every three months for the first year and then periodically |
| **Sulfonylureas** (glipizide, gliclazide) | Weight gain of approximately 2 kg over 12 months[16] | High | ■ Other medicines are preferable in patients with increased risk of hypoglycaemia, including patients with renal impairment or severe hepatic impairment [19, 27]<br>■ Contraindicated in patients with ketoacidosis or acute porphyria | ■ Effects on $HbA_{1c}$ may not persist as long as other oral options, requiring a change in medicine earlier[17] |
| **Pioglitazone** | Weight gain of approximately 2 kg over 12 months[16] | Low | ■ Avoid in patients with hepatic impairment, e.g. ALT levels >2.5 times the upper limit of normal<br>■ Use is not advised in patients with renal failure | Increased risk of:<br>■ Oedema and heart failure<br>■ Fractures<br>■ Bladder cancer; avoid use in patients with risk factors for or a history of bladder cancer |
| **Insulin** | Weight gain of 3 – 9 kg over 12 months[18] | High | ■ Dose reduction not usually required in patients with hepatic or renal impairment | ■ Injection site reactions are a common adverse reaction |

* While in many cases eGFR will be sufficient to estimate renal function in patients taking metformin, the NZF recommends using the Cockcroft-Gault equation for a more accurate calculation of creatinine clearance, which may be particularly useful in people with more severe renal impairment.[9] A calculator is available here: **www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation**

† The combination vildagliptin + metformin formulation is not recommended in patients with eGFR < 60 mL/min/1.73m$^2$; prescribing metformin and vildagliptin in separate tablets may be preferable to allow for an appropriate reduced dose of metformin.

There is very little clinical trial evidence to guide choice of which third non-insulin medicine to add. In general, the incremental effect of adding a third oral medicine is likely to be less than when these medicines are used alone or in dual treatment combinations.[8]

In international guidelines, adding a GLP-1 receptor agonist is the preferred next step for patients requiring escalation to injectable treatment, however, not all patients will be eligible for funded treatment in New Zealand.[3, 8] Initiating dulaglutide may be more acceptable to patients than insulin. While both are injectable treatments, dulaglutide is administered once weekly and self-monitoring of blood glucose levels is not necessary (unless their regimen includes a sulfonylurea).

Combination SGLT-2 inhibitor and GLP-1 receptor agonist treatment, in addition to metformin, is the recommended next step for people at high risk of cardiovascular or renal complications who were previously treated with just one of these medicine classes, however, dual treatment is not currently funded.[3]

## Step 3: Insulin

Discuss insulin initiation with patients who have $HbA_{1c}$ levels above the desired target despite optimal use of two oral medicines and lifestyle approaches, or where a rapid escalation of pharmacological treatment is required because of high $HbA_{1c}$ levels. Insulin has the largest effect on reducing $HbA_{1c}$ levels of all glucose-lowering medicines, however, it is also associated with greater weight gain and a higher risk of hypoglycaemia than other glucose-lowering medicines (Table 2).[8] Weight gain typically plateaus after the first one to three years of treatment and is dose-dependent.[19, 20]

Reassurance and advice is often required when discussing the possibility of initiating insulin with patients to ensure that any anxieties about insulin are addressed, e.g. feeling that it signifies an escalation in the seriousness of their condition, being worried or embarrassed about self-injection, needles or calculating doses, and fear of weight gain or hypoglycaemia. After discussing options some patients may wish to trial more intensive changes to their dietary or physical activity approaches instead of initiating insulin. If this is the case, agree to a time frame for review to ensure that insulin treatment is not unduly delayed.

**Summary of key points for initiating patients with type 2 diabetes on insulin:**[3]

A detailed discussion on initiating and up-titrating insulin, including the different regimens, insulins and devices, is available in: "Initiating insulin for people with type 2 diabetes", Page 33

- Most patients are initiated on once-daily basal insulin, injected at night; isophane insulin (an intermediate-acting insulin) is an appropriate choice for most patients
- A weight-based approach is recommended to determine the initial basal insulin dose:
  - 0.1 units/kg daily if at least one of:
    - $HbA_{1c}$ < 64 mmol/mol
    - BMI < 18 kg/m$^2$ (less likely to have type 2 diabetes)
    - Older (e.g. aged > 65 years) or frailty
    - Renal or liver failure
  - 0.2 units/kg daily if $HbA_{1c}$ > 64 mmol/mol and BMI > 18 kg/m$^2$
- Patients initiating basal insulin should begin self-monitoring blood glucose levels; a once daily measurement before breakfast (if insulin is taken at night) is sufficient; the aim of treatment is to achieve blood glucose levels between 6 – 8 mmol/L
- Patients will need to titrate the insulin dose upwards from this starting point based on their fasting blood glucose levels
- Patients who continue to have elevated $HbA_{1c}$ levels while using a basal insulin regimen may require intensification of insulin treatment. This could include switching to a biphasic insulin formulation, which includes long-acting and short-acting insulins in a premixed solution, or continuing with a basal insulin and adding a short-acting insulin at mealtimes.
- More frequent blood glucose monitoring is advised when introducing other insulin regimens, e.g. adding a fast-acting insulin at mealtimes. Monitoring before meals and before bed is useful.
- Ask patients to check their blood glucose levels if they experience symptoms consistent with hypoglycaemia. If an obvious cause is not apparent, e.g. missed meals, changes to carbohydrate intake or exercise regimen, patients should reduce their insulin dose by 10 – 20%.

Patient information on recognising and responding to hypoglycaemia is available at: **www.healthnavigator.org.nz/health-a-z/l/low-blood-glucose**

## Continuing other medicines

**Metformin is usually continued** when insulin is started as it can result in less weight gain and lower doses of insulin being required to meet $HbA_{1c}$ targets.[21]

**Empagliflozin is usually continued** when insulin is initiated; combining SGLT-2 inhibitor and insulin treatment can result in less weight gain and greater reduction in $HbA_{1c}$ levels without increasing the risk of hypoglycaemia.[22] Empagliflozin also provides cardiovascular and renal benefits independent of its actions on glycaemia.[3]

**Dulaglutide is usually continued** when insulin is initiated; combining GLP-1 receptor agonist and insulin treatment can result in less weight gain and greater reduction in $HbA_{1c}$ levels without increasing the risk of hypoglycaemia.[23] Dulaglutide also provides cardiovascular and renal benefits independent of its actions on glycaemia.[3]

**Vildagliptin may be continued** when insulin is initiated, but in practice is often withdrawn to simplify the regimen. The formulation of vildagliptin + metformin is also approved for use in combination with insulin.

**Sulfonylureas may be continued** if patients are using basal insulin as a lower dose of insulin is required to meet the $HbA_{1c}$ target.[3] However, there is an increased risk of hypoglycaemia when these medicines are used in combination.[3] Sulfonylureas are titrated down and withdrawn if treatment with a short-acting insulin is initiated.[21]

**Pioglitazone is typically discontinued** when insulin is initiated as combined use increases the risk of oedema.[24]

## Regularly revise treatment approaches and goals

Most people with type 2 diabetes will have it for the rest of their lives. Regular review of treatment is necessary to optimise individual goals of treatment and ensure medicine regimens remain appropriate.

**Measuring $HbA_{1c}$ levels at three to six month intervals** is recommended to determine the effect of lifestyle and pharmacological approaches (Figure 1).[3] Treatment can then be optimised by checking and reinforcing lifestyle approaches, adjusting doses, adding or withdrawing medicines, or adjusting $HbA_{1c}$ targets, as appropriate. An annual check is sufficient for patients with stable, well controlled $HbA_{1c}$ levels.

**Discuss diet and physical activity.** For all patients, sustaining lifestyle changes and maintaining weight loss is required for long term improvements in $HbA_{1c}$ levels and cardiovascular risk factors. Achieving this can be difficult; offer regular encouragement and assess barriers the patient is experiencing. Monitor body weight and ideally waist circumference annually.[3]

For further information on lifestyle management, see: "Weight loss for the prevention and treatment of type 2 diabetes", Page 15

**Discuss medicine use and adverse effects.** Ask patients about adverse effects or any difficulties they are having with their prescribed medicines which could contribute to reduced adherence.

**Consider the simplicity of the patient's medicine regimen,** including medicines prescribed for co-morbidities, and whether any changes are possible to improve adherence.[5]

**Ask about hypoglycaemia** if the patient is taking a sulfonylurea or insulin. If patients have symptoms of hypoglycaemia, discuss when they occurred, and the circumstances involved, e.g. a missed meal, acute illness. Ensure the patient is aware of symptoms of nocturnal hypoglycaemia, such as nightmares or disturbed sleep, being particularly hungry in the morning or waking with wet sheets due to sweating.[3] Problems with hypoglycaemia should prompt consideration of reducing doses of medicines, changing medicines or adjusting $HbA_{1c}$ targets.

## Diabetes medicines can affect fitness to drive

People with type 2 diabetes generally have no restrictions for holding a private vehicle licence (Class 1 or 6 licence). However, the NZTA advises that people taking sulfonylureas or insulin need to receive appropriate education regarding the possibility of hypoglycaemia, how to recognise it and how to respond. Avoiding driving for 24 hours is recommended if an episode of hypoglycaemia occurs. A person may need to stop driving for a few days after initiating insulin to check that they do not experience hypoglycaemia.

People with type 2 diabetes using either oral medicines or insulin may be considered fit to hold heavy vehicle licences (Classes 2 – 5) and endorsements P, V, I and O, however, assessments from both a general practitioner and a diabetes specialist (if taking insulin) are required and patients must meet specific conditions to continue driving.

For further information on diabetes and driving, see: **www.nzta.govt.nz/assets/resources/medical-aspects/Medical-aspects-of-fitness-to-drive-a-guide-for-health-practitioners.pdf**

**Review management of cardiovascular and renal risk factors:** Annual review of cardiovascular and renal risk factors, including blood pressure and lipid levels, albumin:creatinine ratio and eGFR, is recommended.[3] In addition, an annual foot check and recall for retinopathy screening at least every two years is recommended. Many PHOs have funding for this review. N.B. More frequent review may be indicated depending on the patient's risk factors.

A calculator to assess CVD risk in people with type 2 diabetes is available here: **www.nzssd.org.nz/calculators/calculator/1/cvd-risk-assessment/**

For further information on an annual diabetes review, see: "The annual diabetes review: screening, monitoring and managing complications", Page 43

## Patient information

- Patient information on type 2 diabetes, the importance of diet and physical activity, and recognising and responding to hypoglycaemia is available from:
  - Diabetes New Zealand: **www.diabetes.org.nz**
  - Ministry of Health "Keeping well with diabetes" booklet, available in English, Māori, Cook Islands Māori, Samoan, Tongan and Niuean: **www.healthed.govt.nz/search?topic%5B0%5D=3&type=resource&mode=picture-view**
  - Health Navigator: **https://www.healthnavigator.org.nz/health-a-z/d/diabetes-type-2/**
- A guide to initiating insulin for patients with type 2 diabetes, produced by the Waitematā District Health Board, is available in various languages: **http://www.saferx.co.nz/patient-guides/**

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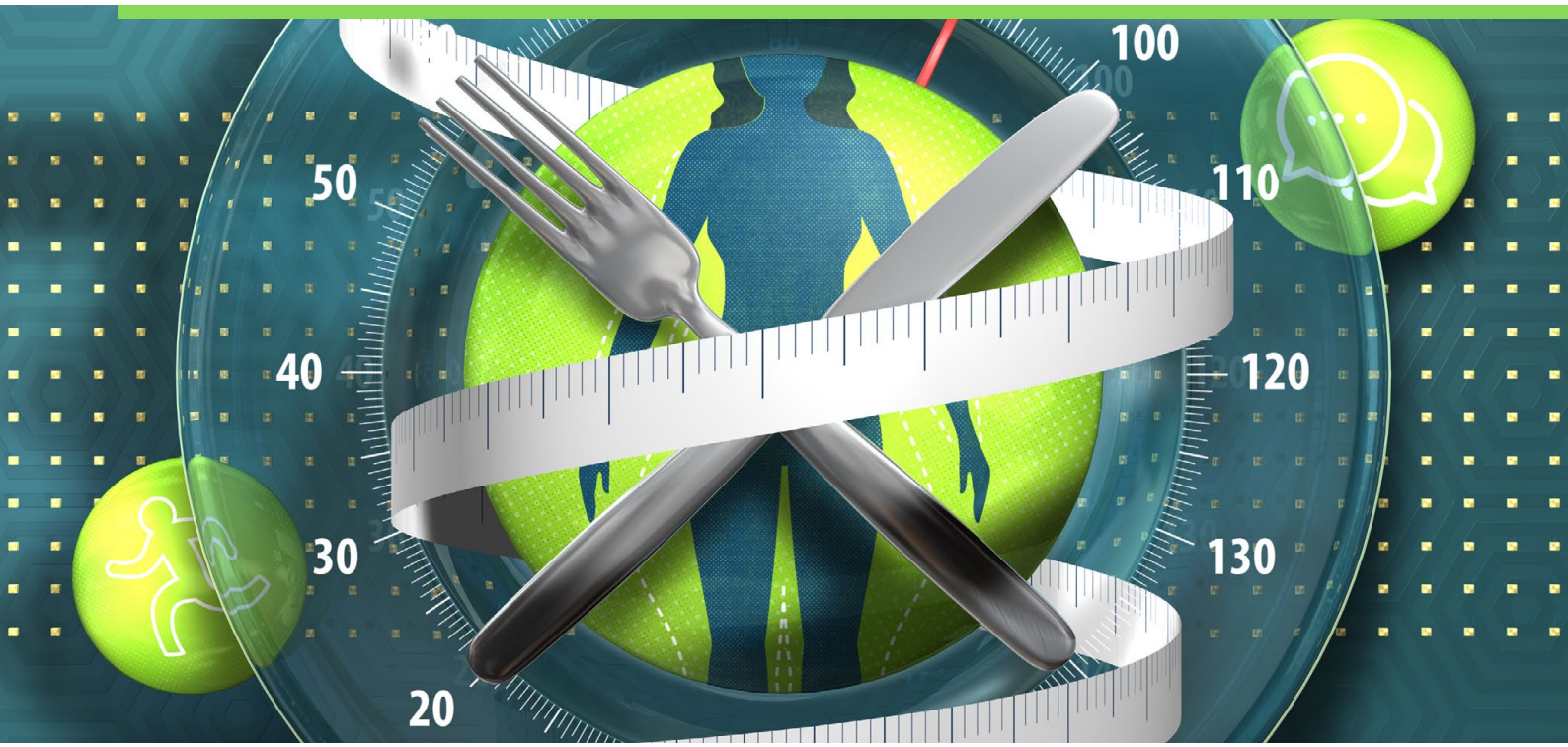



# Weight loss for the prevention and treatment of type 2 diabetes

Obesity is contributing to the increasing rate of type 2 diabetes in New Zealand, most notably in people aged under 40 years. The outcomes for these people are worse than for adults diagnosed later in life as end-organ damage, e.g. diabetic kidney disease, retinopathy and neuropathy, develop over time and the lifetime risk of cardiovascular disease (CVD) and early mortality is higher at a younger age. Weight loss achieved through lifestyle interventions, pharmacological treatments or surgery can be successful in preventing or delaying the onset of diabetes, inducing diabetes remission and improving cardiovascular outcomes in people who have, or are at high risk for type 2 diabetes.

## Lifestyle change can prevent type 2 diabetes in people who are overweight or obese

In people who are at high risk for type 2 diabetes, a healthy diet, physical activity and weight management can prevent or delay the onset of diabetes.[1] Changes in dietary composition and increased physical activity are thought to be the two most significant modifiable factors that contribute to a lower incidence of diabetes.[2] Patients can be encouraged to consume low calorie, low glycaemic index (GI) foods, increase vegetable intake and minimise the consumption of dietary fat, energy-dense foods, sugar and alcohol to form a nutritionally balanced dietary regimen. A healthy diet should be undertaken in combination with physical activity (ideally 150 minutes per week) to maximise the benefits.

There is a large evidence base for the benefits that lifestyle changes have on the risk of developing type 2 diabetes including:

- In a 7.4-year follow-up of The Finnish National Diabetes Prevention Program, 10,149 participants at high risk for type 2 diabetes (average BMI > 30 kg/m$^2$) engaged in a one-year primary care-led lifestyle counselling intervention (i.e. on weight reduction, healthy diet and physical activity). Of the 2,730 participants who completed the intervention, those who achieved weight loss between 2.5% – 4.9%, and ≥ 5%, had a reduced incidence of type 2 diabetes of 37% and 29%, respectively, compared with people who did not lose weight.[3]
- In a German study, 2,227 participants who were obese (BMI 30 – 40 kg/m$^2$) completed a 12-month lifestyle intervention delivered in a primary care setting which consisted of physical activity (41 exercycle sessions with

progressive intensity), dietary modifications (reduction in the intake of dietary fat and energy-dense foods with a focus on consuming low GI foods) and behavioural changes (using cognitive-behavioural strategies to set action-based goals, identify potential barriers and enable self-monitoring).[4] Body weight significantly reduced by 6% and approximately 38% of the participants who had initially elevated $HbA_{1c}$ levels achieved normal levels by the end of the trial.[4] During a six-year follow up, participants who had normalised $HbA_{1c}$ levels from the intervention had significantly lower risk of type 2 diabetes than those whose $HbA_{1c}$ levels did not normalise during the initial study.[4]

- In an observational follow-up of the Chinese Da Qing Diabetes Prevention study, 577 people (average BMI 25.7 kg/m$^2$) with impaired glucose tolerance were each assigned to a control group (no intervention) or an intervention group of diet, exercise, or diet and exercise for six years, and followed for up to 30 years to assess the effect of the intervention.[2] Interventions aimed to increase vegetable intake, lower alcohol and sugar intake and increase the amount of exercise undertaken during spare time; people who were overweight or obese were encouraged to reduce calorie intake.[2] During the 30 year follow-up, those assigned to diet and exercise achieved a delay in diabetes onset of approximately four years and subsequently had a lower incidence of serious diabetes complications and diabetes-related mortality compared with those who had no intervention.[2]

## Remission of type 2 diabetes with weight loss

A substantial proportion of people with type 2 diabetes who are overweight can achieve a non-diabetic state if they are able to lose enough body weight. In a European population-based study, weight loss of ≥ 10% in the first year following a diagnosis of type 2 diabetes was associated with twice the likelihood of remission at five years.[5] Remission becomes much less likely as the duration of diabetes increases, but it is never too late to try.[6] Low-energy, low GI and modified macronutrient dietary approaches, e.g. low carbohydrate, low fat and high protein diets, have been effective in achieving weight loss and type 2 diabetes remission, however, there is no conclusive evidence that one approach is more effective than another.[7]

There has been increased focus in recent years on the benefits of low/very low carbohydrate diets for type 2 diabetes. The effectiveness and safety of this type of diet in people with type 2 diabetes was recently assessed in a systematic review and meta-analysis of 23 trials (1,357 participants).[8] Participants were assigned to low (< 130 g/day or < 26% of a 2000 kcal/day) or very low (< 10% of calories from carbohydrates) carbohydrate diet intervention groups for at least 12 weeks.[8] The group following the low carbohydrate diet (LCD) achieved a 32% increase in diabetes remission at six months compared with people following low-fat control diets.[8] Very low carbohydrate diets were less effective than LCDs at inducing diabetes remission, likely due to lower adherence.[8] Remission rates were lower in people using insulin likely due to people having had diabetes for longer and/or higher $HbA_{1c}$ levels.[8]

Remission was also demonstrated in the DiRECT trial which involved 306 participants with type 2 diabetes in the United Kingdom. The intervention involved replacing half of the groups' meals with a nutritionally balanced liquid diet (825 – 853 kcal/day) for three to five months:[9]

- At 12 months, the mean weight of the intervention group had fallen by 10% and 46% of individuals had achieved diabetes remission
- At 24 months, the mean weight loss of the intervention group was 7.6% and 36% had diabetes remission
- Post-hoc analysis concluded 24% of participants maintained ≥ 10 kg weight loss and 64% of those sustained remission

The balance of evidence suggests that the magnitude of weight loss is the key factor in achieving diabetes remission and it does not matter how this is achieved, as long as it is sustainable.[9, 10] If appropriate, pharmacological and surgical treatments may be considered to achieve weight loss if lifestyle interventions alone are not adequate.

### Type 2 diabetes remission and relapse following bariatric surgery

In people who have type 2 diabetes and are obese, bariatric surgery can induce remission, as well as reduce the risk of diabetes complications, cardiovascular disease and some cancers.[11] A New Zealand study following 224 people with type 2 diabetes who underwent bariatric surgery found a remission* rate of 80%.[12] The relapse rate at five years was 34% and 47% at ten years.[12] Relapse rates were higher in those who had a longer duration of diabetes, were taking insulin at referral and who had less reduction in BMI following surgery.[12]

* Defined as $HbA_{1c}$ < 50 mmol/mol in the absence of insulin or other diabetes medicines

The Ministry of Health's criteria for consideration of publicly funded bariatric surgery are:[11]

- A BMI 35 – 55 kg/m$^2$, but body weight less than 160 kg, and co-morbidities, e.g. diabetes, sleep apnoea, hypertension, hypercholesterolaemia, infertility or arthritis

- Stable living arrangements and strong social supports
- No substance addiction, including nicotine; smoking cessation is required at least six weeks prior to surgery
- A willingness to accept life-long monitoring

Referrals for surgery are reviewed within each DHB by a team who apply a national scoring system to determine who will receive the greatest benefit.[3] Bariatric surgery can also be accessed privately; acceptance criteria is likely to vary between clinics.

## Weight loss may improve cardiovascular outcomes in people with diabetes

If people with diabetes do not achieve remission after losing weight, it is likely that they will still benefit from the improved cardiovascular outcomes associated with weight loss. A healthy diet, exercise and weight control in people at high risk of type 2 diabetes enables improved management of cardiovascular risk factors.[3, 13]

Benefits on cardiovascular health from weight loss achieved through lifestyle interventions have been demonstrated in the:

- Chinese Da Qing Diabetes Prevention study, where after ten years of follow-up participants experienced:[3, 14]
  - Fewer CVD events and deaths
  - Lower incidence of microvascular complications
- Look AHEAD trial post-hoc analysis, where there was an association between the extent of weight loss and the incidence of CVD. In participants with ≥ 10% weight loss, there was a:[14]
  - 21% reduction in the risk of CVD
  - 24% reduction in the first occurrence of myocardial infarction or stroke, hospitalisation for angina, congestive heart failure or death

### The impact of exercise on type 2 diabetes and cardiovascular health

To maximise the benefit to cardiovascular health, weight loss should be coupled with exercise. Regular exercise is a critical component in the management of type 2 diabetes. Exercise improves glycaemic control and weight loss, and contributes to reductions in cardiovascular risk factors through enhancing cardiometabolic health and fitness.[15] Exercise has also been shown to reduce CVD mortality, coronary heart disease, diabetes, myocardial infarction and stroke.[16, 17] Walking is a cost-effective and accessible exercise for most people. A systematic review and meta-analysis including 20 randomised controlled trials and 866 participants with type 2 diabetes concluded that walking alone (i.e. in the absence of dietary interventions or in combination with other exercises) was effective in reducing $HbA_{1c}$ on average by 5.5 mmol/mol.[15] Only interventions lasting eight weeks or more were included in the study, and people in supervised programmes achieved better results than those who were unsupervised.[15]

Before recommending an exercise regimen, consider the patient's medical history.[15] Concomitant medications such as beta-blockers can lower the exercise intensity threshold, and some anti-diabetic medicines can cause hypoglycaemia which could be exacerbated by exertion.[15] If a patient has peripheral neuropathy and accompanying foot problems, suggest non-weight bearing exercises (see below).[15]

To maximise patient engagement and adherence, recommend that they initiate exercises that are less intensive which can then be escalated as tolerance of the regimen improves.[15]

Besides providing general advice on engaging in at least 30 minutes of physical activity per day, other useful recommendations can be made on how to achieve this; consider suggesting:[15]

- Alternative ways to walk, such as brisk walking (e.g. 15 minutes fast walking instead of 30 minutes slow walking for those short on time), interval walking (e.g. alternating 1 – 3 minutes fast walking with 1 – 3 minutes slow walking), Nordic walking (using poles to intensify walking by including upper body exercise), joining a walking group, walking on a treadmill
- Increasing energy expenditure by walking on sand or through water, uphill or downhill
- Walking around the room during television ad breaks or for three minutes every 30 minutes, to interrupt sedentary behaviour
- Using a step-counter as motivation to reach at least 10,000 steps per day
- If the patient has co-morbidities that prevent walking, try alternative activities, e.g. arm and leg exercises while seated, stationary exercise biking, leisure cycling or water-based activities

## Maintaining and sustaining lifestyle change

Lack of adherence to lifestyle changes is a common issue and patients may need support with strategies to maintain motivation. A multi-targeted approach encompassing physiological, psychological and external factors is best.[18] Motivational interviewing may be a useful tool as well as constructive feedback sessions to reinforce accountability.[18]

For example, a strategy to improve long-term adherence to lifestyle changes is to assess patient's emotional needs that are currently managed by unhealthy behaviours, i.e. stress eating or low-mood overindulgence.[19] Suggest alternative coping

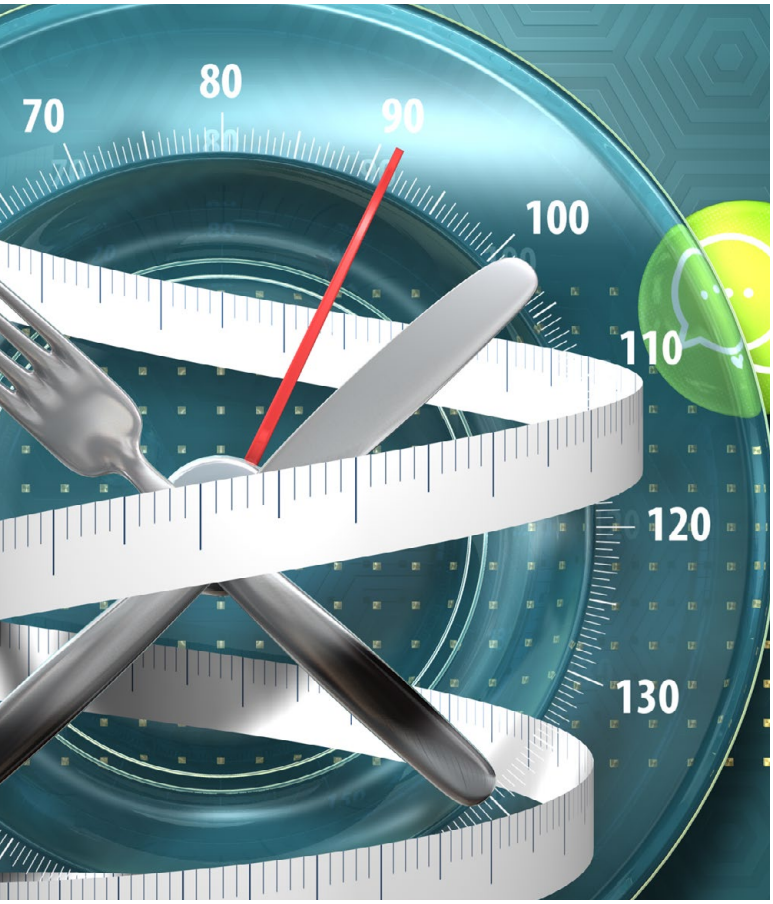
mechanisms, e.g. relaxation or mindfulness techniques when feeling stressed, or counselling if suppressed mood remains problematic.[19]

Other strategies that may be useful in sustaining lifestyle changes include:[15, 18, 19]

- Celebrating achievements of any size without fixating on weight loss
- Engaging in exercises that are enjoyable
- Focusing on healthy eating habits that are less restrictive
- Group based physical activity with friends for socialisation, pleasure and accountability
- Encouraging a positive attitude that is flexible and self-forgiving
- Set achievable goals that are self-guided and non-restrictive; some may find setting long-term goals more helpful (and achievable) than short-term goals
- Setting up prompts, e.g. having sneakers by the door, or having healthy pre-prepared meals in the fridge

Further information on motivation interviewing is available from: **bpac.org.nz/2019/motivational.aspx**

Further information on weight loss is available from: **bpac.org.nz/2019/weight-loss.aspx**

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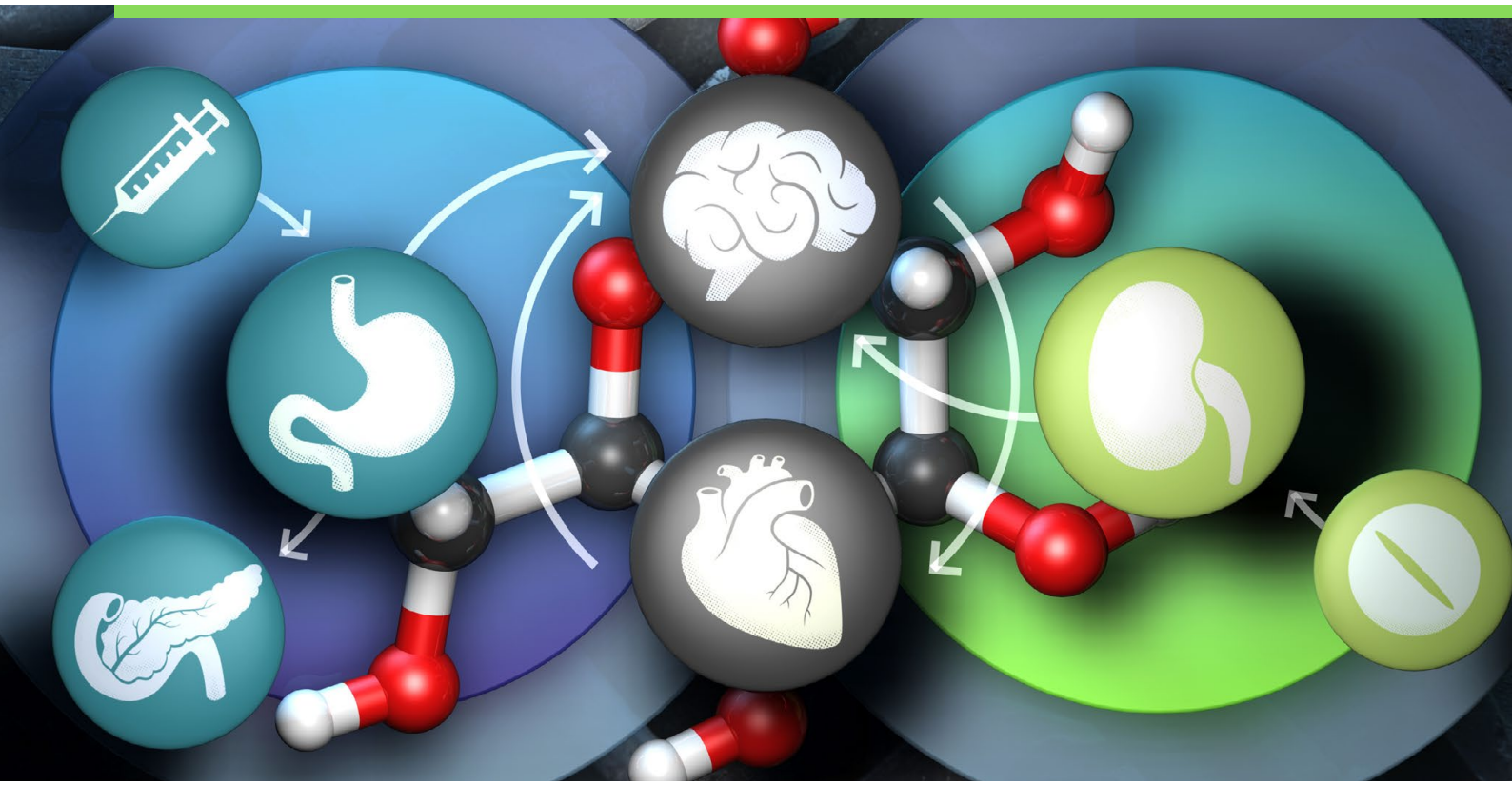
This article is available online at:
**www.bpac.org.nz/2021/diabetes-weight.aspx**



# New diabetes medicines funded: **empagliflozin and dulaglutide**

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have been recommended for the treatment of type 2 diabetes for some time, but until now have not been funded in New Zealand. As of 1 February, 2021, empagliflozin, a SGLT-2 inhibitor, has been available fully funded for the treatment of people with type 2 diabetes who are at high risk of cardiovascular disease or have renal complications, including all Māori and Pacific peoples. Dulaglutide, a GLP-1 receptor agonist, has been available fully funded since 1 September, 2021.

## KEY PRACTICE POINTS:

- Lifestyle interventions, i.e. diet and exercise to achieve weight loss, and metformin remain the cornerstone of type 2 diabetes management
- Empagliflozin, an oral SGLT-2 inhibitor (with or without metformin) and dulaglutide, an injectable GLP-1 receptor agonist, are newly funded options for eligible people with type 2 diabetes to add to lifestyle interventions and metformin
- Empagliflozin and dulaglutide are funded for people with $HbA_{1c}$ levels > 53 mmol/mol who are at high risk of, or with established, cardiovascular disease, diabetic kidney disease, heart failure or who are of Māori or Pacific ethnicity. Dual treatment with these medicines is not funded, although some patients may choose to self-fund.
- Empagliflozin and dulaglutide reduce the risk of cardiovascular and renal complications in people with type 2 diabetes; empagliflozin in particular reduces hospital admission with heart failure. Both classes of medicine also promote weight loss, especially dulaglutide.
- Adverse effects of SGLT-2 inhibitors such as empagliflozin include polyuria and urogenital infections. This medicine class also increases the risk of diabetic ketoacidosis; discuss this risk with patients when initiating treatment and inform them of the key symptoms and signs that should prompt them to seek medical advice.
- Adverse effects of GLP-1 receptor agonists such as dulaglutide include gastrointestinal disturbance and injection site reactions

## More tools for the diabetes management toolbox

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have been recommended internationally in type 2 diabetes management guidelines for some time, but, until now, have been inaccessible to most people in New Zealand due to cost. **Epagliflozin** (with and without metformin), an oral SGLT-2 inhibitor, has been available fully funded with Special Authority approval since 1 February, 2021 (see: "Initiating funded treatment").[1] As of 1 September, 2021, **dulaglutide**, an injectable GLP-1 receptor agonist, has also been available fully funded with Special Authority approval.[1] Both medicines will be the sole subsidised brands until at least 2024.[1]

SGLT-2 inhibitors lower blood glucose levels by inhibiting glucose reabsorption in the renal tubule. In contrast, GLP-1 receptor agonists lower blood glucose levels by stimulating insulin secretion after meals. When added to metformin, SGLT-2 inhibitors and GLP-1 receptor agonists may reduce $HbA_{1c}$ levels by a further 7 to 15 mmol/mol.[2–4]

For further information on the decision to fund these medicines, see: **pharmac.govt.nz/news-and-resources/consultations-and-decisions/decision-to-fund-two-new-medicines-for-type-2-diabetes/**

### People at high risk of cardiovascular and renal complications will benefit

Several large randomised controlled trials (RCTs) have shown that treatment with a SGLT-2 inhibitor or GLP-1 receptor agonist provides significant cardiovascular benefit to people with type 2 diabetes.[5] A recent meta-analysis of 764 RCTs including 421,346 people with type 2 diabetes found that both medicine classes reduced:[6]

- All-cause mortality
- Cardiovascular mortality
- Non-fatal myocardial infarction
- Kidney failure

The mechanism by which these medicines reduce adverse cardiovascular outcomes remains uncertain; trials are currently underway to explore the pathways involved, including investigating reductions in oxidative stress and cardiac pre-load.[7]

Table 1 describes the estimated absolute difference in outcomes with SGLT-2 inhibitors and GLP-1 receptor agonists compared with placebo per 1,000 people with type 2 diabetes with moderate or very high cardiovascular risk.[6]*

* Moderate risk defined as people with cardiovascular disease; very high risk defined as people with both cardiovascular disease and chronic kidney disease

**Funding criteria is intended to help reduce inequities**

For the first time, Māori and Pacific peoples have been specifically identified within Special Authority criteria for funding (see: "Initiating funded treatment" for the full criteria). The prevalence of type 2 diabetes is two to three times higher in these ethnic groups than others.[8] Māori and Pacific peoples with type 2 diabetes have worse health outcomes compared to Europeans.[9, 10] Improved access to medicines with established cardiovascular and renal benefits is hoped to reduce the inequities in diabetes health outcomes in these populations.

**Table 1.** Estimated absolute differences in outcomes with SGLT-2 inhibitors and GLP-1 receptor agonists compared with placebo per 1,000 people with type 2 diabetes with moderate and very high cardiovascular risk, treated for five years. Adapted from Palmer et al. (2021).[6]

| | CVD risk category* | All-cause mortality | Cardiovascular mortality | Non-fatal myocardial infarction | Non-fatal stroke | Kidney failure | Hospital admission for heart failure |
|---|---|---|---|---|---|---|---|
| **SGLT-2 inhibitor** | Moderate | 25 fewer (32 fewer – 18 fewer) | 12 fewer (18 fewer – 6 fewer) | 13 fewer (21 fewer – 3 fewer) | 1 more (11 fewer – 13 more) | 6 fewer (9 fewer – 2 fewer) | 23 fewer (28 fewer – 17 fewer) |
| | Very high | 48 fewer (61 fewer – 35 fewer) | 24 fewer (36 fewer – 12 fewer) | 21 fewer (34 fewer – 5 fewer) | 2 more (17 fewer – 21 more) | 38 fewer (58 fewer – 14 fewer) | 58 fewer (73 fewer – 44 fewer) |
| **GLP-1 receptor agonist** | Moderate | 13 fewer (18 fewer – 6 fewer) | 9 fewer (15 fewer – 1 fewer) | 8 fewer (15 fewer – 1 fewer) | 16 fewer (24 fewer – 7 fewer) | 4 fewer (7 fewer – 2 fewer) | 4 fewer (11 fewer – 2 more) |
| | Very high | 24 fewer (35 fewer – 12 fewer) | 18 fewer (30 fewer – 6 fewer) | 13 fewer (24 fewer – 2 fewer) | 25 fewer (39 fewer – 11 fewer) | 29 fewer (44 fewer – 10 fewer) | 11 fewer (28 fewer – 5 fewer) |

* Moderate risk defined as people with CVD; very high risk defined as people with both CVD and chronic kidney disease

## The place of empagliflozin and dulaglutide in type 2 diabetes management

Type 2 diabetes management follows a stepwise progression. Lifestyle interventions and metformin are the cornerstone of type 2 diabetes management (Step 1). If a sufficient reduction in $HbA_{1c}$ levels is not achieved with metformin, treatment is typically escalated by reinforcing the importance of diet and exercise to induce weight loss, and adding a second non-insulin pharmacological treatment (Step 2a). If further intensification is required, a third non-insulin pharmacological treatment can be added (Step 2b) or insulin can be initiated (Step 3).

N.B. Consider starting at Step 2 at diagnosis for patients with $HbA_{1c}$ levels > 64 mmol/mol, i.e. two pharmacological treatments (e.g. metformin and vildagliptin) and lifestyle management.[11] Consider initiating insulin at diagnosis if very high $HbA_{1c}$ levels, e.g. > 80 – 90 mmol/mol*, or significant symptoms of hyperglycaemia.[11] Insulin may be withdrawn once $HbA_{1c}$ levels are controlled.

* This is a higher level than in previous guidance (75 mmol/mol) due to the availability of more medicines to manage hyperglycaemia[12]

Treatment options at Step 2 (typically added to metformin) include:

- **Empagliflozin** (oral, funded with Special Authority – see: "Initiating funded treatment" and "Prescribing empagliflozin"), taken either as separate metformin and empagliflozin tablets, or a combination empagliflozin + metformin formulation
- **Dulaglutide** (injectable, funded with Special Authority – see: "Initiating funded treatment" and "Prescribing dulaglutide")
- **Vildagliptin** (oral, funded), taken either as separate metformin and vildagliptin tablets, or a combination vildagliptin + metformin formulation
- A sulfonylurea (oral, funded), such as **gliclazide** or **glipizide**
- **Pioglitazone** (oral, funded)

The decision about which medicine to use should take into account any contraindications, cardiovascular co-morbidities, risk of hypoglycaemia, effects on weight, medicines interactions, adverse effects and eligibility for funding (see: Table 2 and "Initiating funded treatment").[5]

**Empagliflozin or dulaglutide** are preferred at Step 2 for people with or at high risk of CVD, diabetic kidney disease or heart failure, regardless of their $HbA_{1c}$ levels; currently only people with $HbA_{1c}$ levels > 53 mmol/mol are eligible for funded treatment (see: "Initiating funded treatment").[11] Both medicine classes can be used together with likely additive benefits, however, dual treatment with empagliflozin and dulaglutide is not funded.[11] There is little risk of hypoglycaemia with these medicines without concomitant use of sulfonylureas or insulin.

N.B. A SGLT-2 inhibitor or GLP-1 receptor agonist are also preferred in some international guidelines if there is a need to minimise weight gain or promote weight loss, however, they are not funded for these indications in New Zealand.[5,13]

**Table 2.** Effects of diabetes medicines (excluding insulin) on $HbA_{1c}$, cardiovascular co-morbidities, progression of kidney disease, weight and risk of hypoglycaemia and diabetic ketoacidosis. Adapted from the American Diabetes Association (2021) and NZSSD (2021).[5, 11]

| Medicine | Efficacy for lowering $HbA_{1c}$ | Cardiovascular effects | | Renal effects: progression of DKD | Effects on weight | Risk of hypoglycaemia | Risk of DKA |
|---|---|---|---|---|---|---|---|
| | | CVD | HF | | | | |
| **Metformin** | High | Potential benefit | Neutral | Neutral | Neutral with potential for modest loss | Low | Low |
| **Empagliflozin** | Intermediate | Benefit | Benefit | Benefit | Loss | Low | High |
| **Dulaglutide** | High | Benefit | Neutral | Benefit | Loss | Low | Low |
| **Vildagliptin** | Intermediate | Neutral | Neutral | Neutral | Neutral | Low | Low |
| **Sulfonylureas** | High | Neutral | Neutral | Neutral | Gain | High | Low |
| **Pioglitazone** | High | Potential benefit | Increased risk | Neutral | Gain | Low | Low |

CVD = cardiovascular disease HF = heart failure DKD = diabetic kidney disease DKA = diabetic ketoacidosis

## Clinical scenarios where empagliflozin or dulaglutide are recommended, but not funded

The recently released type 2 diabetes management guidelines developed by the New Zealand Society for the Study of Diabetes (NZSSD), and supported by the Ministry of Health, states that while the Special Authority criteria for empagliflozin and dulaglutide ensure access for those at high risk of cardiovascular and renal disease, the funding restriction is not fully consistent with best practice.[11]

Patients with type 2 diabetes who are likely to benefit from these medicines but who do not meet the criteria for funded treatment are those:[11]

- With CVD (or five-year CVD risk ≥ 15%), renal disease or heart failure with a $HbA_{1c}$ < 53 mmol/mol or eGFR 60 – 90 mL/min/1.73 $m^2$ without albuminuria
- With CVD (or five-year CVD risk ≥ 15%), renal disease or heart failure who are already taking funded empagliflozin or dulaglutide (i.e. dual treatment with these medicines is recommended, but only one can be funded at a time)
- Who are overweight or obese and have $HbA_{1c}$ levels above target despite regular use of or inability to tolerate metformin, but who do not have cardiovascular or renal disease and are not of Māori or Pacific ethnicity
- With a $HbA_{1c}$ above target despite regular use of or inability to tolerate metformin and vildagliptin, but who do not have cardiovascular or renal disease and are not of Māori or Pacific ethnicity
- With a $HbA_{1c}$ within the target range but where a SGLT-2 inhibitor is preferred to reduce adverse effects, e.g. weight gain or hypoglycaemia with a thiazolidinedione or sulfonylurea, respectively
- Who may benefit from dual treatment with both empagliflozin and dulaglutide

Discuss the recommendation with patients and the option to self-fund treatment, unless there are contraindications or significant cautions. This may be a challenging conversation to negotiate as there will be patients who are unable to meet the financial burden of self-funding treatment and may find this distressing.

**Vildagliptin** is recommended at Step 2 for people with type 2 diabetes who are not eligible for funded SGLT-2 inhibitor or GLP-1 receptor agonist treatment (also see: "Clinical scenarios where empagliflozin or dulaglutide are recommended, but not funded").[11] Vildagliptin is particularly useful in older patients, either combined with metformin or alone if metformin is contraindicated or not tolerated.

A new type 2 diabetes management guideline published by the New Zealand Society for the Study of Diabetes and the Ministry of Health is available here: **t2dm.nzssd.org.nz/**

### Initiating funded treatment

To initiate funded empagliflozin or dulaglutide treatment, patients must meet **either** of the following criteria:[1]

1. Have type 2 diabetes; **and**
2. Have at **least one** of the following characteristics:
   a) Māori or any Pacific ethnicity; or
   b) Pre-existing CVD or risk equivalent*; or
   c) An absolute five-year CVD risk of ≥ 15% according to a validated cardiovascular risk assessment calculator; or
   d) A high lifetime cardiovascular risk due to being diagnosed with type 2 diabetes during childhood or as a young adult; or
   e) Diabetic kidney disease†; **and**
3. Have an $HbA_{1c}$ level > 53 mmol/mol despite the regular use of at least one blood-glucose lowering agent (e.g. metformin, vildagliptin or insulin) for at least three months**

**Or**

Have previously received an initial approval for a SGLT-2 inhibitor if the current application is for a GLP-1 agonist, or vice versa

* Defined as: prior cardiovascular disease event (i.e. angina, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, transient ischaemic attack, ischaemic stroke, peripheral vascular disease), congestive heart failure or familial hypercholesterolaemia

† Defined as: persistent albuminuria (albumin:creatinine ratio greater than or equal to 3 mg/mmol, in at least two out of three samples over a 3 – 6-month period) and/or eGFR less than 60 mL/min/1.73$m^2$ in the presence of diabetes, without alternative cause

** If $HbA_{1c}$ is very high at diagnosis, e.g. > 64 mmol/mol, they would not be eligible for funded treatment with empagliflozin or dulaglutide until they have been treated with at least one glucose-lowering agent for three months; patients with high $HbA_{1c}$ at diagnosis could be initiated on metformin + vildagliptin or, if $HbA_{1c}$ are very high at diagnosis, metformin and insulin (which could then be withdrawn once $HbA_{1c}$ has stabilised)

Applications can be made by any relevant practitioner and are valid without further renewal (unless notified) for eligible

patients. Dual SGLT-2 inhibitor/GLP-1 receptor agonist treatment is not currently funded.

A calculator to assess cardiovascular disease risk in people with type 2 diabetes is available here: **www.nzssd.org.nz/calculators/calculator/1/cvd-risk-assessment**

### Choosing between empagliflozin and dulaglutide

The decision to initiate a SGLT-2 inhibitor versus a GLP-1 receptor agonist is based primarily on the predominant co-morbidity, i.e. CVD, heart failure or diabetic kidney disease, and patient preference, particularly regarding the route of administration (Figure 1).[11] If heart failure or diabetic kidney disease predominates, a SGLT-2 inhibitor (i.e. empagliflozin) is preferred. Otherwise either a SGLT-2 inhibitor or a GLP-1 receptor agonist (i.e. dulaglutide) is recommended; GLP-1 receptor agonist treatment will likely lead to greater improvements in glycaemic control and greater weight loss than SGLT-2 inhibitor treatment (although SGLT-2 inhibitors are still associated with weight loss).[11]

An interactive decision support tool for choosing between a SGLT-2 inhibitor and GLP-1 receptor agonist is available here: **magicevidence.org/match-it/200820dist**

**Dulaglutide is administered as a once weekly injection**

Patients may be reluctant to take dulaglutide as it is an injectable treatment rather than an oral medicine. However, unlike insulin, which requires one or more daily injections, dulaglutide is administered once weekly. Furthermore, self-monitoring blood glucose is not necessary for patients taking dulaglutide, unless their regimen also includes a sulfonylurea or insulin. Providing patients who are hesitant about initiating an injectable treatment with this information may help them to feel more confident with this treatment option. A treatment trial of dulaglutide may be very useful before initiating insulin.

## Prescribing empagliflozin

When initiating empagliflozin, reinforce lifestyle advice, i.e. dietary and exercise interventions, and offer support as required. Metformin should be continued unless it is contraindicated or not tolerated; combination empagliflozin + metformin formulations are available (Table 3).[11] Other glucose-lowering treatments (e.g. vildagliptin, a sulfonylurea, dulaglutide,* or insulin) should be continued if needed for glycaemic control or cardiovascular or renal protection.[11] If the patient is taking insulin or a sulfonylurea, the dose may need to be reduced; a reduction of 15 – 20% of the daily total insulin or 50% of the sulfonylurea dose is recommended as a starting point.[11] People with a $HbA_{1c}$ > 75 mmol/mol do not usually require a reduction in insulin or sulfonylurea, unless they have a history of hypoglycaemia.[11] Patients taking SGLT-2 inhibitors must discontinue treatment during an acute illness or three days before an elective medical procedure.[11]

* Dual empagliflozin and dulaglutide treatment is not currently funded under the Special Authority criteria

**Table 3.** Key empagliflozin prescribing information.[11, 14, 15]

| | Formulation | Dose information | Notes |
|---|---|---|---|
| **Empagliflozin** | 10 mg and 25 mg, tablet | ■ Initiate at 10 mg daily<br>■ Increase to maximum of 25 mg daily after several weeks if no adverse effects AND as required for glycaemic control | ■ Maximum dose 10 mg, once daily, in patients with eGFR < 30 mL/min/1.73m$^2$ (efficacy of empagliflozin likely reduced as it is dependent on renal function, so additional glucose lowering treatment may be required)<br>■ Not recommended in patients on dialysis<br>■ No dose adjustment required for people with mild renal impairment |
| **Empagliflozin with metformin hydrochloride** | 5 mg empagliflozin with 500 mg or 1000 mg metformin, tablet | ■ Initiate at 5 mg empagliflozin twice daily (10 mg total daily dose); choose the dose of metformin similar to the dose already being taken | ■ Contraindicated for people with eGFR < 30 mL/min/1.73 m$^2$ due to metformin component |
| | 12.5 mg empagliflozin with 500 mg or 1000 mg metformin, tablet | ■ Maximum recommended daily dose is 25 mg empagliflozin and 2000 mg metformin | ■ Reduce metformin dose for people with renal impairment; no empagliflozin dose adjustment is required for people with mild renal impairment |

## At diagnosis:

**Discuss non-pharmacological treatment:**

- Lifestyle changes are the cornerstone of management; emphasise the importance of diet and exercise approaches regardless of which medicines are used
- Support and encourage patients to make lifestyle changes throughout follow-up
- Refer patients to support services, e.g. Green Prescription or dietitian, to assist with lifestyle changes

## Determine an appropriate $HbA_{1c}$ target:

**Prescribe an appropriate medicine regimen based on the extent of hyperglycaemia:**

- Initiate metformin at, or soon after diagnosis, unless contraindicated
- Consider initiating two pharmacological treatments at diagnosis (e.g. metformin and vildagliptin) if $HbA_{1c}$ > 64 mmol/mol
- Consider initiating insulin at diagnosis if patients have high $HbA_{1c}$ levels at diagnosis, e.g. > 80 – 90 mmol/mol

## Escalating treatment:

**DKD* or HF or known CVD or five-year CVD risk ≥ 15%?**

* DKD = urinary albumin:creatinine ratio > 3 mg/mmol and/or reduced eGFR

Yes

**HF or DKD predominates?**

Yes

**SGL T-2 inhibitor preferred**
(i.e. empagliflozin)†

No

**GLP-1 receptor agonist**
(i.e. dulaglutide)†
or **SGL T-2 inhibitor**
(i.e. empagliflozin)†

**Treatment not tolerated or $HbA_{1c}$ above target**

**Add another pharmacological treatment:**

- GLP-1 receptor agonist preferred treatment to add to SGLT-2 inhibitor
- SGLT-2 inhibitor preferred treatment to add to GLP-1 receptor agonist

N.B. Dual SGLT-2 inhibitor/GLP-1 receptor agonist treatment not currently funded

*Alternatives:*

- Vildagliptin, if not on GLP-1 receptor agonist
- Pioglitazone (unless heart failure)
- A sulfonylurea
- Insulin

No

**Add another pharmacological treatment:**

- SGLT-2 inhibitor†
- GLP-1 receptor agonist†
- Vildagliptin

*Alternatives*:

- Pioglitazone
- A sulfonylurea
- Insulin

† Special Authority criteria apply

DKD = diabetic kidney disease

HF = heart failure

CVD = cardiovascular disease

**Figure 1.** An overview of management of patients with type 2 diabetes. Adapted from the New Zealand Society for the Study of Diabetes type 2 diabetes guideline (2021).[11]

For further information on sick-day management, see: **t2dm.nzssd.org.nz/Section-95-Sick-day-management-in-patients-with-diabetes**

### Contraindications and cautions to empagliflozin treatment

If the patient's eGFR is < 30 mL/minute/1.73 $m^2$, the maximum recommended dose of empagliflozin is 10 mg, once daily. However, efficacy is dependent on renal function, and empagliflozin may be ineffective at reducing glucose levels in patients with this degree of renal impairment; additional glucose lowering treatment should be considered, as needed.[14] Empagliflozin should not be taken by patients on dialysis.[14]

Empagliflozin is not recommended for use in people with type 2 diabetes who:[11]

- Are pregnant or breastfeeding
- Have a history of severe genitourinary infections
- Are on a ketogenic diet (due to the increased risk of diabetic ketoacidosis – see below)

N.B. Previously, empagliflozin was only approved for use in people with type 2 diabetes aged ≥ 18 years. Since November, 2023, empagliflozin is now indicated in people aged ≥ 10 years as a monotherapy if metformin is not tolerated (and diet and exercise alone do not provide adequate glycaemic control), or in combination with other glucose-lowering medicines (under specialist supervision) if glycaemic control remains poor.

**Cautions.** Use of empagliflozin in people with nephrolithiasis/recurrent renal calculi was previously not recommended in the NZSSD guidance. However, updated advice is that empagliflozin may be used with caution in patients with a history of renal calculi if good hydration is ensured; extra caution is needed in those with recurrent calculi. Caution is also required when using empagliflozin in patients aged ≥ 75 years as they may be at risk of volume depletion.[14] Use was previously not recommended in patients aged ≥ 85 years, but this advice has been removed from the datasheet (Nov, 2023).

For further information, refer to the New Zealand Formulary: **www.nzf.org.nz/nzf_70809**

### Discuss potential adverse effects before initiating treatment

Adverse effects of SGLT-2 inhibitors such as empagliflozin include:[11]

- Polyuria – consider reducing diuretics before initiating treatment
- Genitourinary infections, e.g. urinary tract infection, vaginal thrush, balantitis – this is thought to be due to the increased urinary excretion of glucose. Ensure patients are given information on hygiene measures and the rare risk of necrotising fasciitis of the perineum (Fournier's gangrene).
- Hypotension – consider reducing antihypertensive medicines before initiating treatment or before a dose increase
- Diabetic ketoacidosis (DKA) – increased risk (see below)

**SGLT-2 inhibitor use is associated with an increased risk of severe DKA**

People taking SGLT-2 inhibitors are at increased risk of DKA, particularly in the first few months of treatment or peri-operatively.[11] **This can occur with normal blood glucose levels (euglycaemia).**[11] While this is a rare adverse effect (ranging from one in 1,000 to one in 3,000 people), this should be discussed with patients before initiating treatment, with advice provided on the symptoms and signs of DKA and when to seek medical attention to get their blood ketones checked (i.e. if they experience nausea, vomiting or abdominal pain).[11] In general, it is advisable to temporarily stop empagliflozin if patients are unwell and febrile, especially if they are not eating or vomiting.

N.B. Patients with type 2 diabetes taking a SGLT-2 inhibitor do not currently qualify for a funded CareSens Dual glucometer (measures both blood glucose and blood ketone levels).

For further information on SGLT-2 inhibitors and DKA, see: **diabetessociety.com.au/documents/ADS_DKA_SGLT2i_Alert_update_2020.pdf**

## Prescribing dulaglutide

When initiating dulaglutide, reinforce lifestyle advice and offer support as required, and provide information on how to administer treatment (see below). Metformin should be continued unless it is contraindicated or not tolerated.[11] Dipeptidyl peptidase-4 (DPP-4) inhibitors (i.e. vildagliptin) must be stopped before initiating a GLP-1 receptor agonist as they have similar mechanisms of action.[11] Other glucose-lowering treatments can be continued if needed for glycaemic control or cardiovascular or renal protection, with the dose of insulin or a sulfonylurea reduced to prevent hypoglycaemia, if required (see: "Prescribing empagliflozin" for guidance on dose reduction).[11] Advise patients to stop treatment if they have an acute gastrointestinal illness (and resume treatment once they have recovered).[11]

**Table 4.** Key dulaglutide prescribing information.[11, 16]

| Funded GLP-1 receptor agonist* | Formulation | Dose information |
|---|---|---|
| **Dulaglutide** | 1.5 mg per 0.5 ml prefilled pen, injectable | ■ Administered subcutaneously, once weekly; each pen contains one dose of dulaglutide and should only be used once |

* Other non-funded GLP-1 receptor agonists approved in New Zealand include liraglutide, exenatide and exenatide extended release (soon to be withdrawn from the local market)

**Dulaglutide administration guide:**[16]

- Dulaglutide is administered once weekly, at any time of day, with or without food
- Patients can inject dulaglutide in the abdomen, thigh or upper arm
- Injection sites should be rotated with each dose
- If a dose is missed, it should be administered as soon as possible if there are ≥ 3 days until the next scheduled dose; if < 3 days until the next dose, the missed dose should not be taken, and the next dose taken at the normal time
- If the regimen includes insulin, these should be administered as separate injections, i.e. not mixed. If injected in the same body region, ensure the injections are not next to each other.
- The single-use pen should be disposed of in a specified sharps container or a closable puncture-resistant container, i.e. not in the household rubbish*

* Community pharmacies and some Diabetes NZ branches offer sharps disposal services; patients can return their sharps in a specified sharps container (available to purchase) or other suitable container

Patient instructions for use of dulaglutide (with images) are available from: **uspl.lilly.com/trulicity/trulicity.html#ug**

### Contraindications and cautions to dulaglutide treatment

Dulaglutide is contraindicated in people with personal or family history of medullary thyroid carcinoma or a personal history of multiple endocrine neoplasia syndrome type 2.[11, 16] Rodent studies have shown an increased incidence of thyroid C-cell adenomas and carcinomas with GLP-1 receptor agonist treatment.[17] While a causal relationship has not been established and there is no evidence of increased prevalence of any form of thyroid cancer in humans with long-term use, dulaglutide is not recommended for use in people at increased risk of thyroid cancer, e.g. due to family history, radiation exposure.[11] Advise patients prescribed dulaglutide to seek medical advice if they develop any symptoms that could indicate thyroid cancer, e.g. a mass in the neck, dysphagia, dyspnoea, persistent hoarseness.[16]

Dulaglutide is not recommended for people:[11]

- Aged < 18 years
- Who are pregnant or breastfeeding
- With severe gastrointestinal disease, including gastroparesis
- With previous pancreatitis

### Mild adverse effects with dulaglutide are usually transient

Common adverse effects of GLP-1 receptor agonists include gastrointestinal disturbance (nausea [most common], vomiting, anorexia and diarrhoea) and injection site reactions (e.g. nodules, pruritus, bruising, erythema).[11, 18] These are usually transient and improve with continued treatment.[11] Rare adverse effects include pancreatitis, myalgias and muscle weakness, Stevens-Johnson's syndrome and thromocytopaenia.[11]

## Reviewing treatment and ongoing monitoring

Regular review of treatment is necessary for all patients with type 2 diabetes to optimise individual goals and ensure medicine regimens remain appropriate. Nutrition, physical activity and body weight monitoring should be discussed with patients at all stages of management. $HbA_{1c}$ levels should be checked every three months if they are above target and the treatment regimen has changed.[11] Once target $HbA_{1c}$ levels have been achieved, repeat measurement every six months and complete a diabetes review annually.[11] Renal function should be assessed at least annually in patients taking empagliflozin (with or without metformin) and prior to initiating any medicines that may reduce renal function.[14] No additional monitoring is required for patients taking dulaglutide.

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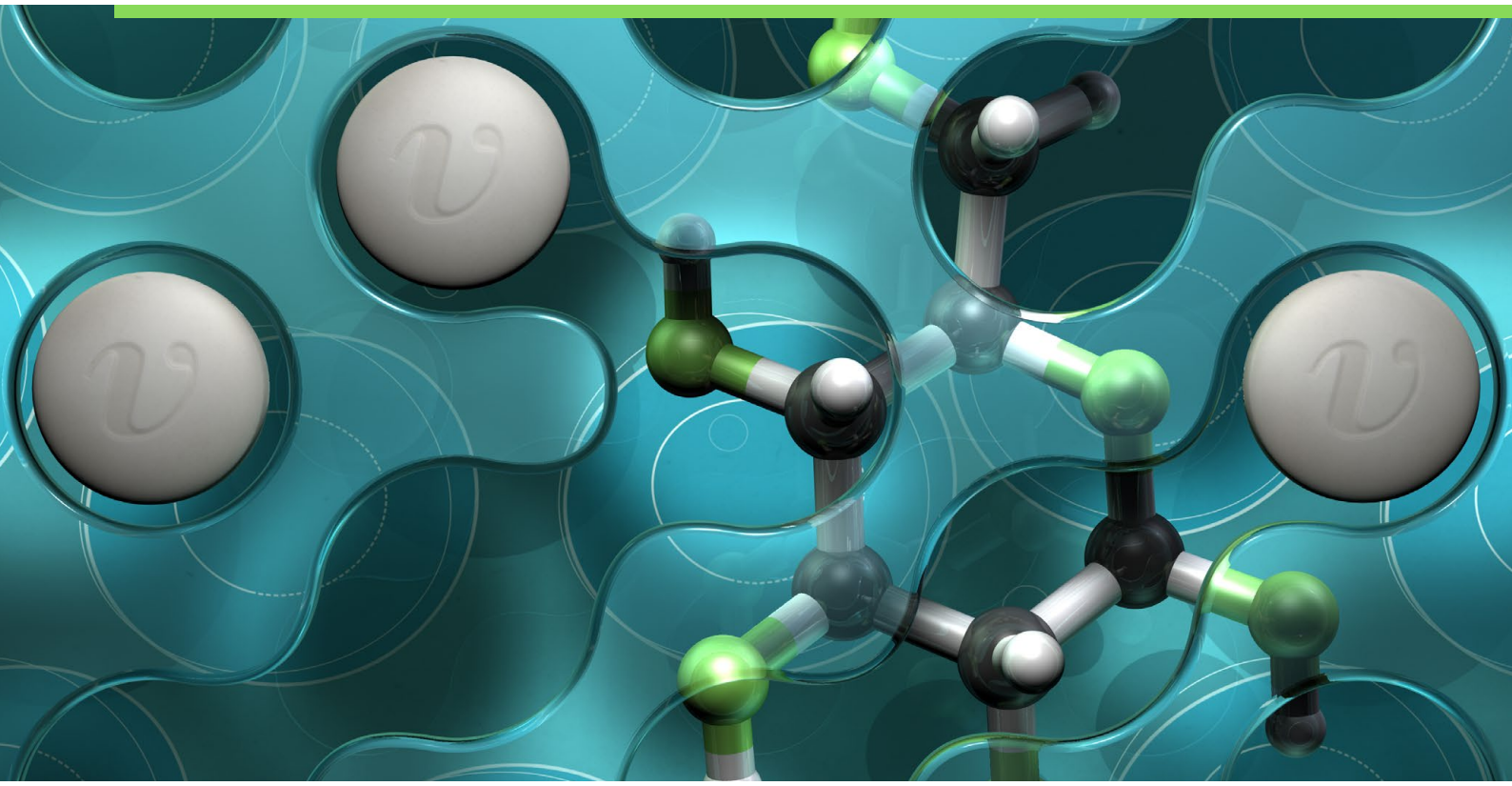

# Prescribing vildagliptin for type 2 diabetes

With two new medicines, empagliflozin and dulaglutide, available in New Zealand* for the management of type 2 diabetes, the place of vildagliptin in treatment has been revised. Vildagliptin is an option for patients who have not achieved sufficient lowering of $HbA_{1c}$ levels with metformin and are not eligible for funded treatment with empagliflozin or dulaglutide; other options include a sulfonylurea or pioglitazone.

* Special authority criteria apply

## KEY PRACTICE POINTS:

- Lifestyle interventions and metformin are the first-line treatments for people with type 2 diabetes
- If an additional pharmacological treatment is required, empagliflozin or dulaglutide are preferred for eligible patients, i.e. those who are at high risk of cardiovascular disease or have renal complications; vildagliptin is preferred for patients who are not eligible for funded treatment
- Vildagliptin is taken once or twice daily, and is available alone or in combination with metformin
- Vildagliptin results in reductions in $HbA_{1c}$ levels of 6 – 12 mmol/mol
- Vildagliptin does not cause weight gain and has less risk of hypoglycaemia than sulfonylurea medicines but is slightly less effective at reducing $HbA_{1c}$ levels
- Nasopharyngitis, headache and dizziness are the most common adverse effects associated with vildagliptin, occurring in 6 – 9% of patients

This is a revision of a previously published article. What's new for this update:

- Vildagliptin has been funded without restriction since October, 2018. It continues to have a place in the treatment of type 2 diabetes, even though new treatments are available.
- Vildagliptin is recommended for patients who require a step up in treatment but are not eligible for funded empagliflozin or dulaglutide treatment

## Vildagliptin is a DPP-4 inhibitor approved for the treatment of type 2 diabetes

Glucagon-like peptide-1 (GLP-1) is a hormone that is rapidly released from the intestine after eating.[1] GLP-1 signals to the pancreas to increase insulin release, and reduce glucagon release, after a meal. In combination, these effects lead to higher insulin levels and a lowering of blood glucose levels. The effects of GLP-1 are usually confined to the period immediately after eating, as it is broken down within minutes by the enzyme dipeptidyl peptidase-4 (DPP-4).[1]

Several anti-diabetic medicines have been developed which aim to amplify the effects of GLP-1. These include oral DPP-4 inhibitors (e.g. vildagliptin), which inhibit the DPP-4 enzyme and result in increased and prolonged action of GLP-1, and injectable synthetic versions of GLP-1 which are not broken down by DPP-4, known as GLP-1 mimetics or receptor agonists (e.g. dulaglutide).

Vildagliptin is typically used in combination with metformin, but can also be used concurrently with empagliflozin, a sulfonylurea, pioglitazone or basal insulin.[2] It cannot be used concurrently with GLP-1 receptor agonists, e.g. dulaglutide, due to a similar mechanism of action. In people with type 2 diabetes who are already taking metformin, adding vildagliptin once or twice daily to their treatment regimen reduces $HbA_{1c}$ levels by a further 7 – 12 mmol/mol after 12 weeks of treatment.[3, 4] When vildagliptin is used alone in people who do not tolerate metformin, it reduces $HbA_{1c}$ levels by an average of 6 – 9 mmol/mol.[5]

## Guidelines recommend lifestyle measures and metformin as first-line approaches

Lifestyle interventions and metformin are the cornerstone of treatment for people with type 2 diabetes (Step 1).[2] If a sufficient reduction in $HbA_{1c}$ levels is not achieved with metformin, treatment is typically escalated by reinforcing the importance of diet and exercise, and adding a second pharmacological treatment. Funded options at Step 2 include:

- Empagliflozin*†
- Dulaglutide†
- Vildagliptin*
- A sulfonylurea, such as gliclazide or glipizide
- Pioglitazone
- Arcabose

* Available in a single formulation and in combination with metformin

† Special Authority criteria apply for funded treatment. For further information, see: Page 22

For patients with higher $HbA_{1c}$ levels at diagnosis, e.g. > 64 mmol/mol, starting at Step 2 is recommended, i.e. initiating two oral medicines simultaneously (e.g. metformin and vildagliptin)*.[2] The use of insulin (Step 3) in addition to metformin is recommended for patients with marked hyperglycaemia at diagnosis (e.g. > 80 – 90 mmol/mol) to reduce $HbA_{1c}$ levels rapidly.[2]

People who have contraindications to, or cannot tolerate, metformin can initiate one of these other medicines alone.

* Other combinations may be preferable depending on the patient's risk factors, however, the Special Authority criteria for funded empagliflozin or dulaglutide treatment specify that the patient must have been taking another glucose-lowering medicine for at least three months to be eligible

### Vildagliptin is the preferred next step for people who are not eligible for funded empagliflozin or dulaglutide

Vildagliptin is recommended for patients who require a step up in pharmacological treatment but are not eligible for funded empagliflozin or dulaglutide treatment (or are unable to self-fund treatment as some patients may choose to do this).[2]

Vildagliptin is generally well tolerated, weight neutral, i.e. does not cause weight gain or weight loss, does not cause hypoglycaemia, and can be used safely in people with renal impairment.[2] N.B. Dose adjustment is required for patients with moderate or severe renal impairment (see: "Prescribing in patients with renal impairment", Page 31).

### Vildagliptin can be continued if insulin is initiated

Clinical trials have found that adding vildagliptin to insulin treatment results in an additional 6 – 7 mmol/mol reduction in $HbA_{1c}$ levels, without an increase in episodes of hypoglycaemia.[6] If patients initiate more complex insulin regimens, e.g. by adding rapid-acting insulin at meal-times, continuing the use of vildagliptin is possible.[7] However, in clinical practice, oral glucose-lowering medicines are often withdrawn if patients initiate complex insulin regimens in order to simplify their treatment.[8]

For further information on lifestyle management, escalating treatment and initiating insulin, see: "Type 2 diabetes management toolbox: from lifestyle to insulin", Page 6

## Prescribing vildagliptin

Vildagliptin is available in three formulations, all taken either once or twice daily:[9]

- 50 mg vildagliptin tablet
- 50 mg vildagliptin + 850 mg metformin tablet
- 50 mg vildagliptin + 1000 mg metformin tablet

Vildagliptin is prescribed as one 50 mg tablet (with or without metformin), either once or twice daily, depending on the extent of $HbA_{1c}$ reduction required and whether patients have renal impairment (Table 1).

If vildagliptin is prescribed concurrently with a sulfonylurea, e.g. in patients who are unable to tolerate metformin and require more than one oral glucose-lowering medicine, once daily dosing should be used as twice daily dosing does not provide any additional benefit.[10]

## Formulations of vildagliptin in combination with metformin may be simpler for patients and more effective

Observational data suggest patients are more likely to reach their target $HbA_{1c}$ level if vildagliptin and metformin are prescribed as a single tablet, which may be due to increased adherence with a simpler regimen.[11]

When taken alone vildagliptin does not need to be taken with food, however, patients prescribed a combination vildagliptin + metformin tablet should be advised to take their medicine with food as they would if taking metformin alone.

Rates of gastrointestinal adverse effects with vildagliptin + metformin treatment are similar to rates when metformin is taken alone.[12]

## Contraindications and cautions

Vildagliptin should not be taken by people who are in a state of ketoacidosis.[9] Prescribing vildagliptin to people aged < 18 years or to women who are pregnant or breastfeeding is not recommended due to a lack of clinical trials or data in these patient populations (Table 1).[9] Vildagliptin has been studied in people with heart failure, however, those with severe heart failure (New York Heart Association functional class IV) were excluded from trials and therefore prescribing in patients with severe heart failure is not recommended due to a lack of data.[10]

Vildagliptin should not be used at the same time as dulaglutide as they have similar mechanisms of action.

**Table 1:** Cautions and associated dosing recommendations for prescribing vildagliptin.[2, 9, 10, 14]

| Patient population | Prescribing or dosing recommendation | Explanations |
|---|---|---|
| Women who are pregnant or breastfeeding | Prescribing not recommended | There is a lack of safety data in women who are pregnant or breastfeeding |
| Patients with renal impairment: | | |
| Prescribing vildagliptin | Maximum once daily dosing of vildagliptin recommended in patients with eGFR < 50 mL/min/1.73m$^2$ | Some vildagliptin is excreted unchanged by the kidneys |
| Prescribing vildagliptin + metformin | Prescribing not recommended in patients with eGFR < 60 mL/min/1.73m$^2$ | Prescribing metformin and vildagliptin in separate tablets may be preferable to allow for an appropriate reduced dose of metformin |
| Patients with severe heart failure (New York Heart Association functional class IV) | Prescribing not recommended | There is a lack of safety data in this patient population |
| Patients with elevations of ALT or AST to over 2.5 times the upper limit of normal prior to initiation | Prescribing not recommended (see: "Contraindications and cautions") | A minority of patients (0.5%) have shown increases in ALT and AST levels to over three times the upper of normal in clinical trials |

**Testing liver function prior to initiation and monitoring during treatment is recommended**

In clinical trials a small proportion of people (0.5% or fewer) have experienced elevations in ALT or AST* levels to greater than three times the upper limit of normal.[13] Assessing liver function tests before initiating treatment and monitoring every three months for the first year is recommended.[2] Initiating vildagliptin is not recommended if patients have ALT or AST levels over two and a half times the upper limit of normal prior to treatment.[2] When prescribing vildagliptin, inform patients of symptoms associated with acute liver dysfunction, including nausea, jaundice, vomiting, abdominal pain and fatigue and advise them to seek medical attention if these occur.[9] If elevations in ALT or AST to greater than two and a half times the upper limit of normal occur during treatment, re-test liver function after considering and addressing other possible causes of hepatic dysfunction. New Zealand guidelines recommended withdrawing vildagliptin if patients persistently have ALT or AST levels greater than two and a half times the upper limit of normal; this is more conservative than the NZF and the manufacturer.[2, 9, 10]

* AST is not always routinely measured as part of LFTs in New Zealand, but can be requested

**Prescribing in patients with renal impairment**

Approximately one-quarter of a dose of vildagliptin is excreted unchanged by the kidneys, and the remainder metabolised by hydrolysis. In patients with an eGFR < 50 mL/min/1.73m$^2$, dosing should be once daily only.[9]

The manufacturer recommends to avoid prescribing vildagliptin + metformin formulations in patients with an eGFR < 60 mL/min/1.73m$^2$ due to the risk of metformin accumulation in patients with impaired renal function.[14] However, in clinical practice metformin can be prescribed to patients with impaired renal function provided appropriate dose reductions are used and renal function is monitored. For patients with an eGFR < 60 mL/min/1.73m$^2$, prescribing vildagliptin and metformin in separate tablets may be easier to allow an appropriate dose of metformin to be used in combination with vildagliptin.

## Adverse effects of vildagliptin

A minority of people taking vildagliptin experience adverse effects, including:[15]

- Nasopharyngitis: 9%
- Headache: 7%
- Dizziness: 6%
- Back pain: 6%
- Diarrhoea: 6%

These adverse effects are typically mild; approximately 2 – 5% of people choose to discontinue vildagliptin due to adverse effects.[16, 17]

The use of DPP-4 inhibitors is associated with an increased risk of pancreatitis, however, there is still considerable uncertainty regarding the strength of this association. A meta-analysis of three randomised controlled trials reported a statistically significant increased odds of acute pancreatitis in participants taking DPP-4 inhibitors, however, the difference in absolute risk was low, at 0.13%.[18] Bullous pemphigoid is a rare but serious complication of vildaglitpin treatment. The median time to onset is 11 months after treatment initiation.[19]

**Patients taking ACE inhibitors have a higher risk of angioedema, but the absolute rate is still low**

Patients with type 2 diabetes are often prescribed ACE inhibitors to treat hypertension or to reduce the risk or progression of diabetic nephropathy. Evidence suggests there may be an interaction between vildagliptin and ACE inhibitors which leads to an increased risk of angioedema, with a meta-analysis reporting an increased odds of angioedema of 4.57 (95% CI: 1.57 – 13.28) in people taking an ACE inhibitor who were also taking vildagliptin, compared to ACE inhibitor use alone.[20] However, the absolute risk remains small with an incidence rate of 0.5% or lower.[20] Reported cases have often occurred in the first three months of initiating vildagliptin in people already taking an ACE inhibitor.[21] Vildagliptin use alone is not associated with angioedema.[20]

## Switching patients from a sulfonylurea or pioglitazone

Patients who have been taking a sulfonylurea or pioglitazone but are experiencing adverse effects such as hypoglycaemia may wish to switch to vildagliptin. The half-life and duration of effect of sulfonylurea medicines is less than 24 hours, and patients taking these medicines could switch to vildagliptin the next day.[22] Pioglitazone has a half-life of seven hours or less, however, it is expected to have a prolonged duration of effect as a result of increasing insulin sensitivity.[22] Patients taking pioglitazone could initiate vildagliptin the next day with a more cautious approach to avoid hypoglycaemia, e.g. initially only taking vildagliptin once daily, before increasing to twice daily use.

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# **Initiating insulin** for people with **type 2 diabetes**

Due to its progressive nature, many people with type 2 diabetes will eventually require insulin treatment. In most cases, insulin can be initiated in primary care. A team approach with close follow-up is essential to enable patients with type 2 diabetes to optimally self-manage their insulin regimen.

## KEY PRACTICE POINTS:

- Consider insulin treatment for any person with type 2 diabetes who has not met their $HbA_{1c}$ target despite optimal lifestyle modification and pharmacological management with non-insulin glucose-lowering medicines
- Insulin initiation is recommended for all patients with significant hyperglycaemia (e.g. $HbA_{1c}$ > 90 mmol/mol) at any stage, including diagnosis
- Patients with type 2 diabetes are typically initiated on basal insulin; isophane insulin is an appropriate choice of basal insulin for most people
- Treatment intensification to a basal-bolus or biphasic insulin regimen should be considered for patients who have not reached their $HbA_{1c}$ target despite taking basal insulin for three months at 0.5 units/kg/day and/or achieving fasting blood glucose levels < 7 mmol/L
- The choice of a basal-bolus or biphasic regimen should be based on patient characteristics and preference, e.g. flexibility of meal times, carbohydrate intake and exercise, blood glucose monitoring and injection frequency, any cognitive or physical limitations on regimen complexity
- Ongoing advice, education and support are essential to ensure patients are confident with their prescribed insulin regimen; consider referral to a diabetes nurse specialist or education programme if available locally

This is a revision of a previously published article. What's new for this update:

- Insulin initiation is recommended for all patients with $HbA_{1c}$ > 80 – 90 mmol/mol at any stage, including diagnosis. This is higher than previously recommended (75 mmol/mol) due to the availability of more options to manage hyperglycaemia.
- Tables added to show the funded short-, intermediate- and long-acting and biphasic insulins available in New Zealand
- Information provided on calculating correction insulin doses
- Up to 30 g (rather than 12 – 15 g) of carbohydrate is now recommended for managing hypoglycaemia

## Insulin depletion is probable over time

Type 2 diabetes is a progressive disease characterised by insulin resistance and a decreasing ability of pancreatic β-cells to produce insulin. Both of these factors contribute to hyperglycaemia. Alongside lifestyle modifications, most patients with diabetes begin treatment with metformin (with or without other glucose-lowering medicines). However, due to the progressive nature of type 2 diabetes, treatment with insulin is eventually required in some patients.

### Making the decision to initiate insulin

New Zealand guidelines recommend that insulin treatment be considered for any person with type 2 diabetes who has not met their $HbA_{1c}$ target despite optimal lifestyle modification and pharmacological management with non-insulin glucose-lowering medicines.[1] Insulin initiation is recommended for all patients with significant hyperglycaemia (e.g. $HbA_{1c}$ > 80 – 90 mmol/mol)* at any stage, including diagnosis.[1]

* This is higher than previously recommended (75 mmol/mol) due to the availability of more options to manage hyperglycaemia[2]

**Reinforce the importance of lifestyle interventions**

Emphasise to all patients initiating insulin that this is not a substitute for a healthy lifestyle and that behavioural strategies such as exercise, healthy eating and smoking cessation should still continue. Alcohol consumption should be limited as this increases the risk of hypoglycaemia in patients taking insulin.

It may be possible for some people with type 2 diabetes, following significant weight loss, to stop taking insulin, especially if they have had diabetes for a short period, now have a body mass index (BMI) < 30 kg/m$^2$ and are close to or at their $HbA_{1c}$ target.

For further information on weight management, see: "Weight loss for the prevention and treatment of type 2 diabetes", Page 15 and **bpac.org.nz/2022/weight-loss.aspx**

**When to seek further advice**

Advice about an insulin regimen should be sought from a diabetes clinic in cases where:[3]

- The patient is a child or adolescent
- The patient is very lean or has lost weight rapidly – testing for glutamic acid decarboxylase (GAD) autoantibodies indicating type 1 diabetes may be appropriate
- There is repeated hypoglycaemia
- The patient is a vocational driver
- $HbA_{1c}$ levels remain above target following insulin initiation and titration – the $HbA_{1c}$ target should ideally be reached within three to six months of treatment initiation and optimisation[4]

## Choosing an insulin regimen

There are three main types of insulin regimens used by people with type 2 diabetes: basal, basal-bolus and biphasic. Selection of a regimen should be guided by the pattern of blood glucose results and individual patient factors (also see: "Treatment intensification: basal-bolus or biphasic?"). Typically, people with type 2 diabetes are initiated on basal insulin.

For a schematic representation comparing the duration of different insulins, see: **www.nzf.org.nz/nzf_3629**

**Basal regimens** use an intermediate/long-acting insulin (basal insulin) injected once or twice daily. Basal insulin reduces $HbA_{1c}$ by controlling hepatic glucose production. There are two types of basal insulin available fully funded in New Zealand (see: "Funded insulins available in New Zealand" for brand names and product variations):

- Isophane insulin (e.g. Humulin NPH or Protaphane), also known as NPH* insulin, is an intermediate-acting insulin – suitable for most patients
- Insulin glargine (e.g. Lantus), an insulin analogue, is a long-acting insulin – consider switching to this insulin if patients have significant hypoglycaemia with isophane insulin[5]

* Neutral Protamine Hagedorn (NPH)

**Basal-bolus regimens** use a rapid/short-acting (bolus) insulin injected before or with meals and snacks and an intermediate/long-acting (basal) insulin injected once or twice daily. Rapid/short-acting formulations reduce $HbA_{1c}$ by decreasing post-prandial glucose levels. Basal-bolus insulin regimens are usually administered as a flexible dose (i.e. carbohydrate counting to match insulin requirements to the carbohydrate content of the upcoming meal) but some patients may use a fixed dose, depending on their circumstances, e.g. if they are unable to count carbohydrates.

For information on carbohydrate counting, see: **bpac.org.nz/2019/diabetes-insulin.aspx**

**Biphasic regimens** use an intermediate-acting insulin mixed with a short-acting insulin, injected twice daily, i.e. before breakfast and dinner. Biphasic regimens are an alternative to basal-bolus regimens for patients who are taking basal insulin and require treatment intensification. A variety of pre-mixed biphasic insulins with differing proportions of intermediate-acting and short-acting insulin are funded (Table 2). A reasonable initial choice is a biphasic insulin containing a rapid-acting insulin analogue, e.g. Humalog Mix25 (biphasic insulin lispro) or Novomix30 (insulin aspart), because of the faster onset of action than those containing human neutral insulin, allowing patients to "inject and eat". Humalog Mix50

## Funded insulins available in New Zealand

Tables 1 and 2 show the funded insulin brand names and product variations available in New Zealand. The delivery device depends on the type of insulin used. There is some variability in the pens provided by different manufacturers which may make one preferable to another, e.g. maximum number of doses, whether they deliver insulin in half-unit increments, size of the dial, pressure needed on the injection button to deliver the dose.[11] "Memory pens" that remember the time and size of the last dose are also available.

In order to reduce the risk of prescription errors with insulin ensure:

- To use the full brand name of the insulin when prescribing – take care with products that have similar names, e.g. Humalog, Humalog Mix and Humulin; Novomix and Novorapid
- The patient understands their regimen, i.e. the type(s) of insulin and when to use, and knows to discuss with the prescriber if their prescription is different from usual
- The patient knows to discuss with the pharmacist if the product or packaging looks different from what they usually receive
- Ensure that any changes in insulin regimen are explained to the patient and clearly understood

**Table 1:** Funded short, intermediate and long-acting insulins as of June, 2022.[12]

| Insulin | Manufacturer | Brand | Formulation* | Injection device** | Time course (subcutaneous injection) |
|---|---|---|---|---|---|
| **Rapid/short-acting insulin** | | | | | |
| Insulin aspart | Novo Nordisk | Novorapid | 10 mL vial × 1 | Prescribe injection syringes with attached needle | Onset: 10 – 20 minutes<br>Peak: 1 hour<br>Duration: 2 – 5 hours |
| | | Novorapid Penfill | 3 mL cartridge × 5 | Use with Novo Nordisk insulin delivery systems | |
| | | Novorapid FlexPen | 3 mL prefilled disposable device × 5 | | |
| Insulin glulisine | Sanofi-Aventis | Apidra | 10 mL vial × 1 | Prescribe injection syringes with attached needle | |
| | | | 3 mL cartridge × 5 | Use with the following reusable injection pens:<br>■ AllStar<br>■ AllStar Pro<br>■ JuniorStar<br>■ ClikStar | |
| | | Apidra Solostar | 3 mL disposable device × 5 | | |
| Insulin lispro | Eli Lilly | Humalog | 10 mL vial × 1 | Prescribe injection syringes with attached needle | |
| | | | 3 mL cartridge × 5 | Use with HumaPen injection device | |

*Table continued on next page*

| Insulin | Manufacturer | Brand | Formulation* | Injection device** | Time course (subcutaneous injection) |
|---|---|---|---|---|---|
| **Short-acting insulin** | | | | | |
| Human neutral insulin | Novo Nordisk | Actrapid | 10 mL vial × 1 | Prescribe injection syringes with attached needle | Onset: 30 – 60 minutes<br>Peak: 2 – 4 hours<br>Duration: up to 8 hours |
| | | | 3 mL cartridge × 5 | Use with Novo Nordisk insulin delivery systems | |
| | Eli Lilly | Humulin | 10 mL vial × 1 | Prescribe injection syringes with attached needle | |
| | | Humulin R | 3 mL cartridge × 5 | Use with HumaPen injection device | |
| **Intermediate-acting insulin** | | | | | |
| Isophane insulin | Eli Lilly | Humulin NPH | 10 mL vial × 1 | Prescribe injection syringes with attached needle | Onset: 1 – 2 hours<br>Peak: 4 – 12 hours<br>Duration: 8 – 24 hours |
| | | | 3 mL cartridge × 5 | Use with HumaPen injection device | |
| | Novo Nordisk | Protaphane | 10 mL vial × 1 | Prescribe injection syringes with attached needle | |
| | | Protaphane Penfill | 3 mL cartridge × 5 | Use with Novo Nordisk insulin delivery systems | |
| **Long-acting insulin** | | | | | |
| Insulin glargine | Sanofi-Aventis | Lantus | 10 mL vial × 1 | Prescribe injection syringes with attached needle | Onset: 1 – 2 hours<br>No pronounced peak<br>Duration: 24 hours |
| | | | 3 mL cartridge × 5 | Use with the following reusable injection pens:<br>■ AllStar<br>■ AllStar Pro<br>■ JuniorStar<br>■ ClikStar | |
| | | Lantus SoloStar | 3 mL disposable device × 5 | | |

* All funded insulin formulations are at a concentration of 100 units/mL. Three months' supply may be dispensed at one time if endorsed "certified exemption" by the prescriber or pharmacist.

** Injection syringes and pen needles may be prescribed with subsidy if prescribed on the same form as insulin or if the patient has previously had a prescription of insulin and the prescription is endorsed; pharmacists may endorse the prescription if there is a prior record of insulin dispensing[13]

**Table 2:** Funded biphasic insulins as of June, 2022.[12]

| Insulin | Manufacturer | Brand | Mix | Rapid/short-acting insulin component | Intermediate-acting insulin component | Formulation* | Injection devices** |
|---|---|---|---|---|---|---|---|
| **Biphasic insulin lispro** | Eli Lilly | Humalog Mix25 | 25/75 | Insulin lispro 25 units/mL | Insulin lispro protamine‡ 75 units/mL | 3 mL cartridges × 5 | For use with HumaPen injection device |
| | | Humalog Mix50 | 50/50 | Insulin lispro 50 units/mL | Insulin lispro protamine‡ 50 units/mL | 3 mL cartridges × 5 | |
| **Biphasic isophane insulin** | Eli Lilly | Humulin 30/70 | 30/70 | Neutral human insulin 30 units/mL | Isophane insulin 70 units/mL | 10 mL vial × 1 | Prescribe injection syringes with attached needle |
| | | | | | | 3 mL cartridge × 5 | For use with HumaPen injection device |
| | Novo Nordisk† | Mixtard 30 | 30/70 | Neutral human insulin 30 units/mL | Isophane insulin 70 units/mL | 10 mL vial × 1 | Prescribe injection syringes with attached needle |
| | | Penmix 30 | 30/70 | Neutral human insulin 30 units/mL | Isophane insulin 70 units/mL | 3 mL cartridge × 5 | For use with Novo Nordisk insulin delivery systems |
| | | Penmix 50 | 50/50 | Neutral human insulin 50 units/mL | Isophane insulin 50 units/mL | 3 mL cartridge × 5 | |
| **Biphasic insulin aspart** | Novo Nordisk | Novomix 30 | 30/70 | Insulin aspart 30 units/mL | Insulin aspart protamine‡ 70 units/mL | Prefilled disposable devices × 5 (FlexPen) | |

* All funded insulin formulations are at a concentration of 100 international units/mL. Three months' supply may be dispensed at one time if endorsed "certified exemption" by the prescriber or pharmacist.

† Novo Nordisk brands of biphasic insulin isophane with insulin neutral (Mixtard 30, Penmix 30 and Penmix 50) **are being discontinued**. Penmix 40 was discontinued in 2022. Mixtard 30, Penmix 30 and Penmix 50 will continue to be listed on the Pharmaceutical Schedule until stock is exhausted (final shipment due by 30th September, 2024).

** Injection syringes, needles and pen needles are subsidised if prescribed on the same form as insulin or if the patient has previously had a prescription of insulin and the prescription is endorsed; pharmacists may endorse the prescription if there is a prior record of insulin dispensing[13]

‡ Insulin lispro protamine and insulin aspart protamine are intermediate-acting insulins that are only available as part of premixed biphasic preparations in New Zealand

may be helpful if the premixed insulin is administered with a large carbohydrate-based meal, particularly if the patient has postprandial hyperglycaemia with mixes containing 25% or 30% rapid/short-acting insulin.[1]

## Patients using insulin should begin self-monitoring of blood glucose

Self-monitoring of blood glucose is recommended to help guide insulin dosing and meal planning. For patients with type 2 diabetes initiating basal insulin, a once daily measurement is usually sufficient, taken either:

- Before breakfast (fasting) if initiating insulin injections in the evening; OR
- Prior to evening dinner if initiating insulin injections in the morning

The aim of treatment is to achieve blood glucose levels between 6 – 8 mmol/L at these times.[3]

For some patients self-monitoring of blood glucose levels may be useful before initiating insulin to determine their daily pattern of glycaemia, e.g. before and after main meals for three days prior to initiation.

**Various blood glucose meters are available fully funded**

There are three blood glucose testing meters currently fully funded* for people with type 2 diabetes who are taking insulin:[6, 7]

- CareSens N – big screen and large numbers
- CareSens N Pop – small, slim meter; backlit for testing in low light environments
- CareSens N Premier – big screen and large numbers; bluetooth functionality

These meters all use the CareSens N blood glucose test strips. Patients should be encouraged to keep a record of their blood glucose measurements, as well as noting any changes to their normal diet, routine or health. Logbooks are available from diabetes clinics or diabetes medicine manufacturers. All funded blood glucose meters can be read by the SmartLog software supplied by the manufacturer at no cost to the patient. Patients should bring their meter and logbook to their appointments. A variety of smartphone apps are also available to record data.

* The CareSens-Dual meter measures blood glucose and blood ketones (using the CareSens PRO and KetoSens test strips); this meter is not funded for people with type 2 diabetes

N.B. Although mainly used by people with type 1 diabetes, continuous blood glucose monitoring may be useful in some people with type 2 diabetes taking insulin.[8] For further information on continuous blood glucose monitoring, see: **bpac.org.nz/2019/diabetes-insulin.aspx**

Patient information on diabetes smartphone apps is available from: **www.healthnavigator.org.nz/apps/d/diabetes-apps/**

## Recommended initial isophane treatment regimen

New Zealand guidelines recommend starting with once daily basal insulin, administered in the evening to help reduce high blood glucose levels in the morning.[1] However, administering the injection in the morning may be appropriate for some patients who have increases in blood glucose levels throughout the day (Table 3).

**Table 3.** Patient characteristics to guide once daily dosing of basal insulin[9]

| Once daily injections at night are suitable for patients: | Once daily injections in the morning are suitable for patients with: |
|---|---|
| ■ With high blood glucose levels in the morning<br>■ At lower risk of nocturnal hypoglycaemia<br>■ Who can respond to a nocturnal hypoglycaemic event, e.g. have no mobility issues or can rely on assistance from others | ■ Blood glucose levels that increase throughout the day<br>■ Increased risk of nocturnal hypoglycaemia<br>■ Increased risk of consequences of a nocturnal hypoglycaemia event, e.g. living alone, frailty, risk of falls |

**A weight-based approach is recommended to determine the initial basal insulin dose:**[1]

- 0.1 units/kg daily if any of:
  - $HbA_{1c}$ < 64 mmol/mol
  - BMI < 18 kg/m$^2$ (less likely to have type 2 diabetes)
  - Older (e.g. aged > 65 years) or frailty
  - Renal or liver failure
- 0.2 units/kg daily if $HbA_{1c}$ > 64 mmol/mol and BMI > 18 kg/m$^2$

Patients will need to titrate the insulin dose upwards from this starting point based on their fasting blood glucose levels. Having patients adjust their own doses, rather than waiting for instructions from a clinician, is usually a more successful approach for achieving $HbA_{1c}$ targets.[10]

There are different methods for titration; New Zealand guidelines recommend increasing the dose by 10% or 2 units if patients have three consecutive days of fasting blood glucose levels > 7 mmol/L (i.e. the dose can be increased every three days).[1]

The upwards titration of basal insulin should be stopped if:[1]

- Hypoglycaemia occurs (blood glucose levels < 4 mmol/L); OR
- Fasting blood glucose levels are < 7 mmol/L; OR
- Dose > 0.5 units/kg/day – consider adding a rapid/short-acting insulin (usually one dose with the largest meal)

If fasting blood glucose levels < 6 mmol/L are recorded, insulin doses should be reduced:[3]

- Between 4 – 6 mmol/L: decrease insulin dose by 2 units
- < 4 mmol/L: decrease insulin dose by 4 units

## Treatment intensification: basal-bolus or biphasic?

Treatment intensification should be considered for patients who have not reached their $HbA_{1c}$ target after three months' treatment with basal insulin, despite achieving fasting blood glucose levels < 7 mmol/L and/or taking a dose of 0.5 units/kg/day.[1] The choice of intensification to a basal-bolus or biphasic regimen should be based on patient characteristics and preference (Table 4).

**Table 4**. Factors influencing the choice between a basal-bolus and biphasic regimen[1]

| Factor/characteristic | Basal-bolus | Biphasic (i.e. premixed) |
|---|---|---|
| Allows flexibility, e.g. for work patterns, exercise | Yes | No |
| Allows for varied diet and meal times | Yes | No |
| Likely requires rapid treatment intensification | Yes | No |
| Level of ability required to manage injections, e.g. cognitive, dexterity | Higher | Lower |
| Frequency of blood glucose monitoring | More frequent | Less frequent |
| Frequency of injections | More frequent | Less frequent |

A treatment algorithm from the NZSSD type 2 diabetes management guideline (2021) is available from: **t2dm.nzssd.org.nz/Insulin-Algorithm.html**

## Initiating a basal-bolus regimen

When adding bolus insulin to a basal regimen, start with a rapid-acting insulin immediately before the largest meal (also known as a "basal plus" regimen):[1]

- Start with 4 units or 10% of the basal dose (maximum starting dose is 10 units)
- Stop sulfonylurea once established on bolus insulin
- Continue lifestyle management and other glucose-lowering medicines
- Monitor blood glucose levels before and two hours after that meal
- Basal insulin dose may need to be reduced to prevent hypoglycaemia, particularly if $HbA_{1c}$ levels < 64 mmol/mol

**Increase the dose** of rapid-acting insulin by 2 units if blood glucose level increase with the meal is > 3 mmol/L on three occasions. Adherence and injection technique should be checked before increasing doses.

**Add bolus insulin at other meals** if $HbA_{1c}$ remains above the target or blood glucose levels increase by > 3 mmol/L at other meals. N.B. The doses of bolus insulin are likely to be different at different meals.

**Add correction doses of** rapid-acting insulin to treat pre-meal hyperglycaemia. The calculation is: 1 unit for every x mmol over 8 mmol/L, based on the total daily dose of basal + bolus insulin (see: Table 5 and Table 6). Initially it may be safer to limit the correction dose to a maximum of 6 – 10 units. Other correction doses may be added, e.g. before bed, but there should be at least three hours before correction doses.[1]

**Table 5.** Correction insulin dose calculation based on total daily insulin dose[1]

| Total daily dose of basal + bolus insulin | Correction dose calculation |
|---|---|
| ≤ 25 units/day | 1 unit for every 4 mmol > 8 mmol/L |
| 26 – 40 units/day | 1 unit for every 3 mmol > 8 mmol/L |
| 41 – 75 units/day | 1 unit for every 2 mmol > 8 mmol/L |
| ≥ 76 units/day | 1 unit for every 1 mmol > 8 mmol/L |

## Managing hypoglycaemia

Symptomatic hypoglycaemia can occur when a person's blood glucose level falls below 4.0 mmol/L.[1] People taking insulin need to be alert for the symptoms of hypoglycaemia and know how to manage the condition. The most common reasons for hypoglycaemia occurring in a person with type 2 diabetes are a lack of food, an increase in physical activity, administration of insulin or less commonly, a sulfonylurea, administering insulin into new sites if previous sites had lipohypertrophy, declining renal function or consumption of alcohol without food.[1]

Symptoms of hypoglycaemia include:[1]

- Hunger
- Blurred vision, headache, light-headedness
- Loss of concentration, confusion, irritability, fatigue
- Sweating, tingling around mouth and lips, trembling, weakness and possible loss of consciousness

A person with diabetes who suspects they are hypoglycaemic should stop what they are doing, sit down and check their blood glucose level. Hypoglycaemia is treated by consuming rapid-acting carbohydrate: 0.3 g/kg of body weight **OR** 30 g total (see below). N.B. weight-based management of hypoglycaemia is more effective.[1]

**Examples of 30 g* of rapid-acting carbohydrate include:**[1]

- 10 Dextro-Energy or Vita glucose tablets or 6 BD brand glucose tablets
- 30 g of glucose powder
- 6 teaspoons of sugar dissolved in water
- 350 mL of fruit juice or non-diet/zero soft drink
- 18 jellybeans
- 2 tablespoons of honey
- 3 tablespoons of jam
- 2 Hypofit gels

* Previously, a lower dose, e.g. 12 – 15 g was recommended. However, data from a 2018 New Zealand-based study has shown that 30 g glucose is more effective than the lower doses at resolving hypoglycaemia in people with type 2 diabetes.[14]

After ten minutes blood glucose levels should be reassessed and more glucose taken if required. This process should continue until blood glucose levels are above 4.0 mmol/L. A carbohydrate snack such as a slice of toast, two biscuits or crackers with cheese should then be eaten and blood glucose levels rechecked after 30 minutes.[1] Encourage patients to report any episodes of hypoglycaemia to their general practice as a change in insulin dose may be needed. The use of a MedicAlert bracelet is also recommended.

Ensure patients and their family/whānau are aware that if they experience a lowered level of consciousness, unusual behaviour or seizures, immediate medical attention must be sought (i.e. call an ambulance).

**Best Practice tip:** Patients who believe they may be experiencing nocturnal hypoglycaemia can confirm this by setting an alarm and performing a blood glucose test during the night (e.g. at 3 am) on several occasions.

## Example of how to calculate a correction dose of insulin

If a patient is taking 40 units of basal insulin once daily (evening dosing) and 10 units of bolus insulin with meals their total daily dose is 70 units per day, so their starting correction is 1 unit for every 2 mmol > 8 mmol/L.

**Table 6.** Example correction insulin dose based on blood glucose levels and total daily dose of 70 units insulin daily[1]

| Blood glucose level (mmol/L) | Correction dose of insulin (unit) | Total insulin dose (bolus + correction) with meal (unit) |
|---|---|---|
| < 10 | 0 | 10 |
| 10 – 11.9 | 1 | 11 |
| 12 – 13.9 | 2 | 12 |
| 14 – 15.9 | 3 | 13 |
| 16 – 17.9 | 4 | 14 |
| 18 – 19.9 | 5 | 15 |
| ≥ 20 | 6 | 16 |

### Initiating a biphasic regimen

Emphasise to patients the importance of premixing insulin by gently inverting the device before each use to reduce the risk of hypoglycaemia.

The type of biphasic regimen depends on whether the patient predominantly has one large meal per day or multiple meals per day (Table 7). Adherence and injection technique should be checked before any dose increases.

**If after three months of optimised treatment $HbA_{1c}$ levels remain above the target,** consider:[1]

- Switching one or both injections to Humalog Mix50 if significant hyperglycaemia after meals
- Adding bolus insulin at other meals if blood glucose levels increase > 3 mmol/L at these times (e.g. lunch, large snacks)
- Switching to a basal-bolus regimen

## Education is key for patients initiating insulin

Ongoing advice and education are paramount to ensure patients are confident with their prescribed insulin regimen.

An initial session for patients starting insulin should cover:[1, 3, 4]

- Self-monitoring of blood glucose levels
- How to use their injection device, injection technique and rotation of injection sites

**Table 7.** Guide for initiating biphasic insulin in people with type 2 diabetes[1]

| Predominately one large meal per day | Multiple meals per day |
|---|---|
| Start **once daily** premixed insulin:<br>■ Convert the daily dose of basal insulin to premixed insulin<br>■ Administer before the largest meal<br>■ Monitor blood glucose levels before and two hours after that meal<br>■ Increase dose by 10% if blood glucose level increase with that meal is > 3 mmol/L and fasting blood glucose level is > 10 mmol/L | Start **twice daily** premixed insulin:<br>■ Convert the daily of dose basal insulin to premixed insulin<br>■ Administer half the dose before breakfast and the other half before dinner; consider a different ratio if there is a large difference in meal sizes or the patient is older, e.g. 2/3 of the total daily insulin dose before the larger meal and 1/3 before the smaller meal; older people should have lower evening doses<br>■ Monitor blood glucose levels before and two hours after that meal<br>■ If on three occasions blood glucose levels increase > 3 mmol/L with breakfast and pre-dinner blood glucose levels are > 10 mmol/L, increase the breakfast dose by 10%<br>■ If on three occasions blood glucose levels increase > 3 mmol/L with dinner and pre-breakfast blood glucose levels are > 10 mmol/L, increase the dinner dose by 10% |

- Appropriate storage of insulin and disposal of injection devices and needles
- How to titrate the insulin dose based on self-measurement of blood glucose levels
- What to do during disruptions to their typical daily routine, such as if they are acutely unwell, miss meals or are travelling
- Managing hypoglycaemia (see "Managing hypoglycaemia", Page 40), including how diet and exercise can affect the risk, recognising symptoms, testing blood glucose levels during suspected hypoglycaemia and how to respond if levels are too low
- Driving safely while using insulin and any impact using insulin may have on their fitness to drive (see: **t2dm.nzssd.org.nz/Section-100-Diabetes-and-driving**)
- Use of a Medic Alert bracelet

The initial session will likely require a longer consultation time and/or a team approach with the general practitioner, nurse practitioner or practice nurse; consider referral to a diabetes nurse specialist or education programme covering the above points if offered by the local DHB or PHO.

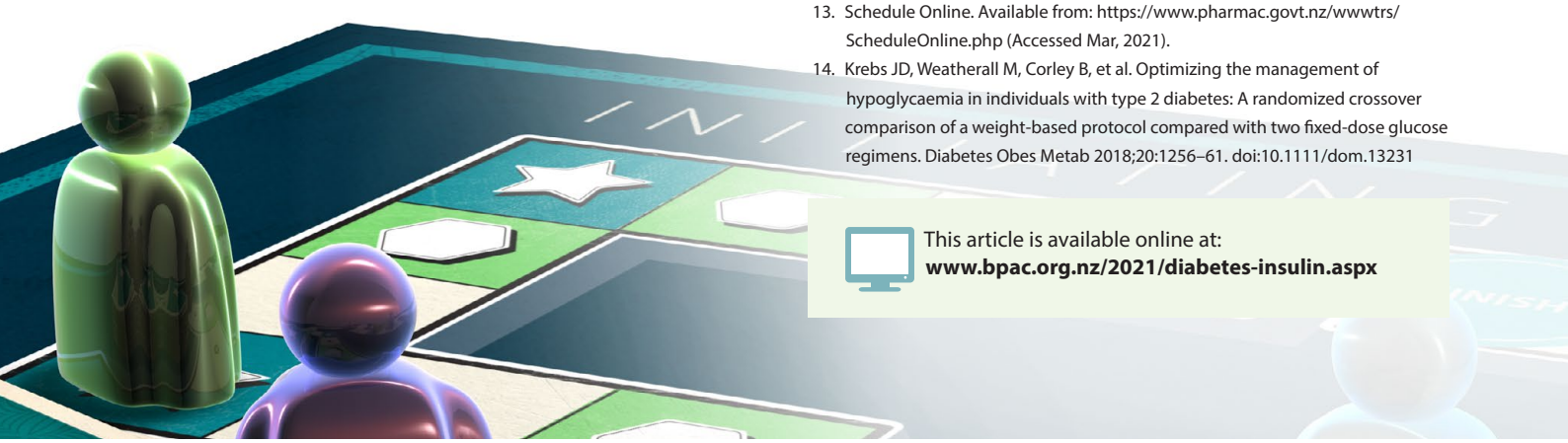
After the initiation of insulin, make regular contact with the patient, e.g. phone calls from the practice nurse with in-person or virtual consultations, as required, until satisfactory glycaemic control is achieved.

## Further resources

Diabetes group education classes are offered by local Diabetes Centres. Diabetes New Zealand provides additional information on subjects such as healthy eating and exercise as well as providing links to support groups and research publications.

Pamphlets for patients can be downloaded or ordered from: **www.diabetes.org.nz/pamphlet-ordering**

The Diabetes New Zealand "Take Control Toolkit" for patients is available at no cost as a smartphone app: **https://www.diabetes.org.nz/take-control-toolkit**



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N.B. Expert reviewers do not write the articles and are not responsible for the final content. bpac[nz] retains editorial oversight of all content.

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This article is available online at:
**www.bpac.org.nz/2021/diabetes-insulin.aspx**

# The annual diabetes review: **screening, monitoring and managing complications**

An annual diabetes review allows for assessment of glycaemic control and earlier detection of, and intervention for, diabetes-related complications. It also creates an opportunity to regularly review and assess individual treatment plans and provide support if required.

**KEY PRACTICE POINTS:**

- Regular review of patients with diabetes is essential to prevent or delay the onset of diabetes complications and slow their progression
- Every patient with type 2 diabetes should be reviewed at least annually; more frequent review may be indicated depending on the patient's risk factors
- The main components of a diabetes review are an examination of the feet, assessing cardiovascular disease (CVD) risk, requesting $HbA_{1c}$, lipid levels, renal and liver function tests, assessing mental health and general wellbeing, and ensuring retinal photoscreening is up to date
- The cornerstones of managing CVD risk and preventing or delaying microvascular complications are lifestyle interventions, optimising glycaemic control, blood pressure and lipid levels; pharmacological treatment is often indicated depending on the patient's risk factors and individualised treatment targets

## Diabetes complications: prevention and early detection are key

Diabetes is associated with a range of complications that are a major cause of disability, morbidity and mortality, including vision loss, lower-limb amputation, renal and cardiovascular disease.[1] With the prevalence of type 2 diabetes in New Zealand predicted to increase by 70 – 90% in the next 20 years, the burden of diabetes complications on patients and the healthcare system will also increase.[2] Ensuring patients are regularly reviewed is essential to preventing or delaying the onset of diabetes complications and slowing their progression.

### Types of diabetes complications

The main complications of diabetes are classified as microvascular or macrovascular complications.

Microvascular complications of diabetes include:[3]

- Retinopathy
- Nephropathy
- Neuropathy – peripheral and autonomic (e.g. erectile dysfunction)

Macrovascular complications of diabetes include:[3]

- Cardiovascular disease (CVD)
- Cerebrovascular disease
- Peripheral vascular disease

Other conditions that are commonly associated with diabetes include:[3]

- Increased risk of infection, e.g. skin, recurrent genitourinary infection, fungal infection
- Dermatological, e.g. diabetic dermopathy, acanthosis nigricans, psoriasis
- Dental and periodontal disease
- Gout
- Polycystic ovary syndrome
- Mental illness, e.g. depression, dementia and disordered eating
- Musculoskeletal, e.g. frozen shoulder, carpal tunnel, Dupuytren's contractures
- Gastrointestinal, e.g. non-alcoholic fatty liver disease, diarrhoea or constipation (due to diabetic autonomic neuropathy)[4]
- Solid cancers, e.g. breast, bowel, lung, pancreatic, ovarian

## Risk factors for diabetes complications

All people with type 2 diabetes are at risk of long-term complications. Factors that increase this include:[3]

- Early onset diabetes
- Older age
- Māori or Pacific ethnicity; any non-European ethnicity
- Low socioeconomic status
- Long duration of diabetes
- Poor glycaemic control
- Pre-existing complications or co-morbidities, e.g. established CVD, microalbuminura and/or reduced estimated glomerular filtration rate (eGFR), hypertension, dyslipidaemia, obesity
- Smoking
- Reduced engagement with health services
- Poor adherence to treatment

## The basic components of an annual diabetes review

The following list describes the basic components of an annual diabetes review. In practice, these may be reviewed at different times, but all should be performed at least once per year.[3] More frequent review may be indicated depending on the patient's risk factors.

N.B. An annual review is a quality standard of care for all people with type 2 diabetes in New Zealand.[5]

- **Measure:**
  - ☐ Weight and waist circumference*
  - ☐ Blood pressure
- **Examine:**
  - ☐ Neurovascular examination of the feet (also include skin, nails, deformity)
  - ☐ Teeth and gums
- **Request:**
  - ☐ $HbA_{1c}$
  - ☐ Urinary albumin:creatinine ratio
  - ☐ Serum creatinine
  - ☐ Liver function tests
  - ☐ Non-fasting lipid studies
- **Review:**
  - ☐ Ensure retinal photoscreening is up to date (every two years)
  - ☐ Cardiovascular symptoms (e.g. chest pain) and risk – using a validated CVD risk calculator (see below)
  - ☐ Smoking status
  - ☐ Alcohol intake and recreational drug use
  - ☐ Mental health – see: "Stay vigilant for diabetes burnout and distress"
  - ☐ Influenza, pneumococcal and COVID-19 immunisation status – people with diabetes are eligible for funded annual influenza vaccination and early access to COVID-19 vaccination; pneumococcal vaccination is recommended, but not funded. See the Immunisation Handbook 2020 for further information: **www.health.govt.nz/our-work/immunisation-handbook-2020**
  - ☐ Contraception – pregnancy planning is recommended for women with known diabetes who wish to conceive, e.g. ensure glycaemic control is optimal and the medicine regimen is appropriate while pregnant and breastfeeding
  - ☐ Ensure cervical, breast and bowel cancer screening up to date
  - ☐ Any other associated complications, e.g. sexual dysfunction, recurrent skin or genitourinary infection

* Although waist circumference measurement is recommended in guidelines, in practice this may be of limited usefulness and is therefore not essential

The recommended CVD risk calculator for people with type 2 diabetes is available from the New Zealand Society for the Study of Diabetes**: www.nzssd.org.nz/calculators/calculator/1/cvd-risk-assessment**

Further information on managing diabetes in pregnancy is available in the New Zealand Society for the Study of Diabetes type 2 diabetes management guidance, available from: **https://t2dm.nzssd.org.nz/Section-99-Diabetes-in-pregnancy**

## Managing type 2 diabetes complications

Lifestyle interventions (i.e. exercise and dietary management for weight loss, smoking cessation, reducing alcohol intake) and optimisation of glycaemic control, blood pressure and lipid levels are the cornerstones of managing CVD risk and preventing or delaying microvascular complications. Pharmacological treatment is often indicated, depending on the patient's risk factors and individualised treatment targets.

For further information on optimising glycaemic targets in older people, see: **bpac.org.nz/2019/diabetes-elderly.aspx**

For further information on weight loss for people with type 2 diabetes, see: "Weight loss for the prevention and treatment of type 2 diabetes", Page 15

### Managing CVD risk in people with type 2 diabetes

**Hypertension**

Individualised blood pressure targets are recommended for people with hypertension and type 2 diabetes (Table 1). Less stringent targets may be indicated for patients at higher risk from hypotension, e.g. older people, diabetic autonomic neuropathy.[3]

A CVD risk calculator validated for use in people with type 2 diabetes is available here: **www.nzssd.org.nz/calculators/calculator/1/cvd-risk-assessment**

N.B. CVD risk calculators may underestimate risk in younger patients or those with a strong family history.[3]

**Pharmacological treatment choice is guided by the presence of diabetic kidney disease**

The type of pharmacological treatment for patients with type 2 diabetes and hypertension is determined by whether they have diabetic kidney disease (DKD):[3]

- **If DKD present:** Initiate an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB)
- **If DKD absent:** Initiate an ACE inhibitor, ARB, calcium channel blocker or thiazide diuretic first-line; an ACE inhibitor is recommended first-line for patients with heart failure[6]

Multiple antihypertensives are often required to achieve a blood pressure < 130/80 mmHg and there should be a low threshold for initiation of a second antihypertensive, e.g. a calcium channel blocker.[3]

For further information on selecting an antihypertensive, see: **bpac.org.nz/2021/ace.aspx**

For further information on managing DKD, see: **bpac.org.nz/2019/renal.aspx**

**Dyslipidaemia**

The decision to initiate a statin in people with type 2 diabetes is determined by the patient's CVD risk and whether they have established macrovascular or renal complications (Table 2).[3] A target LDL cholesterol of < 1.8 mmol/L is recommended for patients with CVD risk > 15% or a TC/HDL-C ratio ≥ 8, with treatment titrated based on non-fasting lipid studies every three to six months until the target is reached.[3] Patients who have a five-year CVD risk > 15% and LDL cholesterol > 2 mmol/L despite taking the maximum tolerated dose and potency of statin should have ezetimibe added to their regimen (Special Authority approval required).[3]

**Table 1.** Blood pressure targets for people with type 2 diabetes and hypertension[3]

| Patient category | Blood pressure (BP) target | |
|---|---|---|
| | Systolic | Diastolic |
| Known microvascular or macrovascular complications OR five-year CVD risk > 15% | < 130 mmHg | < 80 mmHg |
| No microvascular or macrovascular complications AND five-year CVD risk < 5% | < 140 mmHg | < 90 mmHg |
| Five-year CVD risk 5 – 15% | < 130 mmHg | < 80 mmHg |
| Young patients with microvascular or macrovascular complications | < 125 mmHg | < 75 mmHg |

## Stay vigilant for diabetes burnout and distress

Emotional distress due to living with diabetes and the burden of self-management, termed "diabetes distress", is common among people with diabetes, affecting one in five people with type 2 diabetes who are treated with insulin and one in six people who are not treated with insulin.[12] Diabetes distress ranges in severity and can fluctuate over time; following diagnosis, major changes in treatment, diagnosis or worsening of complications, and heightened life stress, are times when the emotional burden of diabetes management can peak.[12] Diabetes distress is a risk factor for worsening diabetes control (see below), worsening severity of diabetes distress, and depression or anxiety disorders.[12]

Routinely ask people with type 2 diabetes about how they are coping with self-management and how they feel about living with type 2 diabetes and life in general; diabetes distress relates specifically to living with and managing diabetes, while depression affects how they feel about life in general (which may include how they feel about living with diabetes).[12] If the conversation suggests symptoms of depression or anxiety, a screening inventory, e.g. the PHQ-9 or GAD-7 questionnaires, can be used to aid diagnosis and assess severity (see below).[12]

**Non-adherence is a risk factor for worsening diabetes control**

Treatment adherence is essential for preventing or delaying diabetes complications, yet many patients experience issues with adherence at some point along their diabetes journey. Factors contributing to treatment non-adherence include: [13, 14]

- Younger age
- Longer duration of disease
- Lack of perceived benefit of medicines
- Hypoglycaemia
- Regimen complexity and inconvenience
- Clinician-patient relationship
- Access to healthcare

Patient self-reporting, regular monitoring of $HbA_{1c}$, review of blood glucose monitoring (for patients taking insulin) and whether patients return for repeat prescriptions on time, are the most practical indicators about adherence for prescribers. Asking patients in a non-judgemental manner how they are managing with their medicines may be a helpful way to initiate the conversation.

Strategies to improve adherence could include:[13, 14]

- Patient education that includes discussion of the importance of good diabetes control for future health and addresses patient fears, misconceptions or misgivings about treatment
- Regular treatment review to:
  - Assess dose or treatment type, e.g. if adverse effects are intolerable
  - Assess regimen and consider simplification, including medicines for co-morbidities
- Establishing a plan for monitoring and communicating issues with hypoglycaemia in patients who are initiating sulfonylureas or insulin
- Encouraging use of smartphone apps or reminders to take their medicines; for examples, see: **www.healthnavigator.org.nz/apps/m/medication-reminder-apps/**
- Flag patients with a history of non-adherence or who are at risk of non-adherence for follow up with a practice nurse by phone or text at the time of prescription renewal

*bestpractice* by BPAC Clinical Solutions offers a range of electronic decision support tools for assessing and managing patients with depression. These modules are part of a nationally-funded suite of resources available free-of-charge to all primary care practices in New Zealand. There are separate modules for managing adults, elderly people, young people and women in the antenatal and postnatal periods with depression. The assessments incorporate the PHQ-9, GAD-7, and EPDS questionnaires and the K10 checklist. For further information, see: **www.bestpractice.net.nz/feat_mod_NatFunded.php**

The PHQ-9 questionnaire is available from: **www.healthnavigator.org.nz/tools/p/patient-health-questionnaire-9-phq-9/**

The GAD-7 questionnaire is available from: **www.healthnavigator.org.nz/tools/g/general-anxiety-scale-gad-7/**

**Table 2.** Statin treatment recommendations for people with type 2 diabetes[3]

| Patient category | Treatment recommendation |
|---|---|
| Established macrovascular complications OR five-year CVD risk > 15% | Statin recommended |
| Five-year CVD risk 5 – 15% | Consider statin |
| Five-year CVD risk < 5% | Consider statin if one of the following:<br>■ Young<br>■ Strong family history of early cardiovascular disease<br>■ History of familial hypercholesterolaemia |
| DKD | Statins recommended regardless of CVD risk |

For further information on prescribing statins, see: **bpac.org.nz/2021/statins.aspx**

**Consider antiplatelet treatment for patients with high CVD risk**

Aspirin, 100 mg daily, is recommended for secondary prevention in all patients with type 2 diabetes; clopidogrel can be used if aspirin is not tolerated.[3] Consider aspirin for primary prevention for patients with five-year CVD risk > 15% AND a low risk of bleeding.[3] People with diabetes have a small increased risk of bleeding[7]; this risk may outweigh the benefits of treatment for primary prevention in patients with lower CVD risk.[3]

For further information on prescribing aspirin for CVD risk management, see: **bpac.org.nz/2018/aspirin.aspx**

## Managing microvascular complications

### Diabetic retinopathy

Diabetic retinopathy is a common microvascular complication of diabetes; there are two main types:[8]

- **Non-proliferative retinopathy** – characterised by increasing numbers of microaneurysms; at moderate to severe stages, vascular permeability increases, which can lead to macular oedema
- **Proliferative retinopathy** – characterised by the growth of new blood vessels on the retina and posterior surface of the vitreous; formation of scar tissue can cause the retina to detach, leading to permanent vision loss

Diabetes can also increase the risk of other eye conditions, such as cataracts.[3] The main risk factors for diabetic retinopathy are the duration of diabetes (i.e. the longer the duration the greater the risk) and poor glycaemic control; other risk factors include nephropathy, hypertension, dyslipidaemia and smoking.[4]

Key points for preventing or slowing the progression of diabetic retinopathy:[3, 4, 8]

- Refer all newly diagnosed patients with type 2 diabetes for retinal photoscreening; screening should be repeated at least every two years
- All pregnant women with diabetes prior to pregnancy should undergo additional photoscreening in the first trimester; women who develop gestational diabetes do not require photoscreening
- Ensure that glycaemic control and management of hypertension and dyslipidaemia are optimised
- In patients with macular oedema, stop pioglitazone as this can exacerbate the condition by increasing fluid retention. New Zealand guidelines recommended considering initiation of a fibrate (e.g. bezafibrate [unapproved indication]).[3] There is some evidence that fibrate treatment slows the progression of diabetic retinopathy.[9]
- Urgently refer patients with rapid vision deterioration for ophthalmology assessment

For further information on diabetic retinopathy, see: **bpac.org.nz/bpj/2010/august/retinopathy.aspx**

### Diabetic kidney disease (DKD)

Key points for managing patients with DKD:[3]

- Initiate an ACE inhibitor or ARB in patients with microalbuminuria (two or more urinary albumin:creatinine ratios (ACRs) in > 3 months of > 2.5 mg/mmol in males and > 3.5 mg/mmol in females) or a decline in eGFR:
  - Repeat the measurement of serum creatinine and potassium 7 – 10 days after initiating an ACE inhibitor or ARB. If eGFR decreases by > 25% or potassium > 6 mmol/L, reduce or stop the ACE inhibitor or ARB.

- Consider adding spironolactone for patients with macroalbuminuria (urinary ACR > 30 mg/mmol) and hypertension, but also consider the risk of hyperkalaemia and further decline in eGFR
- Strongly consider initiating empagliflozin, a sodium glucose co-transporter 2 (SGLT-2) inhibitor, or dulaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, as these medicines have direct beneficial effects on the kidney and improve renal outcomes in people with type 2 diabetes (Special Authority approval required)[10]
- Strongly consider initiating a statin – recommended regardless of the patient's CVD risk

Monitor the patient's serum creatinine, potassium levels and urinary ACR every three to six months.[3] Ensure doses of other treatments are adjusted accordingly to any decline in eGFR.[3]

For further information on managing diabetic kidney disease, see: **bpac.org.nz/2019/renal.aspx**

For further information on empagliflozin and dulaglutide, see: "New diabetes medicines funded: empagliflozin and dulaglutide", Page 19

### The "diabetic foot": managing peripheral diabetic neuropathy and peripheral vascular disease

Key points for managing the diabetic foot in primary care include:[3, 11]

- Optimise glycaemic control and management of hypertension and dyslipidaemia
- Recommend and support smoking cessation to slow progression of peripheral vascular disease
- Provide advice on basic foot care:
  - How to self-check feet
  - Wearing suitable footwear
  - Nail care
  - Moisturising dry feet – consider prescribing cetomacrogol aqueous cream + glycerol (e.g. Sorbolene)
  - When to seek medical advice
- Treatment options for neuropathic pain include:
  - Analgesics for mild pain, e.g. paracetamol or a NSAID. N.B. Use NSAIDs with caution in people with renal impairment, particularly if taking an ACE inhibitor or ARB.
  - Low-dose tricyclic antidepressant, e.g. nortriptyline, amitriptyline (unapproved indication for both medicines) taken in the evening to assist sleep and minimise daytime somnolence
  - Pregabalin or gabapentin
  - Carbamazepine
  - Topical capsaicin 0.075% for localised pain (subsidised by endorsement)

Refer to the New Zealand Formulary for dosing information on medicines used for neuropathic pain: **www.nzf.org.nz/nzf_2556**

For further information on managing diabetic peripheral neuropathy, see: **bpac.org.nz/bpj/2014/june/diabetic-peripheral-neuropathy.aspx**

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**www.bpac.org.nz/2021/diabetes-review.aspx**

# A rising tide of type 2 diabetes in younger people: what can primary care do?

An increasing incidence of early onset type 2 diabetes in New Zealand is putting more people at risk of complications and early mortality. Primary healthcare professionals should consider how they can use their role to identify young people at high risk and support them to create a different future.

## KEY PRACTICE POINTS:

- The incidence of type 2 diabetes in younger adults and adolescents in New Zealand is increasing; people of Māori, Pacific and South-Asian ethnicities are particularly at risk
- People with early onset type 2 diabetes have increased morbidity and mortality compared to those with a later onset or to those of similar age with type 1 diabetes
- Preventing, or delaying, onset of type 2 diabetes is paramount to reducing the burden of diabetes complications; this may be possible with careful management
- Test $HbA_{1c}$ levels in patients at high risk, regardless of their age, so that patients and their whānau/family can be supported to make lifestyle changes before or soon after they develop diabetes
- The management of type 2 diabetes in younger people is essentially the same as for older people, i.e. lifestyle interventions and metformin first-line, but treatments need to be more assertive, e.g. pharmacological treatment escalated sooner
- A high degree of patient and whānau/family engagement is crucial to maximise the benefits of lifestyle changes and ensure that medicines are taken as prescribed

This is a revision of a previously published article. What's new for this update:

- Updated data on the estimated prevalence of type 2 diabetes in those aged 25 – 39 years
- Begin CVD risk assessment, including $HbA_{1c,}$ at age 25 years for people with severe mental illness
- Updated recommendations on screening and management of type 2 diabetes in children and adolescents

## Early onset type 2 diabetes: increasingly common and associated with higher risks

New Zealand has a diabetes problem, fuelled in part by one of the highest rates of obesity in the world.[1] Approximately 5% of the total population has type 2 diabetes; this is predicted to increase to 7% of the population by 2040 (equating to an estimated 430,000 people with type 2 diabetes).[2] The prevalence of diabetes is highest in older age groups, reaching approximately 15 – 20% in people aged over 65 years; however, the prevalence is also increasing in younger people in New Zealand.[3] Data from the Ministry of Health's Virtual Diabetes Register show the prevalence of type 2 diabetes* in people aged 30 – 39 years has nearly doubled between 2006 and 2018 (Figure 1). Increases in diagnoses in children aged under 15 years have also been observed, although absolute numbers are still small.[4] People of Māori, Pacific and South-Asian ethnicity, and people who are socioeconomically disadvantaged, bear a disproportionate burden of obesity and type 2 diabetes. The prevalence of diabetes is approximately two to three times higher in adults aged 25 – 39 years of Māori and Pacific ethnicity compared to those of European ethnicity (Figure 2).

N.B. Increasing rates of type 2 diabetes may partially reflect greater awareness and testing over the years.

* The Virtual Diabetes Register does not distinguish between type 1 and type 2 diabetes. Therefore, the prevalence of type 2 diabetes was estimated based on the assumed ratio of 90% type 2 diabetes to 10% type 1 diabetes;[2] this is a limitation when interpreting the data in younger age groups where type 1 diabetes is more prevalent.

### Many young people are at high risk of developing type 2 diabetes

People with $HbA_{1c}$ levels of 41 – 49 mmol/mol are classified as having "pre-diabetes", which is associated with an increased risk of cardiovascular disease and progression to type 2 diabetes. Data from the most recent national nutrition survey identified that 16% of the population aged under 45 years had pre-diabetes.[5] It is estimated that in the Auckland region, over 40% of people of Māori, Pacific or Indian ethnicity aged 35 – 39 years have pre-diabetes.[3]

### Early onset results in worse health outcomes

Younger people diagnosed with type 2 diabetes, e.g. before the age of 40 years, have a higher risk of early mortality, cardiovascular disease, chronic kidney disease and retinopathy than older adults diagnosed with type 2 diabetes or people with type 1 diabetes at a similar age.[6–8] This is largely because people diagnosed younger have diabetes for longer and are therefore exposed to more risk, but also because glycaemic control tends to be worse and younger people are more likely to have sporadic contact with healthcare services.[6, 9]

## Test people at high risk

**$HbA_{1c}$ should be tested in people at high risk of type 2 diabetes of any age** to aid early detection and therefore reduce their risk of future cardiovascular and renal complications. As type 2 diabetes is not necessarily associated with any symptoms, patients may not even recognise that they are at risk.

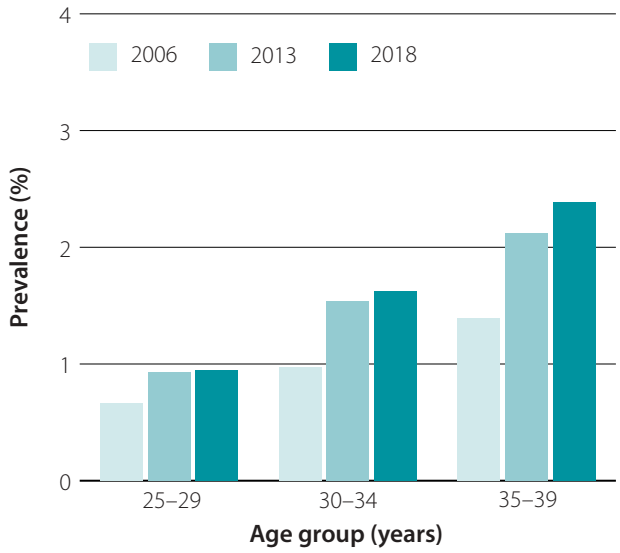



**Figure 1.** Changes in the estimated prevalence of type 2 diabetes from 2006 to 2018 in adults aged 25 – 39 years in New Zealand. Source: Virtual Diabetes Register and Statistics NZ.

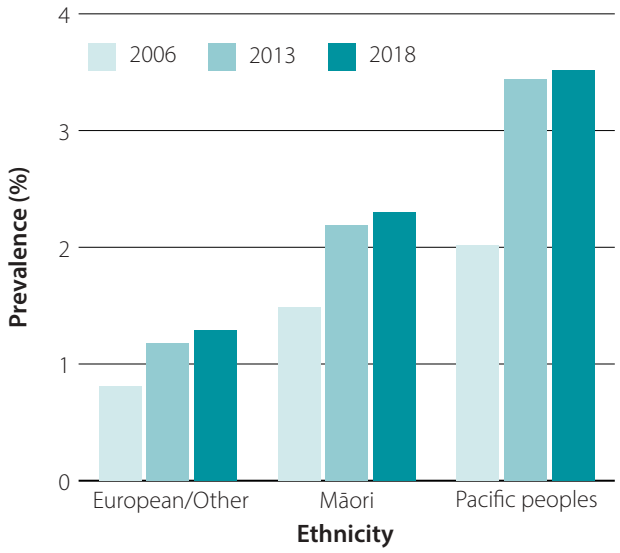



**Figure 2.** The change in prevalence of diabetes in adults aged 25 – 39 years from 2006 to 2018, by ethnicity. Source: Virtual Diabetes Register and Statistics NZ.

## Identifying people at elevated risk

Ministry of Health guidelines recommend $HbA_{1c}$ testing in adults (age > 18 years) with **any** of the following risk factors:[3]

- A BMI of ≥ 27 kg/m² for people of Māori, Pacific or South Asian ethnicities, or ≥ 30 kg/m² for people of other ethnicities*
- A first-degree relative who developed type 2 diabetes at an early age, e.g. < 40 years
- Long-term use of oral corticosteroids
- Females with a personal history of gestational diabetes
- Females with polycystic ovary syndrome
- Severe mental illness, particularly those on long-term antipsychotic treatment
- Known ischaemic heart, cerebrovascular or peripheral vascular disease

A specific opportunity to incorporate $HbA_{1c}$ testing into routine practice is the cardiovascular risk assessment; the age at which to start assessments is now recommended as:[10]

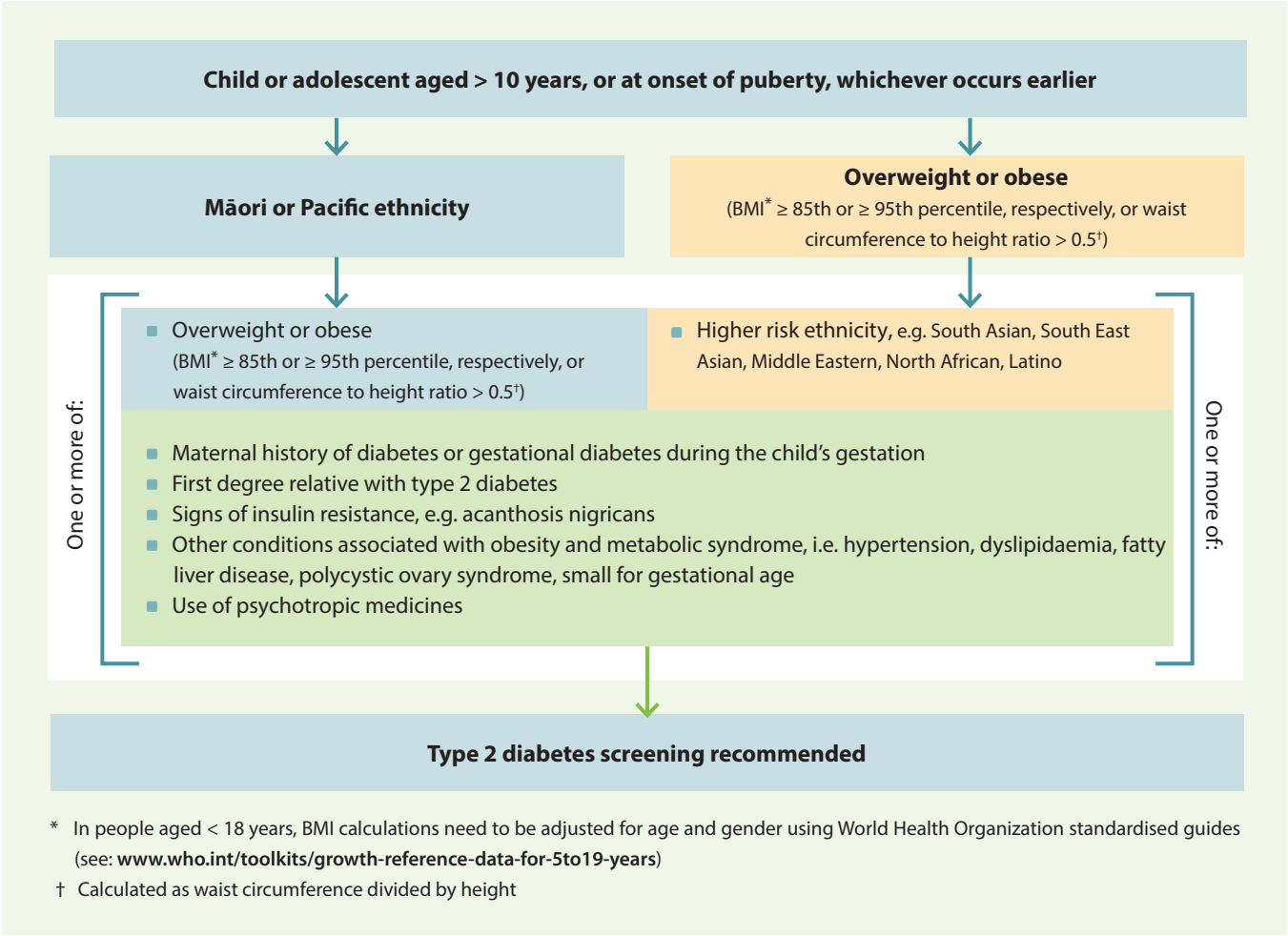
- 45 years for males and 55 years for females with no known risk factors
- 30 years for males and 40 years for females of Māori, Pacific or South-Asian ethnicity
- 35 years for males and 45 years for females with known cardiovascular risk factors or at high risk of developing diabetes†
- 25 years for people with severe mental illness

* A lower BMI threshold is recommended for people of Māori, Pacific or South Asian ethnicities due to the higher risk people of these ethnicities have of developing type 2 diabetes.[3] South Asian ethnicities include Indian, Fijian Indian, Sri Lankan, Afghani, Bangladeshi, Nepalese, Pakistani and Tibetan. People of South or East Asian ethnicity may develop type 2 diabetes at lower BMI levels than people of European ethnicity, likely due to differences in the accumulation of visceral fat.[11]

† Further information on family and personal risk factors is available at: **www.health.govt.nz/publication/cardiovascular-disease-risk-assessment-and-management-primary-care**

## Screening for type 2 diabetes in high-risk children and adolescents

Screening recommendations for type 2 diabetes in children and adolescents are guided by risk factors (Figure 3). A lower threshold for screening is recommended for Māori and Pacific children due to the higher rates of type 2 diabetes, obesity and CVD at younger ages in these groups.[12]




* In people aged < 18 years, BMI calculations need to be adjusted for age and gender using World Health Organization standardised guides (see: **www.who.int/toolkits/growth-reference-data-for-5to19-years**)

† Calculated as waist circumference divided by height

**Figure 3.** Type 2 diabetes screening recommendations for children and adolescents.[12]

Diagnosis of type 2 diabetes can be based on:[12]

- Symptoms of diabetes or hyperglycaemic crisis and a random plasma glucose ≥ 11.1 mmol/L
- Fasting plasma glucose ≥ 7.0 mmol/L
- 2-hour plasma glucose ≥ 11.1 mmol during an OGTT
- $HbA_{1c}$ ≥ 50 mmol/mol*

* The diagnostic threshold used in the Australasian guidelines is $HbA_{1c}$ ≥ 48 mmol/mol, but it is generally accepted in New Zealand that diabetes is diagnosed at 50 mmol/mol

A screening frequency of two to three years is recommended, although earlier testing may be indicated in cases where there has been excessive weight gain.[12]

**Consider the possibility of type 1 diabetes or a monogenic form of diabetes** in children or younger adults with an elevated $HbA_{1c}$ without obesity, a family history or other typical features such as hypertension, dyslipidaemia or non-alcoholic fatty liver disease. Its incidence peaks in children aged 10 – 19 years, but over half of cases are diagnosed in people aged over 20 years.[13, 14] Monogenic diabetes is estimated to be present in up to 8% of children with features of type 2 diabetes.[12]

An algorithm to help clinicians diagnose monogenic diabetes has been developed by the New Zealand Society for the Study of Diabetes: **www.nzssd.org.nz/resources-and-calculators.html**

## Lifestyle change is a cornerstone of managing and reducing the risk of type 2 diabetes at all ages

One of the most important points to convey to people who have type 2 diabetes or pre-diabetes and their whānau/family is that the course is modifiable. Lifestyle changes, i.e. ensuring a healthy, balanced diet and engaging in regular physical exercise, may be difficult at first, but they can substantially improve their future health. The patient or their parent/caregiver will have to take the lead role in making those changes, but with support from their primary care team. Setting small, incremental goals can be helpful if patients are feeling overwhelmed by the extent of changes recommended.[15]

### Lifestyle recommendations for adults

**Weight loss has the potential to induce remission of type 2 diabetes** in people who are overweight or obese, i.e. to achieve an $HbA_{1c}$ < 50 mmol/mol without the use of medicines,[16] and should be regarded as a core focus of treatment.

For further information on weight loss, see: Page 15 and **www.bpac.org.nz/2022/weight-loss.aspx**

**Lifestyle change in people with pre-diabetes** reduces their chance of developing diabetes by approximately 50 – 60% over three years and 27% over 15 years.[17, 18] This includes aiming for a 5 – 10% weight loss, 2.5 hours per week of moderate intensity physical activity and following healthy diet recommendations.[19]

**Referral for bariatric surgery** may be appropriate for some people with a BMI between 35 – 55 kg/$m^2$ to assist with weight loss.[15] Bariatric surgery can reduce the likelihood of developing type 2 diabetes, and in those who already have type 2 diabetes, can induce remission, as well as reduce the risk of diabetes complications, cardiovascular disease and some cancers.[15, 20] Māori and Pacific peoples may require more support to ensure they get bariatric surgery; fewer publicly funded bariatric surgeries are conducted for Māori or Pacific peoples than Europeans.[21] Research has shown there are higher rates of withdrawal prior to surgery in Māori and Pacific peoples.[22] Discussing potential barriers with patients can help them to prepare and plan ahead for some of the difficulties they may face if they are accepted for surgery. Regular follow-up contact is also likely to be helpful once a patient has been accepted for surgery.

For further information on bariatric surgery, see: "Weight loss for the prevention and treatment of type 2 diabetes", Page 15

### Lifestyle recommendations for children and adolescents

**Diet and weight management.** Ensure that the diet is nutritionally adequate for the child or adolescent's growth and developmental stage.[11] The goal is to prevent further weight gain in those who are overweight and encourage weight loss in those who are obese, while maintaining normal linear growth.[11]

**Encourage physical activity**. At least 60 minutes per day of moderate to vigorous intensity exercise is recommended for children and adolescents, with strengthening exercises included three days per week.[12] Body weight exercises and light resistance bands or weights are appropriate for children; external resistance, e.g. gym equipment, can be added for adolescents who have reached skeletal maturity.[12]

**Reduce recreational screen time.** All children, including those with type 2 diabetes, should spend no more than two hours per day on recreational screen time, e.g. smartphones, tablets, computers, television; approximately four out of five children in the general population do not meet this target.[12, 23]

**Ensure adequate sleep.** Children aged 5 to 13 years should be getting 9 – 11 hours of sleep per night; 8 – 10 hours of sleep per night is recommended for adolescents aged 14 – 17 years.[12]

Recommend sleep hygiene measures such as earlier and consistent bed and wake times, and reduced use of electronic media and devices at night.[11]

### Engaging people to make changes

**Identify what motivates people.** Reactions to a diagnosis of type 2 diabetes, or being told they are at high risk, can differ between people. Motivational strategies should be individualised, but a key message is that it is never too late to "step back from the edge" and the course of type 2 diabetes is not pre-determined.

**Avoid stigma and blame.** Discussing lifestyle changes can be challenging, as the advice required often carries an unspoken implication that the person has brought the disease on themselves or their child. Conveying that the risk of type 2 diabetes and obesity is influenced by factors which are out of a person's control, e.g. genetics, exposures in utero or early childhood, or factors in the environment, may help alleviate some of the stigma and embarrassment associated with obesity and type 2 diabetes. Advice on language which can help avoid blame when discussing type 2 diabetes is provided in Table 1 (Page 54).

**Regular follow-up is essential.** Develop an agreed plan that can be used to track progress, e.g. appointment with a practice nurse, providing advice or support via telephone or text message. A randomised controlled trial in the United States found that participants who had completed a lifestyle intervention were less likely to regain weight if they had telephone follow up rather than written education alone.[24] Encourage patients to make one change at a time with subsequent goals added at follow-up appointments; focus on the changes that will bring the greatest benefit, e.g. weight loss or smoking cessation.

**Connect patients to services that can assist with lifestyle changes,** including referring patients to a dietitian, providing them with a Green Prescription, or referring to programmes offered by a local PHO, DHB or Māori health provider.

## Pharmacological management of people with early onset type 2 diabetes

The approach to pharmacological management of type 2 diabetes in patients with early onset is essentially the same as for any patients with type 2 diabetes, i.e. metformin first-line, followed by other oral and injectable glucose-lowering medicines, as appropriate (also see: "Managing type 2 diabetes in children and adolescents"). However, faster escalation of treatments may be required and lower targets for glycaemic control are justified.[25] Patients with early onset type 2 diabetes can have a more rapid increase in $HbA_{1c}$ levels, despite treatment, and are likely to require more frequent dose increases, use of multiple oral medicines or earlier addition of insulin than older patients with type 2 diabetes.[26] Effective communication and engagement with patients and their whānau/family in regards to the importance of adhering to their prescribed medicines is of particular importance in this age group. Reinforce that if they can gain control with assertive treatment and lifestyle, it may be possible to dial treatment back over time.

For further information on setting a $HbA_{1c}$ target and prescribing glucose-lowering medicines for patients with type 2 diabetes, see: "Type 2 diabetes management toolbox: from lifestyle to insulin", Page 6

For further information on initiating insulin, see: "Initiating insulin for people with type 2 diabetes ", Page 33

**Metformin for patients with "pre-diabetes"**

Metformin can be prescribed (unapproved indication) to reduce the risk of developing type 2 diabetes in patients at high risk (e.g. $HbA_{1c}$ of 46 – 49 mmol/mol), but should be considered an adjunct treatment in addition to changes in diet and activity levels.[17] Metformin reduces the risk of developing type 2 diabetes by approximately one-third after three years, and approximately 20% after ten years, compared to a placebo medicine in patients at high risk.[27]

### Managing type 2 diabetes in children and adolescents

Children and adolescents with type 2 diabetes are typically managed in secondary care, with primary care providing additional support to the patient and their whānau/family. A $HbA_{1c}$ target of < 48 mmol/mol is recommended for children and adolescents to reduce the long-term risk of developing diabetes complications.[12] Metformin is the first-line pharmacological treatment, up to a maximum dose of 2 g, daily.[12] If the patient's $HbA_{1c}$ level is ≥ 69 mmol/mol or they are symptomatic at diagnosis, insulin is initiated in addition to metformin. Once $HbA_{1c}$ levels have reduced to target, insulin can be titrated down and withdrawn.[12]

Previously, metformin and insulin were the only medicines approved in New Zealand for use in people with type 2 diabetes aged < 18 years.[12] Since November, 2023, empagliflozin is now indicated in children aged ≥ 10 years as monotherapy if metformin is not tolerated (and diet and exercise alone do not provide adequate glycaemic control), or in combination with other glucose-lowering medicines (under specialist supervision) if glycaemic control remains poor. Other glucose-lowering medicines approved for use in adults only, e.g. dulaglutide, vildagliptin, sulfonylureas and pioglitazone, may be considered for children and adolescents with type 2 diabetes, on the recommendation of a paediatric endocrinologist.[12]

**Table 1:** Using language which can help avoid blame when discussing diabetes. Adapted from the American Association of Diabetes Educators and American Diabetes Association.[29]

| Language/tone of conversation which may have negative connotations | Suggestions for replacement concepts and phrases | Things to consider |
|---|---|---|
| **Compliance/adherence**<br><br>e.g. "You must take metformin twice a day" | Concepts such as engagement, participation, involvement<br><br>Explain the benefits of medicine use and encourage patients to follow dosing instructions, e.g.: "Taking metformin twice a day will make it easier for you to reduce your $HbA_{1c}$ level than taking it less often" | Focus on using factual statements to emphasise how the person's health could improve by following the advice |
| **Regimen/rules**<br><br>e.g. "You need to do 30 minutes of moderate intensity exercise per day" | e.g. "You're doing around 15 minutes per day of walking. This is great - do you think you could now do a bit more? Are there other types of exercise you would like to try? What are some of the things that might stop you from doing more?" | Encourage people to identify changes they want to make and help them to achieve those goals, rather than dictating what those changes should be and judging their progress based on what you think they should achieve |
| **Control:**<br><br>e.g. "Your diabetes is not well-controlled" | Instead of referring to "good/bad control" explain what $HbA_{1c}$ level is being aimed for and the effects of the current approach to treatment:<br><br>e.g. "Your $HbA_{1c}$ level is 70 mmol/mol. That is an improvement, but how about we make another goal to try to get it even lower."<br><br>"We started metformin last time, but it is not bringing down your $HbA_{1c}$ levels enough. We might need to increase the dose." | Control may be impossible to achieve given the body's systems for regulating glucose levels are failing. Try to focus on the underlying physiology and what a patient is doing well. |
| **Can't/shouldn't/don't**<br><br>e.g. "Don't have fizzy drinks" | "Have you tried..."<br><br>"Would you consider...."<br><br>"I've found what has worked for other people is..."<br><br>e.g. encourage alternatives, such as "try water with a slice of lemon" | This type of statement (can't/shouldn't/don't) can make people feel they are being given orders |
| **Lacking motivation or unwilling to engage**<br><br>e.g. "So you are not willing to start insulin?" | Focus on perceived barriers and why a patient doesn't want to proceed with a plan of action. This may lead to potential solutions.<br><br>e.g. "From what you are saying, your main concerns around starting insulin are weight gain and the potential embarrassment of injecting yourself at work?" | Most people want to live a healthy life. The challenge with managing diabetes and weight is that people can feel there are barriers stopping them from changing, or may not appreciate the benefits of doing things differently. People may feel it is not worth the effort or is unachievable. |

## Regular review is essential to minimise the risk of long-term diabetes complications

Despite being young, people diagnosed with diabetes at an early age may already have complications and should have their retinal, foot, renal and cardiovascular health fully assessed and managed at diagnosis. Also consider associated co-morbidities, such as sleep apnoea or non-alcoholic fatty liver disease.

### Managing cardiovascular and renal risk

Cardiovascular and renal diseases are the main causes of early mortality in people with type 2 diabetes, and preventing the onset or progression of these conditions in young people should be a focus of management.[28] Lifestyle changes can improve markers of cardiovascular risk, such as blood pressure and lipid levels, however, pharmacological treatment should be initiated if lifestyle changes result in insufficient improvements, or if the patient's CVD risk is high.

For further information on managing cardiovascular and renal risk in patients with type 2 diabetes, see: **www.health.govt.nz/publication/cardiovascular-disease-risk-assessment-and-management-primary-care**

An online calculator for determining the risk of cardiovascular and renal disease in patients with type 2 diabetes is available at: **www.nzssd.org.nz/cvd_renal/**

### Transition stages are a risk time for worsening diabetes management

Guidelines recommend that all adolescents with type 2 diabetes transition to an adult diabetes service.[12] This transition period can be a time when issues with appointment attendance, adherence to medicines and lifestyle interventions, worsening glycaemic control, acute and chronic complications arise.[12] Primary care should establish who is responsible for the patient's diabetes care and ensure that they are regularly followed up, including reviews of their glycaemic control, medicines regimen, mental health and wellbeing, and undergo a diabetes review annually.

For further information on the annual diabetes review, see: "The annual diabetes review: screening, monitoring and managing complications", Page 43

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