A RESEARCH REVIEW™
SPECIAL REPORT

Type 2 diabetes management guidance

Updated 2023 Recommendations from the NZSSD

Making Education Easy 2023

Specialist contributor:

Ryan G Paul
BHB, MBChB (Auckland), FRACP, PhD

Dr Ryan Paul (Ngāti Maru) is an endocrinologist in Te Whatu Ora Health New Zealand Waikato and is a Senior Lecturer at the University of Waikato. He is also an honorary Senior Lecturer at the University of Auckland and a Clinical Associate of the Maurice Wilkins Centre, with a key research focus of trying to reduce inequities for Māori and Pacific peoples with diabetes. He is the Immediate Past-President of the New Zealand Society of Endocrinology (NZSE) and is an Executive Member of the New Zealand Society for the Study of Diabetes (NZSSD). He has many advisory roles including for Manatū Hauora (Ministry of Health) and has key roles in teaching including being a member of the Royal Australasian College of Physicians New Zealand Adult Medicine Committee. Ryan was awarded the Clinical Educator of the Year by the New Zealand Medical Council in 2019.

Abbreviations used in this review
ACEi = angiotensin converting enzyme inhibitor
ARB = angiotensin receptor blocker
BGL = blood glucose level
BMI = body mass index
BP = blood pressure
CBG = capillary blood glucose
CCB = calcium channel blocker
CGM = continuous glucose monitoring
CV = cardiovascular
DPPIVi = dipeptidyl peptidase-IV inhibitors
DSMES = diabetes self-management education and support
eGFR = estimated glomerular filtration rate
FBG = fasting blood glucose
GAD = glutamic acid decarboxylase
GI = glycaemic index
GLP1RA = glucagon-like peptide-1 receptor agonist
GP = general practitioner
GTT = glucose tolerance test
HbA1c = haemoglobin A_{1c}
IA2 = islet-cell
LDL = low-density lipoprotein
NSAID = non-steroidal anti-inflammatory drugs
OSA = obstructive sleep apnoea
PCOS = polycystic ovarian syndrome
RBC = red blood cell
SGLT2i = sodium glucose co-transporter 2 inhibitor
SMBG = self-monitoring of blood glucose
T1D = type 1 diabetes
T2D = type 2 diabetes
TIR = time in range
UACR = urinary albumin:creatinine ratio
ZnT8 = zinc transporter 8

What's new in the guidelines?

Changes in lifestyle management

- New emphasis on individualised weight management plans aiming for 10-15% weight loss in early disease to achieve T2D remission
- The emphasis on patient education and support to facilitate self-management has increased
- New section on healthy sleep to improve glycaemic control and weight loss
- Cancer screening and influenza vaccination should be included in wrap-around care

Changes in guidance for glucose-lowering medicines

The aim of this section was to recognise 'off-label' prescribing given the delay in updating data sheets.

- Metformin dosing does not need to be reduced unless the patient's eGFR <45 mL/min
- Empagliflozin and/or dulaglutide or liraglutide should be considered in patients aged 10-17 years based on safety and efficacy data*
- Empagliflozin can now be initiated in patients with eGFR >20 mL/min* (previous eGFR cut-off 30 mL/min)
- Multiple weekly dulaglutide injections may be considered if the patient is tolerating treatment and has not reached their HbA1c target – the maximum dose is 4.5 mg per week*
- Vildagliptin is redundant if a GLP-1RA is introduced and should be withdrawn
- Sulfonylureas and/or insulin can be reduced or withdrawn, where appropriate, when newer agents are introduced
- **Liraglutide (Victoza®)** is now available under the same Special Authority as dulaglutide – prescribe funded Novofine® or BD® 4 or 5-mm needles
  - There is no evidence that either dulaglutide or liraglutide is superior in terms of glycaemic control
  - Liraglutide may be preferable if T2D patients cannot obtain or are intolerant to dulaglutide or prefer daily injections

Management of hypoglycaemia

- Hypoglycaemia management in T2D has been simplified to prevent both under and over-treatment
  - If body weight ≥70 kg take 30 g of rapid acting carbohydrate OR
  - If body weight <70 kg take 15 g of rapid acting carbohydrate, repeat after 15 minutes if glucose levels <4 mmol/L

Other changes

- The **target LDL has been lowered from 1.8 mmol/L to < 1.4 mmol/L**
- Lipid-lowering therapy is important to reduce microvascular complications – rosuvastatin is available if LDL cholesterol is above target
- Endorsement of all licenses for Waka Kotahi can now be performed by GPs, nurse practitioners and diabetes nurse specialists
- Continuous glucose monitoring (CGM) has been included with targets, e.g. TIR >70%
- Sulfonylureas are useful for steroid-induced hyperglycaemia
- Acarbose should be taken with meals

*Recommendation is unapproved and prescribing in this way is 'off-label'

Misinformation regarding dulaglutide supply has resulted in stockpiling, particularly by wholesalers. To date, there has been no shortage of dulaglutide in New Zealand and this is unlikely to occur in the immediate future. The supply of dulaglutide to New Zealand will be prioritised and Pharmac and the supplier have agreed to consistent messaging.

Screening and diagnosis of type 2 diabetes

All people aged >18 years who are overweight or obese (BMI >25 kg/m^2 or >23 kg/m^2 if Asian ethnicity) with at least one other risk factor for diabetes should have an HbA1c performed at least every 3 years. Risk factors for T2D include:

- Non-European ethnicity
- Previous prediabetes or T2D in remission
- A first-degree relative with T2D <40 years of age
- Clinical features of insulin resistance, e.g. PCOS, acanthosis nigricans, hypertension, dyslipidaemia
- History of CV disease
- Current long-term corticosteroid or antipsychotic treatment
- Post-transplant
- Smoker

HbA1c testing should be routinely included in all CV risk assessments, beginning at age 45 years for men and 55 years for women. CV assessments should start at age 30 years for males and 40 for females of Māori, Pacific or Indo-Asian ethnicity.

Diagnosing T2D in an asymptomatic person requires two abnormal tests (HbA1c ≥ 50 mmol/mol or fasting glucose ≥ 7 mmol/L) either on the same day or without delay. Pre-diabetes is defined as either HbA1c 41-49 mmol/mol (single measurement if the patient is otherwise well), fasting glucose 6.1-6.9 mmol/L or 2-hour glucose 7.8-11 mmol/L on 75 g glucose tolerance test (GTT).

Practice point: Do not wait three months to confirm a T2D diagnosis, particularly as lifestyle management and metformin should also be used to treat high-risk prediabetes.

People with prediabetes or females with a history of gestational diabetes should have their HbA1c tested at least annually. An HbA1c test is not appropriate for patients with altered RBC turnover or those in the second or third trimester of pregnancy; perform a fasting glucose or 75 g GTT in these situations.

Testing symptomatic people

An HbA1c and fasting or random glucose test should be requested for all patients with symptoms of hyperglycaemia, i.e. polyuria, polydipsia, weight loss, recurrent fungal, skin or genitourinary infections. Diabetes in symptomatic patients is confirmed following a single HbA1c > 50 mmol/mol or a fasting glucose ≥ 7 mmol/L or a random glucose ≥ 11.1 mmol/L.

Determining the type of diabetes

At least 5% of adult-onset diabetes is not T2D. Therefore, other causes of diabetes should always be considered since this alters management, e.g. all patients with T1D require insulin and should be screened for other autoimmune diseases. T1D may develop at any age with an insidious onset and many patients are now overweight at diagnosis due to the prevalence of obesity in the general population. A positive anti-GAD, anti-IA2 or anti-ZnT8 antibody titre or low C-peptide, e.g. < 250 pmol/L fasting or < 600 pmol/L post meal if glucose is > 8 mmol/L, at diagnosis is suggestive of T1D. Suspicion of T1D, diabetes due to pancreatic failure or monogenic diabetes should be discussed with secondary care.

Further information on the screening and diagnosis of T2D is available from the NZSSD guidelines.

Glycaemic monitoring and HbA1c targets

Glycaemic targets should be individualised and reassessed at least yearly, including as part of the annual diabetes review. **HbA1c testing is preferred for assessing glycaemic control and should be performed every three months until the patient is to target, then every six months once at target**.

Many NZ health care professionals believe the target HbA1c for most T2D patients is < 64 mmol/mol because this remains a performance target for many PHOs and the Ministry of Health. However, **the target HbA1c for most people with diabetes is < 53 mmol/mol** because microvascular complications exponentially increase from this point.

More aggressive targets, e.g. HbA1c < 48 mmol/mol, are often appropriate for patients with a low risk of hypoglycaemia who are either:

- Young
- Considering pregnancy or pregnant
- Have microvascular complications, especially retinopathy and nephropathy

A more relaxed target, e.g. HbA1c 54-70 mmol/mol, is more appropriate if the risks of hypoglycaemia are greater than the benefits of tight control. For example, patients with:

- Reduced life expectancy due to non-diabetic co-morbidities
- A history of severe hypoglycaemia
- Significant hypoglycaemic unawareness
- Old age and frailty or cognitive impairment
- Functional dependency

Practice point: Significant medication-induced hypoglycaemia only occurs in patients taking insulin and/or sulfonylureas. Consequently, patients with T2D can be treated with metformin, vildagliptin, SGLT2i, GLP1RA and pioglitazone, alone or in combination with each other, without causing hypoglycaemia or needing to routinely self-monitor blood glucose (SMBG). An HbA1c < 45 mmol/mol is not concerning in these patients, but medications that do not reduce CV or renal disease, such as vildagliptin may be stopped.

Reducing cardiovascular and renal disease

Most of the morbidity and mortality associated with T2D is caused by CV and renal disease and this is especially true for Māori and Pacific peoples. The focus for T2D management therefore now includes reducing CV and renal risk alongside glycaemic control. All glucose-lowering medicines reduce CV and renal risk by improving glycaemic control. Metformin, SGLT2i and GLP1RA are also likely to reduce CV and/or renal risk and bodyweight independently of their effect on glucose levels, without causing hypoglycaemia unless combined with insulin and/or sulfonylureas. Metformin therefore remains the first line pharmacological intervention and SGLT2i and GLP1RA are now the preferred second-line interventions since becoming available in New Zealand.

Practice point: The PREDICT calculator is currently the recommended CV risk calculator for T2D. This tool is embedded in most practice management systems and is also available on the NZSSD website.

The benefits of metformin, SGLT2i and GLP1RA on reducing bodyweight and progression of CV and renal disease are additive. Therefore, **all patients with T2D and either diabetic renal disease (UACR > 3 mg/mmol and/or eGFR < 60 mL/min) OR heart failure OR CV disease OR five-year CV risk > 15% should ideally be on metformin and an SGLT2i or GLP1RA regardless of their glycaemic control or other glucose-lowering therapies**.

Notably, the benefits of SGLT2i and GLP1RA in reducing CV disease and renal risk are additional to the benefits associated with statin and ACEi/ARB therapy. Thus, **unless contraindicated, all patients with T2D and renal disease and/or established macrovascular disease or a five-year CVD risk >15% should be taking a statin and those with renal disease and/or heart failure should also be taking a ACEi/ARB unless contraindicated or not tolerated.** Rosuvastatin should be considered for all patients who cannot reach the LDL target on maximally tolerated doses of atorvastatin or simvastatin.

Practice point: The target LDL has been lowered to <1.4 mmol/L (previously <1.8 mmol/L).

BP targets remain <130 mmHg systolic and <80 mmHg diastolic in this high-risk group, if tolerated. A BP target <125/75 mmHg is likely to be beneficial for younger patients with a complicated disease burden.

If renal disease is present, ACEi or ARB dosing (not in combination) should ideally be maximised before adding another antihypertensive. As it is now known that ACEi/ARBs do not prevent diabetic renal disease, if a patient has a normal UACR and eGFR either a CCB, thiazide or ACEi/ARB can be used to treat hypertension. In patients with no microvascular or macrovascular complications and a five-year CV risk < 15%, a target systolic BP < 140 mmHg and diastolic BP < 90 mmHg is reasonable. All patients with a previous vascular event should take aspirin for secondary prevention, unless contraindicated. Aspirin is now no longer generally used for primary prevention in patients with diabetes because the benefits are reduced and the bleeding risk increased, compared to patients without diabetes. Smoking cessation is, as always, important.

Reducing clinical inertia

Clinical inertia is likely the largest barrier to effective diabetes management in NZ and worldwide. Indeed, despite suboptimal management being largely attributed to patient barriers, pre-COVID data indicates that 99% of patients with diabetes in Auckland were enrolled with a GP practice and over 90% were attending this practice at least twice a year.[3] In patients with the poorest glycaemic control (HbA1c > 75 mmol/mol), more than 75% attended their practice at least twice a year and at least 85% attended their annual diabetes review and regularly received scripts for glucose-lowering therapy.[3] Therefore, **the key to reducing clinical inertia is to proactively optimise diabetes management at every opportunity.** Action is important as almost all patients with an HbA1c > 75 mmol/mol have an HbA1c test at least once per year, but approximately two-thirds had a similar level for the past 12 months.[3]

The most important changes in the guidance aimed at reducing clinical inertia are:

1. Confirm T2D diagnosis in asymptomatic patients as early as possible.
2. Start lifestyle management and metformin together at diagnosis to delay progression of T2D, reduce CV risk and assist weight loss. Commencing metformin should not, however, diminish the importance of lifestyle management.
3. Strongly consider starting a second-line agent with metformin at diagnosis if the patient's HbA1c > 64 mmol/mol as the majority of these will not reach an HbA1c target < 53 mmol/mol with metformin alone.
4. Repeat HbA1c testing every three months with intensification of treatment until the target is met, HbA1c testing is then every six months. Ideally, patients should have their blood pressure and lipids assessed at the same time with escalation of appropriate treatment as required.
5. Start weight-based basal insulin (rather than the traditional 6-10 unit starting dose) and add prandial insulin once basal insulin doses reach 0.5 units/kg/day.
6. Strong consideration should also be given to starting insulin immediately if the HbA1c is > 90 mmol/mol at any time, as these patients typically will not reach their glycaemic targets despite lifestyle management and all other glucose-lowering therapies.

Reinforcing the new 'algorithm' for managing T2D

The availability of SGLT2i and GLP1RA and the shift towards reducing CV and renal risk and obesity, in addition to improving glycaemic control, has led to major changes to T2D management in Aotearoa New Zealand (**Figure 1**). In the new algorithm, lifestyle management and metformin remain the first-line interventions for all T2D patients and the recent changes are further emphasised.

Lifestyle management

Lifestyle changes with healthy eating, physical activity, healthy sleeping, education and support continues to be the cornerstone of T2D management. Individualised DSMES is essential to ensure effective diabetes care. Lifestyle modifications should target a 5-10% reduction in total bodyweight if the patient has a BMI > 30 kg/m^2 OR a BMI > 25 kg/m^2 and a waist circumference > 88 cm for females or > 102 cm for males. Aim for a 10-15% reduction in total body weight to achieve T2D remission, although this may not be possible for patients with long-standing T2D.

Practice point: Explain to patients that a brisk 5-6 minute walk each day is associated with four additional years of life.[2]

Self-monitoring of blood glucose levels is an important component of diabetes management that helps patients understand the effect lifestyle changes and medicines have on their glycaemic control. Self-monitoring can be performed via CBG or CGM. The glucose targets for most adults with T2D who are not pregnant are:

- Fasting glucose levels < 7 mmol/L
- 2-3 hour post-meal glucose levels < 10 mmol/L
- Time in target range (3.9 - 10 mmol/L) > 70% on CGM
- No hypoglycaemia (< 4 mmol/L) in patients treated with sulfonylureas and/or insulin

Practice point: Ideally, every patient with diabetes should be provided with a CareSens™ N or N POP glucometer and CareSens™ N glucose test strips to check CBG levels, however, only those on sulfonylureas and/or insulin or who are pregnant are eligible for funded monitoring.

Self-monitoring is recommended for patients considering or taking a sulfonylurea or insulin, or during preconception or pregnancy, for the acutely unwell or those concerned about hypoglycaemia and for patients unable to return reliable HbA1c results.

CGM is potentially very beneficial when regular CBG cannot be obtained. Consider recommending CGM when insufficient CBG is potentially compromising patient safety and/or timely treatment decisions. Currently, all CGM systems in Aotearoa New Zealand are unfunded and expensive.

Nutritional education from a registered dietitian is best practice at diagnosis and then annually for ongoing assessment, when starting prandial insulin or at any time if required. Recent evidence suggests that low-energy, low-GI and modified macronutrient dietary approaches can be as effective as bariatric surgery in achieving weight loss and T2D remission. However, there is no conclusive evidence that one dietary strategy is more effective than another in achieving sustained weight loss and improved glycaemic control. In particular, meta-analyses show that the benefits of ketogenic diets are unlikely to be sustained. Consequently, the choice of dietary strategy will depend on factors including patient preference, tolerance, income, co-morbidities, cultural suitability and nutritional needs. Indeed, it is important to ensure adequate nutrition in young people, pregnant or lactating women or those considering pregnancy, and the elderly.

Dietary recommendations and activity guidelines are available from: www.health.govt.nz/our-work/eating-and-activity-guidelines. Patients who are unable to meet the recommended activity levels should be supported to complete as much exercise as they are able. Smoking cessation, reduced alcohol intake, green prescriptions, discussing healthy sleep and improving sleep hygiene, annual influenza vaccinations, cancer screening and screening for depression (e.g. PHQ-9) with referral for psychology input as required are important components of wrap-around care.

Practice point: Discuss sleep with all T2D patients as 50% of this population has OSA. Treatment of OSA can significantly improve blood glucose levels. The optimal duration of sleep to benefit glucose levels and bodyweight appears to be 6-8 hours per night.

Metformin

Metformin remains the first-line pharmacological agent for patients with T2D because it reduces CV risk independently of glycaemic control. The mean maximal reduction in HbA1c with metformin monotherapy is 16 mmol/mol, but importantly this is associated with modest weight loss, without the risk of hypoglycaemia. **Many patients with gastrointestinal adverse effects are labelled 'intolerant to metformin', but most will tolerate it well when it is started at 250-500 mg, once or twice daily, with food and titrated up weekly.**

Anecdotally, patients tolerate metformin much better in combination tablets with vildagliptin or empagliflozin, compared to metformin alone. The therapeutic benefit of metformin > 2 g/day is minimal, but the risk of adverse effects is increased. Therefore, **the maximum recommended dose of metformin is 1 g, twice daily**.

Practice point: International guidelines now recommend that metformin at 2 g daily is safe if the patient's eGFR is >45 mL/min.

Despite it being 'off-label', it is now best practice to only reduce the dose of metformin due to renal dysfunction when the eGFR is <45 mL/min:[1,4,5]

- eGFR 30-45 mL/min maximum -recommended dose is 1 g per day
- eGFR 15-30 mL/min maximum recommended dose is 500 mg per day
- eGFR < 15 mL/min stop metformin

Escalation of therapy

The choice of second-line agent is dependent on co-morbidities, primarily CV and renal disease. All patients with T2D with either diabetic renal disease OR heart failure OR CV disease OR five-year CV disease risk > 15% should ideally be on metformin, an SGLT2i and/or GLP1RA regardless of their glycaemic control or other glucose-lowering therapies. The choice between an SGLT2i or GLP1RA can be difficult, but an SGLT2i is typically preferable if renal disease or heart failure predominates, and a GLP1RA is likely preferable if cerebrovascular disease predominates. If the HbA1c remains above target in this high-risk group, dual SGLT2i and GLP1RA therapy is recommended but not funded (see page 6: Mismatch between recommendations and Special Authority criteria).

To date, the benefits of SGLT2i and GLP1RA in reducing CV and/or renal risk in prospective studies have largely been demonstrated in patients with existing CV and/or renal disease.[6] More evidence for the role of SGLT2i and GLP1RA in primary prevention is awaited, particularly confirming the potential for GLP1RA to reduce CV events in those with multiple risk factors. Retrospective data suggest that SGLT2i regimens and combinations of SGLT2i and GLP1RA may provide primary prevention of cardiac and cerebrovascular events and heart failure in those with T2D.[7] Obesity and its complications are also very common and are major causes of morbidity. Therefore, **SGLT2i or GLP1RA are still the likely preferred second-line agents when escalation of metformin therapy is required in T2D (including aged 10-17 years) patients without CV or renal disease who are overweight or obese.**[8-10] This is because GLP1RA and SGLT2i both cause weight loss without hypoglycaemia, whilst vildagliptin is weight neutral and pioglitazone, sulfonylureas and insulin cause weight gain. Patients of Māori or Pacific ethnicity or with early onset T2D (i.e. diagnosis at < 40 years of age) are still eligible for funded SGLT2i or GLP1RA therapy and many others may choose to self-fund in this scenario. GLP1RA typically lead to greater reductions in weight and glucose levels than SGLT2i, but patient preference is likely the greatest influencer on which agent is used.

Vildagliptin is likely the preferred second-line agent when patients cannot afford to self-fund SGLT2i and/or GLP1RA therapy OR when escalation of metformin therapy is required in patients with T2D without CV or renal disease who are of normal weight. This is because vildagliptin is the only agent to date shown to delay the need for insulin, when used in combination with metformin, and it does not cause weight gain or hypoglycaemia. Pioglitazone, sulfonylureas and insulin are now third- and fourth-line agents due to the associated weight gain, risk of hypoglycaemia and the need to SMBG with insulin and sulfonylureas.

SGLT2 inhibitors

SGLT2i are a preferred second-line treatment for patients with T2D and CV disease, especially heart failure and renal disease, as they reduce CV mortality and progression of established renal disease independently of glycaemic control.[11-13] SGLT2i are associated with an average 6-13 mmol/mol reduction in HbA1c.

How to prescribe SGLT2i: Empagliflozin is available in 10 mg and 25 mg tablets and in combination with metformin (5mg/500mg, 5mg/1000mg, 12.5mg/500mg, 12.5mg/1000mg). Empagliflozin is initiated at 10 mg, daily, with the patient's HbA1c, eGFR and blood pressure retested in three months and the dose increased to 25 mg, daily, if the HbA1c is above target and treatment is tolerated. Dose adjustments are not necessary for other glucose-lowering medicines unless sulfonylureas and/or insulin are prescribed. It is safe to initiate empagliflozin in combination with another SGLT2i if the patient's eGFR >20 mL/min, although treatment should be withdrawn in the case of intolerance or if renal replacement therapy is begun.[1]

The most common adverse effects of empagliflozin include polyuria (proportional to glucose levels and transient) volume depletion, a transient decrease in eGFR (up to 25% is acceptable), skin reactions and genitourinary infections, particularly vaginal thrush and balanitis.[14] Current recommendations for genital hygiene with empagliflozin use are for women to wash and change pads at least twice daily, and men to wash at least once daily. Very rare adverse effects include diabetic ketoacidosis (glucose levels may be normal) and necrotising fasciitis of the perineum (Fournier's gangrene).[14] Empagliflozin should not be prescribed to women who are pregnant or breastfeeding, patients aged <10 years*, patients with an eGFR < 20 mL/min at commencement or T1D, and should be used with caution in those with recurrent genitourinary infections and/or are aged > 75 years.[14]

*Recommendation is unapproved and Product Information recommends not prescribing to patients aged <18 years.

GLP-1 receptor agonists

GLP1RA are a preferred second-line medicine in T2D patients and CV and renal disease because they reduce CV outcomes and likely progression of diabetic renal disease, independently of glycaemic control.[15,16] GLP1RA are associated with greater reductions in glucose levels and weight than any other class of non-insulin glucose-lowering therapies, as well as reduced blood pressure, without causing hypoglycaemia in monotherapy.[17] As such, GLP1RA are a useful alternative to basal insulin.

How to prescribe GLP1RA: Dulaglutide is initiated at 1.5 mg subcutaneously, weekly, at any time of the day. Metformin and other glucose-lowering medicines should be continued, although vildagliptin should be withdrawn. Dose adjustments are not necessary for other glucose-lowering medicines unless sulfonylureas and/or insulin are prescribed. More than one injection of dulaglutide per week may be considered if the patient's HbA1c is above target and they are tolerating treatment well.1 The weekly dose should not exceed 4.5 mg.

Liraglutide (Victoza® not Saxenda®) has been funded since March 2023 as an alternative for patients who cannot tolerate or obtain dulaglutide or who prefer daily injections or for those taking ≤1.8 mg/day of liraglutide (Saxenda®) for obesity. Liraglutide (Victoza®) is initiated at 0.6 mg daily and is increased to 1.2 mg daily after 1 week, although the increase may be delayed if there are significant adverse effects. The dose may need to be increased to 1.8 mg daily if the patient's HbA1c remains above target and they are tolerating treatment well or earlier after 2-3 weeks if elevated glucose levels persist. If a patient is switching from dulaglutide to liraglutide, a similarly titrated regimen to a dose of 1.8 mg daily is recommended.

Advise patients that the most common adverse effects of dulaglutide or liraglutide typically resolve if treatment is continued, e.g. nausea, diarrhoea and constipation, and mild injection site reactions.[1] Less common adverse effects may include vomiting and rarely myalgia or muscle weakness. The patient's HbA1c, eGFR and blood pressure should be retested in three months and if the HbA1c is above target, other glucose-lowering treatments should be intensified.

GLP1RA should not be prescribed to women who are pregnant or breastfeeding, patients aged <10 years*, patients with an eGFR < 15 mL/min, T1D or those with severe gastrointestinal disease, previous pancreatitis or medullary thyroid carcinoma or history of the rare genetic disorder MEN2 syndrome.

The limited head-to-head and real-world data that is available on dulaglutide vs liraglutide suggests both agents provide similar glycaemic control and their safety profiles are similar.[18,19]

DPPIV inhibitors

DPPIV inhibitors are a second-line medicine that are weight neutral and do not cause hypoglycaemia in monotherapy. DPPIVi are well tolerated in older people and can be used safely in those with renal dysfunction. Vildagliptin is the only DPPIVi funded and is currently the only glucose-lowering therapy shown to delay the need for insulin therapy in T2D when combined with metformin.[20] Vildagliptin should be withdrawn if a GLP1RA is initiated due to redundancy and an increased risk of adverse effects associated with continued treatment.

Sulfonylureas

Sulfonylureas are now typically a third or fourth-line medicine that may cause weight gain and hypoglycaemia and do not reduce CV or renal disease independently of glycaemic control. Sulfonylureas can be reduced or withdrawn, if appropriate, when newer agents are introduced, although this class of medicine remains useful, particularly in steroid-induced hyperglycaemia. Patients taking sulfonylureas need to SMBG and be educated about: hypoglycaemia management, how the medicine may affect driving ability, and sick day management.

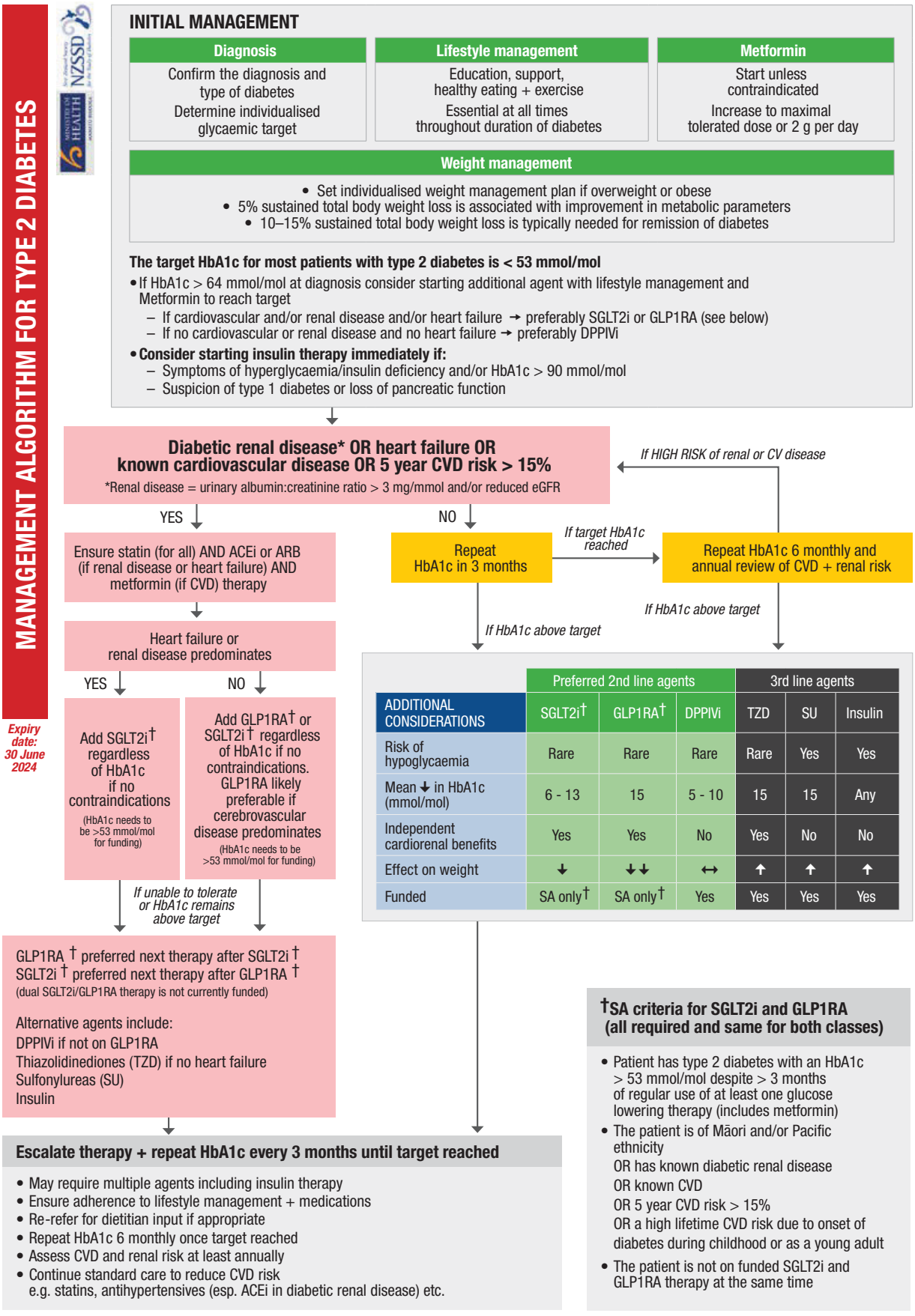
Pioglitazone

Pioglitazone is a third or fourth-line medicine that is likely to reduce CV disease independently of glycaemic control and does not cause hypoglycaemia alone. However, the adverse effects of weight gain and increased fracture risk limit its use. The greatest benefit of pioglitazone is likely to occur in obese patients with insulin resistance and fatty liver disease with the benefits likely to be increased in women.

Acarbose

Acarbose limits carbohydrate absorption and is weight neutral and will not cause hypoglycaemia in monotherapy. Acarbose should be taken with meals. Significant GI adverse effects mean that acarbose is seldom used.

Figure 1: Management algorithm for T2D adapted from NZSSD[1]



ADDITIONAL CONSIDERATIONS	Preferred 2nd line agents			3rd line agents		
	SGLT2i†	GLP1RA†	DPPIVi	TZD	SU	Insulin
Risk of hypoglycaemia	Rare	Rare	Rare	Rare	Yes	Yes
Mean ↓ in HbA1c (mmol/mol)	6 - 13	15	5 - 10	15	15	Any
Independent cardiorenal benefits	Yes	Yes	No	Yes	No	No
Effect on weight	↓	↓↓	↔	↑	↑	↑
Funded	SA only†	SA only†	Yes	Yes	Yes	Yes

†SA criteria for SGLT2i and GLP1RA (all required and same for both classes)

- Patient has type 2 diabetes with an HbA1c > 53 mmol/mol despite > 3 months of regular use of at least one glucose lowering therapy (includes metformin)
- The patient is of Māori and/or Pacific ethnicity
  OR has known diabetic renal disease
  OR known CVD
  OR 5 year CVD risk > 15%
  OR a high lifetime CVD risk due to onset of diabetes during childhood or as a young adult
- The patient is not on funded SGLT2i and GLP1RA therapy at the same time

Mismatch between recommendations and Special Authority criteria

Approximately 33-50% of T2D patients will meet the SA funding criteria for empagliflozin (SGLT2i) or dulaglutide or liraglutide (GLP1RA) which is:

T2D with an HbA1c > 53 mmol/mol, despite regularly using metformin and/or an alternative glucose-lowering medicine (except empagliflozin, dulaglutide or liraglutide) for at least three months **AND** any of the following:

- Māori or Pacific ethnicity OR
- Diabetic renal disease OR
- Known CV disease (ischaemic heart disease, cerebrovascular event, peripheral vascular disease, congestive heart failure or familial hypercholesterolaemia) OR
- Five-year CV risk > 15% OR
- Diabetes onset in childhood or as a young adult

NB: The inclusion of the ethnicity and age-group clauses is to reduce barriers in these high-risk populations, but there is no evidence to date that these agents are more or less effective in these groups.

Patients cannot be on funded empagliflozin and dulaglutide or liraglutide at the same time, but this is only due to financial constraints. Dual SGLT2i/GLP1RA therapy leads to additional reductions in glucose levels and weight and likely provides additional benefit in reducing CV disease. **Therefore, the Special Authority does not fully match best practice**.

Patients should be offered the opportunity to self-fund empagliflozin and/or liraglutide or dulaglutide in the following situations:

- All patients who meet the Special Authority criteria for one agent, but who would benefit from dual SGLT2i/GLP1RA therapy
- Patients with diabetic renal disease and/or heart failure, and/or CV disease, and/or five-year CV risk > 15% with an HbA1c < 53 mmol/mol, i.e. do not qualify because HbA1c is to target
- Non-Māori/ non-Pacific patients without early onset diabetes who are overweight or obese with an HbA1c above target despite taking metformin or are intolerant to metformin
- Non-Māori, non-Pacific patients without early onset diabetes of normal weight with an HbA1c above target who are taking metformin and vildagliptin or are intolerant to this combination
- All patients with an HbA1c at target where the adverse effects of a thiazolidinedione, sulfonylurea and/or insulin need to be avoided

The most cost effective way to self-fund dual SGLT2i/GLP1RA therapy, is for patients to receive funded dulaglutide or liraglutide and pay for empagliflozin.

Patients should be encouraged to compare pharmacy prices as the mark-up varies significantly and online pharmacies are often the cheapest.

The progressive nature of T2D means many patients will require insulin in the advanced stages of disease, despite maximal doses of other glucose-lowering therapies. However, many patients fail to reach glycaemic targets on insulin therapy due to subtherapeutic dosing or ineffectual dose titration.

Patients starting insulin need clear instructions on how to administer and self-titrate doses, how to SMBG levels and to recognise and manage hypoglycaemia. Patients should be provided with a sick day management plan and referred to a dietitian.

Insulin may be reduced or withdrawn, where appropriate, following initiation of newer agents.

Patients taking insulin need to understand their obligations if driving. Factors influencing fitness to drive include vision, peripheral vascular disease and neuropathy, risk of hypoglycaemia, cognitive impairment and other co-morbidities, e.g. obstructive sleep apnoea. Driving assessments for patients can now be performed by medical practitioners or diabetes nurse specialists in secondary care. Further information about diabetes and driving is available from the NZSSD guidelines.

Prescribing insulin

Basal insulin is required by patients with any of the following:

- Likely or confirmed T1D
- Significant hyperglycaemia at any time, e.g. HbA1c > 90 mmol/mol (including at diagnosis)
- Symptoms of insulin deficiency, e.g. weight loss, polyuria, polydipsia
- Unable to meet glycaemic targets after lifestyle management and maximal oral/GLP1RA treatment
- Previous diabetic ketoacidosis or hyperosmolar hyperglycaemic syndrome

Weight-based dosing of isophane or glargine is safe and effective (**Figure 2**) and typically results in faster glycaemic control than the traditional starting dose of 6 –10 units. Basal insulin is most effective when taken at night to offset hepatic glucogenesis.

The recommended starting doses for weight-based basal insulin are:

- 0.1 units/kg daily if there are concerns over hypoglycaemia, e.g. HbA1c < 64 mmol/mol or BMI < 18 kg/m^2 or elderly or renal/liver failure; OR
- 0.2 units/kg daily if HbA1c > 64 mmol/mol and BMI > 18 kg/m^2

Safety remains paramount and regardless of the starting dose regular dose titration results in most patients reaching their glycaemic target.

FBG should be monitored while taking basal insulin and if three consecutive levels > 7 mmol/L occur, increase the dose by 10% or 2 units.

The dose should not be increased if any hypoglycaemia occurs OR the FBG < 7 mmol/L OR doses reach 0.5 units/kg/day.

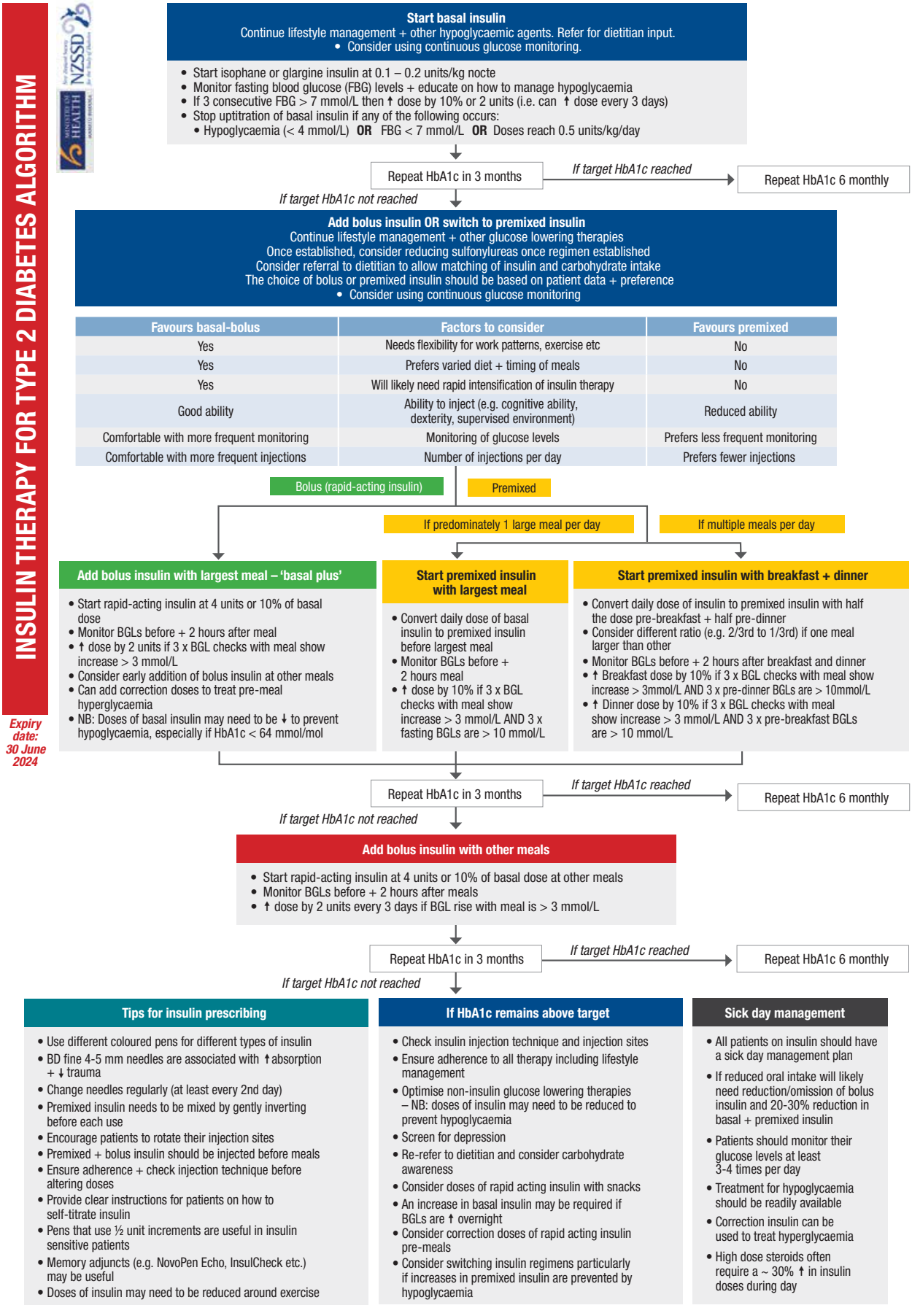
Doses of basal insulin above 0.5 units/kg/day typically do not reduce glucose levels further but lead to weight gain. Clinicians should confirm injection technique and adherence before adjusting insulin doses.

If a patient has not reached their glycaemic target on 0.5 units/kg/day of basal insulin they require prandial insulin with either premixed or bolus insulin.

The choice of bolus or premixed insulin is based on the patient's clinical characteristics and preference. Premixed insulin is only appropriate for patients who eat regular meals.

Correction insulin involves adding doses of rapid-acting insulin to bolus insulin to correct pre-prandial hyperglycaemia. This is administered separately if the patient is taking basal or premixed insulin alone.

Figure 2: Insulin treatment algorithm adapted from NZSSD[1]



TAKE-HOME MESSAGES

- Screen for T2D in high-risk populations from age 15 years
- Confirm a diagnosis of T2D on the same or next day if possible; waiting three months is no longer advised
- The target HbA1c for most patients with T2D is < 53 mmol/mol
- Start lifestyle management and metformin together at diagnosis, in combination with individualised self-management education and support
- Consider starting metformin and a second-line medicine at diagnosis if the HbA1c is > 64 mmol/mol; SGLT2i and GLP1RA are the preferred second-line medicines for most patients with T2D
- Monitor HbA1c levels every three months and escalate treatment if the target is not met
- Prescribe an SGLT2i and/or GLP1RA to all T2D patients with diabetic renal disease and/or CV disease and/or five-year CV risk > 15%, regardless of their glycaemic control, if no contraindications
- Initiate insulin at any time if patients have symptoms of insulin deficiency, e.g. weight loss, polyuria, polydipsia, and consider starting insulin at any time if the HbA1c is > 90 mmol/mol
- Initiate basal insulin with weight-based dosing; introduce prandial insulin if HbA1c above target despite doses of 0.5 units/kg/day.

REFERENCES

1. New Zealand Society for the Study of Diabetes. Type 2 diabetes management guidance. Published online 2021. https://t2dm.nzssd.org.nz/Home.html (Accessed Apr, 2023)
2. ElSayed N. A., et al. Standards of Care in Diabetes. *Diabetes Care.* 2023;46(S1).
3. Chan WC, Lee M (AW). Understanding the heterogeneity of the diabetes population in Metro Auckland in 2018. Published online 2020. https://countiesmanukau.health.nz/assets/About-CMH/Reports-and-planning/Diabetes/2020_Understanding_the_Heterogeneity_of_the_diabetes_pop.pdf (Accessed Apr, 2021)
4. de Boer IH, et al. Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes Care.* 2022;45(12):3075-3090.
5. New Zealand Formulary. NZF. Published online 2022. https://nzf.org.nz
6. Sattar N, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol. 2021;9(10):653-662.
7. Wright AK, et al. Primary Prevention of Cardiovascular and Heart Failure Events With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Their Combination in Type 2 Diabetes. *Diabetes Care.* 2022;45(4):909-918.
8. Tamborlane WV, et al. Liraglutide in Children and Adolescents with Type 2 Diabetes. N Engl J Med. 2019;381(7):637-646.
9. Arslanian SA, et al. Once-Weekly Dulaglutide for the Treatment of Youths with Type 2 Diabetes. N Engl J Med. 2022;387(5):433-443.
10. Laffel LM, et al. Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial. Lancet Diabetes Endocrinol. 2023;11(3):169-181."
11. Palmer SC, et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ.* 2021;372:m4573.
12. Toyama T, et al. Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: A systematic review and meta-analysis. *Diabetes Obes Metab.* 2019;21(5):1237-1250.
13. Zelniker TA, Wiviott SD, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet.* 2019;393(10166):31-39.
14. Boehringer Ingelheim (N.Z.) Limited. Jardiance datasheet. Published online 2021. www.medsafe.govt.nz/profs/Datasheet/j/jardiancetab.pdf
15. Bethel MA, et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. *Lancet Diabetes Endocrinol.* 2018;6(2):105-113.
16. Giugliano D, et al. GLP-1 receptor agonists for prevention of cardiorenal outcomes in type 2 diabetes: An updated meta-analysis including the REWIND and PIONEER 6 trials. *Diabetes Obes Metab.* 2019;21(11):2576-2580.
17. Hinnen D. Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes. *Diabetes Spectr.* 2017;30(3):202-210.
18. Dungan KM, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet.* 2014;384(9951):1349-1357.
19. Tanaka K, et al. Real-world effectiveness of liraglutide versus dulaglutide in Japanese patients with type 2 diabetes: a retrospective study. *Sci Rep.* 2022;12(1):154.
20. Matthews DR, et al. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. *Lancet.* 2019;394(10208):1519-1529.

ABOUT RESEARCH REVIEW

Research Review is an independent medical publishing organisation producing electronic publications in a wide variety of specialist areas.

SUBSCRIBE AT NO COST TO ANY RESEARCH REVIEW

Health professionals can subscribe to or download previous editions of Research Review publications at www.researchreview.co.nz Publications are free to receive for health care professionals, keeping them up to date with their chosen clinical area.

Privacy Policy: Research Review will record your email details on a secure database and will not release them to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time.

New Zealand Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our **CPD page**.