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DULAGLUTIDE DECISIONS

Linda Bryant, Penny Clark and Leanne Te Karu

New Zealand Doctor
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How much do you already know?

Try this quiz

1. Dulaglutide reduces the risk of progression to end-stage renal disease by approximately one-third. True/False
2. Dulaglutide and vildagliptin should not be used together. True/False
3. Dulaglutide and empagliflozin should not be used together. True/False

Answers on page 7

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Decisions abound now dulaglutide is funded for people with type 2 diabetes

PHARMACOTHERAPY

Dulaglutide has been funded for patients with type 2 diabetes since 1 September under Special Authority criteria. This case study summarises its potential benefits and risks, and how these should be considered when tailoring treatment to the individual

Linda Bryant, Penny Clark and Leanne Te Karu

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Sam, who works on traffic control for a roading crew, faces a slight detour in the management of his diabetes and associated risk factors

Sam is a 64-year-old Pacific man who works on traffic control for a roading crew. He was a keen sportsperson, having played representative rugby when he was younger, and he was a regular diver. He currently plays golf off a 10 handicap and still likes to go tramping and hunting with his sons when he can. He also helps coach his grandson's rugby team and laughs that he is learning about hockey as a supporter of his granddaughter's hockey team, and he may start coaching them as well.

Sam is 190cm tall, appears muscular and, although his BMI in March was 33kg/m^2, his waist circumference is only 105cm. He has never smoked, and his alcohol intake is only very occasional.

Sam's past medical history includes long-standing hypertension since 2003, which has been difficult to control. He was diagnosed with type 2 diabetes in 2015 and albuminuria in 2018. In 2017, he had a presumed transient ischaemic attack (TIA), and he recovered from symptoms quickly. He has no history of pancreatitis.

His history of investigations is shown in Table 1. Sam's complete blood count, liver enzymes and lipid profile have all been within target.

Table 2 provides a summary of the medicines currently prescribed to Sam.

Treatment decisions

Due to Sam's albuminuria, he was started on the sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin (Jardiance) after it became funded in February. The benefit was soon noted, with a reduction in albumin:creatinine ratio (ACR) from 72mg/mol to 38mg/mol after three months, and then to 27mg/mol after another three months.

As expected, there was also an initial reduction in estimated glomerular filtration rate (eGFR), as occurs when ACE inhibitors are introduced, but this recovered over time. A benefit for HbA1c was also noted, with a reduction from 72mmol/mol to 62mmol/mol after three months, and then a further reduction to 57mmol/mol after another three months.

Sam initially found the empagliflozin-induced increase in urination

Key points

- Prioritising the potential benefits of SGLT2 inhibitors and GLP-1 receptor agonists is difficult (current Special Authority criteria allow only one class of medicine to be funded for each person).
- Empagliflozin reduces the risk of progression to end-stage renal disease and heart failure, while dulaglutide reduces the risk of stroke.
- There is increasing evidence of synergistic benefit from combining empagliflozin and dulaglutide, so it is important to discuss the option of self-funding empagliflozin if there is a clinical reason for both medicines.

annoying at work, but this reduced over the first three months or so, and is now manageable. He has experienced no other adverse effects on empagliflozin and says he feels much better – he feels "lighter" and like he has more energy.

With the recent approval and funding of the glucagon-like peptide-1 (GLP-1) receptor agonist dulaglutide (Trulicity), a decision now needs to be made whether to:

- continue with empagliflozin only
- switch to dulaglutide
- add dulaglutide to empagliflozin.

Applying the comparisons shown in Table 3 and Sam's perspective, you work through the options.

Option 1: Continue with empagliflozin only

Empagliflozin is beneficial for Sam's kidneys, reducing the risk of progression to end-stage renal disease (ESRD) by approximately one-third. With a rate of ESRD in people with type 2 diabetes of up to 20 per cent, especially in Māori and Pacific peoples, this is a significant reduction.

Already, there has been a reduction in Sam's ACR, indicating a benefit. He has also lost approximately 4kg in weight, reduced his HbA1c by 15mmol/mol, had a marginal drop in blood pressure, and says he feels better on the empagliflozin, with no unacceptable adverse effects. His HbA1c of 57mmol/mol is "heading in the right direction" with the increased empagliflozin dosage.

The added benefit of empagliflozin is that it also reduces his risk of progression to heart failure. Although Sam has not had a cardiac event, he is at risk of heart failure due to his long-standing, hard-to-control hypertension.

These two classes of medicine are very suitable to use together, and international guidance is to use them together

Option 2: Switch to dulaglutide

Sam has done well on empagliflozin, but there is concern about his history of a potential TIA. Further exploration of his medical notes and discharge summary reveals there is a strong possibility this was a TIA. This would make dulaglutide suitable for Sam, especially with his hard-to-control hypertension.

Should Sam be started on dulaglutide, the vildagliptin would need to be stopped.

Both dulaglutide and vildagliptin act on the incretin hormone system – vildagliptin inhibits the metabolism of incretin, and dulaglutide mimics the hormone.

To use both a GLP-1 receptor agonist (dulaglutide) and a dipeptidyl peptidase-4 inhibitor (vildagliptin) is redundant and increases the risk of adverse effects, especially the gastrointestinal adverse effects of dulaglutide.

Dulaglutide-induced gastrointestinal adverse effects occur in up to 25 per cent of people and result in 2 to 3 per cent discontinuing therapy.

Sam is already injecting insulin, so the concerns raised by some people about starting injections is not an issue for him.

Prioritising the potential benefits of SGLT2 inhibitors and GLP-1 receptor agonists is difficult. It usually requires discussion of what is most important to the person in terms of kidney complications versus stroke, especially when it is difficult to quantify the likelihood of progression and who will specifically benefit from the different treatments.

Option 3: Add dulaglutide to empagliflozin

The options of continuing only on empagliflozin or switching from empagliflozin to dulaglutide are funding driven. The current Special Authority criteria allow only one class of medicine to be funded for each person. Clinically, these two classes of medicine are very suitable to use together, and international guidance is to use them together.

There is increasing evidence of synergistic benefit from combining GLP-1 receptor agonists and SGLT2 inhibitors, with further improvements seen in the surrogate endpoints of HBA1c, blood pressure, weight and renal indicators. However, there is a need for longer-term studies relating to the definitive endpoints of ESRD, heart failure and cardiovascular/cerebrovascular outcomes.[1–7]

For Sam, it is expected he would have an improvement in HbA1c with the combination, perhaps even allowing him to discontinue insulin, which may further aid weight loss. Further reductions in blood pressure and ACR are also possible and reduce the risk of ESRD and stroke.

Because of Sam's current HbA1c of 57mmol/mol, a reduction in insulin dosage is likely, although this needs to be balanced against the effects of stopping vildagliptin when dulaglutide is started.

If Special Authority funding is transferred to dulaglutide, Sam would need to self-fund the less expensive

Table 1. **Investigations up to September 2021**

Test	February 2020	July 2020	December 2020	March 2021[a]	July 2021[b]	September 2021
HbA1c (mmol/mol)	74	89	76	72	62	57
ACR (mg/mol)	56	49	77	72	38	27
eGFR (ml/min/1.73m^2)	72	76	74	72	61	70
Blood pressure (mmHg)	148/85	144/82	142/82	146/80	138/82	134/80
Weight (kg)	118	122	120	119	116	115

a) empagliflozin 10mg daily added in March 2021; b) empagliflozin increased to 25mg daily in July 2021
ACR, albumin:creatinine ratio; eGFR, estimated glomerular filtration rate

empagliflozin. This is generally $80 to $85 a month, depending on which pharmacy it is purchased from.

Decision

It is important to discuss the option of self-funding empagliflozin with all people if there is a clinical reason for both medicines. People will then prioritise their potential health outcomes.

Sam takes up the offer of discussing this with his wife, Naomi, and brings her back to an appointment. Together, they decide to decrease the risk of Sam having a stroke, but protecting his kidneys is still important to them. They can budget up to $20 a week to fund empagliflozin, with a hope that the price will reduce and a generic will become available, as happens with many medicines.

When Sam starts dulaglutide, the vildagliptin/metformin (Galvumet) will need to be stopped. Fortunately, having had his empagliflozin dose titrated, Sam can be moved to empagliflozin 12.5mg with metformin 1000mg (Jardiamet), one tablet twice daily. This reduces the daily number of tablets (pill burden), and there is no extra cost for the combination product.

Although a lower absolute reduction in HbA1c is expected with a lower baseline HbA1c, and Sam's HbA1c is 57mmol/mol, it is prudent to reduce Sam's insulin dose by 10–20 per cent to avoid potential hypoglycaemia. As Sam is conscientious about monitoring his blood glucose levels and understands the symptoms of hypoglycaemia, he agrees to reduce his insulin glargine (Lantus) dose to 23 units once daily.

Advice for Sam

- Stop the vildagliptin/metformin and empagliflozin-only tablets, and use empagliflozin/metformin instead.
- Reduce insulin glargine from 28 units to 23 units every morning, monitor blood glucose level every morning and monitor for any signs of hypoglycaemia. If Sam wasn't on insulin or a sulphonylurea, there wouldn't be a concern about hypoglycaemia. Because he is on insulin, his agreed target blood glucose range is 5–8mmol/L, instead of 4–8mmol/L, for safety. You explain there will likely be some initial adjustment of doses. Naomi adds that she always checks the morning readings and will advise you if any are less than 5mmol/L.
- Explain the possibility of stomach upset with dulaglutide for one in four people during the first week, but this usually goes away by the second or third week. Eating smaller meals more slowly, not eating just before bed, and maintaining hydration may minimise stomach upsets. Sam may prefer to wait for two weeks to do his second injection of dulaglutide if he has severe stomach upset, then continue weekly.
- If severe stomach upset occurs, it is important to still eat because he is taking empagliflozin, which has a risk of diabetic ketoacidosis. If Sam does stop eating, he should temporarily stop the empagliflozin and contact the clinic or after-hours clinic. There is minimal extra risk of diabetic ketoacidosis when you add a GLP-1 receptor agonist to an SGLT2 inhibitor, but the risk remains from taking empagliflozin, so remind him to seek medical advice if he experiences any warning signs of euglycaemic diabetic ketoacidosis, including severe abdominal pain, nausea, vomiting or shortness of breath (see "Pharmacotherapy", *New Zealand Doctor*, 3 February).
- Demonstrate the correct injection technique for dulaglutide (YouTube and Health Navigator are useful).
- Explain that if Sam forgets his injection, he can inject it up to three days late; otherwise, just wait until his usual day for the injection.
- Explain that dulaglutide is kept in the fridge, though it can be kept at room temperature for two weeks, providing

If Sam forgets his injection, he can inject it up to three days late

Table 2. **Sam's prescriptions, as at September 2021**

Medicine	Dosage	Comment
Cilazapril	5mg daily	Has been prescribed since 2010, but Sam is aware he may need to switch at some stage due to decreased global supply
Amlodipine	10mg daily	
Chlorthalidone	25mg daily	
Doxazosin	4mg daily	Used for hypertension; no apparent prostate problems
Atorvastatin	40mg daily	
Aspirin	100mg daily	Started for presumed TIA in 2017
Vildagliptin/metformin (Galvumet)	50mg/1000mg twice daily	
Insulin glargine (Lantus)	28 units every morning	Sam was initially hesitant about using insulin, and he still worries about hypoglycaemia, especially when tramping
Empagliflozin (Jardiance)	25mg daily	Started at 10mg daily in March 2021; increased to 25mg daily in July 2021

it is under 30°C. Fortunately, Sam lives in a temperate climate.

- Be clear that despite the benefits of dulaglutide, Sam still needs to take his other medicines.

It is very helpful to set a task for Sam to be contacted in two weeks to check how he is getting on. When this is done, Sam explains that he did feel unwell for a few days after the first dulaglutide injection, but he decided to inject himself again in one week, rather than wait for two weeks. He is feeling better now. His morning blood glucose level has been down to 4.1–4.5mmol/L on four mornings, so his insulin dosage is reduced to 20 units in the morning.

Three months later

Sam has his follow-up blood test three months later, and his HbA1c is 52mmol/mol. He explains that his morning blood glucose level continued to be low, so he reduced his insulin to 16 units in the morning. Sometimes, his morning blood glucose level is still below 5mmol/L, so he reduces his insulin dose to 14 units.

For some people who were on doses of insulin of less than 20 units before commencing dulaglutide, it is possible to eventually discontinue insulin.

At follow-up, Sam's ACR is 23mg/mol, eGFR is 78ml/min/1.73m^2, his weight is 112kg and his blood pressure is 130/76mmHg. ■

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Details have been changed to protect patient confidentiality

The references for this article are available with the online version on nzdoctor.co.nz

For free clinical resources on empagliflozin and dulaglutide, visit akohiringa.co.nz/tags/diabetes

Table 3. **Comparison of empagliflozin and dulaglutide**

	Empagliflozin	Dulaglutide
Renal	**Preferred** Evidence of reduced risk of end-stage renal disease Should not be used for people with an eGFR <30ml/min/1.73m^2	Reduces progression of albuminuria, but less evidence for reduced risk of end-stage renal disease Can be used for people with an eGFR down to 15ml/min/1.73m^2
Cardiovascular	Secondary prevention of major adverse coronary events (MACE), and cardiovascular risk reduction in high-risk people	*Primary* and secondary MACE prevention, driven primarily by stroke risk reduction
Stroke	No current evidence of benefit	**Preferred** Reduced risk of stroke
Heart failure	**Preferred** Reduced risk of hospitalisation with heart failure; effective in people with preserved ejection fraction	Less evidence of benefit
Blood glucose	HbA1c reduction is dependent on baseline – higher HbA1c produces greater absolute reduction Generally, a smaller reduction than with dulaglutide	HbA1c reduction is dependent on baseline – higher HbA1c produces greater absolute reduction Generally, a greater reduction than with empagliflozin
Weight loss	Approximately 2–3kg (on average, so some people have greater weight loss, and others less) Lifestyle measures are still important	Approximately 2–3kg (on average, so some people have greater weight loss, and others less) Lifestyle measures are still important
Adverse effects	Increased urination Increased risk of urinary tract infection and genital infections Risk of diabetic ketoacidosis, especially with low-carbohydrate diets or low food intake Small risk of Fournier gangrene	Gastrointestinal upset Contraindicated if there is history of pancreatitis or medullary thyroid cancer Minor injection site reactions

Quiz answers

1. False **2.** True **3.** False

This publication has been reprinted with the support of Eli Lilly and Company (NZ) Ltd to provide an update on treatment decisions now dulaglutide is funded for people with type 2 diabetes. The content is entirely independent and based on published studies and the author's opinion.

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†Trulicity demonstrated significant HbA1c reductions of -12 mmol/mol to -18 mmol/mol in people with T2D.[1,4-12]

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‡As an adjunct to standard of care therapy, Trulicity significantly reduced the risk of MACE in adults with T2D with established CV disease or multiple CV risk factors (HR: 0.88, 95% CI 0.79-0.99, p=0.026; ARR 1.4%).[1,13]
§MACE: composite of CV death, non-fatal MI or non-fatal stroke.[1,13]

Simple delivery^[1,15,16]

^Once weekly dosing with a ready-to-use pen that 99% of injection naïve patients found easy to use. Titration is not required.[1,15,16]

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TRULICITY® (dulaglutide 1.5mg/0.5mL solution for injection, pre-filled pen [autoinjector]). **PRESCRIPTION MEDICINE.** TRULICITY is funded under the New Zealand Pharmaceutical Schedule from 1 September 2021. Special Authority Criteria apply. **INDICATIONS** – TRULICITY is indicated for adult patients with Type 2 diabetes as 1) an adjunct to diet and exercise to improve glycaemic control; and 2) as an adjunct to standard of care therapy to reduce the risk of major adverse cardiovascular events in those with either established cardiovascular disease or multiple risk factors for cardiovascular disease. **CONTRAINDICATIONS** – Hypersensitivity to dulaglutide or any of the excipients. **PRECAUTIONS** – should not be used in patients with Type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis; severe gastrointestinal disease – not recommended; acute pancreatitis – discontinue treatment if suspected; hypoglycaemia – combining treatment with sulfonylurea or insulin may increase risk; congestive heart failure – limited therapeutic experience; Use in Pregnancy Category B3. **ADVERSE EFFECTS Clinical Trials Experience** – Very Common (≥10%) gastrointestinal disorders (nausea, vomiting and diarrhoea), hypoglycaemia (in combination with insulin non-/secretagogues and/or insulin); Common (≥1 and <10%) abdominal pain, decreased appetite, dyspepsia, fatigue, hypoglycaemia (as monotherapy), immunogenicity, atrial fibrillation. **DOSAGE AND ADMINISTRATION** – Dosage: Adults (≥ 18 years): 1.5 mg once weekly, at any time of day, independently of meals. Elderly Patients (≥65 years): dose adjustment not required. Children and adolescents (<18 years): safety and effectiveness have not been established. Renal Impairment: no dose adjustment is required in mild, moderate or severe renal impairment; not recommended in end-stage renal disease. Hepatic Impairment: no dose adjustment required. Administration: subcutaneous injection in the abdomen, thigh or upper arm. Should not be administered intravenously or intramuscularly. Single-use in one patient only. Discard the pen once the injection is completed. Please review full Data Sheet before prescribing. Full Data Sheet is available on request from Eli Lilly. Eli Lilly and Company (NZ) Limited, PO Box 109 197, Newmarket, Auckland 1149. Phone 0800 500 056. Based on Data Sheet approved 12 August 2021.

ABBREVIATIONS: ARR, absolute risk reduction; CV, cardiovascular; GLP-1 RA, Glucagon-like peptide-1 receptor agonist; MACE, Major Adverse Cardiovascular Events; MI, myocardial infarction; T2D, type 2 diabetes.

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