Clinical Quality and Education
Medicines Update Bulletin
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Type 2 Diabetes: Update on Oral Antihyperglycaemics

Key messages

- **SGLT-2 inhibitors** (empagliflozin) and **GLP-1 receptor agonists** (dulaglutide) are new antihyperglycaemic classes funded via Special Authority
- They are second-line options after metformin and preferred in patients at high risk of cardiovascular (CV) or renal complications. Patients likely to benefit the most are those of older age, prior heart failure or CV events, or diabetic kidney disease
- SGLT-2 inhibitors and GLP-1 agonists reduce major CV events and progression of renal disease in high-risk patients, independent of HbA1c. SGLT-2 inhibitors also reduce admission to hospital with heart failure
- SGLT-2 inhibitors and GLP-1 agonists also lower weight and blood pressure, and do not cause hypoglycaemia unless used with insulin or sulfonylureas
- Second-line antihyperglycaemic choice now depends on presence (or high risk of) CV disease, heart failure or kidney disease. Otherwise, the decision is based on patient preference, efficacy, contraindications, adverse effects and interactions
- Other second-line options include DPP-4 inhibitors (vildagliptin), sulfonylureas (e.g. gliclazide and glipizide), and thiazolidinediones/glitazones (e.g. pioglitazone)
- Continue standard care to reduce CV risk, such as aspirin, statins and antihypertensives

Clinical Quality and Education Team comment: SGLT-2 inhibitors and GLP-1 agonists reduce the risk of death and improve CV and renal outcomes in patients with type 2 diabetes who are at increased CVD risk. Their efficacy in patients at lower risk is less clear, and both medication classes have important adverse effects. They may be useful therapeutic options in selected patients. Treatment decisions should be based on an individualised assessment of benefit, harms and patient preference.

Newly funded classes of antihyperglycaemics

Pharmac has recently funded two classes of antihyperglycaemics for the treatment of type 2 diabetes:

- *Sodium-glucose cotransporter-2 (SGLT-2) inhibitor*: empagliflozin (oral)
- *Glucagon-like peptide (GLP-1) receptor agonist:* dulaglutide (subcutaneous injection)

These classes have been used overseas for many years and are now funded via Special Authority.

SGLT-2 inhibitors and GLP-1 agonists reduce mortality, major CV events, progression of renal disease, and heart failure (for SGLT-2 inhibitors) in high-risk patients with diabetes, irrespective of HbA1c. Patients likely to benefit the most are those of older age, history of heart failure (HF) or CV events (or high risk of CVD), or diabetic kidney disease[2]. They are currently only funded if HbA1c is >53 mmol/mol.

SGLT-2 inhibitors and GLP-1 agonists also reduce weight and blood pressure, and do not cause hypoglycaemia unless used with sulfonylureas or insulin.

Special Authority criteria:

Empagliflozin and dulaglutide are funded in patients on at least one antihyperglycaemic with an HbA1c >53 mmol/mol, and at high risk:

- Māori or Pacific ethnicity, **or**
- CV disease (or 5-year risk ≥15%), **or**
- Diabetic kidney disease*

*albumin:creatine ratio ≥3 mg/mmol or eGFR<60 mL/min/1.73m2

See Pharmac for exact criteria. Dual use is not funded.

Self-funding: Patients who do not meet the criteria may wish to self-fund. Cost is approximately $85/month for empagliflozin and $240/month for dulaglutide.

Evidence for SGLT-2 inhibitors and GLP-1 agonists

Multiple large CV outcome trials have found SGLT-2 inhibitors and GLP-1 receptor agonists similarly reduced risk of major adverse CV events in type 2 diabetes, independent of HbA1c.

These effects have been confirmed in recent meta-analyses. Palmer 2021[3] (764 RCTs, n=421,346) found:

- SGLT-2 inhibitors and GLP-1 agonists reduced all-cause mortality, CV mortality, non-fatal MI, and kidney failure when added to existing diabetes treatment (high certainty)
- SGLT-2 inhibitors reduced hospital admission with HF
- GLP-1 agonists reduced risk of non-fatal stroke
- Absolute benefits were much greater as individual risk increased, e.g., SGLT-2 inhibitors prevented 5 deaths per 1000 patients per 5 years in patients with no CV risk factors, vs. 48 in very high-risk patients. See Table 1.
- Compared with GLP-1 agonists, SGLT-2 inhibitors had greater effect on mortality (OR 0.88; 95% CI 0.79-0.97) and hospital admissions for HF (OR 0.74; 95% CI 0.65-0.85), but higher odds of non-fatal stroke (OR 1.20; 95% CI 1.03-1.41)

Other meta-analyses have shown SGLT-2 inhibitors are superior to GLP-1 agonists in reducing renal risk [2,4,5].

The decision-making tool MATCH-IT can be used to estimate individual patient benefits and risks of treatment.

Choosing between SGLT-2 inhibitor or GLP-1 agonist

There are no head-to-head studies comparing the two classes, therefore, patient preference and co-morbidities are likely to be the most important considerations. They can be used together with potential extra benefit[6,10,11], but dual use is not funded.

SGLT-2 inhibitors may be preferred if:

- HF or renal disease predominates
- Oral treatment or daily administration is preferred

GLP-1 agonists may be preferred if:

- Cerebrovascular disease predominates
- A greater reduction in HbA1c or weight is required
- Weekly administration is preferred
- eGFR 15-30 mL/min/1.73m^2

Prescribing a SGLT-2 inhibitor (empagliflozin)

Mechanism: blocks glucose reabsorption in kidneys

Dosage: 10mg po daily, increasing to 25 mg if needed

- Consider reducing dose of sulfonylurea (e.g., 50%) and insulin (e.g., by 20%) if HbA1c is <64 mmol/mol[6]
- Consider reducing dose of antihypertensives

Adverse effects: Genitourinary infections, volume depletion, polyuria, rarely ketoacidosis (euglycaemic) – discuss sick day management, Fournier's gangrene.

Route of elimination: Glucuronidation (mostly hepatic)

Prescribing a GLP-1 agonist (dulaglutide)

Mechanism: stimulates insulin secretion after meals and reduces glucagon secretion, gastric emptying and appetite

Dosage: 1.5mg subcutaneous once weekly (no titration)

- Consider reducing dose of sulfonylurea (e.g., by 50%) and insulin (e.g., by 20%) if HbA1c <64 mmol/mol[6]
- Avoid DPP4-inhibtors (vildagliptin) as no extra benefit

Adverse effects: Commonly, gastrointestinal symptoms such as nausea, anorexia, diarrhoea (usually transient). Occasionally effects are severe. Transient injection site reactions. Discuss sick day management.[6]

Route of elimination: Protein catabolism

Table 1: Palmer 2021 meta-analysis: Comparison of SGLT-2 inhibitors or GLP-1 agonists vs. placebo treatment[3]

	All-cause mortality	CV mortality	Non-fatal MI	Non-fatal stroke	Kidney failure	Hospital admissions with HF
SGLT-2 inhibitor						
Odds ratio (95% CI)	**0.77** (0.71 - 0.83)	**0.84** (0.76 - 0.92)	**0.87** (0.79 - 0.97)	**1.01** (0.89 - 1.14)	**0.71** (0.57 - 0.89)	**0.70** (0.63 - 0.77)
Absolute effect*						
Moderate CV risk	25 less	12 less	13 less	not significant	6 less	23 less
Very high CV risk	48 less	24 less	21 less	not significant	38 less	58 less
GLP-1 agonist						
Odds ratio (95% CI)	**0.88** (0.83 - 0.94)	**0.88** (0.80 - 0.96)	**0.92** (0.85 - 0.99)	**0.84** (0.76 - 0.93)	**0.78** (0.67 - 0.92)	**0.94** (0.85 - 1.03)
Absolute effect*						
Moderate CV risk	13 less	9 less	8 less	16 less	4 less	not significant
Very high CV risk	24 less	18 less	13 less	25 less	29 less	11 less

*Reduction in number of events per 1000 patients over 5 years. *Moderate* CV risk defined as patients with established CV disease and *very high* risk as established CV and diabetic kidney disease

Pharmacological management of type 2 diabetes[1,6,8]

First-line: Metformin + lifestyle management

Second-line:

- *Cardiovascular disease, renal disease, or heart failure* → *SGLT-2 inhibitor* or *GLP-1 agonist* preferred
  - Heart failure → SGLT-2 inhibitor preferred
  - Renal disease → SGLT-2 inhibitor preferred
  - Cerebrovascular disease → *GLP-1 agonist* likely preferred[6]
- *No CV or renal disease or heart failure* → Consider patient preference, efficacy, impact on weight, adverse effects, interactions, and contraindications. NZSSD suggests sulfonylureas and glitazones as **third-line** since they cause weight gain and hypoglycaemia.
- For more information on treating type 2 diabetes, see NZSSD and BPAC.

Inequity in diabetes care

Māori and Pacific peoples are at a higher risk of developing diabetes and have increased mortality and morbidity once it has developed. However, they receive inequitable delivery of healthcare, including prescribing of antihyperglycaemics[1.] To help reduce inequity and improve health outcomes for these patients, ethnicity has been identified as a major criterion for obtaining Special Authority funding for empagliflozin and dulaglutide.

Table 2: Considerations when selecting antihyperglycaemic treatment[6,7,8,9]

		Route	Efficacy (HbA1c)	Hypo	Weight	Renal benefit	CV benefit		Other info
							CVD	HF	
1st-line	**Metformin**	Oral	High	No	↔ ↓	↔	?Yes	↔	**Caution:** eGFR <60mL/min/1.73m^2 - dose adjust, sick day management **Contraindicated**: eGFR<15mL/min/1.73m^2; liver or heart failure
2nd-line	**SGLT-2 inhibitor** Empagliflozin	Oral	Medium	No	↓	Yes	Yes	Yes	**Caution**: risk of DKA (withhold in acute illness or surgery), sick day management, patients at risk of volume depletion, hypos with insulin and sulfonylureas **Contraindicated:** eGFR <30mL/min/1.73m^2, under 18yo, pregnancy, breastfeeding, previous severe genitourinary infections
	GLP-1 agonist Dulaglutide	Subcut	High#	No	↓↓	Yes	Yes	↔	**Caution:** eGFR<15 mL/min/1.73m^2 - seek specialist advice, monitor eGFR, sick day management **Contraindicated:** <18yo, pregnancy, breastfeeding, severe GI disease, DPP-4 inhibitor use, history of pancreatitis, medullary thyroid carcinoma, MEN2 syndrome
	DPP-4 inhibitor Vildagliptin	Oral	Medium	No	↔	↔	↔	↔	**Caution:** eGFR<50mL/min/1.73m^2 - reduce dose**;** ACE inhibitor use (rare reports of angioedema), history of acute pancreatitis, GLP-1 agonist use, hypos with sulfonylureas **Contraindicated:** <18yo, pregnancy, breastfeeding, unstable CHF
3rd -line*	**Sulfonylurea** Gliclazide Glipizide	Oral	High	Yes	↑	↔	↔	↔	**Caution:** Renal impairment – dose reduce**,** sick day management, hypos, G6PD deficiency **Contraindicated:** <18yo, pregnancy, breastfeeding, renal or liver failure, ketoacidosis
	Glitazones Pioglitazone	Oral	High	No	↑	↔	?Yes	↑ risk	**Cautions:** Fluid retention - avoid in HF, sick day management, hypos with insulin or sulfonylureas, monitor LFTs **Contraindicated:** osteoporosis, oedematous conditions, history of bladder cancer
	Insulin	Subcut	Highest	Yes	↑	↔	↔	↔	**Caution:** Lower doses required in renal impairment, hypos, sick day management **Contraindicated:** hypoglycaemia

Effect is greatest when HbA1c is high. Glycaemic efficacy was found to be similar or greater than basal insulin in comparative trials.
*As per NZSSD guidelines. Sulfonylureas and glitazones are suggested as third-line since they cause weight gain and hypos.
Hypo = hypoglycaemia

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