PHARMAC
TE PĀTAKA WHAIORANGA

PHARMACEUTICAL SCHEDULE CHANGE

To: Obesity Treatment Advisory Group

From: Therapeutic Group Manager

Date: December 2025

Seeking advice on proposal to amend the Special Authority criteria for SGLT2 inhibitors and GLP1 agonists for the treatment of type 2 diabetes mellitus with cardio-renal risk

SUMMARY OF PHARMACEUTICAL			
Brand Name	Jardiance/ Jardiamet	**Chemical Name**	Empagliflozin / Empagliflozin with metformin
Current Subsidy	s 9(2)(b)(ii)	**Proposed Restriction**	Special Authority
Proposed Subsidy	Gross s 9(2)(b)(ii) Tab 10mg (30), Tab 25 mg (30), Tab 5mg /500mg (60), Tab 5mg/1000mg (60), Tab 12.5mg/500mg (60), Tab 12.5mg/1000mg (60)	**Approved by Medsafe for this indication**	Yes
Supplier	Boehringer Ingelheim	**Application Date**	n/a
MOH Restrictions	Prescription medicine	**Proposal type**	Widen access

SUMMARY OF PHARMACEUTICAL			
Brand Name	Trulicity	**Chemical Name**	Dulaglutide
Current Subsidy	s 9(2)(b)(ii)	**Proposed Restriction**	Special Authority
Proposed Subsidy	Gross s 9(2)(b)(ii) per 4 x 1.5mg prefilled pens (s 9(2)(b)(ii) per 4 x 1.5mg prefilled pens)	**Approved by Medsafe for this indication**	Yes
Supplier	Eli Lilly	**Application Date**	n/a
MOH Restrictions	Prescription medicine	**Proposal type**	Widen access

SUMMARY OF PHARMACEUTICAL			
Brand Name	Victoza	**Chemical Name**	Liraglutide
Current Subsidy	s 9(2)(b)(ii)	**Proposed Restriction**	Special Authority
Proposed Subsidy	Gross s 9(2)(b)(ii) per 3 x 6mg per ml, 3 ml prefilled pens	**Approved by Medsafe for this indication**	Yes
Supplier	Novo Nordisk	**Application Date**	n/a
MOH Restrictions	Prescription medicine	**Proposal type**	Widen access

QUESTIONS TO THE COMMITTEE

1. Does the information in the PICO table accurately reflect the intended population, intervention, comparator, and outcome, if SGLT2i / GLP-1a were to be funded for individuals with T2DM with a five-year CVD risk of 10% or more? If not, how should this be adjusted?
2. What are the Committee's views on the health benefits gained by individuals with a five-year CVD risk of 10-14%, when receiving SGLT2i or GLP1a instead of standard of care? Specifically, can any of the following benefits be assumed?
    - Decrease in all-cause mortality
    - Decrease in heart failure hospitalisation
    - Improved renal outcomes (Delay in progression to macroalbuminuria and renal replacement therapy)
    - Delayed progression to insulin
3. Can we assume a class effect for SGLT2i, meaning that health benefits would be comparable across different agents within this class? Note that previous advice suggested this may be plausible but was uncertain at the time.
4. How do the health benefits due to empagliflozin/SGLT2i for individuals with a five-year CVD risk of 10-14% compare to those for individuals with a risk of 15% or higher?

    4.1. Is it reasonable to assume that relative treatment effects remain consistent regardless of baseline absolute CVD risk?
5. How do the health benefits due to GLP1a for individuals with a five-year CVD risk of 10-14% compare to those for individuals with a risk of 15% or higher?

    5.1. Is it reasonable to assume that relative treatment effects remain consistent regardless of baseline absolute CVD risk?
6. Would the meta-analysis by Palmer et al. 2021 be appropriate to use to reflect the treatment benefit of SGLT2i and GLP1a in a moderate or low CVD risk population?

    6.1. If yes, what risk group best reflects the population under assessment?

    6.2. If not, what other evidence would best represent the health benefit in individuals with T2DM with a CVD risk of 10-14% for these two treatment classes?
7. What is the Committee's views on the strength and quality of the evidence, including its relevance to New Zealand, for health benefits that may be gained from SGLT2i and GLP1a for individuals with T2DM and a five-year CVD risk of 10-14%?
8. Would the baseline characteristics of DECLARE-TIMI 58 (dapaglifozin) or the CANVAS trials (canagliflozin) be more reflective of the population under assessment than the EMPA-REG OUTCOME trial?

    8.1. Specifically, characteristics related to renal function and number of patients on insulin as outlined in Table 6.
9. Would the baseline characteristics of DECLARE-TIMI 58 (dapaglifozin) or the CANVAS trials (canagliflozin) be more reflective of the population under assessment than the EMPA-REG OUTCOME trial?

10. Is it appropriate to assume that all patients not on insulin at baseline will progress to requiring insulin after three months regardless of treatment with an SGLT2i or GLP1a?
11. Pharmac seeks the Committee's advice on the likelihood that individuals diagnosed with T2DM in childhood or early adulthood would have a CVD risk of 10–14%, given their elevated lifetime risk.
    11.1. If overlap is likely, what proportion of this group is expected to fall within that risk range?
12. Would the reduction in the CVD risk score from ≥15% to ≥10% capture the majority of people with T2DM likely to benefit from treatment with an SGLT2i or GLP1a medicine?
    12.1. Would this change in the CVD risk score criteria also ensure that the majority of Māori / Pacific people who currently have access via the specific ethnicity criteria would also be able to access treatment based on defined clinical criteria alone?

PURPOSE OF THIS PAPER

This paper seeks the Committee's advice on a proposed change to the Special Authority criteria for empagliflozin/GLP1a medicines in the treatment of type 2 diabetes mellitus (T2DM). The proposal involves lowering the five-year cardiovascular disease (CVD) risk threshold from 15% to 10%.

The paper also requests guidance on the potential impact of removing the current ethnicity-based criteria for empagliflozin/GLP1a medicines, and the extent to which lowering the CVD risk threshold may offset that impact.

DISCUSSION

BACKGROUND

Empagliflozin, a sodium-glucose co-transporter 2 inhibitor (SGLT2i), was recommended for listing on the Pharmaceutical Schedule for individuals with T2DM with high cardiovascular risk with a high priority by PTAC in 2017. Empagliflozin (Jardiance) and empagliflozin with metformin (Jardiamet), supplied by Boehringer Ingelheim, were listed 1 February 2021.

The current Special Authority criteria used for empagliflozin (*with or without metformin*) for the treatment of T2DM are presented below, with the criteria under consideration in this proposal underlined

Initial application from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:

Prerequisites (select where appropriate)

1. Patient has previously received an initial approval for a GLP-1 agonist, OR

All of the following:

2. Patient has type 2 diabetes; and
3. Any of the following:
    - 3.1. Patient is Māori or any Pacific ethnicity*; or
    - 3.2. Patient has pre-existing cardiovascular disease or risk equivalent (see note a)*; or
    - 3.3. Patient has an absolute 5-year cardiovascular disease risk of 15% or greater according to a validated cardiovascular risk assessment calculator*; or
    - 3.4. Patient has a high lifetime cardiovascular risk due to being diagnosed with type 2 diabetes during childhood or as a young adult*; or
    - 3.5. Patient has diabetic kidney disease (see note b)*; and
4. Target HbA1c (of 53 mmol/mol or less) has not been achieved despite the regular use of one blood-glucose lowering agent (e.g., metformin, vildagliptin or insulin) for at least 3 months.

Note:

* Criteria 3.1-3.5 describe patients at high risk of cardiovascular or renal complications of diabetes.

a) Pre-existing cardiovascular disease or risk equivalent 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.

b) Diabetic kidney disease 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/1.73m2 in the presence of diabetes, without alternative cause.

c) Funded [empagliflozin / empagliflozin with metformin hydrochloride] treatment is not to be given in combination with a funded GLP-1 unless receiving (empagliflozin / empagliflozin with metformin hydrochloride] for the treatment of heart failure.

Dulaglutide and liraglutide, both glucagon-like peptide 1 inhibitors (GLP1a), are listed on the Pharmaceutical Schedule for individuals with T2DM with high cardiovascular risk.

The current Special Authority criteria used for GLP1a inhibitors for the treatment of T2DM are presented below, with the criteria under consideration in this proposal in bold.

> Initial application from any relevant practitioner. Approvals valid without further renewal unless notified.
>
> Prerequisites (select where appropriate)
>
> 1. Patient has type 2 diabetes; and
> 2. Target HbA1c (of 53 mmol/mol or less) achieved despite the regular use of all of the following funded blood glucose lowering agents for a period of least 6 months, where clinically appropriate: empagliflozin, metformin, and vildagliptin; and
> 3. Any of the following:
>   - 3.1. **Patient is Māori or any Pacific ethnicity*;** or
>   - 3.2. Patient has pre-existing cardiovascular disease or risk equivalent (see note a)*; or
>   - 3.3. **Patient has an absolute 5-year cardiovascular disease risk of 15% or greater according to a validated cardiovascular risk assessment calculator***; or
>   - 3.4. Patient has a high lifetime cardiovascular risk due to being diagnosed with type 2 diabetes during childhood or as a young adult*; or
>   - 3.5. Patient has diabetic kidney disease (see note b)*; and
>
> Note:
>
> * Criteria intended to describe patients at high risk of cardiovascular or renal complications of diabetes.
>
> a) Pre-existing cardiovascular disease or risk equivalent 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..
>
> b) Diabetic kidney disease 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/1.73m2 in the presence of diabetes, without alternative cause identified.
>
> c) Funded GLP-1a treatment is not to be given in combination with funded (empagliflozin /empagliflozin with metformin hydrochloride) unless receiving funded (empagliflozin or empagliflozin in combination with metformin hydrochloride) for the treatment of heart failure.

Previous Committee Consideration

The Pharmac Diabetes Advisory Committee met in June 2025 to discuss the proposed removal of specific ethnicity criteria from the special authority criteria for SGLT2i and GLP1a medicines for the treatment of T2DM, and what would be an appropriate mechanism by which those people captured by the ethnicity criteria would still be able to access these medicines.

The key discussion points of that meeting were:

- **Health benefit and access widening**
    - The Committee agreed that broader access to SGLT2i and GLP1a medicines for people with type 2 diabetes - beyond current funding criteria - would likely yield significant health benefits.
- **Special Measures justification**
    - Māori and Pacific peoples face entrenched systemic barriers to healthcare access and ethnicity remains a necessary component of the Special Authority criteria to address these inequities, as no alternative criteria effectively capture the unique risks and needs of these populations.
    - Māori and Pacific peoples have a disproportionately high burden of type 2 diabetes cardio-renal disease (6 - 7 times higher than other groups) and lower dispensing rates.
    - The health system was not adequately meeting their needs, and ethnicity-based criteria were necessary to address entrenched inequities. Māori and Pacific peoples face entrenched systemic barriers to healthcare access.
    - South Asian people, while at higher risk, do not face the same systemic barriers and are adequately captured by other clinical criteria.
- **Pharmac analysis and prescribing trends**
    - The Committee reviewed a December 2023 Pharmac check-up analysis (available on request) of the effectiveness of the access criteria for empagliflozin and dulaglutide and noted that the analysis indicated that ~89% of Māori and Pacific peoples with type 2 diabetes meet current clinical criteria independently of the ethnicity access option.
    - The Committee also noted that the analysis showed cardiovascular risk assessments are more frequently conducted for Māori (91%) than non-Māori (83%), indicating an improvement in access since the original consideration.
    - The Committee reviewed an independent study that found that nearly half of eligible patients were prescribed SGLT2i/GLP1a within 18 months of funding availability, with Māori and Pacific patients having the highest initiation rates (50.8% and 48.8%, respectively).
- **Clinical criteria and risk assessment tools**
    - Multiple cardiovascular risk tools are used in practice and these are somewhat inconsistent, particularly with regards to how they factor in the impact of ethnicity on risk.
    - The current special authority form may inadvertently enable prescribers to avoid undertaking a thorough clinical assessment including cardiovascular risk assessment/scoring for Māori and Pacific peoples.
    - The current 15% 5-year cardiovascular risk threshold may not capture all those who could receive significant benefit from treatment; New Zealand Society for the Study Diabetes (NZSSD) guidelines are under review and this threshold

may be lowered in the new version to a 5 yr risk score of greater than or equal to 10%

- Introducing discretionary criteria based on prescriber judgment of cardio-renal risk could improve inclusivity and capture the intended target population. However, this approach may may result in under or over assessment of clinical risk, inadvertently reduce the use of risk-scoring tools, and may have significant budgetary implications.
- The intent of a criterion is not to explicitly guide clinical practice nor serve as an educational tool but to ensure that funded access was targeted to the defined population for which funded medicine access was intended.

Pharmac staff note the advice received from the Committee continued to support the use of ethnicity criteria where there were no other reasonable means to allow access to individuals with the highest health need.

Pharmac's Board has agreed in principle to consult on removing ethnicity-based criteria for diabetes medicines (SGL2i/GLP1a). At the same time, it would like to consider widening access to empagliflozin and GLP1a by lowering the five-year CVD risk threshold and understand to what extent this widening of access would offset the impact of removing the ethnicity criteria. This proposed change in the CVD risk criteria would be assessed through Pharmac's standard funding processes.

This proposal supports Pharmac's purpose of delivering the best health outcomes from New Zealand's investment in medicines and medical devices, by making choices and managing expenditure and supply. It aims to better identify those with the greatest health need through targeted clinical criteria. This approach aligns with the Cabinet Circular CO (24) 5 of 13 September 2024, titled 'Needs-based Service Provision' (the Cabinet Circular), the Letter of Expectations and Pharmac's position on section 6 and 7 of Pae Ora (Healthy Futures) Act 2022 (the Act).

The proposed PICO for this proposal is presented below.

Table 1. PICO

POPULATION	People with T2DM 2 who have an absolute five-year CVD risk of 10-14% and who have not achieved target HbA1c (of less than 53 mmol/mol) despite maximum tolerated doses of oral antidiabetic agents and/or insulin for at least 3 months
INTERVENTION	SGLT2i (Empagliflozin selected as the agent to represent the class) or GLP1a (Dapagliflozin may be selected as the agent to represent the class)
COMPARISON	Standard of care diabetes treatment
OUTCOME	• Decrease in all-cause mortality • Decrease heart failure hospitalisation • Improved renal outcomes (Delay in progression to macroalbuminuria and renal replacement therapy) • Delayed progression to requiring insulin treatment

EVIDENCE BY CVD RISK CLASSIFICATION

Clinical guidelines, policies and studies vary in how CVD risk is assessed and classified. These differences arise from the choice of risk assessment tools or criteria, the absolute risk thresholds applied, and the time horizon over which risk is calculated. Consequently, an individual considered 'high risk' in one country or study may be classified as 'moderate risk' or ''low risk' elsewhere.

Currently, New Zealand's Special Authority criteria for empagliflozin includes patients with a five-year CVD risk of 15% or higher (as one of the access criteria). This aligns with the 2023 T2DM management guidelines, developed by the New Zealand Society for the Study of Diabetes (NZSSD) and supported by the Ministry of Health, which recommends that "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 GLP1a regardless of their glycaemic control or other glucose-lowering therapies." This threshold in the NZSSD guideline is expected to be lowered in the upcoming guideline update, with indications suggesting a change to a five-year CVD risk of 10% or greater.

Australian guidelines define high risk as a five-year CVD risk of ≥10%, intermediate risk as 5–10%, and low risk as <5% (AusCVDRisk. CD risk category. Last accessed 25 November 2025). The UK's National Institute for Health and Care Excellence (NICE) defines high CVD risk in their T2DM guideline as a QRISK score of ≥10% over 10 years (which will be less than 5% over 5 years) (NICE NG28, updated June 2022), and it is recommended that prescribers should consider an SGLT2i with proven cardiovascular benefit, alongside metformin, for this group. A GLP1i may be considered later on in the treatment pathway (if triple therapy with metformin and two other oral drugs is not effective), but access is not dependant on CVD risk status (NICE NG28, updated June 2022).

The published clinical evidence on SGLT2i and GLP1a identified by Pharmac does not typically report absolute CVD risk for the study populations, meaning there is no data that directly corresponds to people with the assessed CVD risk of 10% or more over five years. Instead, trial participants are generally classified as having established CVD or not. Among those without established CVD, most were considered to be at high cardiovascular risk.

a) *Cardiovascular outcome evidence for SGLT2i and GLP1a previously reviewed by PTAC and Diabetes Advisory Committee*

The long-term trial cardiovascular outcome data for SGLT2i and GLP1a was assessed by PTAC in February 2019 and the Diabetes Advisory Committee in March 2019.

The following primary studies were assessed:

- Canagliflozin: CANVAS and CANVAS R - Neal et al, N Engl J Med. 2017;377:644-57
- Dapagliflozin: DECLARE-TIMI 58 – Wiviott et al, N Engl J Med. 2019;380:347-57
- Empagliflozin: EMPA-REG OUTCOME – Zinman et al, N Engl J Med. 2015;373:2117-28
- Liraglutide: LEADER trial – Maso et al, N Engl J Med. 2016;375:311-22
- Semaglutide: SUSTAIN 6 – Maso et al, N Engl J Med. 2016;375:1834-44
- Exenatide: EXSCEL – Holman et al, N Engl J Med. 2017;377:1228-39
- Albiglutide: HARMONY – Hernandez et al, Lancet. 2018;392:1519-29.

An overview of the study designs and assessed outcomes is provided in the *Evidence Summary* (see pages 20-24). For SGLT2i trials, EMPA-REG OUTCOME included only patients with established CVD, whereas CANVAS and DECLARE-TIMI 58 enrolled patients both with and without established CVD. For GLP-1a trials, HARMONY included only patients with established CVD, whereas LEADER, SUSTAIN-6, and EXSCEL included participants with and without established CVD.

See the meeting records (PTAC February 2019 & Diabetes Advisory Committee March 2019) for more detail on the other studies assessed relating to CVD outcomes. These were mainly systematic reviews, meta-analyses and retrospective cohort studies.

Key themes on SGLT2**i** from the Advisory Committee meetings (PTAC February 2019 & Diabetes Advisory Committee March 2019) based on the evidence available at the time;

- Cardiovascular Benefits
  - Both committees agreed that SGLT2i show benefits in reducing hospitalisations for heart failure and potentially improving cardiovascular outcomes (only reported in some studies).
  - Evidence of cardiovascular benefit is strongest in patients with established CVD, but there is a trend (though not as significant) toward benefit in high-risk populations without established CVD.
  - Some SGLT2i demonstrate reductions in major adverse cardiovascular events (MACE), cardiovascular mortality, and all-cause mortality.
- Renal Outcomes
  - Both committees noted likely benefits in slowing progression of renal disease and composite renal outcomes, particularly for patients with declining eGFR.
  - While long-term data are still emerging, current evidence supports a class effect for renal benefits in T2DM patients.
- Class Effects and Uncertainty
  - Both committees considered that therapeutic benefits are likely consistent within the SGLT2i class.
  - There is however some uncertainty due to variations in trial populations and disease characteristics, but international guidelines acknowledge this and expect clearer evidence over time.

Key themes on GLP1a from the Advisory Committee meetings (PTAC February 2019 & Diabetes Advisory Committee March 2019) based on the evidence available at the time;

- Cardiovascular and Mortality Benefits
  - Evidence consistently indicates a class effect for GLP-1 receptor agonists in reducing all-cause mortality, cardiovascular mortality, and heart failure hospitalisations.
  - These benefits appear to apply broadly, irrespective of baseline cardiovascular or renal risk, and may extend beyond patients with established cardiovascular disease.

b) *Cardiovascular outcome evidence (by CVD risk categorisation) not yet assessed by PTAC and Diabetes Advisory Committee*

Additional systematic reviews and real-world studies that provide insights into the cardiovascular and renal benefits of SGLT2i and GLP1a in lower-risk populations were identified by Pharmac staff. The findings from the systematic review and meta-analysis considered most relevant to this proposal are summarised below (Palmer et al. B*MJ* 2021;372:m4573; PDF available in **Appendix 1**), with details of other identified studies presented in the *Evidence Summary* (see pages 20-24).

Palmer et al (2021) reported the findings from a systematic review and network meta-analysis that evaluated the benefits and harms of SGLT-2i and GLP1a in adults with T2DM.

Data is presented according to five baseline risk categories to estimate absolute effects of treatment on cardiovascular and kidney outcomes. Patient risk categories were defined as follows:

- Very low risk: No or fewer than three cardiovascular risk factors
- Low risk: Three or more cardiovascular risk factors
- Moderate risk: Established cardiovascular disease
- High risk: Chronic kidney disease
- Very high risk: Both cardiovascular disease and chronic kidney disease

In this analysis, baseline absolute risk per 1,000 patients treated over five years was estimated by extrapolating short-term data where necessary, assuming a constant annual risk for each outcome.

A summary of the results is presented in Table 2, Table 3, Table 4 and Table 5. These results are also presented in evidence summaries and decision aids developed in MAGICapp, including an interactive decision support tool for multiple treatment choices (https://magicevidence.org/match-it/200820dist/#!/).

Table 2. Summary of anticipated absolute differences comparing SGLT2i treatment with placebo treatment per 1000 patients with T2DM and with very low to very high CVD risk, treated for five years

Risk*	All cause mortality	Cardiovascular mortality	Non-fatal myocardial infarction	Non-fatal stroke	Kidney failure	Hospital admission for heart failure	Diabetic ketoacidosis	Genital infection	Body weight
Very low	3 fewer (4 fewer to 2 fewer) ⊕⊕⊕	2 fewer (3 fewer to 1 fewer) ⊕⊕⊕	4 fewer (6 fewer to 1 fewer) ⊕⊕⊕	0 more (3 fewer to 4 more) ⊕⊕⊕	1 fewer (1 fewer to 0) ⊕⊕⊕	2 fewer (2 fewer to 1 fewer) ⊕⊕⊕	0 (1 fewer to 2 more) ⊕⊕⊕	143 more (119 more to 170 more) ⊕⊕⊕⊕	1.92 kg lower (2.23 lower to 1.62 lower) over 6 months ⊕⊕
Low	10 fewer (15 fewer to 6 fewer) ⊕⊕⊕⊕	7 fewer (11 fewer to 4 fewer) ⊕⊕⊕⊕	7 fewer (12 fewer to 2 fewer) ⊕⊕⊕⊕	1 more (6 fewer to 8 more) ⊕⊕⊕⊕	3 fewer (4 fewer to 1 fewer) ⊕⊕⊕⊕	9 fewer (11 fewer to 7 fewer) ⊕⊕⊕⊕			
Moderate	18 fewer (25 fewer to 10 fewer) ⊕⊕⊕⊕	12 fewer (18 fewer to 6 fewer) ⊕⊕⊕⊕	13 fewer (21 fewer to 3 fewer) ⊕⊕⊕⊕	1 more (11 fewer to 13 more) ⊕⊕⊕⊕	6 fewer (9 fewer to 2 fewer) ⊕⊕⊕⊕	23 fewer (28 fewer to 17 fewer) ⊕⊕⊕⊕			
High	26 fewer (36 fewer to 14 fewer) ⊕⊕⊕⊕	16 fewer (25 fewer to 8 fewer) ⊕⊕⊕⊕	14 fewer (23 fewer to 3 fewer) ⊕⊕⊕⊕	1 more (12 fewer to 15 more) ⊕⊕⊕⊕	25 fewer (37 fewer to 9 fewer) ⊕⊕⊕⊕	29 fewer (36 fewer to 22 fewer) ⊕⊕⊕⊕			
Very high	40 fewer (56 fewer to 21 fewer) ⊕⊕⊕⊕	24 fewer (36 fewer to 12 fewer) ⊕⊕⊕⊕	21 fewer (34 fewer to 5 fewer) ⊕⊕⊕⊕	2 more (17 fewer to 21 more) ⊕⊕⊕⊕	38 fewer (58 fewer to 14 fewer) ⊕⊕⊕⊕	58 fewer (73 fewer to 44 fewer) ⊕⊕⊕⊕			

Certainty of the evidence for each estimate is shown: high certainty ⊕⊕⊕⊕; moderate certainty ⊕⊕⊕; low certainty ⊕⊕; very low certainty ⊕.

* Risk categories represent the following patient populations: very low=no or less than three cardiovascular risk factors; low=three or more cardiovascular risk factors; moderate=cardiovascular disease; high=chronic kidney disease (reduced glomerular filtration rate or macroalbuminuria); very high=cardiovascular disease and chronic kidney disease.

Table 3. Summary of anticipated absolute differences comparing GLP-1 inhibitor treatment with placebo treatment per 1000 patients with diabetes type 2 and with very low to very high cardiovascular risk, treated for five years

Risk*	All cause mortality	Cardiovascular mortality	Non-fatal myocardial infarction	Non-fatal stroke	Kidney failure	Hospital admission for heart failure	Severe gastrointestinal events	Body weight
Very low	2 fewer (3 fewer to 1 fewer) ⊕⊕⊕	2 fewer (3 fewer to 1 fewer) ⊕⊕⊕	2 fewer (4 fewer to 0) ⊕⊕⊕	5 fewer (7 fewer to 2 fewer) ⊕⊕⊕	0 (1 fewer to 0) ⊕⊕⊕	0 (1 fewer to 0) ⊕⊕⊕	58 more (9 more to 142 more) ⊕⊕	145 kg lower (1.72 lower to 1.18 lower) over 6 months ⊕⊕
Low	8 fewer (11 fewer to 4 fewer) ⊕⊕⊕⊕	5 fewer (9 fewer to 2 fewer) ⊕⊕⊕⊕	4 fewer (8 fewer to 1 fewer) ⊕⊕⊕⊕	9 fewer (13 fewer to 4 fewer) ⊕⊕⊕⊕	2 fewer (1 fewer to 3 fewer) ⊕⊕⊕⊕	2 fewer (4 fewer to 1 more) ⊕⊕⊕⊕		
Moderate	13 fewer (18 fewer to 6 fewer) ⊕⊕⊕⊕	9 fewer (15 fewer to 1 fewer) ⊕⊕⊕⊕	8 fewer (15 fewer to 1 fewer) ⊕⊕⊕⊕	16 fewer (24 fewer to 7 fewer) ⊕⊕⊕⊕	4 fewer (7 fewer to 2 fewer) ⊕⊕⊕⊕	4 fewer (11 fewer to 2 more) ⊕⊕⊕⊕		
High	17 fewer (25 fewer to 9 fewer) ⊕⊕⊕⊕	12 fewer (20 fewer to 4 fewer) ⊕⊕⊕⊕	9 fewer (16 fewer to 1 fewer) ⊕⊕⊕⊕	17 fewer (26 fewer to 7 fewer) ⊕⊕⊕⊕	19 fewer (28 fewer to 7 fewer) ⊕⊕⊕⊕	6 fewer (14 fewer to 3 more) ⊕⊕⊕⊕		
Very high	24 fewer (35 fewer to 12 fewer) ⊕⊕⊕⊕	18 fewer (30 fewer to 6 fewer) ⊕⊕⊕⊕	13 fewer (24 fewer to 2 fewer) ⊕⊕⊕⊕	25 fewer (39 fewer to 11 fewer) ⊕⊕⊕⊕	29 fewer (44 fewer to 10 fewer) ⊕⊕⊕⊕	11 fewer (28 fewer to 5 more) ⊕⊕⊕⊕		

Certainty of the evidence for each estimate is shown: high certainty ⊕⊕⊕⊕; moderate certainty ⊕⊕⊕; low certainty ⊕⊕; very low certainty ⊕.

* Risk categories represent the following patient populations: very low=no or less than three cardiovascular risk factors; low=three or more cardiovascular risk factors; moderate=cardiovascular disease; high=chronic kidney disease (reduced glomerular filtration rate or macroalbuminuria); very high=cardiovascular disease and chronic kidney disease.

Table 4. Summary of anticipated absolute differences comparing SGLT-2 inhibitor treatment with GLP-1 receptor agonist treatment per 1000 patients with diabetes type 2 and with very low to very high cardiovascular risk, treated for five years

Risk*	All cause mortality	Cardiovascular mortality	Non-fatal myocardial infarction	Non-fatal stroke	Kidney failure	Hospital admission for heart failure	Body weight	Diabetic ketoacidosis	Serious hyperglycaemia	Genital infection
Very low	1 fewer (3 fewer to 1 more) ⊕⊕⊕	0 fewer (2 fewer to 1 more) ⊕⊕⊕	1 fewer (4 fewer to 2 more) ⊕⊕⊕	5 more (1 more to 10 more) ⊕⊕⊕	0 (1 fewer to 0) ⊕⊕	1 fewer (2 fewer to 1 fewer) ⊕⊕⊕	0.47 kg lower (0.09 lower to 0.85 lower) over 6 months ⊕⊕⊕	1 more (0 to 3 more) ⊕⊕⊕	5 more (2 fewer to 19 more) ⊕⊕⊕	158 more (64 more to 299 more) ⊕⊕⊕⊕
Low	4 fewer (10 fewer to 4 more) ⊕⊕⊕⊕	2 fewer (6 fewer to 4 more) ⊕⊕⊕⊕	3 fewer (8 fewer to 4 more) ⊕⊕⊕⊕	9 more (1 more to 19 more) ⊕⊕⊕⊕	1 fewer (2 fewer to 2 more) ⊕⊕⊕	7 fewer (10 fewer to 4 fewer) ⊕⊕⊕⊕				
Moderate	6 fewer (17 fewer to 7 more) ⊕⊕⊕⊕	3 fewer (11 fewer to 6 more) ⊕⊕⊕⊕	5 fewer (15 fewer to 7 more) ⊕⊕⊕⊕	16 more (2 more to 33 more) ⊕⊕⊕⊕	1 fewer (5 fewer to 3 more) ⊕⊕⊕	18 fewer (25 fewer to 11 fewer) ⊕⊕⊕⊕				
High	9 fewer (24 fewer to 10 more) ⊕⊕⊕⊕	4 fewer (15 fewer to 8 more) ⊕⊕⊕⊕	5 fewer (16 fewer to 8 more) ⊕⊕⊕⊕	18 more (3 more to 36 more) ⊕⊕⊕⊕	6 fewer (21 fewer to 13 more) ⊕⊕⊕	24 fewer (32 fewer to 13 fewer) ⊕⊕⊕⊕				
Very high	13 fewer (37 fewer to 16 more)	5 fewer (22 fewer to 12 more)	7 fewer (24 fewer to 11 more)	27 more (4 more to 53 more)	10 fewer (34 fewer to 20 more)	48 fewer (66 fewer to 27 fewer)				

Certainty of the evidence for each estimate is shown: high certainty ⊕⊕⊕⊕; moderate certainty ⊕⊕⊕; low certainty ⊕⊕; very low certainty ⊕.

* Risk categories represent the following patient populations: very low=no or less than three cardiovascular risk factors; low=three or more cardiovascular risk factors; moderate=cardiovascular disease; high=chronic kidney disease (reduced glomerular filtration rate or macroalbuminuria); very high=cardiovascular disease and chronic kidney disease.

Table 5. GRADE summary of findings to illustrate absolute effects based on cardiovascular and renal risk, for all cause mortality for SGLT-2 inhibitors and GLP-1 receptor agonists compared with placebo or each other

Comparison	Relative effect (odds ratio (95% CI))	Anticipated absolute effects over five years			Anticipated absolute effects (95% CI) over five years	Certainty in treatment effects (GRADE)	Plain text summary
		Baseline risk*	Risk with control	Risk with intervention			
SGLT-2 inhibitor *v* placebo	0.85 (0.79 to 0.92)	Very low	Placebo: 20 per 1000	SGLT-2 inhibitor: 17 per 1000	3 fewer per 1000 (from 2 fewer to 4 fewer)	Moderate due to indirectness	SGLT-2 inhibitor treatment probably reduces all cause mortality in people with diabetes and few or no cardiovascular risk factors
		Low	Placebo: 70 per 1000	SGLT-2 inhibitor: 60 per 1000	10 fewer per 1000 (from 6 fewer to 15 fewer)	High	SGLT-2 inhibitor treatment reduces all cause mortality in people with diabetes and cardiovascular risk factors
		Moderate	Placebo: 120 per 1000	SGLT-2 inhibitor: 102 per 1000	18 fewer per 1000 (from 10 fewer to 25 fewer)	High	SGLT-2 inhibitor treatment reduces all cause mortality in people with diabetes and established cardiovascular disease
		High	Placebo: 170 per 1000	SGLT-2 inhibitor: 144 per 1000	26 fewer per 1000 (from 14 fewer to 36 fewer)	High	SGLT-2 inhibitor treatment reduces all cause mortality in people with diabetes and chronic kidney disease
		Very high	Placebo: 265 per 1000	SGLT-2 inhibitor: 225 per 1000	40 fewer per 1000 (from 21 fewer to 56 fewer)	High	SGLT-2 inhibitor treatment reduces all cause mortality in people with diabetes and established cardiovascular disease and chronic kidney disease
GLP-1 receptor agonist *v* placebo	0.88 (0.83 to 0.94)	Very low	Placebo: 20 per 1000	GLP-1 receptor agonist: 18 per 1000	2 fewer per 1000 (from 1 fewer to 3 fewer)	Moderate due to indirectness	GLP-1 receptor agonist treatment probably reduces all cause mortality in people with diabetes

Comparison	Relative effect (odds ratio (95% CI))	Anticipated absolute effects over five years			Anticipated absolute effects (95% CI) over five years	Certainty in treatment effects (GRADE)	Plain text summary
		Baseline risk*	Risk with control	Risk with intervention			
							and few or no cardiovascular risk factors
		Low	Placebo: 70 per 1000	GLP-1 receptor agonist: 62 per 1000	8 fewer per 1000 (from 4 fewer to 11 fewer)	High	GLP-1 receptor agonist treatment reduces all cause mortality in people with diabetes and cardiovascular risk factors
		Moderate	Placebo: 120 per 1000	GLP-1 receptor agonist: 107 per 1000	13 fewer per 1000 (from 6 fewer to 18 fewer)	High	GLP-1 receptor agonist treatment reduces all cause mortality in people with diabetes and established cardiovascular disease
		High	Placebo: 170 per 1000	GLP-1 receptor agonist: 153 per 1000	17 fewer per 1000 (from 9 fewer to 25 fewer)	High	GLP-1 receptor agonist treatment reduces all cause mortality in people with diabetes and chronic kidney disease
		Very high	Placebo: 265 per 1000	GLP-1 receptor agonist: 241 per 1000	24 fewer per 1000 (from 12 fewer to 35 fewer)	High	GLP-1 receptor agonist treatment reduces all cause mortality in people with diabetes and established cardiovascular disease and chronic kidney disease
SGLT-2 inhibitor *v* GLP-1 receptor agonist	0.95 (0.86 to 1.06)	Very low	GLP-1 receptor agonist: 18 per 1000	SGLT-2 inhibitor: 17 per 1000	1 fewer per 1000 (from 1 more to 3 fewer)	Moderate due to indirectness	SGLT-2 inhibitor treatment and GLP-1 receptor agonist treatment probably have similar effects on all cause mortality in people with diabetes and few or no cardiovascular risk factors

Comparison	Relative effect (odds ratio (95% CI))	Anticipated absolute effects over five years			Anticipated absolute effects (95% CI) over five years	Certainty in treatment effects (GRADE)	Plain text summary
		Baseline risk*	Risk with control	Risk with intervention			
		Low	GLP-1 receptor agonist: 62 per 1000	SGLT-2 inhibitor: 58 per 1000	4 fewer per 1000 (from 4 more to 10 fewer)	High	SGLT-2 inhibitor treatment and GLP-1 receptor agonist treatment have similar effects on all cause mortality in people with diabetes and cardiovascular risk factors
		Moderate	GLP-1 receptor agonist: 107 per 1000	SGLT-2 inhibitor: 101 per 1000	6 fewer per 1000 (from 7 more to 17 fewer)	High	SGLT-2 inhibitor treatment and GLP-1 receptor agonist treatment have similar effects on all cause mortality in people with diabetes and established cardiovascular disease
		High	GLP-1 receptor agonist: 153 per 1000	SGLT-2 inhibitor: 144 per 1000	9 fewer per 1000 (from 10 more to 24 fewer)	High	SGLT-2 inhibitor treatment and GLP-1 receptor agonist treatment have similar effects on all cause mortality in people with diabetes and chronic kidney disease
		Very high	GLP-1 receptor agonist: 241 per 1000	SGLT-2 inhibitor: 228 per 1000	13 fewer per 1000 (from 16 more to 37 fewer)	High	SGLT-2 inhibitor treatment and GLP-1 receptor agonist treatment have similar effects on all cause mortality in people with diabetes and established cardiovascular disease and chronic kidney disease

GRADE=grading of recommendations assessment, development, and evaluation.

The point estimate of the absolute effect for GLP-1 receptor agonist treatment, obtained from GLP-1 receptor agonist treatment versus placebo, was used to calculate the absolute effect for SGLT-2 inhibitors versus GLP-1 receptor agonists.

* Risk categories represent the following patient populations: very low=no or less than three cardiovascular risk factors; low=three or more cardiovascular risk factors; moderate=cardiovascular disease; high=chronic kidney disease (reduced glomerular filtration rate or macroalbuminuria); very high=cardiovascular disease and chronic kidney disease.

Questions to the Committee:

- *What are the Committee's views on the health benefits gained by individuals with a five-year CVD risk of 10% or higher, when receiving SGLT2i or GLP1a instead of standard of care? Specifically, can any of the following benefits be assumed?*
  - *Decrease in all-cause mortality*
  - *Decrease in heart failure hospitalisation*
  - *Improved renal outcomes (Delay in progression to macroalbuminuria and renal replacement therapy)*
  - *Delayed progression to insulin*
- *How do the health benefits due to SGLT2i for individuals with a five-year CVD risk of 10% or higher compare to those for individuals with a risk of 15% or higher?*
  - *Is it reasonable to assume that relative treatment effects remain consistent regardless of baseline absolute CVD risk?*
- *How do the health benefits due to GLP1a for individuals with a five-year CVD risk of 10% or higher compare to those for individuals with a risk of 15% or higher?*
  - *Is it reasonable to assume that relative treatment effects remain consistent regardless of baseline absolute CVD risk?*
- *Can we assume a class effect for SGLT2 inhibitors, meaning that health benefits would be comparable across different agents within this class? Note that previous advice suggested this may be plausible but was uncertain at the time.*
- *Would the meta-analysis by Palmer et al. 2021 be appropriate to use to reflect the treatment benefit of SGLT2i and GLP1a in a moderate to low CVD risk population?*
  - *If yes, what risk group best reflects the population under assessment?*
  - *If not, what other evidence would best represent the health benefit in individuals with T2DM with a CVD risk of 10% or more for these two treatment classes?*
- *What is the Committee's views on the strength and quality of the evidence, including its relevance to New Zealand, for health benefits that may be gained from empagliflozin when the individual has T2DM when their five-year CVD risk is 10% or higher?*

Baseline characteristics population with a CVD risk of 10% or greater

Previous modelling for empagliflozin in a population with a CVD risk of 15% or greater used the baseline proportion of individuals on insulin or with macroalbuminuria from the EMPA-REG trial. See the baseline proportions in the EMPA-REG, DECLARE-TIMI 58, and CANVAS studies in Table 6 below.

Table 6. Baseline characteristics - probability of being on insulin or having macroalbuminuria

Drug class	Trial	Proportion on insulin at baseline	Proportion with macroalbuminuria at baseline
SGLT2i	EMPA-REG	48%	41%
	DECLARE-TIMI 58	41.6%	-
	CANVAS	-	7.6%

A large retrospective observational study across Europe (n = 803,836) examined how well the general population of people with T2DM met the key inclusion criteria of these four major cardiovascular outcome trials: CANVAS (canagliflozin), DECLARE-TIMI 58 (dapagliflozin),

EMPA-REG OUTCOME (empagliflozin), and VERTIS-CV (ertugliflozin) (Birkeland et al., Diabetes Obes Metab. 2018. doi:10.1111/d). Compared with trial participants, the broader T2DM population had a lower prevalence of CVD and was slightly older. Among the trials, DECLARE-TIMI 58 showed the greatest representativeness, with 59% of the general T2DM population meeting its criteria - nearly 2-, 3-, and 4-fold higher than CANVAS (34%), EMPA-REG OUTCOME (21%), and VERTIS-CV (17%), respectively (Birkeland et al., 2018).

Questions to the Committee:

- *Would the baseline characteristics of DECLARE-TIMI 58 (dapaglifozin) or the CANVAS trials (canagliflozin) be more reflective of the population under assessment than the EMPA-REG OUTCOME trial?*
    - *Specifically, characteristics related to renal function and number of patients on insulin as outlined in Table 6.*

Probability of initiating insulin

A previous Pharmac assessment of an SGLT2i and GLP1a for people with T2DM with a CVD risk 15% or greater assumed that initiating one of these treatments would delay the progression to insulin treatment by three months. This assumption was based on the T2DM treatment paradigm outlined in 'Guidance on the Management of type 2 diabetes' published by the Ministry of Health. This advised that if HbA1c is not within the target range of 50-55mmol/mol after 3 months, the treatment regimen should be intensified. Results from the EMPA-REG and LEADER trials reported that despite a small reduction in HbA1c post initiation of SGLT2i or GLP1a therapy, the average HbA1c after a year or more of treatment was still 7.5-8% (58-64 mmol/mol). It was therefore assumed that all individuals on an SGLT2i or GLP1a would progress to insulin after three months.

Question to the Committee:

- *Is it appropriate to assume that all patients not on insulin at baseline will require insulin after three months regardless of treatment with an SGLT2i or GLP1a?*

Overlap between access criteria

People diagnosed with T2DM during childhood or as a young adult can already access SGLT2i and GLP1a. It is unclear how many of these patients may also have a CVD risk of 10-14%.

Pharmac is collaborating with s 9(2)(a) and his team at the University of Auckland to quantify the affected patient populations and assess the impact of the proposed change. However, it is uncertain whether their data can address this specific question of overlapping populations.

Questions to the Committee:

- *Pharmac seeks the Committee's advice on the likelihood that individuals diagnosed with T2DM in childhood or early adulthood would have a CVD risk of 10–14%, given their elevated lifetime risk.*
    - *If overlap is likely, what proportion of this group is expected to fall within that risk range?*

EVIDENCE SUMMARY: DESIGN OF PRIMARY STUDIES

Summary of primary studies for SGLT2i and GLP1a

Primary study paper and trial name (study type and no. of countries)	Sample size	Intervention (mode of administration)	Comparator (drug class, mode of administration)	Population	Duration of follow-up	Outcomes of interest
SGLT2i						
Neal et al 2017 - CANVAS program (DB, PC, RCT, 30 countries)	10,142 4,330 (CANVAS) 5,812 (CANVAS-R)	Canagliflozin 100 mg or 300 mg (oral)	Placebo	Adults with T2D aged ≥30 years with a history of CVD or aged ≥50 years with ≥2 *or more CVD risk factors*. The study excluded people with an eGFR <30.	Mean 188.2 weeks	• CV mortality • MI • Stroke • Hospitalisation for heart failure • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • Discontinuation due to adverse events • 3-point MACE
Wiviott et al 2019 - DECLARE-TIMI 58 (DB, PC, RCT, 33 countries)	17,160	Dapagliflozin 10 mg (oral)	Placebo	Adults with T2D aged ≥40 years with a HbA1c of 48-108 mmol/mol (6.5% - 12%) and a creatinine clearance of ≥60 ml/minute.	Median 4.2 years	• CV mortality • MI • Stroke • Hospitalisation for heart failure • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • Discontinuation due to adverse events • 3-point MACE
Zinman et al 2015 - EMPA-REG (DB, PC, RCT, 42 countries)	7,020	Empagliflozin 10 mg or 25 mg (oral)	Placebo	Adults with T2D aged ≥18 years and with a BMI ≤45 and *established CVD*. Those with an eGFR <30 were excluded.	Median 3.1 years	• CV mortality • MI • Stroke • Hospitalisation for heart failure • Hospitalisation for unstable angina • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • Discontinuation due to adverse events • 3-point MACE

Primary study paper and trial name (study type and no. of countries)	Sample size	Intervention (mode of administration)	Comparator (drug class, mode of administration)	Population	Duration of follow-up	Outcomes of interest
GLP1a						
Marso et al 2016 LEADER (DB, PC, RCT 32 countries)	9,340	Liraglutide 1.8 mg (once daily subcutaneous injection)	Placebo	Adults with T2D aged ≥50 years with a HbA1c ≥53 mmol/mol (≥7.0%) and ≥1 CVD or ≥60 years with CVD risk factors (no exclusions for renal disease reported).	Median 3.8 years	• CV mortality • MI • Stroke • Hospitalisation for heart failure • Hospitalisation for unstable angina • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Discontinuation due to adverse events • 3-point MACE
Marso et al 2016 SUSTAIN-6 (DB, PC, RCT 20 countries)	3,297	Semaglutide 0.5 mg or 1.0 mg (once weekly subcutaneous injection)	Placebo	Adults with T2D aged ≥50 years with HbA1c ≥53 mmol/mol (≥7%) with established CVD or renal disease, or aged ≥60 years with CVD risk factors (no exclusions for renal disease reported).	Planned 109-week treatment and follow-up period.	• CV mortality • MI • Stroke • Hospitalisation for heart failure • Hospitalisation for unstable angina • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • Discontinuation due to adverse events • 3-point MACE
Holman et al 2017 EXSCEL (DB, PC, RCT 35 countries)	14,752	Exenatide 2 mg (once weekly subcutaneous injection)	Placebo	Adults with T2D with a HbA1c of 48-86 mmol/mol (6.5% - 10%), trial designed so that 70% of the population had established CVD. Those with an eGFR <30 were excluded.	Median 3.2 years	• CV mortality • MI • Stroke • Hospitalisation for heart failure • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • Discontinuation due to adverse events

Primary study paper and trial name (study type and no. of countries)	Sample size	Intervention (mode of administration)	Comparator (drug class, mode of administration)	Population	Duration of follow-up	Outcomes of interest
						• 3-point MACE
Hernandez et al 2018 HARMONY (DB, PC, RCT 28 countries)	9463	Albiglutide 30-50mg, based on glycaemic response and tolerability (once weekly subcutaneous injection)	Placebo	People with T2DM aged 40 years or older with HbA1c of more than 7·0% (53 mmol/mol) and established CVD.	Median 3.8 years	• CV mortality • MI • Stroke • Hospitalisation for heart failure • All-cause mortality • Weight/BMI • Severe hypoglycaemia • Any discontinuation • Discontinuation due to adverse events • 3-point MACE

CV-cardiovascular, DB-double-blind, MACE-Major Adverse Cardiovascular Event, PC-placebo-controlled, RCT-randomised controlled trial

Table 7. Summary of newly identified evidence that indicate the health benefits of SGLT2i and GLP1a in people with T2DM and different levels of CVD risk

Trial & Study Design	Summary of Evidence
Network meta-analysis assessing the effects of DPP-4 inhibitors, GLP1a, SGLT2i and sulphonylureas on mortality, cardiovascular and renal outcomes in T2DM Brønden et al. Diabet Med. 2023 Aug;40(8):e15157	The comparison between the different classes of glucose-lowering drugs included analyses of T2D populations with low risk and high risk for cardiovascular disease including populations with established cardiovascular disease and/or kidney disease. The magnitude of the observed beneficial effects of SGLT2i and GLP1a were determined by baseline cardiovascular risk, and thus, the effect estimates for the low-risk subgroup were small and not considered to be of clinical relevance according to the predefined cut-off values. Evaluation by GRADE identified the general lack of low-risk patients in the clinical trials as the most consistent challenge for the quality of evidence.
Post hoc analysis of randomised CV outcome trial (EMPAG-REG OUTCOME) Inzucchi et al. J Clin Endocrinol Metab. 2020 Sep 1;105(9):3025–35	Post-hoc analysis found that the benefit of empagliflozin was consistent across levels of baseline risk-factor control (e.g., those achieving more or fewer cardiovascular risk factor goals) in EMPA-REG.
Meta-analysis of RCT trials assessing cardiovascular safety of empagliflozin in patients with T2DM at low/medium CVD risk (placebo-controlled Phase III studies excluding EMPA-REG OUTCOME) or high CV risk (EMPA-REG OUTCOME) Salsali et al. Diabetes Obes Metab. 2016 Oct;18(10):1034-40	The EMPA-REG OUTCOME trial was considered representative of a T2DM population at high cardiovascular risk (≥15% over five years), whereas the other seven trials in this meta-analysis reflected patients at low to moderate CV risk. This classification was based on placebo-group event rates for 3-point MACE, which ranged from 4.6 to 28.7 per 1,000 patient-years in the other trials, compared with 43.9 per 1,000 patient-years in EMPA-REG OUTCOME. The authors reported that CV outcomes were consistent between the high and low/medium CV risk patients. Findings in low/medium CV risk group: - Reduced risk of 4-point MACE with empagliflozin compared with placebo [HR: 0.59 (95% CI 0.36, 0.95)] (Figure 6). - Results for 3-point MACE, CV death, MI, non-fatal MI, stroke, non-fatal stroke, hospitalisation for unstable angina or all-cause mortality were consistent with the larger meta-analysis comprising patients at low/medium and high CV risk; however, because of the smaller number of events, HRs for 3-point MACE, CV death, all-cause mortality and hospitalization for heart failure missed significance, with confidence intervals crossing unity. - The composite endpoint of hospitalisation for heart failure or CV death occurred at a significantly lower rate with empagliflozin than with placebo.
Meta-analysis Aronow et al. Ann Transl Med. 2017 Dec;5(23):455.	- The observed improvement in patient outcomes is attributable to the largest RCT, EMPA-REG OUTCOME. - Sensitivity analyses excluding this RCT demonstrate no protective effects from empagliflozin against all-cause and cardiovascular mortality in all other RCTs combined. There are no differences in the risk of stroke or coronary events between empagliflozin and placebo.

Trial & Study Design	Summary of Evidence
Meta-Analysis of Randomized Trials and Systematic Review Rahman et al. J Am Heart Assoc. 2023 Aug 15;12(16):e030578	- Included large-scale cardiovascular outcome randomised controlled trials, or their prespecified subgroup analyses. Evaluated SGLT2 inhibitors versus placebo for primary prevention of atherosclerotic cardiovascular disease (ASCVD). - For T2D patients without prior ASCVD, SGLT2 inhibitors may reduce all-cause mortality (RR ~0.85, not significant) but the evidence for reducing atherosclerotic MACE is weaker in pure "risk-factor only" populations.
Meta-analysis using data from patients with T2DM from six SGLT2 inhibitor outcomes trials McGuire et al. JAMA Cardiol. 2021 Feb 1;6(2):148-158	- Assessed CV and kidney outcomes of all 4 available SGLT2 inhibitors in patients with type 2 diabetes. - Overall, SGLT2 inhibitors were associated with a reduced risk of major adverse CV events (HR, 0.90; 95% CI, 0.85-0.95; Q statistic, P = .27), HHF/CV death (HR, 0.78; 95% CI, 0.73-0.84; Q statistic, P = .09), and kidney outcomes (HR, 0.62; 95% CI, 0.56-0.70; Q statistic, P = .09), with no significant heterogeneity of associations with outcome. - Associated risk reduction for HHF was consistent across the trials (HR, 0.68; 95% CI, 0.61-0.76; I2 = 0.0%), whereas significant heterogeneity of associations with outcome was observed for CV death (HR, 0.85; 95% CI, 0.78-0.93; Q statistic, P = .02; I2 = 64.3%). - The presence or absence of atherosclerotic CV disease did not modify the association with outcomes for major adverse CV events (HR, 0.89; 95% CI, 0.84-0.95 and HR, 0.94; 95% CI, 0.83-1.07, respectively; P = .63 for interaction), with similar absence of associations with outcome modification by prevalent atherosclerotic CV disease for HHF/CV death (P = .62 for interaction), HHF (P = .26 for interaction), or kidney outcomes (P = .73 for interaction).
Systematic review that informed NICE Guideline 28 (NG28) Evidence review on pharmacological therapies with cardiovascular and other benefits in people with type 2 diabetes	- Four SGLT2 inhibitors were considered as part of this review: canagliflozin, dapagliflozin, ertugliflozin and empagliflozin Key consideration of the Clinical Guideline Committee: - Relative efficacy: "The committee discussed whether people with type 2 diabetes and CV risk factors are likely to respond in the same way to treatment interventions to those people with established CVD. The committee agreed that for the treatments under review in this update it was reasonable to assume that the relative treatment effects would be similar, but that baseline risks may be different between these CVD risk groups." - Applicability of the evidence: "The committee agreed that the results of the analyses carried out in this review and the associated model are most applicable to people with established CV disease and people at high risk of developing CV disease." - ICER results for each SGLT2 inhibitor drug were similar across the five population groups assessed: (1) a high CVD risk population with a prior event, (2) a high CV risk population without a prior event, (3) a pooled high CV risk population, (4) one with BMI greater than or equal to 30 and (4) one representing everyone with type 2 diabetes. The difference in baseline risks was considered as part of the economic modelling work.

APPENDIX

Appendix 1: PDF Copy of Palmer et al. BMJ 2021;372:m4573