

**APPLICATION
FOR
THE INCLUSION OF SODIUM-GLUCOSE CO-
TRANSPORTER-2 (SGLT-2) INHIBITORS
AS
ADD-ON TREATMENT
FOR
TYPE 2 DIABETES
ON
THE WHO MODEL LIST OF ESSENTIAL
MEDICINES 2021**

INTERNATIONAL DIABETES FEDERATION



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Application for the inclusion of Sodium-Glucose Co-transporter-2 (SGLT-2) inhibitors as add-on treatments for type 2 diabetes on the WHO Model List of Essential Medicines 2021

1. Summary statement of the proposal for inclusion

This application concerns updating section 18.5 Insulins and other medicines used for diabetes of the WHO Model List of Essential Medicines (WHO EML) for adults and children (1).

The application focuses on expanding the core list of 18.5.2 Oral Hypoglycaemic Medications to include Sodium-Glucose Co-transporter-2 (SGLT-2) inhibitors as add-on treatments for adults with type 2 diabetes (T2D).

SGLT-2 inhibitors are a class of medications used to treat T2D. They are also called sodium-glucose co-transport protein 2 inhibitors or gliflozins. SGLT-2 inhibitors modulate sodium/glucose channels and prevent the reabsorption of glucose from blood that is filtered through the kidneys, therefore facilitating glucose excretion in the urine.

Initial therapy for T2D traditionally begins with lifestyle interventions and metformin monotherapy. If these do not satisfactorily control the diabetes, additional oral or injectable agents are added. Sulfonylureas and insulin have been the preferred additional therapies based on considerations of efficacy, side-effect profiles, long-term safety, and relative cost. Both insulin and sulfonylurea are listed as essential medicines, along with metformin.

In recent years newer classes of medications have become available for the treatment of T2D including two oral medications, DPP-4 inhibitors and SGLT-2 inhibitors, and an injectable treatment, GLP-1 receptor agonists (GLP-1 RA). A growing body of evidence has demonstrated that two of these medications, SGLT-2 inhibitors and GLP-1 RA, are associated with cardiovascular and renal benefits beyond their glycaemic effects. Consequently, international guidelines recommend their use in people with T2D with or at high risk of cardiovascular disease (CVD) and with evidence of diabetic nephropathy.

In line with recommendations of international guidelines, the focus of this application is the addition of SGLT-2 inhibitors as add on treatment for non-pregnant adults with T2D with or at high risk of CVD and/or diabetic nephropathy.

This application also provides an assessment of GLP-1RA compared with SGLT-2 inhibitors and outlines the reasons why the focus of this application is SGLT-2 inhibitors and not GLP-1 RAs.

Previous submissions to the Expert Committee of Essential Medicines Selection and Use.

In 2013, the Expert Committee evaluated evidence comparing DPP-4 inhibitors, thiazolidinediones (TZDs), alpha-glucosidase inhibitors and meglitinides against metformin and sulfonylureas (2). That review indicated no apparent differences in efficacy across drug classes, and that sulfonylureas were the most cost-effective treatment option. The 2013 Expert Committee concluded that “there was insufficient evidence to show that any of the medicines in the four groups (DPP-4 inhibitors, alpha glucosidase inhibitors, meglitinides, or thiazolidinediones) offered any efficacy or safety advantages over the existing medicines included in the EML”, (i.e. metformin first line and sulfonylurea second line).

In 2017 an application was made for second line therapy for T2D to be expanded to include meglitinides, alpha-glucosidase inhibitors, TZDs, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 RA, basal insulins, bolus insulins, and biphasic insulins, including analogues based on an update of the 2013 Canadian Agency for Drugs and Technologies in Health (CADTH) review(3, 4).

This was based on newer agents approved in many countries and additional randomized controlled trial (RCT) evidence on the beneficial impact on CVD outcomes with some drugs (SGLT-2 inhibitors and GLP-1 RA). The 2017 Expert Committee did not recommend inclusion of second-line medicines for T2D on the

Essential Medicines List (5). Of the second-line therapies considered, the Committee noted that SGLT-2 inhibitors have shown a relevant clinical benefit as second-line therapy in patients at high risk of cardiovascular events, with a reduction in overall mortality, but that more data were needed to confirm this finding.

These data are now available with several reviews demonstrating CVD and renal benefits of SGLT-2 inhibitors and consequently these agents are routinely recommended by international guidelines.

2. Relevant WHO technical department and focal point.

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The application is supported by the Medicines Patent Pool which provided the summary of available data on comparative cost and cost-effectiveness of the SGLT-2 inhibitors and GLP-1 RAs (Section 11).

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code

ATC code	INN
A10BK01	dapagliflozin
A10BK02	canagliflozin
A10BK03	empagliflozin

5. Dose forms and strengths proposed for inclusion for adults

Dapagliflozin: tablet 5 mg, 10 mg

Canagliflozin: tablet 100 mg, 300 mg

Empagliflozin: tablet 10 mg, 25 mg

6. Listing request

Listing is requested for empagliflozin as the representative of the pharmacological class of SGLT-2 inhibitors, with therapeutically equivalent alternatives limited to dapagliflozin and canagliflozin. Dapagliflozin, canagliflozin and empagliflozin are the most established agents in this class and are accompanied by the most robust clinical and outcome data.

Empagliflozin was the first of these agents to demonstrate CVD benefits (6). Subsequent CVD and renal outcomes studies with dapagliflozin and canagliflozin support a class effect of benefits with SGLT-2 inhibitors. These agents are available in many global markets. While newer SGLT-2 inhibitors are coming onto the market, supportive outcome data are not as robust at this time and their availability is limited.

7. Treatment details

WHO Guidelines on Second- and Third-line Medicines for the Control of Blood Glucose Levels in Non-pregnant Adults with Diabetes Mellitus (7, 8).

In 2018 WHO published guidelines to provide public health guidance on pharmacological agents for managing hyperglycaemia in type 1 and type 2 diabetes for use in primary health-care in low-resource settings which updated the WHO Package of Essential NCD Interventions (8). Several newer oral agents were reviewed including DPP-4 inhibitors, SGLT-2 inhibitors and TZDs. However, GLP-1 RAs were outside the scope of these guidelines.

The evidence summary for treatment intensification beyond metformin was obtained from the systematic review and network meta-analysis carried out by the Methods and Applications Group for Indirect Treatment Comparisons (MAGIC) for the Canadian Agency for Drugs and Technologies in Health (3). The systematic review included 166 RCTs that reported at least one of the outcomes of interest. The network meta-analysis included sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors, TZDs and basal insulins, as well as bolus insulins, biphasic insulins, meglitinides, alpha-glucosidase inhibitors, and GLP-1 RAs (which were not of interest for these guidelines).

All evaluated hypoglycaemic agents added to metformin performed similarly in lowering HbA1c compared to placebo. There was lower risk of severe hypoglycaemia with SGLT-2 inhibitors (OR 0.09, 95% CI: 0.02, 0.44) compared to sulfonylurea and SGLT-2 inhibitors were associated with weight loss. Evidence on quality of life and microvascular complications were not available. There were no significant differences for CVD incidence (myocardial infarction or stroke) or CVD mortality, but the network meta-analysis model was not robust (very few events and a large number of trials with no events). In a separate analysis of patients at high risk of CVD, there was no significant difference in CVD mortality. The Guideline Group acknowledged that SGLT-2 inhibitors look particularly promising. Empagliflozin, when compared to placebo, had a protective effect on a composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke in one study in people with T2D at high CVD risk (6) with more evidence needed to determine whether this is a class effect and whether there is a cardioprotective effect in the general population of people with T2D. Because SGLT-2 inhibitors are a relatively new class of drugs, more safety data are likely to emerge from ongoing trials and from their use outside trial populations.

The evidence summary for medicines added to metformin and sulfonylurea was obtained from a systematic review and network meta-analysis published in 2016 (9). The WHO Guideline Group considered insulin to be comparable to SGLT-2 inhibitors when weighing desirable and undesirable effects. Insulin performed best for lowering HbA1c while SGLT-2 inhibitors performed better in lowering body weight. All drug classes were associated with an increased risk of hypoglycaemia compared to placebo, but there were no statistically significant differences between the drug classes. The long-term benefits and harms of triple therapy with three oral agents were unclear. There were very few events of CVD mortality and no significant differences between treatments. Insufficient observations were available to generate evidence networks for CVD incidence. Preferred treatment characteristics indicated that most patients prefer oral agents to insulin if glycaemic control is comparable. However, patient preference for newer oral agents

was not deemed a sufficiently strong reason to recommend them in the context of a public health approach because the price of newer oral medicines is currently higher than that of human insulin.

Based on these data, the following recommendations were made for second and third-line treatment in type 2 diabetes:

1. Give a sulfonylurea* to patients with type 2 diabetes who do not achieve glycaemic control with metformin alone or who have contraindications to metformin (strong recommendation, moderate quality evidence).

* Glibenclamide should be avoided in patients aged 60 years and older. Sulfonylureas with a better safety record for hypoglycaemia (e.g. gliclazide) are preferred in patients for whom hypoglycaemia is a concern (people who are at risk of falls, people who have impaired awareness of hypoglycaemia, people who live alone, people who drive or operate machinery as part of their job).

2. Introduce human insulin treatment to patients with type 2 diabetes who do not achieve glycaemic control with metformin and/or sulfonylurea (strong recommendation, very low-quality evidence).

3. If insulin is unsuitable*, a DPP-4 inhibitor, SGLT-2 inhibitor or a TZD may be added (weak recommendation, very low-quality evidence).

* *Insulin treatment could be unsuitable when circumstances make its use difficult (e.g. persons who live alone and are dependent on others to inject them with insulin).*

Since these WHO guidelines were published considerably more robust outcome data have emerged for both SGLT-2 inhibitors and GLP-1 RAs in people with T2D which have results in international guidelines recommending their use in people with T2D with or at high risk of CVD and/or renal disease and even in lower risk individuals. These international guidelines include the Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)(10), the 2019 ESC and EASD guidelines (11) and the recently approved Australian guidelines (12).

8. Information supporting the public health relevance.

1. **Epidemiological information on disease burden**

Diabetes is a serious threat to global health and ranks fifth among causes of deaths worldwide (13, 14). The burden of diabetes is projected to increase to affect 700 million people in 2045(13). The majority of diabetes cases (90%) is attributed to T2D (15). Three in four people living with diabetes are between 20 and 64 years old, impacting the working population, productivity and economic growth (13). Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke, and lower limb amputation (13). In 2019, an estimated 4.2 million deaths were related to diabetes and its complications. Globally 11.3% of deaths are correlated to diabetes. People with diabetes commonly have comorbidities including cardiovascular diseases or chronic kidney disease (13). The annual global healthcare expenditure on people with diabetes is estimated to be USD 850 billion, which amounts to 12% of the overall global healthcare expenditure.

2. **Assessment of current use of diabetes medications**

Type 2 diabetes commonly requires pharmacologic treatment and its progressive nature means that most patients will need increasingly intensive pharmacotherapy. Current guidelines recommend lifestyle modification with metformin being the initial first-line pharmacological treatment. If diabetes control assessed by HbA1c does not improve, additional pharmacological treatment is recommended. There are several options with availability, accessibility and affordability varying across countries. International guidelines are increasingly recommending prioritising the use of new classes of blood glucose lowering therapies, especially SGLT-2 inhibitors and GLP-1 RA, because of their additional benefits in improving CVD and renal outcomes, especially in people with or at high risk of CVD. The three most frequently used SGLT-2 inhibitors are empagliflozin, dapagliflozin and canagliflozin. Guidelines recommend their use at various points in the treatment cascade, even as first line therapy (11), however the evidence base for improved CVD and renal outcomes relates to add-on therapy to a range of other blood glucose lowering treatments.

Little data are available on global patterns of diabetes pharmacotherapy use. The DISCOVER study which included 15,992 subjects from 38 countries reported that the most common combination therapy was metformin and sulfonylureas. Although this treatment combination is given a low priority in the hierarchy of therapies suggested by some recent international guidelines, this study suggests that the choice of this combination is driven by the low cost of these medications. Second-line therapies varied greatly across regions with combinations of metformin and a sulfonylurea the most prescribed in Africa, South-East Asia and the Western Pacific region, and combinations of metformin and a DPP-4 inhibitor most prescribed in the Americas, Europe and the Eastern Mediterranean region (16).

The pattern of pharmacotherapy use is changing in western countries. A study of 70,657 people with T2D investigated the trend of diabetes medication use from 2000 until 2015 in the US, France, Germany, Italy, Spain, and the UK. Combinations which included newer drug classes (DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 RA) increased among primary care physicians from 4% of patients in 2008 to 33% in 2015 and among specialists from 1% of patients in 2006 to 43% in 2015 (17).

A recent review of management of T2D in developing countries emphasised the need for providing balanced and actionable guidance for global guidelines with context-specific recommendations including affordability and availability when selecting glucose-lowering medications. However, it also acknowledged that *“newer agents certainly have a role to play in the management of type 2 diabetes and may be appropriate as add-on treatments in certain subpopulations, such as those at higher risk of cardiovascular events and where accessibility and cost allow”*(18).

3. *Target population*

SGLT-2 inhibitors are suitable for non-pregnant adults with type 2 diabetes in whom target blood glucose control is not achieved and who do not have a contraindication to their use.

The focus of this application is the use of SGLT-2 inhibitors in a specific sub-population of people with type 2 diabetes – those with or at high risk of cardiovascular disease and/or renal disease.

The specific sub-population which is the focus of this application includes people with type 2 diabetes and:

- With CVD - those with a previous history of myocardial infarction, angina, heart failure or stroke
- With renal disease – those with known renal disease
- At high risk of heart disease – those defined by the CVD risk score assessment according to the HEARTS technical package for cardiovascular disease management in primary health care (19)
- At high risk of renal disease – those with impaired renal function based on an eGFR of 30-60 ml/min/1.73m² and/or the presence of albuminuria. These measures should be part of the annual assessment of a person with T2D. However, it is acknowledged that not all LMIC settings have the resources to routinely perform these tests and therefore it may not be possible to identify this subset of this sub-population in some LMIC settings.

4. *Likely impact of treatment on the disease*

Use of SGLT-2 inhibitors in this sub-population of people with T2D will reduce premature mortality, incidence of myocardial infarction, hospitalisation due to heart failure and progression to end stage kidney disease. The reduction in complications will have a significant impact on individual well-being. In addition, SGLT-2 inhibitors will improve other important clinical parameters including diabetes control and weight without increasing the risk of hypoglycaemia.

9. Review of benefits: summary of evidence of comparative effectiveness.

The following reviews the evidence to support this application for addition of SGLT-2 inhibitors to the WHO Model List of Essential Medicines. It also includes a brief review of GLP-1 RA and summarises why these agents are not included in this application.

The benefits of SGLT-2 inhibitors in people with T2D include:

- improving diabetes control reflected by a reduction in HbA1c without increasing the risk of hypoglycaemia or increasing weight
- protective effect on cardiovascular and renal disease
- a well-tolerated oral medication

SGLT-2 inhibitors prevent the reabsorption of glucose from glomerular filtrate by blocking the action of the sodium-glucose co-transporter 2 proteins located in the kidney's proximal convoluted tubules. They result in reduced threshold for glycosuria, which improves overall glycaemic management, however this mechanism contributes to the most common adverse events of genitourinary infections, polyuria and volume depletion. In addition to improving glycaemic management, SGLT-2 inhibitors also reduce blood pressure and body weight.

The following section summarises two recent systematic reviews and network meta-analyses on of the clinical effects of SGLT-2 inhibitors. The first was done to inform the development of the 2020 Australian Evidence-Based Clinical Guidelines - Medications for blood glucose management in adults with type 2 diabetes and the second was very recently published (12, 20). It also includes a summary of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines on the renal benefits of SGLT-2 inhibitors (21).

The Australian Guideline Review.

The key clinical question addressed relevant to this application was:

Should GLP-1 receptor agonist, SGLT-2 inhibitors, sulfonylurea or DPP-4 inhibitor be used as add-on in adults with type 2 diabetes? Will it differ by cardiovascular risk groups?

Methodology: An electronic literature search through to 1 May 2020 yielded 18,248 unique records. Screening and full-text article analysis identified 730 trials including 402,030 patients comparing 11 glucose lowering drugs, placebo, or standard care. The trial sample sizes ranged from 16 to 17,160. The median trial mean age was 57.0 years and median proportion of men was 55.6%. At baseline, the median trial mean HbA1c was 8.1% (65 mmol/mol) and body mass index was 30.1 kg/m². Eligibility criteria included coronary artery disease or macrovascular disease in 33 trials, atrial fibrillation in 1 trial, heart failure in 6 trials, chronic kidney disease and/or albuminuria in 30 trials, dialysis for kidney failure in 4 trials and high risk of cardiovascular or kidney disease in 9 trials. The results of the network meta-analysis and the reference list for included studies is provided in Appendix 1.

Interpretation of the certainty of the evidence based on GRADE (grading of recommendations assessment, development, and evaluation) [www.gradeworking group.org]:

High: We are very sure that the true effect is close to the estimated effect.

Moderate: We are moderately sure of the estimated effect. The true effect is probably close to this one, but there is a possibility that it is significantly different.

Low: We have limited confidence in the estimated effect. The true effect may be significantly different from the estimated effect.

Very low: We have very little confidence in the estimated effect. The true effect is likely to be significantly different from that estimated effect.

For ease of interpretation of the many estimates and outcomes, evidence tables and summaries gave an overview of all outcomes and their relative effects and were colour coded as follows:

High-moderate certainty Most effective
High-moderate certainty Effective
High-moderate certainty No difference
High-moderate certainty Harmful
Low-very low certainty Most effective
Low-very low certainty No difference
Low-very low certainty Potentially harmful

Overview of populations for absolute risk

Some included trials explicitly excluded patients with various comorbidities, however the majority of included trials consisted of a combination of individuals from a range of risk groups. Numerous risk calculators and other tools have been developed in order to quantify baseline risks, thereby allowing the use of indirect evidence to inform recommendations that are applicable to these groups. For the purpose of calculating absolute effects in this review, baseline HbA1c is represented by mean HbA1c at baseline in contributing trials and severe hypoglycaemia is derived from the risk in the placebo arm of contributing trials. Risks of death, hospitalisation due to heart failure and major cardiovascular events were derived from the RECODE risk calculator (<https://sanjaybasu.shinyapps.io/recode/i/>).

Recommendations were based on the results of network meta-analyses of a broad range of medications. For these analyses, members of each class of medication were pooled and no subgroups of any class were considered separately. For example, data relating to the use of SGLT-2 inhibitors were derived from all trials in which an SGLT-2 inhibitor was included (whether dapagliflozin, empagliflozin or canagliflozin).

Recommendation 1 – add-on treatment

We recommend the addition of an SGLT-2 inhibitor to other glucose lowering medication(s) in adults with type 2 diabetes who also have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease (strong recommendation).

This recommendation applies to adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease and are unable to achieve optimal blood glucose levels using their current baseline therapy.

Summary of evidence in relation to SGLT-2 inhibitors (Table 1):

The evidence base for this recommendation includes studies in people with T2D with kidney disease who had an estimated glomerular filtration rate as low as 30 mL per minute per 1.73 m². Multiple cardiovascular risk factors were defined as men 55 years of age or older or women 60 years of age or older with T2D who have one or more additional traditional risk factors, including hypertension, dyslipidaemia, or smoking.

- SGLT-2 inhibitors lowered odds of *all-cause mortality* compared to placebo, DPP-4 inhibitor, sulfonylurea or GLP-1 RA as add-on therapy (high certainty or moderate certainty in lowest risk patients because of indirectness).
- SGLT-2 inhibitors lowered odds of *hospitalisation for heart failure* compared to placebo,

sulfonylurea, DPP-4 inhibitor or GLP-1 RA when added to background treatment (high certainty or moderate certainty in lowest risk patients because of indirectness).

- There was no evidence that SGLT-2 inhibitors lowered odds of a *major cardiovascular event* (3-item MACE - composite of CV death, non-fatal myocardial infarction and non-fatal stroke) compared to placebo when added to background therapy (moderate certainty because of imprecision).
- SGLT-2 inhibitor therapy probably lowered odds of a *major adverse cardiovascular event* (4-item MACE - 3-item MACE plus hospitalization for unstable angina) compared to placebo or a GLP-1 RA added to background therapy (high certainty and moderate certainty in lowest risk patients because of indirectness).
- There was no evidence that an SGLT-2 inhibitor added to background therapy increased *severe hypoglycaemia* to a greater extent than placebo (high certainty or moderate certainty in lowest risk patients because of indirectness).
- SGLT-2 inhibitors decreased *kidney failure* compared to placebo when added to background therapy (high certainty or moderate certainty in lowest risk patients because of indirectness).
- SGLT-2 inhibitor therapy decreased *HbA1c* compared to standard therapy (high certainty).
- SGLT-2 inhibitors incurred lower odds of *serious adverse events* than standard care (high certainty or moderate certainty in lowest risk patients because of indirectness). There was no evidence that other therapies added to background therapy had different odds of serious adverse events (high certainty).

Benefits and Harms

When added to other glucose lowering medications, SGLT-2 inhibitors resulted in reductions in all-cause mortality, heart failure, kidney failure, serious adverse events, events within the 4-item MACE composite outcome and mean HbA1c in people with T2D and HbA1c ≥ 53 mmol/mol (7%). Some trials also found benefit in people with T2D and HbA1c < 53 mmol/mol (7%). The effects on all-cause mortality, heart failure and kidney failure were most clinically significant in people with established cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease. No clinically relevant differences were observed when adding SGLT-2 inhibitors to other glucose lowering medications with regard to severe hypoglycaemia or events within the 3-item MACE composite outcome.

Certainty of evidence

With regard to the addition of SGLT-2 inhibitors to other glucose lowering medication, there was no evidence of serious heterogeneity or inconsistency in the network or incoherence in the direct and indirect estimates across all outcomes. The certainty of evidence for SGLT-2 inhibitors added to other glucose lowering medication was high across all outcomes, with the exception of MACE, in which certainty was downgraded to moderate due to suspicion of selective outcome reporting.

Summary

In formulating this recommendation, the Guideline Development Group placed emphasis on the high certainty of evidence across all outcomes, with the exception of 3-item MACE outcomes, in people with moderate to very high cardiovascular risk. SGLT-2 inhibitors when used as add-on therapy, demonstrated clinically relevant improvements in all-cause mortality, heart failure, kidney failure, serious adverse events, HbA1c and 4-item MACE outcomes over GLP-1 RA, DPP-4 inhibitors and sulfonylureas.

Table 1 Summary of effects of blood glucose medications when added to any standard care.

Summary of treatments added to any standard care								
	All-cause mortality	Heart failure	MACE 3-item*	MACE 4-item*	Severe hypoglycaemia	Kidney failure**	Change in HbA1c %***	Serious adverse events
Among the most effective or safest	SGLT-2	SGLT-2	GLP-1	SGLT-2		SGLT-2	GLP-1	SGLT-2
						GLP-1		
Among the effective	GLP-1						Sulfonylurea	
							SGLT-2	
							DPP-4	
Not convincingly different from placebo	DPP-4	GLP-1	SGLT-2	GLP-1	SGLT-2	DPP-4		GLP-1
	Sulfonylurea	DPP-4	DPP-4		GLP-1	Sulfonylurea		DPP-4
		Sulfonylurea	Sulfonylurea		DPP-4			Sulfonylurea
Among the harmful					Sulfonylurea			
<i>Trials (participants)</i>	228 (283,997)	143 (230,158)	15 (65,408)	2 (10,469)	193 (248,896)	32 (90,038)	587 (236,269)	446 (310,484)

Patients in contributing trials had type 2 diabetes and a mean age of 57 years, and BMI of 30 kg/m².

For very low risk patient the certainty has generally been downgraded by one level as the proportion of very low risk patients in the trials is unclear.

*Major cardiovascular events composite outcome. 3 item MACE is a composite of CV death, nonfatal myocardial infarction and nonfatal stroke. 4 item

MACE is hospitalization for unstable angina added to these three outcomes.

**Kidney failure refers to end-stage kidney disease defined as starting dialysis, receiving a kidney transplant or reaching an estimated glomerular filtration rate below 15 ml/min per 1.73 m².

***Baseline glycated HbA1C is mean HbA1C at baseline (8.1%) in contributing trials, with reductions measured over treatment duration of 9.6 months

The review by Palmer *et al* (20) evaluated SGLT-2 inhibitors and GLP-1 RA in people with T2D at varying cardiovascular and renal risk.

Methodology: The network meta-analysis included RCTs comparing SGLT-2 inhibitors or GLP-1 RA with placebo, standard care, or other glucose lowering treatment in adults with T2D with follow up of 24 weeks or longer. Frequentist random effects network meta-analysis was carried out and GRADE used to assess evidence certainty. Results included estimated absolute effects of treatment per 1000 patients treated for five years for patients at very low risk (no cardiovascular risk factors), low risk (three or more cardiovascular risk factors), moderate risk (cardiovascular disease), high risk (chronic kidney disease), and very high risk (cardiovascular disease and kidney disease). A guideline panel provided oversight of the systematic review. 764 trials including 421,346 patients were included. The absolute benefits for cardiovascular and renal outcomes varied substantially for patients, depending on their absolute cardiovascular risk (very low to very high; <https://magicevidence.org/match-it/200820dist/#/>).

Overall results for SGLT-2 inhibitors:

All results related to the addition of SGLT-2 inhibitors to existing diabetes treatment. SGLT-2 inhibitors lowered all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, and kidney failure (high certainty evidence). SGLT-2 inhibitors reduced mortality and admission to hospital for heart failure more than GLP-1 RA, and GLP-1 RA reduced non-fatal stroke more than SGLT-2 inhibitors (which appeared to have no effect). The absolute benefits varied substantially across patients from low to very high risk of cardiovascular and renal outcomes. There was little or no evidence for an effect of SGLT-2 inhibitors on limb amputation, blindness, eye disease, neuropathic pain, or health related quality of life (Table 2).

Table 2 Summary of effects with SGLT-2 inhibitors (20)

Table 1 Summary of anticipated absolute differences comparing sodium-glucose cotransporter-2 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	Diabetic ketoacidosis	Genital infection	Body weight
Very low	5 fewer (6 fewer to 3 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) ⊕⊕⊕			
Low	15 fewer (19 fewer to 11 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	25 fewer (32 fewer to 18 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) ⊕⊕⊕⊕	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 ⊕⊕
High	34 fewer (43 fewer to 25 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	48 fewer (61 fewer to 35 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) ⊕⊕⊕⊕			

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

Detailed results for SGLT-2 inhibitors

All-cause mortality

238 trials including 290,662 patients reported all-cause mortality. SGLT-2 inhibitors lowered all-cause mortality compared with placebo (odds ratio 0.77 [95% confidence interval 0.71 to 0.83]); 5 fewer per 1000 in five years for very low risk patients (moderate certainty); 15 fewer for low risk patients (high certainty); 25 fewer for moderate risk patients (high certainty); 34 fewer for high risk patients (high certainty); and 48 fewer for very high risk patients (high certainty).

SGLT-2 inhibitors reduced all-cause mortality compared with GLP-1 RA (0.88 [0.79 to 0.97]); 2, 7, 12, 16, and 23 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty.

Cardiovascular mortality

135 trials including 226,701 patients reported cardiovascular mortality. SGLT-2 inhibitors lowered cardiovascular mortality compared with placebo (0.84 [0.76 to 0.92]); 2, 7, 12, 16, and 24 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively.

Non-fatal myocardial infarction

208 trials including 265,921 patients reported non-fatal myocardial infarction. SGLT-2 inhibitors lowered odds of non-fatal myocardial infarction compared with placebo (odds ratio 0.87 [0.79 to 0.97]); 4, 7, 13, 14, and 21 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty.

Non-fatal stroke

176 trials including 261,434 patients reported non-fatal stroke. SGLT-2 inhibitors had little or no effect on non-fatal stroke (odds ratio 1.01 [95% confidence interval 0.89 to 1.14]); moderate to high certainty). SGLT-2 inhibitors had higher odds of non-fatal stroke than GLP-1 RA (1.20 [1.03 to 1.41]); moderate to high certainty.

Kidney failure

33 trials including 98,284 patients reported kidney failure, defined generally as estimated glomerular filtration rate (eGFR) below 15 ml/min per 1.73 m² or start of kidney replacement treatment. SGLT-2 inhibitors reduced kidney failure (odds ratio 0.71 [0.57 to 0.89]); 1, 3, 6, 25, and 38 fewer per 1000 in five

years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty.

Admission to hospital for heart failure

149 trials including 242,361 patients reported admission to hospital for heart failure. SGLT-2 inhibitors reduced admission for heart failure (odds ratio 0.70 [0.63 to 0.77]); 2, 9, 23, 29, and 58 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty. GLP-1 RA had little or no effect on hospitalisation for heart failure (0.94 [0.85 to 1.03]), moderate to high certainty. SGLT-2 inhibitors reduced hospitalisation for heart failure compared with GLP-1 RA (0.74 [0.65 to 0.85]); 1, 7, 18, 24, and 48 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty.

Body weight

469 trials including 226,361 patients reported body weight during a median follow up of six months. SGLT-2 inhibitor treatment might lower body weight (mean difference for SGLT-2 inhibitors –1.92 kg [–2.23 to –1.62]; low certainty. SGLT-2 inhibitors appeared to lower body weight to a greater extent than GLP-1 RA (–0.47 kg [–0.85 to –0.09]); moderate certainty.

Glycated haemoglobin A1c

604 trials including 242,745 patients reported HbA1c during a median follow-up of six months. SGLT-2 inhibitors (mean difference –0.60% [–0.67 to –0.54]) might lower HbA1c levels more than placebo (low certainty). GLP-1 RA reduced HbA1c to a greater extent than SGLT-2 inhibitors (mean difference –0.28% [–0.37 to –0.19]; high certainty).

Clinical uncertainties

SGLT-2 inhibitors failed to reduce non-fatal stroke in the same way that it reduced other cardiovascular endpoints, a finding not scientifically intuitive. Trials generally did not include patients with lowest cardiovascular risk. Accordingly, the certainty of evidence was graded down for the lowest risk patients owing to indirectness.

Comparisons with other studies

This systematic review included substantially more trials and patients than previously published reviews. The results provide evidence to support guideline recommendations that people with T2D at highest risk of cardiovascular disease and kidney disease are likely to have important benefits on risks of cardiovascular events and heart failure with SGLT-2 inhibitors. The network meta-analysis provided additional information of both relative and absolute estimates of a wide range of important clinical outcomes.

The findings are consistent with large scale observational analyses of SGLT-2 inhibitor treatment in a range of countries and settings, which suggest beneficial effects on a range of clinical outcomes, including reduced mortality and heart failure in people with T2D (22, 23). However, the effects of treatment in the available randomised trials were smaller than seen with observational data, as the trial data enable analyses that reduce the risks of confounding by treatment indication.

Conclusions

SGLT-2 inhibitors in people with T2D are associated with absolute benefits which depend on individual risk profiles of patients and supports a risk stratified approach for prescribing SGLT-2 inhibitors to people with T2D.

Kidney Disease Improving Global Outcomes (KDIGO) guidelines

The renal benefits of SGLT-2 inhibitors are the focus of the recently published KDIGO guidelines (21).

There is substantial evidence that SGLT-2 inhibitors confer significant renoprotective and cardioprotective effects derived from 3 large RCTs - EMPAREG (6), CANVAS (24), and DECLARE-TIMI 58 (25); a meta-analysis of these 3 cardiovascular outcome trials which stratified by CKD subgroups(26) an RCT, CREDENCE, specifically designed to evaluate kidney outcomes as the primary outcome but also reporting on secondary outcomes (27); a meta-analysis of 4 trials (EMPA-REG, CANVAS, CREDENCE, DECLARE-TIMI 58) evaluating kidney outcomes (28); and 2 RCTs, DAPA-HF (29) and EMPEROR-Reduced (30), evaluating the primary outcome of heart failure/cardiovascular death, among adults with reduced ejection fraction with and without T2D, and also stratified by eGFR (<60 and ≥ 60 ml/min per 1.73 m^2).

Main Recommendation:

We recommend treating patients with type 2 diabetes, chronic kidney disease, and an eGFR >30 ml/min per 1.73 m^2 with an SGLT-2 inhibitor (Graded 1A using KDIGO criteria).

This recommendation is based on the demonstrated cardiovascular benefits in the EMPA-REG study which enrolled people with T2D and an eGFR of ≥ 30 ml/min per 1.73 m^2 (25.9% had an eGFR <60 ml/min per 1.73 m^2)(6); the CANVAS program, which combined data from 2 RCTs (CANVAS and CANVAS-R) which enrolled people with T2D and an eGFR of ≥ 30 ml/min per 1.73 m^2 of whom 20.1% had CKD with an eGFR <60 ml/min per 1.73 m^2 (24); the DECLARE-TIMI 58 trial which enrolled people with T2D of whom 7.4% had an eGFR <60 ml/min per 1.73 m^2 (31); the CREDENCE trial in people with T2D with CKD (27); the DAPA-HF trial which enrolled people with symptomatic HFrEF with an \geq eGFR 30 ml/min per 1.73 m^2 , including 55% of individuals without diabetes (29) and the EMPEROR-Reduced trial which enrolled people with HFrEF with an eGFR ≥ 20 ml/min per 1.73 m^2 , including 50% of individuals with T2D (30).

The results of these RCTs were also consistent with a real-world registry, with the reduction in risk of hospitalization for heart failure and cardiovascular death associated with SGLT-2 inhibitors mirroring the favourable benefits seen in the RCTs (23).

Kidney benefits have also been demonstrated in studies with prespecified renal outcomes. EMPA-REG evaluated a prespecified kidney outcome of incident or worsening nephropathy, defined as progression to severely increased albuminuria (ACR >300 mg/g [30 mg/mmol]), doubling of serum creatinine, accompanied by an eGFR <45 ml/min per 1.73 m^2 , initiation of kidney replacement therapy, or renal death. This outcome was lower in the empagliflozin group (v placebo) -12.7% versus 18.8% HR 0.61 (95% CI: 0.53–0.70) (32). In the CANVAS program canagliflozin conferred kidney benefit with a 27% lower risk of progression of albuminuria (HR: 0.73; 95% CI: 0.67–0.79) and a 40% lower risk of a composite kidney outcome (40% reduction in eGFR, need for kidney replacement therapy, or death from renal cause; HR: 0.60; 95% CI: 0.47–0.77) (33). The DECLARE-TIMI 58 trial reported that dapagliflozin achieved a 1.3% absolute and 24% relative risk reduction in the secondary kidney outcome (a composite of a 40% decrease in eGFR to <60 ml/min per 1.73 m^2 , ESKD, and cardiovascular or renal death: HR: 0.76; 95% CI: 0.67–0.87)(34).

A 2019 meta-analysis pooled data from the EMPA-REG, CANVAS program, and DECLARE-TIMI 58 trials and examined kidney outcomes among individuals with and without CKD(28). For trial participants with an eGFR of 30 to <60 ml/min per 1.73 m^2 , SGLT-2 inhibitors reduced the risk of adverse kidney outcomes (composite worsening kidney failure, ESKD, or renal death; HR: 0.67; 95% CI: 0.51–0.89).

The CREDENCE trial was specifically powered to examine the effects of an SGLT-2 inhibitor (canagliflozin) on primary kidney outcomes in people with T2D with exclusively albuminuric CKD defined by an eGFR of 30–90 ml/min per 1.73 m^2 with albuminuria (ACR of 300–5000 mg/g [30–500 mg/mmol]) who were

receiving standard of care including a maximum tolerated dose of an ACEi or an ARB(27). The trial was stopped early because of superiority in the canagliflozin arm. The primary outcome occurred in 43.2 and 61.2 per 1000 patient-years in the canagliflozin and placebo arms, which translated to a 30% relative reduction in the primary kidney outcome by canagliflozin (HR: 0.70; 95% CI: 0.59–0.82). The secondary outcome of dialysis, kidney transplant, or renal death also showed a significant benefit (HR: 0.72; 95% CI: 0.54–0.97).

These results are supported by the Dapagliflozin and Prevention of Adverse Outcomes in CKD (DAPA-CKD) study (35). This study randomised 4,304 subjects with an eGFR of 25 to 75 ml per minute per 1.73 m² and a urinary albumin-to-creatinine ratio of 200 to 5000 to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. The study was stopped because of efficacy. Over a median of 2.4 years, a primary outcome event occurred in 197 of 2,152 participants (9.2%) in the dapagliflozin group and 312 of 2,152 participants (14.5%) in the placebo group (hazard ratio, 0.61; 95% confidence interval [CI], 0.51 to 0.72; P<0.001; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15 to 27]). The hazard ratio for the composite of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI, 0.45 to 0.68; P<0.001), and the hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI, 0.55 to 0.92; P = 0.009). Death occurred in 101 participants (4.7%) in the dapagliflozin group and 146 participants (6.8%) in the placebo group (hazard ratio, 0.69; 95% CI, 0.53 to 0.88; P = 0.004). The effects of dapagliflozin were similar in participants with and without T2D. The known safety profile of dapagliflozin was confirmed.

In real-world registry data, after propensity matching, the initiation of SGLT-2 inhibitors was associated with a 51% reduced risk of composite kidney outcome of 50% eGFR decline or ESKD (HR: 0.49; 95% CI: 0.35–0.67). This finding suggests that the kidney benefits seen in clinical trials are generalizable to clinical practice (36).

The overall quality of the evidence for this recommendation is high, supported by high-quality data of double-blinded, placebo-controlled RCTs of SGLT-2 inhibitors. There is moderate to high quality evidence that SGLT-2 inhibitor treatment reduces undesirable consequences in people with T2D and CKD, specifically cardiovascular death, hospitalization for heart failure, and progression of CKD. Risk of bias was considered low, consistency moderate to high, indirectness low, precision good and publication bias low.

Policy implications

The numerous RCTs and systematic reviews have consistently demonstrated with high certainty the benefits of SGLT-2 inhibitors on important CVD and renal outcomes in people with T2D, especially those at higher risk. On the basis of these findings, international guidelines uniformly recommend the use of SGLT-2 inhibitors as add-on therapy for people with T2D who are not achieving glycaemic targets.

The 2017 Expert Committee did not recommend the inclusion of SGLT-2 inhibitors as an option on the Essential Medicines List for T2D (5). The Committee stated (page 397) that although SGLT-2 inhibitors had shown a relevant clinical benefit in patients at high risk of cardiovascular events, more data were needed to confirm this finding. These new additional data (reviewed above) are now available and address previously expressed concerns.

GLP-1 Receptor Agonists

Several studies in recent years have reported the clinical benefits of GLP-1 RAs and most international guidelines recommend these agents as a second option to the use of SGLT-2 inhibitors for people with T2D at high risk.

This application focuses on SGLT-2 inhibitors and does not extend to GLP-1 RA as a treatment option for the reasons listed below. A summary of the evidence in relation to these follows.

1. GLP-1 RA are not considered as a treatment option in the WHO Guidelines on Second- and Third-line Medicines for the Control of Blood Glucose Levels in Non-pregnant Adults with Diabetes Mellitus (5).
2. There are differences in important clinical benefits which favour SGLT-2 inhibitors over GLP-1 RA including greater effect on all-cause mortality, heart failure and broader renal benefits.
3. The majority of available GLP-1 RAs require administration by subcutaneous injection.
4. The higher cost of GLP-1 RA (reviewed in Section 11).

Evidence on the clinical effects of GLP-1 RAs

GLP-1 RAs activate the GLP-1 receptor, an incretin that stimulates glucose-dependent insulin secretion. GLP-1 activation also decreases pancreatic islet glucagon secretion and delays gastric emptying leading to earlier satiety.

The Australian Guideline Review

Recommendation 2 states “*We recommend the addition of a GLP-1 receptor agonist to other glucose lowering medication(s) in adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, and are unable to be prescribed an SGLT-2 inhibitor due to either intolerance or contraindication (strong recommendation)*”.

This recommendation applies to adults with T2D who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, are unable to achieve optimal blood glucose levels on their current baseline therapy, and are unable to be prescribed an SGLT-2 inhibitor due to either intolerance or contraindication. The methodology of the Australian Guidelines is reviewed above.

Summary of evidence in relation to GLP-1 RA (Table 1):

- GLP-1 RA lowered *all-cause mortality* compared to placebo, or a sulfonylurea or DPP-4 inhibitor as add-on therapy (high certainty or moderate certainty in lowest risk patients because of indirectness).
- GLP-1 RA lowered odds of a *major adverse cardiovascular event (3-item MACE* - composite of CV death, non-fatal myocardial infarction and non-fatal stroke) compared to placebo when added to background therapy (high certainty or moderate certainty in lowest risk patients because of indirectness).
- GLP-1 RA decreased *kidney failure* compared to placebo when added to background therapy (high certainty or moderate certainty in lowest risk patients because of indirectness). SGLT-2 inhibitors and GLP-1 RA added to background therapy had similar effects on kidney failure (moderate because of imprecision).
- There was no evidence that GLP-1 RA decreased *hospitalisation for heart failure* compared to placebo or when added to background therapy (moderate certainty because of imprecision).
- There was no evidence that GLP-1 RA lowered odds of *4-item MACE* (3-item MACE plus hospitalization for unstable angina) compared to placebo (moderate certainty because of imprecision).
- There was no evidence that a GLP-1 RA added to background therapy increased *severe hypoglycaemia* to a greater extent than placebo (high certainty or moderate certainty in lowest risk patients because of indirectness).

- GLP-1 RA therapy added to background treatment decreased *HbA1c* to a greater extent than sulfonylurea, DPP-4 inhibitor, and SGLT-2 inhibitor therapy (high certainty).

Palmer Systematic Review and Meta-analysis (20)

The methodology has been reviewed above and all results related to the addition of GLP-1 RA to existing diabetes treatment. The overall results are shown in Table 2.

- GLP-1 RA lowered *all-cause mortality* compared with placebo (0.88 [0.83 to 0.94]); 2, 8, 13, 17, and 24 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty). SGLT-2 inhibitors reduced all-cause mortality compared with GLP-1 RA (0.88 [0.79 to 0.97]); 2, 7, 12, 16, and 23 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty.
- GLP-1 RA lowered *cardiovascular mortality* (0.88 [0.80 to 0.96]); 2, 5, 9, 12, and 18 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty. SGLT-2 inhibitors and GLP-1 RA did not have different effects on cardiovascular mortality (0.96 [0.84 to 1.09]), moderate to high certainty.
- GLP-1 RA lowered *non-fatal myocardial infarction* (0.92 [0.85 to 0.99]); 2, 4, 8, 9, 13 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty. SGLT-2 inhibitors and GLP-1 RA did not have different effects on non-fatal myocardial infarction (0.95 [0.84 to 1.08]), moderate to high certainty.
- GLP-1 RA reduced *non-fatal stroke* (0.84 [0.76 to 0.93]); 5, 9, 16, 17, and 25 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty. SGLT-2 inhibitors had higher odds of non-fatal stroke than GLP-1 RA (1.20 [1.03 to 1.41]); moderate to high certainty.
- GLP-1 RA had little or no effect on *hospitalisation for heart failure* (0.94 [0.85 to 1.03]), moderate to high certainty. SGLT-2 inhibitors reduced hospitalisation for heart failure compared with GLP-1 RA (0.74 [0.65 to 0.85]); 1, 7, 18, 24, and 48 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty.
- GLP-1 RA reduced *kidney failure* (0.78 [0.67 to 0.92]); 0, 2, 4, 19, and 29 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty. SGLT-2 inhibitors and GLP-1 RA probably did not have different effects on kidney failure (0.91 [0.69 to 1.20]); low to moderate certainty.
- During a median follow up of six months GLP-1 RA might lower *body weight* (mean difference for SGLT-2 inhibitors –1.92 kg [–2.23 to –1.62]; low certainty; mean difference for GLP-1 RA –1.45 kg [–1.72 to –1.18]; low certainty. SGLT-2 inhibitors appeared to lower body weight to a greater extent than GLP-1 RA (–0.47 kg [–0.85 to –0.09]); moderate certainty.
- During a median follow-up of six months, GLP-1 RA might lower *HbA1c* levels more than placebo (–0.89% [–0.95 to –0.82]; low certainty) and might reduce *HbA1c* to a greater extent than SGLT-2 inhibitors (mean difference –0.28% [–0.37 to –0.19; high certainty).
- No difference in the odds of *serious hypoglycaemia* was found in a comparison of SGLT-2 inhibitor or GLP-1 RA treatment with placebo or with each other in high or moderate certainty evidence.

Kidney Disease Improving Global Outcomes (KDIGO) guidelines (21) include a recommendation (4.3.1) on GLP-1RA which states “*In patients with T2D and CKD who have not achieved individualized glycaemic targets despite use of metformin and SGLT-2 inhibitors, or who are unable to use those medications, we recommend a long-acting GLP-1 RA (1B)*”.

This recommendation places a high value on the cardiovascular and kidney benefits of long-acting GLP-1 RA treatment in patients with T2D and CKD, and a lower value on the costs and adverse effects associated with this class of drug. This recommendation has a lower grading than the recommendation on SGLT-2 inhibitors.

Cardiovascular outcomes.

Six large RCTs examined cardiovascular outcomes for injectable GLP-1 RA (37-41) (42, 43) and 1 trial of an oral GLP1-RA(44). Of these, 4 studies (LEADER (41), SUSTAIN-6 (40) HARMONY(39), REWIND (37, 38) confirmed cardiovascular benefit of injectable GLP-1 RA with significant reductions in MACE for liraglutide, semaglutide, albiglutide, and dulaglutide, respectively. The other agents (lixisenatide (43), exenatide (42) and oral semaglutide(44) showed cardiovascular safety, but without significant cardiovascular risk reduction.

Kidney outcomes.

A 2019 meta-analysis of 7 cardiovascular outcomes trials of GLP-1 RA (ELIXA, LEADER, SUSTAIN-6, EXSCEL, HARMONY, REWIND, and PIONEER 6) (45) showed that compared to placebo, GLP-1 RA treatment reduced risk for a broad composite kidney outcome (development of new severely increased albuminuria, decline in eGFR, or rise in serum creatinine, progression to ESKD, or death from renal cause); HR: 0.83 [0.78–0.89] in people with T2D, including patients with CKD. In these studies, kidney endpoints were driven largely by reduction in albuminuria. Excluding severely increased albuminuria, the association of GLP-1 RA with kidney endpoints was not significant (HR:0.87; 0.73–1.03).

A major limitation of GLP-1 RA effect on renal endpoints is that there has not been a completed clinical trial enrolling a study population selected for CKD or in which kidney outcomes were the primary outcome as was done in the CREDENCE trial for canagliflozin (27) Such a study is underway examining the effect of semaglutide versus placebo on the progression of renal impairment in subjects with T2D and chronic kidney disease (FLOW trial) and is due to be completed in August 2024 (46).

KDIGO rated the overall evidence as moderate. The quality of the evidence for reduced MACE in people with T2D was downgraded to moderate because of the inconsistency of the data (I^2 59%). The favourable benefits on broad composite kidney outcomes are largely driven by reduction in severely increased albuminuria with less evidence to support benefit for harder kidney outcomes.

Summary of comparison of effects of SGLT-2 inhibitors and GLP-1 RA.

- SGLT-2 inhibitors - greater reduction in all-cause mortality; hospitalisation for heart failure; broader effect on kidney outcomes
- GLP-1 RA - reduction in non-fatal stroke which was not observed with SGLT-2 inhibitors was reported in the Palmer review which commented that this finding was not scientifically intuitive
- No difference in HbA1c, weight loss and severe hypoglycaemia

Route of administration.

WHO conducted a narrative review exploring preferences and values relating to treatment decisions in people living with T2D. The main drivers in deciding between treatment regimens included route of administration, avoiding or reducing the number of injections, side effects (in particular nausea), glycaemic management and avoiding hypoglycaemia, supporting the person's weight management strategy, reducing the risk of cardiovascular disease and reducing the frequency of blood glucose monitoring.

The Australian guideline commented that as GLP-1 RA usually require administration via subcutaneous injection, some people may prefer the use of other medications over GLP-1 RA.

The KDIGO guideline listed among harms that since most GLP-1 RA are administered subcutaneously, some patients may not wish to take an injectable medication.

Cost

GLP-1 RA are more costly than SGLT-2 inhibitors as reviewed in Section 11. KDIGO guidelines comment that although some models have found the use of GLP-1 RA to be a cost-effective, these medications are frequently cost-prohibitive for many patients compared to other cheaper oral diabetes medications.

10. Review of harms and toxicity: summary of evidence of safety.

Estimate of total patient exposure to date

There are few publicly available data on exposure to SGLT-2 inhibitors. They are now common-place in diabetes guidelines and clinical experience indicates their increasing availability and use in countries with developed health systems and universal health coverage. A study from the UK reported that SGLT-2 inhibitors represented 14% of new second line prescriptions and 27% of new third line prescriptions for T2D in primary care in the UK in 2016 (47).

In Australia, unpublished data indicate that SGLT-2 inhibitors are currently used by approximately 300,000 Australians representing 25% of the estimated 1.2 million people with T2D.

The Palmer et al review identified data from 764 trials which included 421,346 people with T2D (20).

Description of the adverse effects/reactions and estimates of their frequency

Adverse effects and SGLT-2 inhibitors

A number of potential adverse effects have been noted in relation to treatment with SGLT-2 inhibitors. The frequency of adverse events reported in clinical trials should be considered in the context that the majority of studies recruited high risk people with T2D (48).

Schorling et al (49) conducted an analysis of the safety and tolerability of empagliflozin in people with T2DM compared with placebo by pooling data from clinical trials which included 16,480 (empagliflozin) and 7,857 (placebo) patient-years. The frequency of serious adverse events (AEs) requiring hospitalization was 18.6% for the empagliflozin group and 21.3% for the placebo group. Empagliflozin was not associated with a higher rate of confirmed hypoglycaemia versus placebo, except in patients co-administered insulin and/or a sulfonylurea (31.5% vs. 30.2%, respectively). The incidence of events consistent with urinary tract infections was similar for empagliflozin versus placebo (9.37 vs. 9.70/100 patient-years, respectively). Events consistent with genital infections occurred more frequently with empagliflozin than placebo (3.54 vs. 0.95/100 patient-years, respectively). The frequency of AEs consistent with volume depletion was similar across groups, but higher with empagliflozin in patients aged 75 to 85 years and those on loop diuretics at baseline.

The Australian guideline review found that SGLT-2 inhibitors incurred lower odds of serious adverse events than standard care (high certainty or moderate certainty in lowest risk patients because of indirectness) and there was no evidence that other therapies added to background therapy had different odds of serious adverse events (high certainty)(12).

Genital infections

The most common adverse effect of SGLT-2 inhibitors is genital infections which is related to the glycosuria resulting from the mode of action of SGLT-2 inhibitors.

The increased risk of genital mycotic infections with SGLT-2 inhibitor treatment in both men and women has been consistent across all clinical trials. SGLT-2 inhibitors increased genital infection compared with placebo with a high certainty - 143 (range 119-170) more genital infections per 1000 patients treated for five years (20). The overall percent of affected individuals is small. For example, in the CREDENCE trial conducted in a population of people with T2D and CKD, genital infections occurred in 2.3% of those treated with canagliflozin versus 0.6% of those receiving placebo (27). Most of the time, such infections can be managed with topical antifungal medications and self-care practices, such as daily bathing (50). Discontinuation from the clinical trial due to genital mycotic infections was uncommon (48).

Fournier's gangrene is a serious but rare adverse event associated with SGLT-2 inhibitor use. It is an aggressive and life-threatening necrotising fasciitis of the external genitalia, perineum and perianal region, much more common in men than in women and diabetes is a predisposing factor. In 2018, the US FDA required a warning about the risk of Fournier's gangrene be added to the prescribing information of all

SGLT-2 inhibitors. In a post-marketing review, 55 cases of Fournier's gangrene were identified by the FDA in 6 years of SGLT-2 inhibitor use compared to 19 cases over a 35-year period for all other blood-glucose-lowering drugs (51). The Palmer et al review reported that the effect of SGLT-2 inhibitor treatment on Fournier gangrene was uncertain which is not surprising given that is a rare event (20).

Urinary tract infection

Initial reports suggested an increase in severe urinary tract infections (UTIs) with SGLT-2 inhibitors but subsequent reports have been conflicting. Dave et al (52) assessed the occurrence of UTIs in people with T2D initiating SGLT-2 inhibitors compared with DPP-4 inhibitors or GLP-1 RA in two large U.S.-based databases of commercial claims, one with 123,752 people and the other with 111,978 people. The primary outcome was a severe UTI event, defined as a hospitalization for primary UTI, sepsis with UTI, or pyelonephritis; the secondary outcome was outpatient UTI treated with antibiotics. In cohort 1, 61 people newly receiving SGLT-2 inhibitors had severe UTI events (incidence rate [IR] per 1000 person-years, 1.76), compared with 57 events in the DPP-4 inhibitor group (IR, 1.77) (HR, 0.98 [0.68 to 1.41]). In cohort 2, there were 73 events with SGLT-2 inhibitors (IR, 2.15), compared with 87 events in the GLP-1 RA group (IR, 2.96) (HR, 0.72 [0.53 to 0.99]). SGLT-2 inhibitors were not associated with increased risk for outpatient UTIs (cohort 1: HR, 0.96 [0.89 to 1.04]; cohort 2: HR, 0.91 [0.84 to 0.99]). This study confirms the increasing clinical trial findings and routine practice experience that the risk for severe and non-severe UTI events among those initiating SGLT-2 inhibitor therapy was similar to that among patients initiating treatment with other add-on blood glucose lowering medications.

Volume depletion / hypotension

Because of the osmotic diuresis induced by glycosuria resulting from SGLT-2 inhibition, volume depletion is a possibility. This is usually accompanied by increased urinary frequency, thirst, and rarely orthostatic hypotension. Risk factors for volume depletion are age >75 years, eGFR <60 mL/min/1.73m² and use of loop diuretics (48).

The risk of SGLT-2 inhibitor associated adverse effects related to intravascular volume depletion, such as hypotension, syncope and dehydration, is small (53). Strategies for minimising risk in euvoaemic patients include reducing the dose of any diuretics to avoid further volume depletion and withholding SGLT-2 inhibitors when a patient is at risk of dehydration, such as during an episode of gastroenteritis, when systemically unwell and around medical and surgical procedures.

Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) usually presents with hyperglycaemia (glucose \geq 13.9 mmol/L [\geq 250 mg/dL]), glycosuria, and hyperketonaemia. Over a third of patients with DKA associated with SGLT-2 inhibitors have normal or only mildly elevated blood glucose levels (<13.9 mmol/L, <250 mg/dL), referred to as euglycaemic diabetic ketoacidosis (euDKA). The absence of hyperglycaemia and the less severe polyuria and polydipsia, owing to the milder degree of hyperglycaemia-induced osmotic diuresis, can delay diagnosis and treatment. Overall, euDKA is pathophysiologically similar to DKA except for the SGLT2-induced glycosuria that artificially lowers plasma glucose levels and predisposes to increased ketogenesis. In May 2015, the US FDA issued a Drug Safety Communication warning that treatment with SGLT-2 inhibitors may increase the risk of ketoacidosis (48).

High quality evidence from a systematic review and meta-analysis including 39 RCTs and 60,580 patients reported an increased risk of DKA with SGLT-2 inhibitors in T2D compared with placebo or other antidiabetic drugs (relative risk 2.13 [1.38 to 3.27]), with an absolute rate of 3 events per 1000 patient-years (54).

Another review and meta-analysis reported a consistent doubling in risk of DKA with SGLT-2 inhibitors compared with placebo (2.20 [1.25–3.87], $p=0.0060$), but with a low event rate (<1 per 1000 patient-years (26). On the other hand, the Palmer et al review concluded that SGLT-2 inhibitor treatment probably did not increase DKA compared with placebo(20).

Bone fractures

The potential for SGLT-2 inhibitors to increase bone fractures was raised as a result of one RCT. In the CANVAS, but not the CANVAS-R, trial, there was a higher rate of fractures attributed to canagliflozin (24). However, in the CREDENCE trial which evaluated 100 mg/d of canagliflozin, there was no excess fracture rate (27).

In 9 pooled clinical trials with a mean duration of exposure to canagliflozin of 85 weeks, the incidence rates of adjudicated bone fractures were 1.1, 1.4, and 1.5 per 100 patient-years of exposure in the comparator (includes placebo and active comparators), canagliflozin 100 mg, and canagliflozin 300 mg groups, respectively. A double-blind, placebo-controlled clinical trial was conducted in 714 patients (mean age 64 years, range 55 to 80 years) with T2D inadequately controlled on current diabetes therapy as part of an FDA-issued post marketing requirement. At 2 years, patients randomized to canagliflozin 100 mg and canagliflozin 300 mg had placebo-corrected declines in bone mineral density (BMD) at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively. A 1.2% decline in BMD translates into a decrease of approximately 0.1 T-score units or 1% of peak bone mass. In post-hoc analysis, change in body weight appeared to explain about 40% of the observed difference in total hip BMD between the pooled canagliflozin group and the placebo group. Available from:

<http://www.fda.gov/Drugs/DrugSafety/ucm461449.htm>.

Recent meta-analyses do not support an increased risk of bone fractures. Li et al (55) identified 27 RCTs that compared the efficacy and safety of SGLT-2 inhibitors to a placebo in 20,895 people with T2DM with an average duration of 64 weeks. The pooled RR was 1.02 (95% CI [0.81, 1.28]) with low heterogeneity, indicating that SGLT-2 inhibitor treatment was not correlated with a higher risk of fracture. Three trials with 1,303 patients reported a change in the BMD from baseline. SGLT-2 inhibitor treatment did not decrease the BMD at four skeletal sites (lumbar spine, femoral neck, total hip, and distal forearm), and the overall WMD was 0.08 (95% CI [-0.09, 0.26]). No significant publication bias was detected. In people with T2DM treated with SGLT-2 inhibitors did not appear to affect bone health in this meta-analysis.

Abrahami et al (56) reported on real world data on SGLT-2 inhibitors and fractures. They conducted a population-based cohort study using the U.K. Clinical Practice Research Datalink. This study included 73,178 patients, with 9,454 SGLT-2 inhibitor users and 18,410 DPP-4 inhibitor users, monitored for a median duration of 1.9 years. Compared with use of DPP-4 inhibitors, use of SGLT-2 inhibitors was not associated with fracture risk (HR 0.97, 95% CI 0.79–1.19). Overall, these data provide further reassurance on the safety of SGLT-2 inhibitors on bone health among people with T2D.

Amputations

An increased risk of lower-limb amputations was seen with canagliflozin in the CANVAS trial (24). However, it was not reproduced in the CREDENCE trial, although this trial implemented special attention to foot care for prevention excluding those at risk for amputation (27). This risk of amputations was also not seen with other SGLT-2 inhibitor (empagliflozin and dapagliflozin) in the EMPA-REG (6) and DECLARE-TIMI 58 trials (34), respectively. In the DAPA-HF trial (29), lower-limb amputation occurred infrequently and were similar between the two treatment groups.

Heyward et al (57) performed a systematic review of RCTs and observational studies to examine the association between SGLT-2 inhibitors and lower extremity amputation. The primary outcome was risk of lower limb amputation. The random effects meta-analysis of 7 RCTs suggested the absence of a statistically significant association between SGLT-2 inhibitor exposure, although there was substantial statistical heterogeneity ($n = 424/23,716$ vs $n = 267/18,737$ in controls; RR 1.28, CI's 0.93–1.76; $I^2 = 62.0\%$; $p = 0.12$) whereas fixed effects analysis showed an increased risk, again with statistical heterogeneity (RR 1.27, 1.09–1.48; $I^2 = 62\%$; $p = 0.003$). Subgroup analysis of canagliflozin vs placebo showed a statistically significantly increased risk in a fixed effects meta-analysis ($n = 2$ RCTs, RR 1.59, 1.26–2.01; $I^2 = 88\%$; $p = 0.0001$) whereas the meta-analysis of dapagliflozin or empagliflozin ($n = 2$ RCTs each) and a single RCT for

ertugliflozin did not show a significantly increased risk. The findings from observational studies were too heterogeneous to be pooled in a meta-analysis and draw meaningful conclusions. Overall, there was no consistent evidence of SGLT-2 inhibitor exposure and increased risk of amputation.

The FDA warning initially imposed on canagliflozin in relation to increasing the risk of amputations was removed in 2020.

<https://www.fda.gov/drugs/drug-safety-and-availability/fda-removes-boxed-warning-about-risk-leg-and-foot-amputations-diabetes-medicine-canagliflozin>

Hypoglycaemia

All RCTs have shown that treatment with SGLT-2 inhibitors does not increase risk of serious hypoglycaemia as confirmed in the recent review by Palmer et al (high or moderate certainty evidence) (20).

Summary

SGLT-2 inhibitors are safe and well-tolerated. A small percentage of users are affected by well documented adverse effects related to their mode of action in inducing glycosuria and an osmotic diuresis. These include an increase in genital mycotic infections and volume depletion. DKA, including euDKA, is increased but rare. The literature is inconsistent in relation to a possible increase in fractures which has only been reported in relation to one agent, canagliflozin, in one RCT.

Because of these potential adverse effects SGLT-2 inhibitors should be used with caution in people with T2D in the following situations:

- frail elderly people especially those using loop diuretics due to the risk of volume depletion
- severe UTI – use should be temporarily discontinued
- history of recurrent UTIs – may need to be permanently discontinued
- genital infections – usually respond to genital hygiene but may need to be discontinued if problem is recurrent
- conditions of fasting and dehydration

The following precautions are required for conditions of fasting and dehydration:

- temporary cessation of SGLT-2 inhibitor with significant intercurrent illness
- cease SGLT-2 inhibitor at least 3 days pre-operatively (2 days prior to surgery and the day of surgery).
- SGLT-2 inhibitors should only be restarted post-operatively when the patient is eating and drinking normally or close to discharge from hospital.
- SGLT-2 inhibitors do not require cessation, excepting on day of procedure, for minor operations with short period of fasting (4 hours), with no risk of dehydration and with rapid resumption of normal food and fluid intake following the procedure <https://diabetessociety.com.au/position-statements.asp>.

There are no data on SGLT-2 inhibitor use in pregnant and breast-feeding women with T2D and consequently use in these women is contra-indicated.

11. Summary of available data on comparative cost and cost-effectiveness.

This section was prepared by Medicines Patent Pool (Dr Dzintars Gotham and Giulia Segafredo).

Comparative cost-effectiveness

This section reviews available evidence on comparative cost-effectiveness of SGLT-2 inhibitors and GLP1-RAs, compared to older antidiabetic medicines.

Systematic reviews of SGLT-2 inhibitors cost-effectiveness

The PubMed database was searched with the query “(sglt2 OR SGLT-2 OR (sodium glucose transporter inhibitor*) OR canagliflozin OR dapagliflozin OR empagliflozin OR ertugliflozin OR ipragliflozin) AND (cost* OR QALY OR ICER OR pric* OR economic*)” and the Systematic Review filter. The search returned 16 results, of which 3 were systematic reviews of SGLT-2 inhibitor cost-effectiveness (58-60).

The 2019 meta-analysis by Bagepally et al (58) considered evidence on the cost-effectiveness of SGLT-2 inhibitor compared to available alternatives for the treatment of people with T2D for whom metformin alone had not achieved glycaemic control. The search strategy was restricted to English-language publications but was not restricted geographically. Thirteen studies were included in the review, including 6 studies comparing SGLT-2 inhibitor to DPP-4 inhibitors, 5 studies comparing to sulfonylureas, 2 studies comparing to GLP-1 RAs, 2 studies comparing to TZDs, 1 study comparing individual SGLT-2 inhibitors, and 1 study comparing SGLT-2 inhibitor to insulin (some studies made more than one comparison). The geographic breakdown of the 13 studies was (some covered more than one country): UK (3), US (3), Greece (2), Canada (1), Denmark (1), Finland (1), Mexico (1), Netherlands (1), Norway (1), Sweden (1), Spain (1).

The results of meta-analysis found that SGLT-2 inhibitors were cost-effective compared to sulfonylureas and had no significant difference in cost-effectiveness compared to DPP-4 inhibitors. Data were insufficient to give pooled meta-analysis of cost-effectiveness comparisons to insulin, TZD, or GLP-1 RAs, but the individual studies found SGLT-2 inhibitors to be cost-effective compared to insulin (1 study) and TZD (1 study), and mixed findings compared to GLP-1RA (2 studies).

The review by Hong et al (59) considered cost-effectiveness of SGLT-2 inhibitors, GLP-1 RAs, and DPP-4 inhibitors against a range of comparators. With this broad scope, the review identified 85 studies for inclusion. Compared to the SGLT-2 inhibitor focussed group of studies identified by Bagepally et al (58), this review identified 2 additional studies on SGLT-2 inhibitors cost-effectiveness, both of which considered SGLT-2 inhibitor cost-effectiveness in China (61, 62).

This review did not undertake a quantitative meta-analysis but gave the following general commentary: *“Among the newer antidiabetic medications, GLP-1 RA tend to be cost effective compared with DPP-4 inhibitors and SGLT-2 inhibitors, and SGLT-2 inhibitors tend to be cost effective compared with DPP-4 inhibitors. However, there are limited number of studies on SGLT-2 inhibitors, and future studies on the cost effectiveness of SGLT-2 inhibitors versus other newer antidiabetic medications are recommended.”*

The review by Yoshida et al (60) identified 24 relevant studies, drawing the conclusion that *“SGLT-2 inhibitors in monotherapy, dual, or triple therapy were cost-effective compared to standard care /metformin or other antidiabetic therapies including DPP-4 inhibitors, sulfonylureas, TZD, alpha-glucosidase inhibitors, or insulin. However, it may not be a favourable option compared to GLP-1 RA.”*

Table 3 below lists studies on SGLT-2 inhibitor cost-effectiveness compared to non-SGLT-2 inhibitor therapies, identified in the Bagepally et al 2019 (58), Hong et al (59) and Yoshida et al (60) reviews, their geographic scope, and bottom-line conclusion.

Table 3. Studies on SGLT-2 inhibitor cost-effectiveness compared to non-SGLT-2 inhibitor therapies.

Study	Country	SGLT	Comparator	Cost-effectiveness SGLT-2 versus comparator
Van Haalen (2014)	Netherlands	Dapagliflozin	Insulin	Cost-effective
Abad Pangiagua (2015)	Spain	Dapagliflozin	SU, DPP4i, TZD	Cost-effective
Charakopou (2015)	UK	Dapagliflozin	DPP4i	Cost-effective
Charakopou (2015)	UK	Dapagliflozin	SU	Cost-effective
Neslusan (2015)	Mexico	Canagliflozin	DPP4i	Cost-effective
Sabale (2015)	Denmark, Finland, Norway, Sweden	Dapagliflozin	SU	Cost-effective
Sabapathy (2016)	Canada	Canagliflozin	DPP4i and SU	Cost-effective
Tzanetakos (2016)	Greece	Dapagliflozin	DPP4i and SU	Cost-effective
Vega-Hernandez (2017)	UK	Dapagliflozin	GLP1	Not cost-effective
Chakravarty (2018)	US	Dapagliflozin	GLP1, SU, DPP4i, TZD	Cost-effective
Gourzoulidis (2018)	Greece	Empagliflozin	Standard of care	Cost-effective
Nguyen (2018)	US	Empagliflozin	Standard of care	Cost-effective
Ramos (2019)	UK	Empagliflozin	Sitagliptin, saxagliptin	Cost-effective
Pawaskar (2019) Pawaskar (2019)	US, UK	SGLT2i	NPH insulin (various combinations/sequencing)	Cost-effective
Kansal (2019)	UK	Empagliflozin	SOC	Cost-effective
Kaku (2019)	Japan	Empagliflozin	SOC	Cost-effective
Gorgojo-Martinez (2019)	Spain	Empagliflozin	Semaglutide (injectable)	Not cost-effective
Cai (2019)	China	Dapagliflozin	Metformin	Cost-effective
Shao (2017)	China	Dapagliflozin	Glimepiride	Cost-effective
Gu (2016)	China	Dapagliflozin	Acarbose	Cost-effective
Ektare (2014)	US	Canagliflozin	Sitagliptin	Cost-effective

For simplicity, we do not use the separate term ‘dominant’ (meaning simultaneously cost-saving and QALY-adding) and note this simply as ‘cost-effective’ in the table above.

Summary of literature review of cost effectiveness of SGLT-2 inhibitors

Nearly all studies identified found SGLT-2 inhibitors to be cost effective over older classes of second-line (post-metformin) glucose-lowering drugs, especially for patients at a high risk of developing cardiovascular disease. Beyond glucose-lowering effects, the beneficial effects of SGLT-2 inhibitors on renal function, cardiovascular outcomes (e.g. risk of mortality from myocardial infarction and heart failure hospitalizations), and obesity are key drivers of cost-effectiveness.

In most comparisons (Table 3), SGLT-2 inhibitors have also been found to be cost-effective compared to DPP-4 inhibitors and GLP-1 RAs. However, the Bagepally et al. 2019 review (58), in which cost-effectiveness data were pooled across national studies and meta-analysed to give a single weighted average cost-effectiveness estimate, found that SGLT-2 inhibitors were not significantly different in terms of cost-effectiveness compared to DPP-4 inhibitors.

The magnitude of incremental benefit, in terms of quality-adjusted life years range from 0.05 to 0.48 QALYs for comparisons to SUs, 0.032–0.704 for comparisons to DPP-4 inhibitors, and 0.8–2.7 for comparisons to standard of care alone. For other comparisons only single studies were identified – 0.0715 incremental QALYs versus TZD, 0.25 versus acarbose, and 0.417 versus insulin (60).

Predictions about SGLT-2 inhibitor cost-effectiveness in LMICs are limited by the fact that cost-effectiveness analyses in LMICs are available only for China and Mexico. Additionally, the determination of cost-effectiveness relies entirely on a country's willingness-to-pay threshold (except in a minority of cases where SGLT-2 inhibitors were found to 'dominate' a comparator, i.e. lead to better health outcomes at lower cost). LMICs are likely to have far lower acceptable cost-effectiveness (incremental cost-effectiveness ratio) thresholds, that is, SGLT-2 inhibitors will have to have significantly lower prices in LMICs than current originator prices in HICs in order to be cost-effective in LMICs.

The situation may be different in countries where resources for managing diabetes complications are more constrained. Diabetes complications, such as microvascular complications (e.g. diabetic retinopathy, neuropathy, nephropathy), are conditions that can be very costly for health systems. Similarly, common comorbidities – heart failure and obesity – are similarly highly costly to health systems and are shown to benefit from SGLT-2 inhibitor therapy. Compared to people living with diabetes in high-income countries, people living with diabetes in LMICs may have a higher risk of developing complications. For example, diabetes is generally detected later in Africa, suggesting a higher risk of complications at the time of diagnosis (63, 64). In addition, the onset of diabetes is generally earlier in Asians, and the increased duration of diabetes may lead to a higher long-term risk of complications (65). Additionally, in broad terms, different oral antidiabetic drug classes can be sequenced to delay the need for insulin therapy. The difficulty of providing effective insulin therapy in many resource-constrained settings implies further LMIC-specific sources of cost savings through all drug classes that can delay the need for insulin therapy in people living with T2D (66).

Interpretation of the cost-effectiveness analyses listed above is limited by the fact that SGLT-2 inhibitor cost-effectiveness compared to TZD, SU, or other comparator, is dependent on the pricing of the comparator in the relevant country, and the pricing of the SGLT-2 inhibitor. Outcomes of cost-effectiveness analyses also depend on what pricing strategy the proprietor of the SGLT-2 inhibitor in question pursues in that country.

In 2018, the Medicines Patent Pool (MPP) published a feasibility study, examining the SGLT-2 inhibitor market in detail, with regard to patient access to SGLT-2 inhibitors (at the time), pricing, the intellectual property landscape, and potential clinical benefits and cost savings if access were expanded by voluntary licensing through the MPP model (67) [Available from: <https://medicinespatentpool.org/news-publications-post/exploring-the-expansion-of-the-medicines-patent-pools-mandate-to-patented-essential-medicines-a-feasibility-study-of-the-public-health-needs-and-potential-impact/>]. While current price differentials between SGLT-2 inhibitors and older drug classes (e.g. sulfonylureas, TZDs) are large (Table 4), MPP estimated that SGLT-2 inhibitor prices could decrease substantially when and where competitive generic manufacture is established. (See also section on current prices, below.)

Cost-effectiveness can result from lower effectiveness at lower cost, compared to the comparator. It is important to note this was not the case for SGLT-2 inhibitors in the majority of cost-effectiveness analyses identified above (Table 3), with the exception of comparisons to GLP-1 RAs.

Table 4. Average price per day of treatment (USD), for SGLT-2 inhibitors, GLP-1 RAs and selected older second-line glucose-lowering drugs.

	Argentina	Brazil	India	Russia	South Africa	UK
Older 2nd line medicines						
gliclazide	\$0.16	\$0.18	\$0.05	\$0.05	\$0.04	\$0.01
pioglitazone	\$0.29	\$0.45	\$0.03		\$0.33	\$0.10
SGLT-2 inhibitors						
canagliflozin	\$1.06	\$0.50	\$1.46			\$1.14
dapagliflozin	\$2.34	\$0.64	\$0.91	\$0.88	\$0.82	\$1.71
empagliflozin	\$2.28	\$0.56	\$0.58	\$0.72	\$0.91	\$1.20
GLP-1 RA						
albiglutide						
dulaglutide	\$7.03	\$1.60	\$3.57			\$2.56
exenatide		\$1.57				\$2.69
liraglutide	\$23.52	\$3.65	\$5.05		\$4.17	\$4.29
lixisenatide		\$1.90	\$3.93	\$1.82		\$2.72
semaglutide (injectable)		\$2.65				\$10.57
semaglutide (oral)						\$5.29

WHO defined daily doses used (https://www.whocc.no/atc_ddd_index/). Price sources: Argentina <https://servicios.pami.org.ar/vademecum/views/consultaPublica/listado.zul>, Brazil <https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/cmed/precos>, India www.1mg.com, Russia <http://grls.rosminzdrav.ru/pricelims.aspx>, South Africa <https://medicineprices.org.za/>, UK bnf.nice.org.uk/. Brazilian and Russian prices are without VAT. Brazilian, Russian, and UK prices are for public procurement, others are private market.

Systematic reviews of GLP-1 RA cost-effectiveness

The PubMed database was searched with the query “(Glucagon-like peptide-1 receptor agonist* OR GLP1 agonist* OR GLP-1 agonist* OR GLP1RA OR GLP-1RA OR incretin mimetic* OR exenatide OR liraglutide OR lixisenatide OR albiglutide OR dulaglutide OR semaglutide) AND (cost* OR QALY OR ICER OR pric* OR economic*)” and the Systematic Review filter. The search for GLP-1 RA returned 23 results, of which 2 were systematic reviews of GLP-1 RA cost-effectiveness (59, 68). A systematic review commissioned by UK NICE that included GLP-1 RAs was excluded for being outdated (69). One systematic review on cost-effectiveness of liraglutide was excluded for covering only one GLP-1 RA(70).

The Bagepally et al. 2020 review (68) restricted the search strategy to English-language publications but was not restricted geographically. Fifty-six studies were included in the review, including 10 studies comparing GLP-1 RAs to DPP-4 inhibitors, 7 comparisons to sulfonylureas, 3 studies comparing to TZDs, 27 comparisons to insulin, 4 comparisons to insulin plus a non-GLP-1 RA second-line medicine, and 7 studies comparing liraglutide plus insulin degludec to insulin. The majority of the identified studies considered cost-effectiveness in the UK, US, or other Western European high-income countries. Studies in LMICs included 2 in China, 1 in Bulgaria, and 1 in Colombia (Table 5).

Table 5. Studies on GLP-1 RA cost-effectiveness compared to non-GLP-1 RA medicines, identified in the Bagepally 2020 review (68).

Study	Country	GLP-1RA	Comparator	Cost-effectiveness of GLP-1 RA versus comparator
Watkins (2006)	USA	Exenatide	SU, TZD, insulin	Cost-effective
Ray (2007)	UK	Exenatide	Insulin	Cost-effective
Minshall (2008)	USA	Exenatide	SU	Cost-effective
Woehl (2008)	UK	Exenatide	Insulin glargine	Not cost-effective
Brandle (2009)	Switzerland	Exenatide	Insulin	Cost-effective
Mittendorf (2009)	Germany	Exenatide	Insulin	Cost-effective
Sinha (2010)	USA	Exenatide	SU, DPP-4I	Not cost-effective
Beaudet (2011)	UK	Exenatide	Insulin glargine	Cost-effective
Goodall (2011)	Spain	Exenatide	Insulin	Cost-effective
Ivanova (2011)	Bulgaria	Liraglutide	Insulin+SU	Cost-effective
Lee (2011)	USA	Liraglutide	SU+TZD	Cost-effective
Davies (2012)	UK	Liraglutide	SU, DPP-4I	Cost-effective
Gaebler (2012)	USA	Exenatide	TZD, insulin	Cost-effective
Gao (2012)	China	Liraglutide	SU	Cost-effective
Guillermin (2012)	USA	Exenatide	DPP-4I, TZD	Cost-effective
Lee (2012)	USA	Liraglutide	DPP-4I	Cost-effective
Samyshkin (2012)	USA	Exenatide	Insulin	Cost-effective
Fonseca (2013)	Spain	Exenatide	Insulin	Cost-effective
Mezquita Raya (2013)	Spain	Liraglutide	DPP-4I	Cost-effective
Kiadaliri (2014)	Sweden	GLP1RA	Insulin, insulin+DPP-4I	Cost-effective
Steen Carlsson (2014)	Sweden	Liraglutide	SU, DPP-4I	Cost-effective
Tzanetakos (2014)	Greece	Liraglutide	Insulin+DPP-4I	Cost-effective
Zhang (2014)	USA	GLP1RA	Insulin, insulin+SU	Cost-effective
Deng (2015)	China	Exenatide	Insulin	Cost-effective
Huetson (2015)	Norway	Lixisenatide	Insulin	Cost-effective
Perez (2015)	Spain	Liraglutide	DPP-4I	Cost-effective
Bruhn (2016)	USA	Albiglutide	Insulin, DPP-4I	Cost-effective
Davies (2016)	UK	Liraglutide + insulin degludec	Insulin	Cost-effective
Gordon (2016)	Sweden	Exenatide	Insulin	Cost-effective
Roussel (2016)	France	Liraglutide	DPP-4I, SU	Cost-effective
Ericsson (2017)	Sweden	Liraglutide + insulin degludec	Insulin	Cost-effective
Hunt (2017)	Netherlands	Liraglutide + insulin degludec	Insulin	Cost-effective
Hunt (2017)	USA	Liraglutide + insulin degludec	Insulin	Cost-effective
Kvapil (2017)	Czech Republic	Liraglutide + insulin degludec	Insulin	Cost-effective
Lasalvia (2017)	Colombia	Dulaglutide	Insulin	Cost-effective
Psota (2017)	Slovakia	Liraglutide + insulin degludec	Insulin	Cost-effective
Barnett (2018)	UK	Liraglutide	DPP-4I	Cost-effective
Drummond (2018)	UK	Liraglutide + insulin degludec	Insulin	Cost-effective
Ishii (2018)	Japan	Dulaglutide	Insulin	Cost-effective
Vega-Hernandez (2017)	UK	Liraglutide	SGLT-2I	Cost-effective
Charkravarty (2018)	USA	GLP1RA	SGLT-2I+SU	Not cost-effective
Lee (2011)	USA	Liraglutide	TZD	Cost-effective
Gu (2017)	China	Exenatide	Insulin	Cost-effective

Table adapted from Bagepally et al. 2020 (68). For simplicity, we do not use the separate term 'dominant' (meaning simultaneously cost-saving and QALY-adding) and note this simply as 'cost-effective' in the table above.

Summary of literature review reviews of GLP-1 RA cost-effectiveness

As is the case for SGLT-2 inhibitors (above), nearly all studies identified here found GLP-1 RAs to be cost effective over older classes of second-line (post-metformin) glucose-lowering drugs.

Beyond glucose-lowering effects, the beneficial effect of GLP-1 RAs on obesity is a key driver of cost-effectiveness.

There only cost-effectiveness analyses available for LMICs were from China, Bulgaria, and Colombia. While current price differentials between GLP-1 RAs and older drug classes (e.g. sulfonylureas, thiazolidinediones) are large (Table 5), MPP estimated that GLP-1 RA prices could decrease substantially when and where competitive generic manufacture is established. However, the fact that GLP-1 RAs are biologics (except exenatide, which is synthetic), unlike the small-molecule SGLT-2 inhibitors, may mean that price decreases are less rapid even when intellectual property barriers are removed.

Recent prices of SGLT-2 inhibitors and GLP-1 RAs in selected countries (Table 4)

Overall, SGLT-2 inhibitors and GLP-1 RAs are significantly more expensive than older second line antidiabetic medicines at present. However, SGLT-2 inhibitors and GLP-1 RAs are still under patent and substantial price reductions can be expected when competitive generic manufacture is established.

Price reductions have already been observed in India with SGLT-2 inhibitors where India-based Natco Pharma recently launched a generic version of dapagliflozin on the basis of the primary patent expiring in 2020. The Natco price for its generic dapagliflozin is Indian Rupee (INR) 15 (US 20 cents) for the 5mg tablet and INR 19.50 (US 27cents) for the 10mg tablet, considerably less than AstraZeneca's dapagliflozin which costs INR 49 (US 67 cents) for the 5mg tablet and INR 57 (US 78 cents) for the 10mg tablet - a 70% discount for the 5mg tablet and a 65% discount for the 10mg tablet.

12. Summary of regulatory status and market availability.

Table 6 provides details of the regulatory status of both SGLT-2 inhibitors and GLP-1 RA in selected jurisdictions.

Table 6. Regulatory approval status of SGLT-2 inhibitors and GLP-1 RAs in selected jurisdictions

	US	EMA	Japan	Australia	Canada
Older 2nd line medicines					
gliclazide	No	Yes*	Yes	Yes	Yes
pioglitazone	Yes	Yes*	Yes	Yes	Yes
SGLT2 inhibitors					
canagliflozin	Yes	Yes	Yes	No***	Yes
dapagliflozin	Yes	Yes	Yes	Yes	Yes
empagliflozin	Yes	Yes	Yes	Yes	Yes
GLP-1 receptor agonists					
albiglutide	No**	No**	No	No	No**
dulaglutide	Yes	Yes	Yes	Yes	Yes
exenatide	Yes	Yes	Yes	Yes	Yes
liraglutide	Yes	Yes	Yes	Yes	Yes
lixisenatide	Yes	Yes	Yes	Yes	Yes
semaglutide (injectable)	Yes	Yes	Yes	Yes	Yes
semaglutide (oral)	Yes	Yes	Yes	No	Yes

*Not authorised through EMA's centralised procedure, as predates establishment of this pathway, but approved in many EU countries nationally.

**Previously approved but originator discontinued manufacture and sales globally in 2018.

***Approved in 2012 but not available on the market since 2015.

Sources

US: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?> ; EMA – <https://www.ema.europa.eu/en/medicines> ; Japan – <https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0002.html> ; Australia – <http://tga-search.clients.funnelback.com/s/search.html?query=&collection=tga-artg> ; Canada – <https://health-products.canada.ca/dpd-bdpp/newSearch-nouvelleRecherche.do?lang=en> .

13. Availability of pharmacopoeial standards.

Table 7 shows the listing of the proposed medicines in the International, British and the United States Pharmacopoeias.

Table 7. Availability of pharmacopoeial standards

	Int P	BP	USP
SGLT-2 inhibitors			
canagliflozin	No	No	No
dapagliflozin	No	No	No
empagliflozin	No	No	No
GLP-1 receptor agonists			
albiglutide	No	No	No
dulaglutide	No	No	No
exenatide	No	No	Yes
liraglutide	No	No	No
lixisenatide	No	No	No
semaglutide (injectable)	No	No	No
semaglutide (oral)	No	No	No

Sources

BP – <https://www.pharmacopoeia.com/Catalogue/SearchProducts>; IP – <https://apps.who.int/phint/en/p/docf/>; USP – <https://usp.org>

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APPENDIX 1: Australian Guidelines Network Meta-Analysis Results

Introduction

Search results

The electronic literature search through to 1 May 2020 yielded 18,248 unique records. Screening and full-text article analysis identified 730 trials including 402,030 patients comparing 11 glucose- lowering drugs, placebo, or standard care. The trial sample sizes ranged from 16 to 17,160. The median trial mean age was 57.0 years and median proportion of men was 55.6%. At baseline, the median trial mean glycated haemoglobin A1C was 8.1% and body mass index was 30.1 kg/m².

Eligibility criteria included coronary artery disease or macrovascular disease in 33 trials (1-33), atrial fibrillation in 1 trial (7), heart failure in 6 trials (34-39), chronic kidney disease and/or albuminuria in 30 trials (40-69), dialysis for kidney failure in 4 trials (70-73) and high risk of cardiovascular or kidney disease in 9 trials (74-82). The reference list for all included studies is provided below.

Evidence tables and summaries

To ease interpretation of the many estimates and outcomes, we have prepared summaries and evidence tables. There are summary evidence tables which give an overview of all outcomes and their relative effects. For specific outcomes where the relative effect were interpreted as clinically relevant differences, we have also prepared tables showing the absolute effect across different risk groups. All tables also show the certainty of the evidence. The interventions will be ranked depending on how effective or safe they are. Colour coded is used to illustrate both how effective a treatment is and how certain we are of the effect.

Colour codes used in the tables

High-moderate certainty Most effective
High-moderate certainty Effective
High-moderate certainty No difference
High-moderate certainty Harmful
Low-very low certainty Most effective
Low-very low certainty No difference
Low-very low certainty Potentially harmful

Interpretation of the certainty of the evidence

High: We are very sure that the true effect is close to the estimated effect.

Moderate: We are moderately sure of the estimated effect. The true effect is probably close to this one, but there is a possibility that it is significantly different.

Low: We have limited confidence in the estimated effect. The true effect may be significantly different from the estimated effect.

Very low: We have very little confidence in the estimated effect. The true effect is likely to be significantly different from that estimated effect.

Overview of populations for absolute risk

The administration of therapeutics for blood glucose control in individuals with type 2 diabetes varies depending on whether the individual has any pre-existing conditions or are at risk of developing cardiovascular disease or have existing cardiovascular disease and/or kidney disease.

Some included trials explicitly exclude patients with various comorbidities, however the majority of included trials consist of a combination of individuals from a range of risk groups. Numerous risk calculators and other tools have been developed in order to quantify baseline risks, thereby allowing the use of indirect evidence to inform recommendations that are applicable to these groups.

For the purpose of calculating absolute effects in this review, baseline glycated HbA1C is represented by mean HbA1c at baseline in contributing trials and severe hypoglycaemia is derived from the risk in the placebo arm of contributing trials. Risks of death, hospitalisation due to heart failure and major cardiovascular events are derived from the RECODE risk calculator (<https://sanjaybasu.shinyapps.io/recodesi/>).

Variables used to calculate baseline risks within the RECODE calculator are as follows:

Risk group	Criteria
Very low risk (no CV risk factors)	Age: 60 years Sex: Male Black: No Hispanic: No Total cholesterol: 5 mmol/l HDL cholesterol: 1 mmol/l HbA1C: 8.0% Serum creatinine: 70 µmol/l UACR: 5 mg/mmol Systolic BP: 140 mmHg Prior MI: No On statins: No On oral diabetes medication: No On blood pressure treatment: No On anticoagulant: No Currently smoking: No
Low risk	<u>Very low risk with the following additions:</u>

(1-3 CV risk factors)	<ul style="list-style-type: none"> - Currently smoking - HbA1c: >9.0% - Systolic blood pressure: 160 mmHg (on treatment)
Moderate risk (established CV disease)	<u>Low risk, with the following additions:</u> <ul style="list-style-type: none"> - Prior MI or stroke
High risk (established kidney disease)	<u>Low risk, with the following additions:</u> <ul style="list-style-type: none"> - Serum creatinine: >120 µmol/l
Very high risk (established CV disease and established kidney disease)	<u>Low risk, with the following additions:</u> <ul style="list-style-type: none"> - Prior MI or stroke - Serum creatinine: >120 µmol/l

Monotherapy

Clinical question: Should you use metformin or a different blood glucose lowering agent (sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT-2 inhibitor, GLP-1 receptor agonist) as first line treatment in adults with type 2 diabetes?

201 trials evaluated metformin or another monotherapy. In these trials, the mean duration of diabetes at baseline was 5.4 years. The mean age at baseline was 56.2 years. The mean glycated haemoglobin A1C was 8.3%. The minimum duration of studies was 6 months and the mean was 8.7 months. The mean body mass index was 29.2 kg/m².

- There was no evidence that metformin or other therapeutics given as first line monotherapy had different effects on **all-cause mortality** than (*low certainty because of very serious imprecision*).
- There was no evidence that metformin or other therapeutics given as first line monotherapy had different effects on **hospitalisation for heart failure** (*low certainty because of very serious imprecision*).
- There were no trials evaluating metformin or other therapeutics given as first line monotherapy on a **major adverse cardiovascular event (3-item or 4-item)**.
- There was no evidence that metformin or other therapeutics given as first line monotherapy had different odds of **severe hypoglycaemia** (*low certainty because of very serious imprecision*).
- There was no evidence that metformin or SGLT-2 inhibitor first line monotherapy had different effects on **kidney failure** (*low certainty because of very serious imprecision*).
- Metformin first line monotherapy may lower **glycated haemoglobin A1C** to a greater extent (by 0.2%) than sulfonylurea, thiazolidinedione, and DPP-4 inhibitor monotherapy.
- GLP-1 receptor agonist first line monotherapy may decrease **glycated haemoglobin A1C** to a greater extent (by 0.2%) than metformin first line monotherapy (*low certainty because of network inconsistency and incoherence*).
- There was no evidence that metformin or other therapeutics given as first line monotherapy had different odds of **serious adverse events** (*low or moderate certainty because of very serious imprecision*).

Monotherapy - Summary of treatments compared to metformin								
GRADE	Classification	All-cause mortality	Heart failure	MACE	Severe hypoglycaemia	Kidney failure *	Change in HbA1c % **	Serious adverse events
Low to very low certainty	Not convincingly different from metformin alone	GLP-1 1.29 (0.29,5.67) ¹	GLP-1 0.24 (0.05,1.25) ¹		GLP-1 0.35 (0.05,2.70) ¹	SGLT-2 0.10 (0.006 to 1.63) ²	GLP-1 -0.21 (-0.02,-0.41) ³	GLP-1 0.94 (0.62,1.42) ¹
		SGLT-2 0.69 (0.21,2.31) ¹	SGLT-2 0.44 (0.01,16.60) ¹		SGLT-2 0.52 (0.14,1.91) ¹	SGLT-2 0.13 (-0.06,0.32) ³	SGLT-2 1.01 (0.68,1.50) ¹	
		Sulfonylurea 0.69 (0.21,2.31) ¹	Sulfonylurea 0.52 (0.25,1.09) ¹		Sulfonylurea 2.97 (0.71,12.46) ¹	Sulfonylurea 0.21 (0.05,0.36) ³	Sulfonylurea 0.86 (0.64,1.16) ¹	
		Thiazolidinedione 1.05 (0.67,1.64) ¹	Thiazolidinedione 1.20 (0.66,2.17) ¹		Thiazolidinedione 0.25 (0.04,1.46) ¹	Thiazolidinedione 0.20 (0.06,0.34) ³	Thiazolidinedione 0.86 (0.66,1.12) ¹	
		DPP4 0.73 (0.39,1.36) ¹	DPP4 0.29 (0.08,1.0)1		DPP4 0.76 (0.19,3.01) ¹	DPP4 0.31 (0.17,0.44) ³	DPP-4 0.93 (0.72,1.20) ¹	
Trials (n)		43 (26,623)	17 (12,501)	0 (0)	24 (14,387)	1 (712)	159 (45,659)	95 (43,051)

Estimates are therapeutics compared to metformin. Estimates are network odds ratios and 95% CI unless specified otherwise. Patients in contributing trials had type 2 diabetes for 5.4 years on average, with a mean age of 56 years and BMI of 29 kg/m².

* Kidney failure refers to end-stage kidney disease defined as starting dialysis, receiving a kidney transplant or reaching an estimated glomerular filtration rate below 15 ml/min per 1.73 m².

** Mean difference. Baseline glycated HbA1C is mean HbA1C at baseline (8.3%) in contributing trials, with changes measured over treatment duration of 8.7 months (average duration of trials).

1) Certainty downgraded due to very serious imprecision

2) Certainty downgraded due to very serious imprecision and risk of selective reporting; direct estimate used.

3) Certainty downgraded due to inconsistency and incoherence

Dual therapy

Clinical question: Which blood glucose lowering drug (sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT-2 inhibitor, GLP-1 receptor agonist) should be used in combination with metformin as dual treatment in adults with type 2 diabetes?

125 trials evaluated metformin, or another therapy added to metformin. In these trials, the mean duration of diabetes at baseline was 6.1 years. The mean age at baseline was 56.4 years. The mean glycated haemoglobin A1C was 8.0%. The minimum duration of studies was 6 months and the mean duration was 9.6 months. The mean body mass index was 30.9 kg/m².

- There was no evidence that therapeutics when added to metformin or metformin alone had different effects on **all-cause mortality** (*low or moderate certainty because of imprecision*).
- Thiazolidinedione therapy added to metformin increased **hospitalisation for heart failure** compared to a sulfonylurea, DPP-4 inhibitor or GLP-1 receptor agonist added to metformin and to metformin alone (*moderate certainty because of imprecision*).
- There was no evidence of different effects of sulfonylurea and DPP-4 inhibitor therapy when added to metformin on a **major adverse cardiovascular event (3-item)** (*low certainty because of imprecision*).
- There were no trials reporting the effects of therapeutics added to metformin compared to metformin alone on a **major adverse cardiovascular event (4-item)**.
- Sulfonylurea therapy added to metformin incurred **severe hypoglycaemia** compared to metformin alone, and compared to a DPP-4 inhibitor, SGLT-2 inhibitor or GLP-1 receptor agonist added to metformin (*high certainty*).
- There was no evidence that therapeutics when added to metformin had different odds of **kidney failure** (*low certainty because of imprecision*). There were no trials reporting the effects of therapeutics added to metformin compared to metformin alone on **kidney failure**.
- All therapeutics added to metformin decreased **glycated haemoglobin A1C** to a greater extent than metformin alone (*high certainty*). There was no evidence that therapeutics added to metformin had different effects on glycated haemoglobin A1C compared with each other (*low certainty due to imprecision*).
- There was no evidence that therapeutics when added to metformin or metformin alone had different odds of **serious adverse events** (*moderate to high certainty because of imprecision or incoherence between direct and indirect estimates*).

Dual therapy - Summary of treatments added to metformin compared to metformin alone							
	All-cause mortality	Heart failure	MACE*	Severe hypoglycaemia	Kidney failure**	Change in HbA1c %***	Serious adverse events
Among the most effective						GLP-1 -0.76 (-0.63,-0.89)	
						Sulfonylurea -0.63 (-0.48,-0.77)	
						Thiazolidinedione -0.63 (-0.46,-0.80)	
						SGLT-2 -0.59 (-0.45,-0.73)	
						DPP-4 -0.55 (-0.44,-0.65)	
Not convincingly different from metformin alone	Thiazolidinedione 0.85 (0.67,1.06) ¹	Sulfonylurea 0.34 (0.10,1.09) ²		SGLT-2 1.08 (0.44,2.62) ¹			SGLT-2 1.03 (0.80,1.32)
	GLP-1 0.76 (0.37,1.54) ¹	GLP-1 0.52 (0.13,2.02) ²		GLP-1 0.99 (0.38,2.57) ¹			GLP-1 0.97 (0.74,1.26) ¹
	DPP-4 0.59 (0.34,1.03) ¹	SGLT-2 0.55 (0.13,2.25) ²		DPP-4 0.82 (0.35,1.91) ¹			DPP-4 1.02 (0.82,1.26)
	Sulfonylurea 0.77 (0.52,1.15) ¹	DPP-4 2.06(0.40,10.7) ³					Sulfonylurea 1.03 (0.81,1.30)
	SGLT-2 0.73 (0.31,1.70) ²						Thiazolidinedione 1.15 (0.88,1.50) ¹
Among the harmful		Thiazolidinedione 2.19 (1.41,3.41) ¹		Sulfonylurea 4.5 (1.58,12.8)			
<i>Trials (n)</i>	<i>38 (38,247)</i>	<i>19 (25,097)</i>	<i>1 (2,620)</i>	<i>28 (23,963)</i>	<i>3 (3,559)</i>	<i>101 (48,474)</i>	<i>85 (55,450)</i>

Estimates are therapeutics added to metformin compared to metformin alone. Estimates are network odds ratios and 95% CI unless specified otherwise. Patients in contributing trials had type 2 diabetes for 6.1 months on average, with a mean age of 56 years, baseline HbA1C of 8.0% and BMI of 31 kg/m²

* Major cardiovascular events, only one study reported on this outcome, in the study there were 25 events, not enough to inform decision making.

** Kidney failure refers to end-stage kidney disease defined as starting dialysis, receiving a kidney transplant or reaching an estimated glomerular filtration rate below 15 ml/min per 1.73 m². There were only three events across three trials, not enough to inform decision making.

*** Mean difference. Baseline glycated HbA1C is mean HbA1C at baseline (8.0%) in contributing trials, with reductions measured over treatment duration of 8.7 months.

1) Certainty downgraded due to serious imprecision

2) Certainty downgraded due to very serious imprecision

3) Certainty downgraded due to very serious imprecision; direct estimate used due to very serious incoherence in the network estimate.

Dual therapy – Hospitalisation for heart failure								
GRADE	Classification	Intervention	Odds ratio for treatment added to metformin vs metformin alone (95% CI)	Intervention vs placebo Absolute effect per 1000 patients per 5 years				
				Very low risk (No CV risk factors)	Low risk (Three CV risk factors)	Moderate risk (CV disease)	High risk (Kidney disease)	Very high risk (CV and kidney disease)
				Baseline risk: 3	Baseline risk: 15	Baseline risk: 40	Baseline risk: 53	Baseline risk: 118
High to moderate certainty	Among the most harmful	Thiazolidine-dione	2.19 (1.41,3.41) ¹	3 more	18 more	47 more	60 more	140 more
Low to very low certainty	Not convincingly different from metformin alone	Sulfonylurea	0.34 (0.10,1.09) ²					
		GLP-1	0.52 (0.13,2.02) ²					
		SGLT-2	0.55 (0.13,2.25) ²					
		DPP-4	2.06 (0.40,10.72) ³					
		n = 25,097	Trials = 19					

Estimates are therapeutics added to metformin compared to metformin alone. Estimates are network odds ratios and 95% CI unless specified otherwise. Absolute risks of heart failure are derived from the RECODE risk calculator <https://sanjaybasu.shinyapps.io/recodesi/>.

1) Certainty downgraded due to serious imprecision

2) Certainty downgraded due to very serious imprecision

3) Certainty downgraded due to very serious imprecision; direct estimate used due to very serious incoherence in the network estimate.

Dual therapy – Severe hypoglycaemia								
GRADE	Classification	Intervention	Odds ratio for treatment added to metformin vs metformin alone (95% CI)	Intervention vs placebo Absolute effect per 1000 patients per 5 years				
				Very low risk (no CV risk factors)	Low risk (Three CV risk factors)	Moderate risk (CV disease)	High risk (kidney disease)	Very high risk (CV and kidney disease)
				Baseline risk: 24	Baseline risk: 24	Baseline risk: 24	Baseline risk: 24	Baseline risk: 24
High to moderate certainty	Not convincingly different from metformin alone	SGLT-2	1.08 (0.44,2.62) ¹					
		GLP-1	0.99 (0.38,2.57) ¹					
		DPP-4	0.82 (0.35,1.91) ¹					
		Thiazolidine-dione	No evidence	-	-	-	-	-
	Among the most harmful	Sulfonylurea	4.5 (1.58,12.8)	84 more	84 more	84 more	84 more	84 more
		n = 23,963	Trials = 28					

Estimates are therapeutics added to metformin compared to metformin alone. Estimates are network odds ratios and 95% CI. Absolute risk of severe hypoglycaemia absolute risk is drawn from the risk in the placebo arm in contributing trials.

1) Certainty downgraded due to serious imprecision

Dual therapy – Change in HbA1c %			
GRADE	Classification	Intervention	Mean difference for treatment added to metformin vs metformin alone (95% CI)
High to moderate certainty	Among the most effective	GLP-1	-0.76% (-0.63,-0.89)
		SGLT-2	-0.59% (-0.45,-0.73)
		Sulfonylurea	-0.63% (-0.48,-0.77)
		Thiazolidinedione	-0.63% (-0.46,-0.80)
		DPP4	-0.55% (-0.44,-0.65)
Baseline HbA1c: 8.0%		n = 48,474	Trials = 101

Estimates are network mean differences and 95% CI. Baseline glycated HbA1C is mean HbA1C at baseline (8.0%) in contributing trials, with reductions measured over treatment duration of 8.7 months.

Add-on to background treatment

Clinical question: Should you use a GLP-1 receptor agonist, SGLT-2 inhibitor, sulfonylurea or DPP-4 inhibitor as add-on in adults with type 2 diabetes? Will it differ by cardiovascular risk groups?

730 trials compared treatments added to background therapy. The median trial mean age was 57.0 years. At baseline, the mean trial mean glycated haemoglobin A1C was 8.1% and body mass index was 30.1 kg/m². The minimum duration of studies was 6 months and the mean duration was 9.7 months.

- SGLT-2 inhibitors lowered odds of **all-cause mortality** compared to placebo, DPP-4 inhibitor, sulfonylurea, GLP-1 receptor agonist as add-on therapy (*high certainty or moderate certainty in lowest risk patients because of indirectness*). GLP-1 receptor agonists lowered **all-cause mortality** compared to placebo, or a sulfonylurea or DPP-4 inhibitor as add-on therapy (*high certainty or moderate certainty in lowest risk patients because of indirectness*).
- SGLT-2 inhibitors lowered odds of **hospitalisation for heart failure** compared to placebo, sulfonylurea, DPP-4 inhibitor, or GLP-1 receptor agonist therapy when added to background treatment (*high certainty or moderate certainty in lowest risk patients because of indirectness*). There was no evidence that a DPP-4 inhibitor or GLP-1 receptor agonist decreased **hospitalisation for heart failure** compared to placebo or each other added to background therapy (*moderate certainty because of imprecision*).
- GLP-1 receptor agonists lowered odds of a **major adverse cardiovascular event (3-item)** compared to placebo when added to background therapy (*high certainty or moderate certainty in lowest risk patients because of indirectness*). There was no evidence that a sulfonylurea, DPP-4 inhibitor, or SGLT-2 inhibitor lowered odds of a **major adverse cardiovascular event (3-item)** compared to placebo or each other when added to background therapy (*moderate certainty because of imprecision*).
- SGLT-2 inhibitor therapy probably lowered odds of a **major adverse cardiovascular event (4-item)** compared to placebo or a GLP-1 receptor agonist added to background therapy (*high certainty and moderate certainty in lowest risk patients because of indirectness*). There was no evidence that a GLP-1 receptor agonist lowered odds of a **major adverse cardiovascular event (4-item)** compared to placebo (*moderate certainty because of imprecision*).
- Sulfonylurea therapy increased **severe hypoglycaemia** compared to placebo, DPP-4 inhibitor, SGLT-2 inhibitor, or GLP-1 receptor agonist therapy added to background treatment (*high certainty or moderate certainty in lowest risk patients because of indirectness*). There was no evidence that a DPP-4 inhibitor, SGLT-2 inhibitor, or GLP-1 receptor agonist added to background therapy increased severe hypoglycaemia to a greater extent than placebo or each other (*high certainty or moderate certainty in lowest risk patients because of indirectness*).
- SGLT-2 inhibitors and GLP-1 receptor agonists decreased **kidney failure** compared to placebo when added to background therapy (*high certainty or moderate certainty in lowest risk patients because of indirectness*). There was no evidence that a sulfonylurea or DPP-4 inhibitor decreased **kidney failure** compared to placebo, other treatments or each other when added to background therapy (*moderate because of imprecision*). SGLT-2 inhibitors and GLP-1 receptor agonists added to background therapy had similar effects on **kidney failure** (*moderate because of imprecision*).

- GLP-1 receptor agonist therapy added to background treatment decreased **glycated haemoglobin A1C** to a greater extent than sulfonylurea, DPP-4 inhibitor, and SGLT-2 inhibitor therapy (*high certainty*). Sulfonylurea, DPP-4 inhibitor and SGLT-2 inhibitor therapy decreased HbA1C compared to standard therapy (*high certainty*). There was no evidence that sulfonylurea, DPP-4 inhibitor and SGLT-2 inhibitor therapy added to background therapy had different effects on HbA1C (*high certainty or moderate certainty in lowest risk patients because of indirectness*).
- SGLT-2 inhibitors incurred lower odds of serious adverse events than standard care (*high certainty or moderate certainty in lowest risk patients because of indirectness*). There was no evidence that other therapies added to background therapy had different odds of serious adverse events (*high certainty*).

The systematic review undertaken to answer this question is currently submitted for publication. To align with the publishing model of the journal, we cannot make the detailed results and evidence profiles based on the results publicly available until the paper is published. We will update this document as soon as the paper is published. The full systematic review was available to the panel in confidence when making the recommendations and is available to the NHMRC and the Department of Health for review purposes.

Summary of treatments added to any standard care								
	All-cause mortality	Heart failure	MACE 3-item*	MACE 4-item*	Severe hypoglycaemia	Kidney failure**	Change in HbA1c %***	Serious adverse events
Among the most effective or safest	SGLT-2	SGLT-2	GLP-1	SGLT-2		SGLT-2	GLP-1	SGLT-2
						GLP-1		
Among the effective	GLP-1						Sulfonylurea	
							SGLT-2	
							DPP-4	
Not convincingly different from placebo	DPP-4	GLP-1	SGLT-2	GLP-1	SGLT-2	DPP-4		GLP-1
	Sulfonylurea	DPP-4	DPP-4		GLP-1	Sulfonylurea		DPP-4
		Sulfonylurea	Sulfonylurea		DPP-4			Sulfonylurea
Among the harmful					Sulfonylurea			
<i>Trials (participants)</i>	228 (283,997)	143 (230,158)	15 (65,408)	2 (10,469)	193 (248,896)	32 (90,038)	587 (236,269)	446 (310,484)

Patients in contributing trials had type 2 diabetes and a mean age of 57 years, and BMI of 30 kg/m².

For very low risk patient the certainty has generally been downgraded by one level as the proportion of very low risk patients in the trials is unclear.

*Major cardiovascular events composite outcome. 3 item MACE is a composite of CV death, nonfatal myocardial infarction and nonfatal stroke. 4 item MACE is hospitalization for unstable angina added to these three outcomes.

**Kidney failure refers to end-stage kidney disease defined as starting dialysis, receiving a kidney transplant or reaching an estimated glomerular filtration rate below 15 ml/min per 1.73 m².

***Baseline glycated HbA1C is mean HbA1C at baseline (8.1%) in contributing trials, with reductions measured over treatment duration of 9.6 months

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