Association of British Clinical Diabetologists

Educating
Representing
Supporting

SGLT-2 inhibitors in type 2 diabetes

An educational resource for health professionals

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Contents

Introduction

Two of the core objectives of the Association of British Clinical Diabetologists (ABCD) are to ensure the highest quality of care for people with diabetes and to provide a resource of information; not only for our members but also the wider multidisciplinary team and colleagues providing care for people with diabetes.

The rapid evolution of the SGLT-2 inhibitors in joining the pharmacological armamentarium to help manage hyperglycaemia in type 2 diabetes is to be celebrated; however, it can pose some clinical conundrums in terms of who to select for this class and how to minimize risks of harm. Over time, there will be increasing clarity as to the best groups of people who will benefit from these medications; even as this goes to the printers there is further emerging data on the benefits of SGLT-2 inhibitors and quantification of risk.

Currently SGLT-2 inhibitors have a role in:

1. Treatment of hyperglycaemia
2. Treatment and prevention of diabetic kidney disease and its progression
3. Treatment and prevention of chronic heart failure

For this document, the term SGLT-2 inhibitors covers medications which inhibit SGLT-1 in addition to SGLT-2.

We hope that this document will pragmatically support those involved in the day-to-day care of people with type 2 diabetes in the “here and now”, with the aim of maximising the benefits and minimising harm.

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What does this document cover and what does it not cover?

By the end of this document, you should understand:

- What the main types of diabetes are and why accurate diagnosis matters
- What SGLT-2 inhibitors are and their mode of action
- The benefits of using SGLT-2 inhibitors in people with type 2 diabetes
- The risks associated with the use of SGLT-2 inhibitors in people with type 2 diabetes
- How to minimise the risk and utilise SGLT-2 inhibitors for the benefits of people with type 2 diabetes

The document will not cover:

- Detailed theoretical aspects for which links can be obtained from the ABCD
- Detailed clinical trial data
- Any new licence that might come up after the preparation date of the course
- Use of SGLT-2 inhibitors in type 1 diabetes or gestational diabetes (SGLT-2 inhibitors not licensed)
- Details of use of SGLT-2 inhibitors in people with diabetes

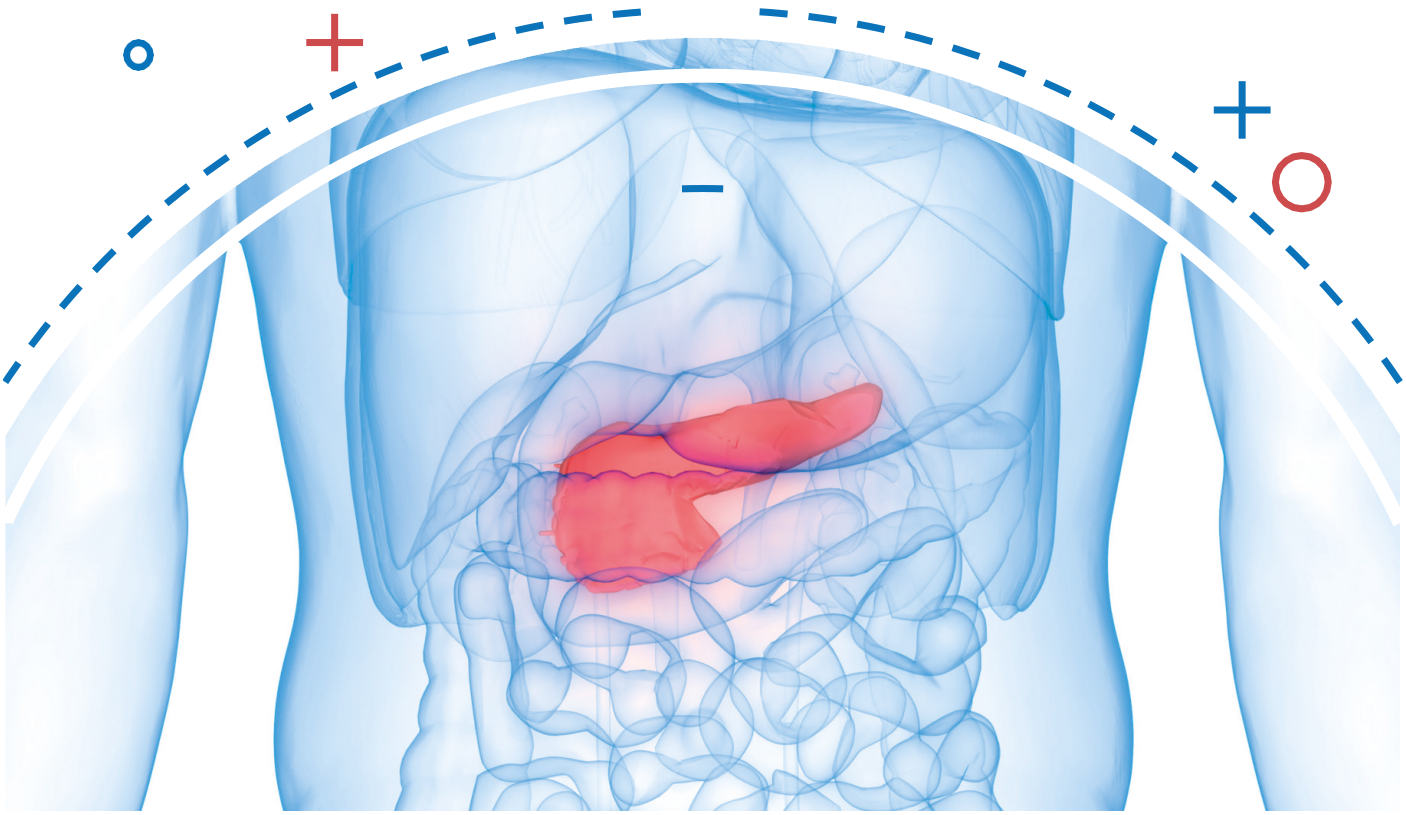
What are the types of diabetes?

Type 1 diabetes

- Clinical diabetes is caused by the destruction of the insulin producing beta cells in the pancreas. In 80-90% of cases one of the disease specific autoantibodies can be detected (GAD, IA2, Zinc Transporter 8)
- People with this type of diabetes rapidly become dependent on insulin for survival
- Insulin should never be stopped even for a short period in these people otherwise they will develop ketoacidosis which can be life threatening
- Some types of secondary diabetes due to destruction of the pancreas also behave in a similar fashion
- The treatment mainly consists of insulin and dietary modifications supported by education, with little role for oral medication

Type 2 diabetes

- This type of diabetes develops because of a mix of resistance to insulin action and deficiency of insulin secretion. The proportion of these components can be different in different people
- This type of diabetes commonly results because of resistance to insulin due to excess body fat – both subcutaneous and visceral (around the abdominal organs predominantly)



- This is initially treated with weight loss, healthy diet, exercise, and improved fitness. Oral medications are often required (including metformin, sodium glucose transporter-2 inhibitors, sulphonylureas, pioglitazone, gliptins, oral GLP1 agonists). As the disease progresses control may require additional or alternative injectable treatment (Glucagon Like Peptide-1 analogues and insulin). Finally with aging and frailty, de-escalation of treatment may be required. Insulin production decreases with diabetes duration, increasing DKA risk
- Some people with apparent type 2 diabetes may have a slowly progressing type 1 diabetes (latent autoimmune diabetes in adults (LADA), with positive GAD antibodies) or damage to their entire pancreas. These people are at higher risk of diabetic ketoacidosis (DKA)
- Some people with type 2 diabetes are unusually ketosis prone, for unknown reasons
- SGLT-2 inhibitors are associated with a small increased risk of ketoacidosis in type 2 diabetes. Given the large number of people with type 2 diabetes, this may translate into a significant number of extra cases hence the need for education

How is diabetes diagnosed?

- In the presence of symptoms (polydipsia, polyuria, and unexplained weight loss) diabetes is diagnosed by a single fasting plasma glucose ≥7 mmol/L (whole blood ≥6.1 mmol/L) or a random venous plasma glucose concentration ≥11.1 mmol/L

OR

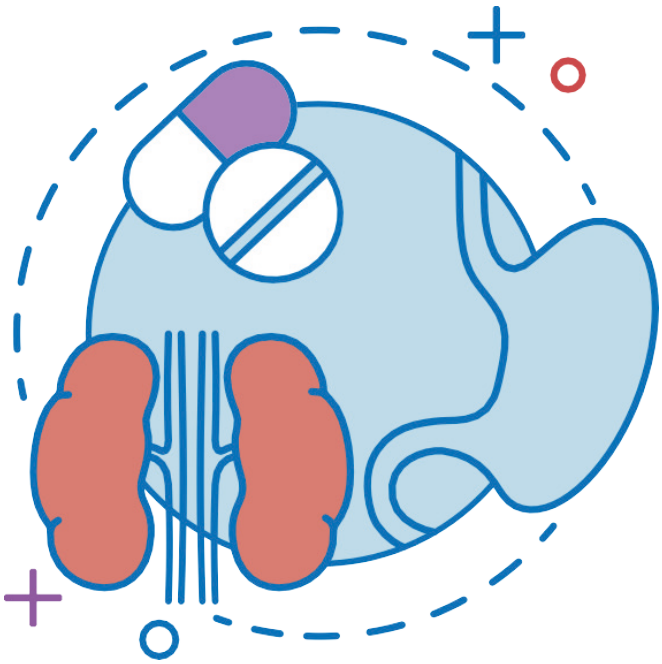
- In the absence of symptoms, diagnostic levels on two different occasions are required to make a diagnosis: a fasting plasma glucose ≥7 mmol/L, a plasma glucose concentration ≥11.1 mmol/L two hours after 75g anhydrous glucose in an oral glucose tolerance test (OGTT) or an HbA1c ≥48 mmol/L. HbA1c can be used for the diagnosis of type 2 diabetes but not for type 1 diabetes
- Up to 90% of people with type 1 diabetes have positive autoantibodies at presentation. Serum or urine C-peptide is inappropriately low, but present. This declines with time, such that C-peptide becomes undetectable in most people five years after diagnosis
- LADA should be considered in people with type 2 diabetes who are either lean or experience large changes in BMI over a short period of time. LADA is confirmed by significant autoantibody levels
- In people with apparent type 2 diabetes but unusual profile (lean, history of DKA, widely varying CBGs, requiring rapid escalation in treatment), consider doing autoantibodies, C-peptide and glucose levels. In people with strong family history and lean body profile, consider doing genetic testing for Maturity Onset Diabetes of Young (MODY). Probability calculators for MODY and differentiating type 1 from type 2 diabetes are available via diabetesgenes.org
- It is good practice to revisit the diagnosis of type of diabetes if things are not evolving as clinically expected

Why do we need more treatment options in people with type 2 diabetes?

	With the current management strategies only 36% of people with type 2 diabetes achieve all the NICE recommended targets for glucose, BP and cholesterol (National Diabetes Audit). This has got worse from previous years
	Inadequate or inappropriately treated type 2 diabetes is associated with acute glycaemia related complications: hypoglycaemia, Hyperglycaemic Hyperosmolar Syndrome, Diabetic Ketoacidosis
	Type 2 diabetes causes chronic microvascular complications: retinopathy, nephropathy, neuropathy, as well as cardiovascular complications
	Very few diabetes medications (metformin, pioglitazone, SGLT-2 inhibitors and GLP-1 agonists) have evidence to show that they reduce cardiovascular disease in people with type 2 diabetes
	Many people either do not tolerate, would not accept, or have contra-indications to the available drugs

What are SGLT-2 inhibitors?

- Sodium glucose cotransporter-2 inhibitors are an established class of drugs which act to decrease blood glucose by preventing reabsorption of glucose, mainly from proximal renal tubule in the kidney. Glucose is therefore lost in urine, decreasing the blood glucose level. The osmotic effect of the glucose loss leads to diuresis and a drop in blood pressure
- These agents act selectively on SGLT-2 receptors (found in kidneys) but may also interact with SGLT-1 receptors which are in the gastrointestinal tract and proximal renal tubules



- These drugs are currently licensed and used widely in people with type 2 diabetes and have shown significant cardiovascular and kidney benefits in different subsets of this group of people
- With the developing evidence more SGLT-2 inhibitors are likely to get licence for indications other than type 2 diabetes (e.g., chronic heart failure and chronic kidney disease)

Preparation and use in the UK (please check the current BNF/SmPC for any updates)

Name of SGLT inhibitor	Theraputic indication
SGLT-2 inhibitors:	
Dapagliflozin	Type 2 diabetes, symptomatic chronic heart failure (CHF) and chronic kidney disease (CKD)
Canagliflozin	Type 2 diabetes
Empagliflozin	Type 2 diabetes and symptomatic chronic heart failure
Ertugliflozin	Type 2 diabetes
SGLT 1+2 inhibitors:	
Sotagliflozin	Not currently licensed

Benefits of using SGLT-2 inhibitors in people with type 2 diabetes

- Reduction in HbA1c
- Up to 10 mmol/mol with some agents, dependent on starting HbA1c level
- Low incidence of hypoglycaemia

- The mechanism of action means that their effect is proportional to blood glucose
- Weight loss (up to 3kg)
- With a significant effect to reduce visceral fat
- Reduces progression of chronic complications affecting cardiovascular system and kidneys (see next pages)

Risks of SGLT-2 inhibitors in type 2 diabetes

- Genital infections
- DKA
- Amputation and fracture in some trials (but not others) with canagliflozin

Rare side effects reported with SGLT-2 inhibitors

Fournier's gangrene. It is a rare (55 cases in 6 years with SGLT inhibitors compared to 19 cases in 35 years with other antidiabetic drugs) but this serious bacterial infection needs urgent treatment

Suspect if there is pain, redness, swelling or discomfort in perineal or genital area. Needs urgent surgery and IV antibiotics

How to reduce the risks from SGLT-2 inhibitors?

Select the right person and an appropriate clinical setting for SGLT-2 inhibitors:

Required *(all three)*		
Age 	eGFR 	Education: 
Age above 18 years	eGFR as per the most recent summary of product characteristics (SmPC) and the indication of use for the specific SGLT-2 inhibitor*	Willing and able to understand the benefits and risks of SGLT-2 inhibitors and how to reduce those risks Willing and able to access or carry out urine and blood ketone checks if not feeling well due to any reason. Knows what to do when Urine ketones are ++ or more and/or blood ketones are >0.6 mmol/L. Blood ketones are more reliable
Advisory		
	BMI >27 kg/m² although diabetes specialists may use them in people with a lower BMI for potential cardiac or renal benefits	
Indication *(one or more)*		
		
People with microalbuminuria or macroalbuminuria	Inadequate glycaemic control despite optimal current treatment and / or at high risk of cardiac and renal adverse outcome For glycaemic management – anyone with eGFR >45 mL/ min/ 1.73 m² High risk of hypoglycaemia with alternative treatments	People with CHF with ongoing symptoms regardless of ejection fraction (use the SGLT-2 inhibitor with evidence and licence) For cardiorenal prevention and management – anyone with eGFR down to 15 regardless of albumin creatinine ratio

* What should be the GFR for optimal benefit of SGLT-2 inhibitors?

	Dapagliflozin	Empagliflozin	Canagliflozin
Do not initiate below eGFR (mL/ min/ 1.73 m²)	< 15	< 30 or < 20 if co-existing heart failure	< 30
If already initiated, continue until	eGFR < 15	eGFR < 20	Can be continued to dialysis or transplantation

Note, the glycaemic benefits of SGLT2i are typically only significant with eGFR > 45 mL/ min/ 1.73 m². Initiating or continuing SGLT-2 inhibitors at lower levels are for cardiorenal benefits.

Contraindications for SGLT-2 inhibitors

- Hypersensitivity

Use with caution in the following groups of people due to higher risk of developing DKA

- Person adhering to restricted food intake
- BMI <27 kg/m² although diabetes and other specialists may use them in people with lower BMI for potential cardiac or renal benefits
- Person at risk of developing high glucose related complications (dehydration, poor compliance to treatment, frequent missed medications)
- Person with history of ketoacidosis unless there was a different precipitant for DKA that has been resolved and type 1 diabetes, LADA or insulin deficiency has been excluded
- Acutely unwell person with medical illness although specialists may like to continue SGLT-2 inhibitors in people admitted with chronic heart failure even in the elderly
- Surgery or planned medical procedure that may require starvation
- Person with excess alcohol consumption or intravenous drug use
- Person with HbA1c >86 mmol/mol. (Additional risk of genitourinary infections in these people)
- Frail and elderly who are at risk of dehydration
- Cognitive impairment
- People who rapidly progressed to needing insulin after diagnosis within 1 year
- Pancreatic disease
- Suspected or possible type 1 diabetes or LADA unless under specialist supervision

Seek advice from the local diabetes team if unsure about the benefits and risks

Use under specialist guidance as not licensed

- People under 18 years of age
- Pregnant, breast feeding, female in the childbearing years and sexually active without contraception
- Genetic diabetes

How best to use SGLT-2 inhibitors?

What to do before you start SGLT-2 drugs

- Treatment with SGLT-2 inhibitors in people with type 2 diabetes should be initiated only after educating the person or those caring for person with diabetes who can't understand the risk themselves
- Explore if the person has a high burden of oral medications and their attitude to injectable therapies
- The education should include information on:
- how SGLT-2 inhibitors work
- the risk of diabetic ketoacidosis
- signs and symptoms of early DKA
- sick day rules
- when to start and stop SGLT-2 drugs
- how to get ketone levels measured when needed depending upon the local set-up. In most places in the country the local hospitals will be able to measure blood ketones when a person with diabetes is not well

What to do when you start SGLT-2 inhibitors

At initiation:

- Document completion of the education and the advice on who to contact if not feeling well
- Other glucose lowering medications including insulin should be reviewed and probably reduced when SGLT-2 inhibitors are started, to avoid hypoglycaemia
- Use with caution or avoid if the diagnosis of type 2 diabetes is not secure and there is a possibility of type 1 diabetes or latent autoimmune diabetes in adults
- Do not check renal function (eGFR) after starting SGLT-2 inhibitors unless it is specifically indicated
- Review diuretic and anti-hypertensive therapy periodically if hypertension improves

What to monitor when continuing SGLT-2 therapy

- Be prepared (have education and systems in place) to measure blood ketones when the person with diabetes is not eating well or is feeling unwell
- Check that the person has an up to date understanding of the benefits and risks of SGLT-2 inhibitors
- Reinforce education about DKA periodically

When to suspend treatment with SGLT-2 inhibitors

Suspend SGLT inhibitors in the following circumstances:

- Acute medical admission due to severe illness
- Admission for elective surgery or procedure requiring starvation
- Vomiting
- Dehydration

Restart the treatment when the potential or possible precipitant of DKA no longer poses a threat. This may be 24 hours to several days based on the original insult. Alternative diabetes treatment may be required in the interim. Consider monitoring blood ketones during the period of suspension of SGLT-2 inhibitors.

When to stop SGLT-2 inhibitors

Stop SGLT-2 inhibitors and do not restart in people who develop DKA on SGLT inhibitors unless there was a clear precipitant that has been resolved and type 1 diabetes, LADA or insulin deficiency has been excluded by a review of history, appropriate antibody tests and C-peptide level (paired with a blood glucose measurement - a low C-peptide would be appropriate in hypoglycaemia) if indicated.

How to reduce the risk: Sick day rules

Education

When a person with diabetes is not well or is unable to eat and drink as normal some simple rules can help further deterioration or DKA

- Measure capillary ketones using self-testing equipment or at the local hospital. If ketones > 0.6mmol/L, then attend the local emergency department immediately for testing for possible DKA
- Take half glass of milk, fruit juice, yogurt or soups (not clear soups), if not able to eat and if taking insulin cover with half the normal dose of insulin
- Drink plenty of water/sugar free fluid to avoid dehydration for up to 24 hours
- Seek medical advice if infection or illness
- Be aware that glucose levels can be normal because of the way SGLT-2 inhibitors work. Ketone levels can be high even with a normal glucose!
- Some medications are not good when you are not well (see below)

Diabetes Medicines to Stop Temporarily when not well (DAMN GlucoSe drugs)

- **D**iuretics: 'water pills' – e.g., furosemide, bendroflumethiazide, indapamide, bumetanide
- **A**CE inhibitors: names ending in '**pril**' e.g., ramipril, lisinopril, perindopril
- **A**RBs: names ending in '**sartan**' e.g., candesartan, losartan, irbesartan
- **M**etformin
- **N**SAIDs: anti-inflammatory pain killers e.g., ibuprofen, naproxen, diclofenac
- **G**LP1 analogues (injectable): names ending in '**tide**' e.g., exenetide, liraglutide, dulaglutide, lixisenatide
- **S**GLT-2 inhibitor: names ending in '**flozin**' e.g., canagliflozin, dapagliflozin, empagliflozin, ertugliflozin

Do not forget to restart medications when the person is well again.

How to reduce the risk: Education

Educate the individual

Advice to people with type 2 diabetes taking SGLT-2 inhibitors:

- Illness, infections, starvation, excessive exercise, alcohol, surgery, reduced insulin dose (if on insulin) and dehydration increase the risk of DKA
- When you are not well you should follow some sick day rules to avoid further problems (as in the page earlier)
- Suspect DKA if you have nausea, vomiting, pain abdomen, stupor, fatigue, and difficulty breathing (even if glucose levels are near normal – this may be because SGLT-2 inhibitors increase glucose excretion in urine)
- Do not rely on urine ketone but test your capillary ketones or present yourself for blood ketone testing at your local hospital
- Useful information from the manufacturers may be available online

Educate the health care professionals

- People with type 2 diabetes taking SGLT-2 inhibitors are at higher risk (the relative risk is around 1.3 per 1000 person- years) of developing diabetic ketoacidosis
- Suspect DKA in presence of nausea, vomiting, abdominal pain, difficulty breathing, confusion, fatigue and drowsiness
- Confirm ketosis by measuring blood ketone (>3.0 mmol/L)
- Confirm acidosis with a venous bicarbonate (<15 mmol/L) or venous pH (<7.30)

- Glucose levels may be normal
- If confirmed to have ketosis with acidosis (regardless of the glucose level) then start a fixed rate intravenous insulin infusion and IV fluids as per JBDS guidelines. Concomitant additional glucose infusion may be required to avoid hypoglycaemia
- Revisit prescribing in those with increasing frailty

Appendix (The evidence section)

Which SGLT-2 inhibitors to use in addition to standard therapy?

The trials have been done in different types of population. Dapagliflozin's trial included people with no previous cardiac events, people on empagliflozin had established cardiovascular disease and people on canagliflozin had CKD. The cardiac and renal benefits appear to be a class effect but are more pronounced in people with renal impairment. Some of the initial trial results are shown in the table below.

	Composite renal outcome/1000 pt.yrs		Cardiac outcomes {Major adverse cardiac events (MACE)/1000 pt.yrs}	
	event rate, placebo	Relative risk reduction {RRR (%)}	event rate, placebo	RRR (%)
EMPA REG (Empagliflozin)	6.3, 11.5	46	37.4, 43.9	14
CANVAS (Canagliflozin)	5.5, 9.0	40	26.9, 31.5	14
DECLARE (Dapagliflozin)	3.7, 7.0	47	22.6, 24.2	7
CREDENCE (Canagliflozin)	43.2, 61.2	30	38.7, 48.7	20
VERTIS CV Ertugliflozin)	9.3, 11.5	19	40.0, 40.3	1

Cardiovascular benefits of SGLT-2 inhibitors added to standard therapy including renin angiotensin aldosterone system (RAAS) blockade

RCT	Trial population Main inclusion criterion	Composite of Cardiovascular (CV) death or worsening of heart failure Placebo	 SGLT-2 inhibitor
DAPA-HF	Heart failure with reduced ejection fraction (HFrEF) with or without diabetes on dapagliflozin or placebo	21.2%	16.3%
EMPEROR-Reduced	HFrEF with or without diabetes on empagliflozin or placebo	24.7%	19.4%
EMPEROR-Preserved	Heart failure with preserved ejection fraction (HFpEF) with or without diabetes on empagliflozin or placebo	17.1%	13.8%
DELIVER trial	HFpEF with or without diabetes on dapagliflozin or placebo	19.5%	16.4%

RCT	Trial population Main inclusion criterion	Composite of Cardiovascular (CV) death or worsening of heart failure Placebo	SGLT-2 inhibitor
EMPEROR-Preserved pre-specified analysis	Left ventricular ejection fraction (LVEF) ≥50% LVEF >40% With or without diabetes on empagliflozin or placebo	17% ↓ in risk of CV death or HHF 29% ↓ in risk of CV death or HHF	

Remote Trial

Trial	Main inclusion criterion	Main outcome
CHIEF-HF	Heart failure regardless of ejection fraction (EF) with or without diabetes on canagliflozin or placebo	Kansan City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ TSS) at 12 weeks reduced by 4.3 points

Renal benefits of SGLT-2 inhibitors added to standard therapy including RAAS blockade

RCT	Trial population Main inclusion criterion	Composite of sustained decline in the estimated GFR (or doubling of serum creatinine in CREDENCE), end stage kidney disease or death from renal or cardiovascular cause Placebo	SGLT-2 inhibitor
CREDENCE	CKD with type 2 diabetes on canagliflozin or placebo	30% relative risk reduction due to event rate being 43.2 in the canagliflozin group vs 61.2 in the placebo group per 1000 patient-years	
DAPA-CKD	CKD with or without type 2 diabetes on dapagliflozin or placebo	14.5%	9.2% (relative risk reduction of primary end point 39%)
EMPA-Kidney	CKD with or without type 2 diabetes on Empagliflozin or placebo	16.9%	13.1% (relative risk reduction of primary end point 28%)

Combined cardio-renal benefits from SGLT-2 inhibitors added to standard therapy including RAAS blockade

Trials	Outcomes in the SGLT-2 inhibitor group vs comparator
13 trials combined by Oxford Population Health renal Studies Group and the SGLT2 meta-analysis Cardio-Renal trialists' Consortium (SMART-C)	37% ↓ kidney disease progression 23% ↓CV death or HHF 21% ↓acute kidney injury 14% ↓CV death
Combined 5 trials (DELIVER, EMPEROR-Preserved, DAPA-HF, EMPEROR Reduced and SOLOIST-WHF	23%↓ in the composite of cardiovascular death of HHF 13% ↓ cardiovascular death 28% ↓ first hospitalisation for heart failure 8% ↓ all-cause mortality