SGLT-2 inhibitors in people with type 2 diabetes-An educational resource for health care professionals who are not diabetes specialists (updated September 2020)

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

By the end of this guide 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.
- What the benefits of using SGLT-2 inhibitors are in people with type 2 diabetes.
- What the side effects associated with the use of SGLT-2 inhibitors are in people with type 2 diabetes.
- How we can minimize the risk and utilise SGLT-2 inhibitors for the benefits of people with type 2 diabetes.

The guide will not cover

- Detailed theoretical aspects for which links can be provided on request.
- Detailed clinical trial data or references for which links can be provided on request.
- Any new data or licence that might come up after the date of preparation of the course.

What are the types of diabetes?

Type 1 diabetes

- Is generally caused by destruction of the insulin producing beta cells in the pancreas. In 80-90% of cases one of the disease specific antibodies 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 can develop ketoacidosis which can be life threatening
- Some other types of secondary diabetes due to destruction of pancreas also behave in a similar fashion.
- The treatment mainly consists of insulin and dietary modifications supported by education.

Type 2 diabetes

- This type of diabetes develops because of a mix of resistance to insulin action & deficiency of insulin secretion with variable genetic susceptibility. The proportion of these components can be different in different patients.
- Type 2 diabetes is initially treated with diet and exercise. Medications are often required if diet and exercise alone are not sufficient. Options for medication include: metformin, sulfonylureas, DPP-4 inhibitors, pioglitazone and SGLT-2 inhibitors. GLP-1 receptor agonists are also an option, especially useful for patients with high HbA_{1c}, severe obesity or those with established/high risk of CV disease. As diabetes progresses, combination therapy may be needed and insulin may be required to manage hyperglycaemia.
- Some people with apparent type 2 diabetes may actually have a slowly progressing type 1 diabetes ("Latent Auto Immune Diabetes" with positive insulin auto-antibodies) or damage to their entire pancreas. These people are at higher risk of DKA.
- Some other people with type 2 diabetes are also ketosis-prone for unknown reason.

How is diabetes diagnosed?

- Diabetes is diagnosed by a single fasting capillary blood glucose ≥ 7 mmol/L or an HbA_{1c} ≥48 mmol/L in the presence of osmotic symptoms (polydipsia, polyuria, tiredness, thirst) or the same levels on two different occasions in the absence of symptoms.
- Up to 90% of people with Type 1 diabetes have positive auto-antibodies at presentation. Serum or urine c-peptide is initially low, but present. This declines with time, such that c-peptide becomes undetectable in most.
- Latent Autoimmune diabetes should be considered in lean people with type 2 diabetes and in those with a raised BMI but rapid, excessive weight loss & is confirmed by significant autoantibody levels and low serum / urinary c peptide.
- It is good practice to revisit the diagnosis of type of diabetes if clinical course in not following expectation.

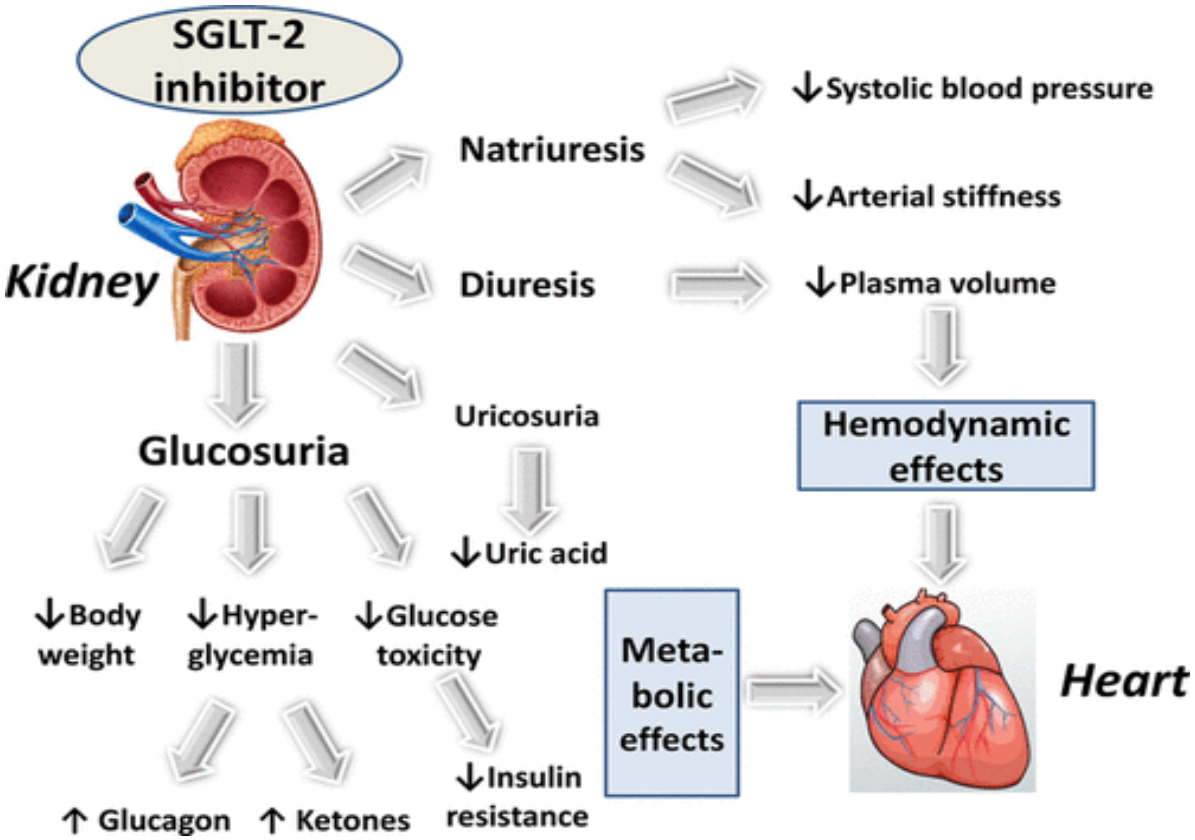
Why do we need any more treatment options in people with type 2 diabetes?

- An important goal of diabetes treatment is to prevent or delay both macro and microvascular complications associated with the condition.
- Setting HbA_{1c} targets and achieving good glycaemic control remains a crucial part of type 2 diabetes management and will help alleviate symptoms of marked hyperglycaemia as well as reduce risk of microvascular complications. However, the effect of improving blood sugar control to reduce cardiovascular risk is less certain.
- 50% of people with diabetes die from cardiovascular disease and increased mortality seen in type 2 diabetes has been strongly attributed to diabetic kidney disease.
- Therefore, drugs with robust evidence of reducing cardiovascular and renal morbidity and mortality in people with type 2 diabetes are needed.
- In the past, there has been a lack of drugs used in the management of type 2 diabetes that have such evidence.
- A number of treatment options are associated with unwanted side-effects such as hypoglycaemia and weight gain. Efficacious drugs not associated with such side effects are also highly desirable.

What are SGLT-2 inhibitors?

- SGLT-2 inhibitors are an established class of anti-diabetic drugs which act by preventing the absorption of glucose and sodium, mainly from the proximal renal tubule in the kidney. Glucose and sodium are therefore lost in urine. This results in decreasing the blood glucose level, weight loss, an osmotic diuresis and a drop in BP.
- These drugs have been 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 patients.

Cardiovascular and renal effects of SGLT-2 inhibitors



André J. Scheen. Circulation Research. Cardiovascular Effects of New Oral Glucose-Lowering Agents, Volume: 122, Issue: 10, Pages: 1439-1459, DOI: (10.1161/CIRCRESAHA.117.311588)

What are the benefits of using SGLT-2 inhibitors in people with type 2 diabetes?

- Strong evidence for reducing risk of major cardiovascular, renal and heart failure events (see table 1- evidence differs for different agents within the class)
- Reduction in HbA_{1c}
  - up to 10 mmol/mol with some agents, dependent on starting HbA_{1c} level and eGFR
- Low incidence of hypoglycaemia
  - The mechanism of action means that their effect is proportional to the blood glucose
- Weight loss (up to 3 Kg)
  - With a significant effect to reduce visceral fat
- Reduction in systolic blood pressure
  - approx. 3-5mmHg
- Reduction in risk of major adverse CV events in patients with established CV disease*
  - Reduction in risk of major renal events*
  - Reduction in risk of hospitalisation for heart failure*

**Evidence varies for different agents. Please refer to table 1 for further information.*

Table 1. Major SGLT-2 Inhibitor Trials- Summary of Outcomes

(Results are from separate trials with different designs and populations- direct comparisons should not be made)

	Cardiovascular Outcome Trials				Renal Outcome Trial	Heart failure Outcome Trial
	CANVAS PROGRAM Canagliflozin	DECLARE TIMI-58 Dapagliflozin	EMPA-REG OUTCOME Empagliflozin	VERTIS-CV Ertugliflozin	CREDENCE Canagliflozin	DAPA-HF Dapagliflozin
Baseline patient characteristics	65% established CVD; 35% risk factors for CVD	40% established CVD; 60% risk factors for CVD	All established CVD	All established CVD	All established Diabetic Kidney Disease	All HFrEF class II-IV (45% T2DM; 55% no diabetes)
Major adverse CV event (MACE)	★ ↓14%	↔	★ ↓14%	Not yet published ↔	★ ↓20%	
CV death and hospitalisation for heart failure	↓22%	★ ↓17%	↓34%	Not yet published ↔	★ ↓31%	★ ↓25%
Major adverse renal events	↓47%	↓47%	↓39%	Not yet published ↔	★ ↓30%	↔
Hospitalisation for heart failure	↓33%	↓27%	↓35%	Not yet published	★ ↓39%	↓30%
CV death	↔	↔	★ ↓38%	Not yet published ↔	↔	↓28%

CVD: Cardiovascular disease; HFrEF: Heart failure with reduced ejection fraction; T2DM: Type 2 diabetes mellitus; HF: Heart failure

★ = CONFIRMED SIGNIFICANT RISK REDUCTION IN PRIMARY OUTCOME TRIAL
GREEN = SIGNIFICANT RISK REDUCTION AS EXPLORATORY OUTCOME
YELLOW = NO SIGNIFICANT REDUCTION/ NEUTRAL EFFECT
GREY = OUTCOME NOT STUDIED

Table 2. Summary of Licenced Indications and Recommended Doses of SGLT-2 Inhibitors in Type 2 Diabetes

		Dose Adjustment Recommendations as per Kidney Function			
SGLT-2 Inhibitor	Licenced Indications	eGFR > 60	eGFR 45-59	eGFR 30-44	eGFR < 30
Canagliflozin	Adults with insufficiently controlled T2DM*	Initiate 100mg; titrate to 300mg if required	Initiate/continue with 100mg only	Initiate /continue with 100mg only if albuminuria > 30mg/mmol at initiation	Continue established treatment with 100mg but do not initiate. Stop if dialysis/transplant
Dapagliflozin	Adults with insufficiently controlled T2DM*	Initiate 10mg	Continue with 10mg but do not initiate	Not recommended	Not recommended
Empagliflozin	Adults with insufficiently controlled T2DM*	Initiate 10mg; titrate to 25mg if required	Continue with 10mg only but do not initiate	Not recommended	Not recommended
Ertugliflozin	Glycaemic control only	Initiate 5mg. Titrate to 15mg if required	Continue with 5mg or 15mg but do not initiate	Not recommended	Not recommended

eGFR: estimated glomerular filtration rate (ml/min/1.73m^2); T2DM: type 2 diabetes mellitus

GREEN = INITIATE
YELLOW = CAN INITIATE IN CERTAIN CIRCUMSTANCES
ORANGE = NO INITIATION BUT CAN CONTINUE ESTABLISHED TREATMENT
RED= TREATMENT NOT RECOMMENDED

In appropriate high-risk patients, a decision to treat with an SGLT-2 inhibitor to reduce risk of cardiovascular (CV), kidney and heart failure events should be considered **independently** of HbA_{1c}.

- Canagliflozin and Empagliflozin have label indication for reducing major adverse CV events.
- Canagliflozin, Dapagliflozin and Empagliflozin have shown reduction in hospitalisation for heart failure and to reduce chronic kidney disease progression in CV trials.
    - Canagliflozin has primary renal outcome data and is licensed for the treatment of Diabetic Kidney Disease in type 2 diabetes
    - Dapagliflozin has primary heart failure outcome data

Further trial results in areas of chronic kidney disease and heart failure are coming which may impact licensed indications in future. Please refer to current SmPC for individual drug for latest information on licenced indications and dose adjustment recommendations.

What are the potential adverse reactions with SGLT-2 Inhibitors in type 2 diabetes

Table 3. Common adverse reactions

Adverse Reaction	Frequency	Notes
Genital Mycotic Infections	Common/ Very Common	Males and females. Provide genital hygiene advice. Most cases can be treated with topical antifungals
Increased urination	Common	Increased frequency and/or increased volume
Urinary-tract Infections	Common	In recent large trials, any increase in risk was small and non-significant
Volume-depletion side-effects (thirst, postural dizziness, hypotension, dehydration…)	Common/ Uncommon (varies with agent)	Caution in frail/elderly. Encourage patients to drink plenty of fluids

Frequency categories
Very common: ≥ 1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1000 to <1/100
Rare: ≥1/10,000 to < 1/1000

Table 4. Uncommon but serious adverse reactions

Adverse Reaction	Frequency	Notes
Diabetic Ketoacidosis (DKA)	DKA: event rate <1/1000 in SmPC (between 0 and 2 additional events/1000 person- years in RCTs); real life events may be higher	•Counsel patients on risk factors, signs and symptoms of DKA •Temporarily stop drug in acute illness or pre-major surgery •Caution if other risk factors for DKA present •Avoid if history of DKA
Amputation	Amputation: event rate <1/100 in SmPC (between 0 and 3 additional events/1000 person-years in RCTs); real life events may be lower	•Caution with all SGLT-2 inhibitors in patients with risk factors for amputation •Encourage routine preventative foot care; regular foot checking •Advise patients to report wounds, discoloration or tender/painful feet •Consider stopping therapy if significant foot problems arise such as infection or skin ulcers

Necrotising Fasciitis (Fournier's Gangrene): Post-marketing reports have been reported (6 yellow card reports in >500,000 patient years. Recent large trials have not shown any increase in risk. Patients should be advised to seek urgent medical attention if they experience fever/malaise along with pain, tenderness or redness in the genital or perineal area.

Selecting the right patient: Who is likely to benefit most from SGLT-2 Inhibitor treatment?

- Adults above 18 years with type 2 diabetes and 1 or more of the following:
  - Established/ high risk of cardiovascular disease*
  - Chronic kidney disease with albuminuria*
  - History of heart failure*
  - Inadequate glycaemic control with need to minimise hypoglycaemia
  - Inadequate glycaemic control with need to minimise weight gain/ encourage weight loss
- Patients with a clear understanding of the risks associated with SGLT-2 inhibitors and how to reduce those risks.

* Please refer to table 1 for evidence of benefit for individual agents.

How to reduce the risk: People in whom SGLT-2 inhibitors should be prescribed with caution or avoided

Use with caution in the following situations:
Person adhering to a ketogenic diet
BMI under 25kg/m^2
Person considered at high risk of acute effects of hyperglycaemia such as dehydration due to non-adherence to medication
Person with very high level of HbA_{1c} >86 mmol/mol (~10% in old HbA_{1c} units)
People diagnosed with or at risk of frailty
Cognitive impairment
On chronic oral steroids
Avoid in the following situations:
Past history of diabetic ketoacidosis
Eating Disorder
eGFR lower than allowed in the up-to-date licensing of the medication being considered
Person with excess alcohol consumption or IVDU
Unwell person (acute medical illness including COVID-19, surgery or planned medical procedure)
Any diagnosis or suspicion of diabetes due to other causes, including type 1 diabetes*, latent autoimmune diabetes (LADA), other genetic causes of diabetes, known pancreatic disease or injury, or people who rapidly progressed to needing insulin within one year of diagnosis.
Pregnant, breast feeding, female in the child bearing years and sexually active without contraception
Age <18
Suspected or possible type 1 diabetes except under specialist supervision (dapagliflozin 5mg only)*
In-patient with acute vascular event who is not stable

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

*Only dapagliflozin 5mg is licensed for use in type 1 Diabetes in certain circumstances and should be initiated and supervised by a specialist. Sotagliflozin (SGLT-1+2 inhibitor) 200 mg is also approved by NICE for similar circumstances but not currently available in the UK.

What to do when initiating SGLT-2 inhibitors- Information for the Patient

- Treatment with SGLT-2 inhibitors should be initiated only after an educational session with the person
  - The educational session should include information on:
    - Benefits of taking SGLT-2 Inhibitors
    - Common side-effects- thrush and ↑ urination volume and/or frequency.
      - Encourage good genital hygiene; most cases of thrush can be treated with OTC topical antifungals
      - Immediately report any pain or redness in genital area with accompanying fever
    - Drink plenty of fluids to avoid dehydration
    - Risks, signs and symptoms of DKA (see next section)
    - Encourage good foot care- check feet regularly; take measures to avoid damage to feet and report wounds, discolouration or tender/painful feet to the healthcare professional.

How to reduce the risk: educate the patient about sick day rules

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 > 0.6 then attend the local emergency department immediately for testing for possible DKA.
- Take half glass of milk, fruit juice, yogurt, soups (not clear soup) 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!
- Urine glucose is not reliable as SGLT-2 inhibitors reduce their excretion.
- Some medications are not good when you are not well (see next section)

Useful information about DKA for people with diabetes

Advise to people with type 2 diabetes taking SGLT-2 inhibitors

- DKA is an uncommon but serious side-effect characterised by the build-up of acidic chemicals in the blood called ketones.
- Illness, infections, starvation, ketogenic diet, excessive exercise, alcohol, surgery, illicit drugs, 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 (see next section).
- If ill with diarrhoea, vomiting or fever and unusual drowsiness- stop drug and don't restart until feeling better and eating/drinking fluids normally.

- Suspect DKA if you have nausea, vomiting, pain abdomen, stupor, fatigue and difficulty breathing.
- Do not rely on urine ketone but test your capillary ketones or present for blood ketone testing at your local hospital.

What to do when initiating SGLT-2 inhibitors- Information for the prescriber

- Document completion of the education session and the advice on who to contact if not feeling well
- Glucose lowering medications that may cause hypoglycaemia, such as insulin and sulphonylureas, should be reviewed and the dose possibly reduced when SGLT-2 inhibitors are started, particularly if individual's HbA_{1c} is at target when initiated
- Review diuretic and anti-hypertensive therapy periodically if hypertension improves

How to reduce the risk: Educate the health professionals

- People with type 2 diabetes taking SGLT-2 inhibitors are at higher risk (1/1000 to 1/10000) of developing diabetic ketoacidosis
    - Suspect DKA in presence of nausea, vomiting, abdominal pain, difficulty breathing, confusion, fatigue, sweeting smell and drowsiness
        - Confirm ketosis by measuring **blood** ketone (>0.6 mmol/L)
        - Confirm acidosis with a venous bicarbonate (<18 mmol/L) or venous pH (<7.38).
        - Glucose levels may be normal
    - If confirmed to have ketoacidosis (regardless of the glucose level) then start a fixed-rate intravenous insulin infusion & IV fluids as per JBDS guidelines. Concomitant additional glucose infusion may be required to avoid hypoglycaemia.

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

- Diuretics : 'water pills' – e.g. frusemide, bendrofluazide, indapamide, bumetanide
- ACE inhibitors: names ending in 'pril' e.g. ramipril, lisinopril, perindopril
- ARBs : names ending in 'sartan' e.g. candesartan, losartan, irbesartan
- Metformin
- NSAIDs : anti-inflammatory pain killers e.g. ibuprofen, naproxen , diclofenac
- GLP1 analogues (injectable): names ending in 'tide' e.g. exenetide, liraglutide, dulaglutide, lixisenatide, semaglutide
- SGLT-2 inhibitors : names ending in 'flozin' e.g. canagliflozin, dapagliflozin, empagliflozin, ertugliflozin

Courtesy:

East and North Hertfordshire NHS
ENHIDE
East and North Herts Institute of Diabetes and Endocrinology

When to suspend treatment with SGLT-2 inhibitors?

- Suspend SGLT-2 inhibitors in the following circumstances:
  - -Acute medical admission including COVID-19
  - -Admission for elective surgery or procedure requiring starvation
  - -Vomiting
  - -Dehydration
- Restart only AFTER patient has been eating normally for AT LEAST 24 hrs. AND no longer acutely unwell
- Alternative diabetes treatment may be required in the interim