



**Educating
Representing
Supporting**

SGLT-2 inhibitors in people with type 2 diabetes:

An educational resource for health professionals

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Contents

Introduction	3
What does this course cover and what it does not cover	3
What are the types of diabetes	4
Type 1 diabetes	
Type 2 diabetes	
How is diabetes diagnosed?	
Why do we need any more treatment options in people with type 2 diabetes?	
What are SGLT inhibitors?	6
Preparations and licences in the UK	
Benefits of using SGLT inhibitors in people with type 2 diabetes	
Which SGLT-2 inhibitors to use?	
Risks of SGLT inhibitors in type 2 diabetes	
Rare side effects reported with SGLT-2 inhibitors	
How to reduce the risk?	8
Select the right person and an appropriate setting for SGLT-2 inhibitors	
Avoid the wrong person and the wrong setting for SGLT-2 inhibitors	
SGLT-2 initiation: The patient journey	9
What to do before you start SGLT-2 drugs	
What to do when you start SGLT-2 inhibitors	
What to monitor when continuing SGLT-2 therapy	
When to suspend treatment with SGLT inhibitors	
When to stop SGLT-2 inhibitors	
How to reduce the risk: Sick day rules	10
Educate the patient about sick day rules	
Diabetes Medicine to Stop Temporarily when not well (DAMN GlucoSe drugs)	
How to reduce the risk: Education	11
Educate the patient	
Educate the health professionals	

Introduction

Two of ABCDs core objectives are to ensure the highest quality of care for patients 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 which patients 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 patients 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.

We hope that this document will help 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 maximizing the benefits and minimizing harm.

ABCD Executive committee

What does this course cover and what it does not cover

By the end of this course you should understand

- ✓ What are the main types of diabetes and why accurate diagnosis matters
- ✓ What are SGLT-2 inhibitors and their mode of action
- ✓ What are the benefits of using SGLT-2 inhibitors in people with type 2 diabetes
- ✓ What are the risks associated with the use of SGLT inhibitors in people with type 2 diabetes
- ✓ How can we minimize the risk and utilize SGLT-2 inhibitors for the benefits of people with type 2 diabetes

The course will not cover

- ✗ Detailed theoretical aspects for which links will be provided
- ✗ Detailed clinical trial data
- ✗ Any new licenses that might come up after the preparation date of the course
- ✗ Use of SGLT-2 inhibitors in Type 1 diabetes



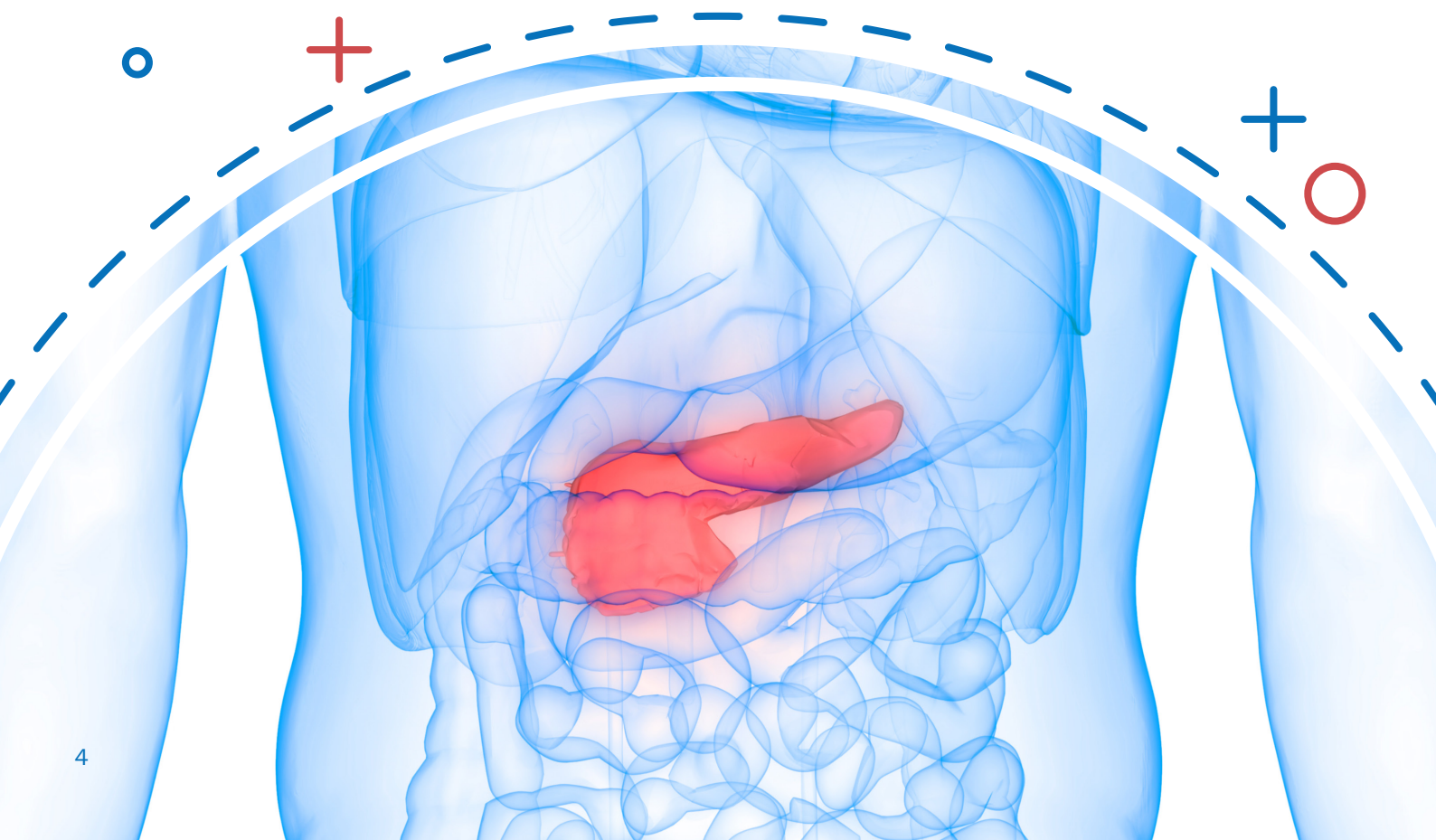
What are the types of diabetes

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 auto 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 will 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. The proportion of these components can be different in different patients.
- This type of diabetes commonly results because of resistance to insulin due to excess body fat – both externally and internally.
- This is initially treated with diet and exercise. Oral medications are often required (classes include: metformin, sulphonylurea, gliptins, pioglitazone, & sodium glucose transporter-2 inhibitors). As the disease progresses control may require injectable treatment (Glucagon Like Peptide-1 analogues and insulin)
- Some people with apparent type 2 diabetes may actually have a slowly progressing type 1 diabetes (late onset autoimmune diabetes in adults (LADA), with positive GAD 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 reasons
- SGLT-2 inhibitors are associated with a small but increased risk of ketoacidosis in Type 2 diabetes. Given the large number of people with type 2 diabetes, this may actually translate into a significant number of extra cases hence the need for education



How is diabetes diagnosed?

- Diabetes is diagnosed by a single fasting capillary blood glucose ≥ 7 mmol/L or an HbA1c ≥ 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 & is confirmed by significant autoantibody levels
 - In people with apparent type 2 diabetes but unusual profile (lean, history of DKA, widely varying CBGs, rapid escalation in treatment requirement), consider doing auto antibodies
- It is good practice to revisit the diagnosis of type of diabetes if things are not evolving as clinically expected

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



With the current management strategies only 40% of people with type 2 diabetes achieve all of the NICE recommended targets for glucose, BP and cholesterol (National Diabetes Audit)



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



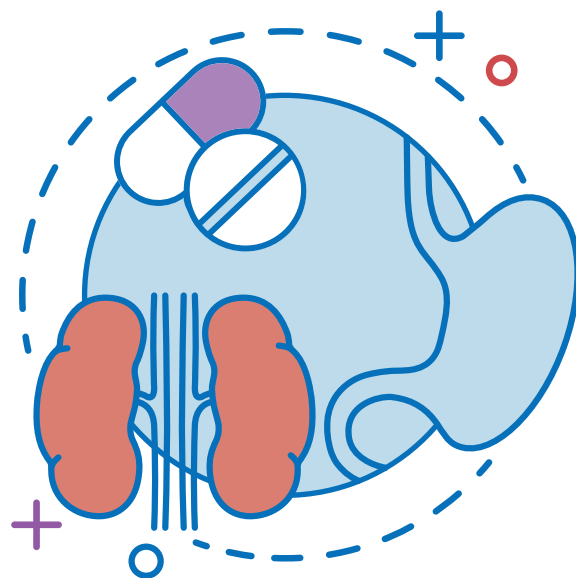
Very few diabetes medications (Metformin, Pioglitazone and GLP-1 analogues) have evidence to show that they reduce cardiovascular disease and mortality in people with type 2 diabetes



Many people either do not tolerate, would not accept or have contra-indications to the available anti-diabetic drugs

What are SGLT inhibitors?

- Sodium glucose cotransporter-2 inhibitors are an established class of anti-diabetic drugs which act 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 BP
- These agents act selectively on SGLT-2 receptors (found in kidneys) but may also interact with SGLT-1 receptors which are located in the gastro intestinal 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 patients



Preparations and licences in the UK

Name of the SGLT inhibitor	Licensed in
SGLT-2 inhibitors:	
Dapagliflozin	Type 1 and Type 2 diabetes
Canagliflozin	Type 2 diabetes
Empagliflozin	Type 2 diabetes
Ertugliflozin	Type 2 diabetes
SGLT 1+2 inhibitors:	
Sotagliflozin	Neither

Benefits of using SGLT 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 the blood glucose
- Weight loss (up to 3 Kg)
 - With a significant effect to reduce visceral fat
- Reduces progression of chronic complications affecting cardiovascular system and kidneys (see next pages)

Which SGLT-2 inhibitors to use?

The trials have been done in different types of population. Dapagliflozin's trial included patients with no previous cardiac events, Emagliflozin patients had established cardiovascular disease and canagliflozin patients had chronic kidney disease. The cardiac and renal benefits appear to be a class effect but are more pronounced in people with renal impairment

	Composite renal outcome/1000 pt.yrs		Cardiac outcomes (MACE/1000 pt.yrs)	
	event rate, placebo	RRR (%)	event rate, placebo	RRR (%)
EMPA REG	6.3, 11.5	46	37.4, 43.9	14
CANVAS	5.5, 9.0	40	26.9, 31.5	14
DECLARE	3.7, 7.0	47	22.6, 24.2	7
CREDESCENCE	43.2, 61.2	30	38.7, 48.7	20

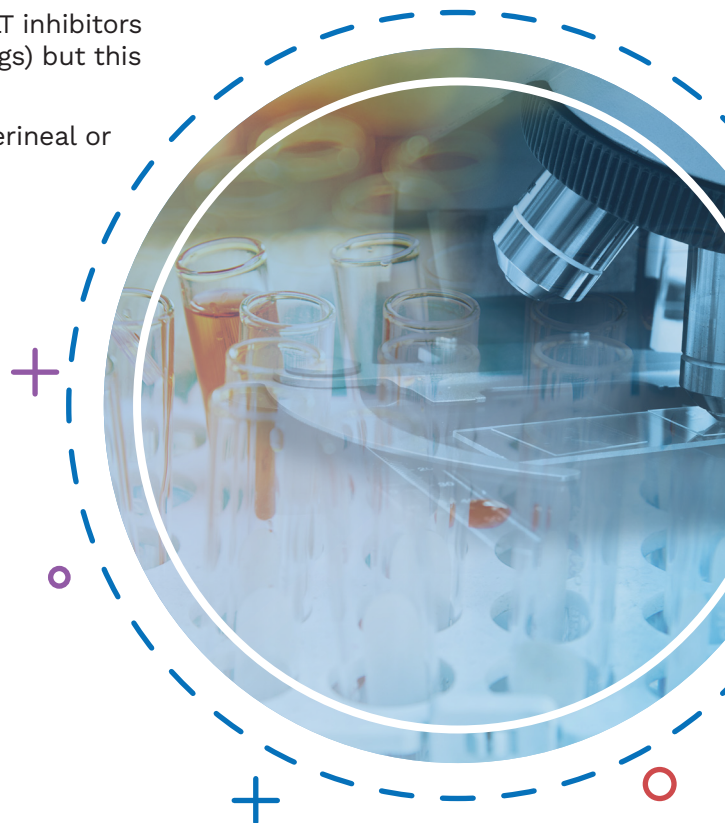
Risks of SGLT inhibitors in type 2 diabetes

risk	DECLARE (Dapagliflozin)	Canvas (Canagliflozin)	EMPA_REG (Empagliflozin)	CREDESCENCE (Canagliflozin)
Genital infections Males	✓	✓	✓	✓
Genital infections Females	✓	✓	✓	✓
UTI		✓		✓
Fracture		✓		
Amputation		✓		
DKA	✓	✓	✓	✓

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 & IV antibiotics



How to reduce the risk?

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

 <p>Age above 18 years</p>		<p>Inadequate glycaemic control in spite of optimal current treatment and / or at high risk of cardiac and renal adverse outcome</p>
 <p>eGFR >60 ml/min/1.73 m² (a lower cut off may be recommended for an individual by a diabetes specialist)</p>		<p>BMI >27 kg/m² although diabetes specialists may use them in people with a lower BMI for potential cardiac or renal benefits</p>
 <p>People with microalbuminuria or macroalbuminuria</p>		<p>High risk of hypoglycaemia with alternative treatments</p>
<p>Education:</p> <ul style="list-style-type: none"> • Willing and able to complete an educational course about the risks of SGLT-2 inhibitors and how to reduce those risks • Able & willing 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 &/or blood ketones are >0.6 mmol/L. Blood ketones are more reliable 		

Avoid the wrong person and the wrong setting for SGLT-2 inhibitors

- Person adhering to a ketogenic diet, with an eating disorder or a BMI <27kg/m² except by a specialist in diabetes
- eGFR <60 ml/min/1.73 m² except by a specialist
- Person at risk of developing glucose related complications (dehydration, poor compliance to treatment, frequent missed medications)
- Person with past history of ketoacidosis
- Unwell person (acute medical illness, surgery or planned medical procedure)
- Person with excess alcohol consumption or IVDU
- Pregnant, breast feeding, female in the child bearing years and sexually active without contraception
- Person with HbA1c >86 mmol/mol (~10% in old HbA1c units)
- Frail and elderly
- 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
- Genetic diabetes
- On loop diuretics unless this is discussed carefully with a specialist and cardiac benefits outweigh the risk of dehydration
- On steroids
- Age <18
- Seek advise from the local diabetes team if unsure about the benefits and risks

SGLT-2 initiation: The patient journey



What to do before you start SGLT-2 drugs

- Treatment with SGLT inhibitors in people with type 2 diabetes should be initiated only after an educational session with the person
- The educational session should include information on
 - how SGLT inhibitors work
 - sick day rules
 - the risk of diabetic ketoacidosis
 - when to start and stop SGLT drugs
 - signs and symptoms of early DKA
- 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 do the blood ketones when a person with diabetes is not well



What to do when you start SGLT-2 inhibitors

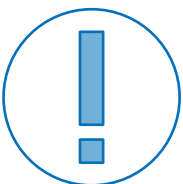
At initiation

- Issue an alert card to people with type 2 diabetes and their carers
- Document completion of the education session 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 inhibitors are started, to avoid hypoglycaemia
- Consider checking U and Es before and after 1 week of starting SGLT-2 inhibitors if the person is taking diuretic or is at risk of dehydration
- 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 feeling unwell
- Check that the person has an up to date alert card
- Reinforce education about DKA periodically



When to suspend treatment with SGLT inhibitors

Suspend SGLT inhibitors in the following circumstances:

- Acute medical admission
- Admission for elective surgery or procedure requiring starvation
- Vomiting
- Dehydration

Restart the treatment when the potential 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



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 resolved

How to reduce the risk: Sick day rules

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 $> 0.6\text{mmol/L}$, 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 SGLT2 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 Medicine to Stop Temporarily when not well (DAMN GlucoSe drugs)

- Diuretics: 'water pills' – e.g. frusemide, bendroflumethiazide, 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. exenatide, liraglutide, dulaglutide, lixisenatide
- SGLT inhibitor : names ending in '**flozin**' e.g. canagliflozin, dapagliflozin, empagliflozin, ertugliflozin

How to reduce the risk: Education

Educate the patient

Advice to people with type 2 diabetes taking SGLT 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 for blood ketone testing at your local hospital
- Useful information from the manufacturer at www.goto.az/forxiga-hcp-uk



Educate the health professionals

- People with type 2 diabetes taking SGLT 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 & IV fluids as per JBDS guidelines. Concomitant additional glucose infusion may be required to avoid hypoglycaemia





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