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# UK Kidney Association Clinical Practice Guideline: Sodium-Glucose Co-transporter-2 (SGLT-2) Inhibition in Adults with Kidney Disease

## Lay Summary

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Final version: 18 October 2021  
Review date: 18 October 2026

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See appendix for list of previous versions/revisions and working group affiliations.

**The full guideline is available at:**

<https://ukkidney.org/health-professionals/guidelines/guidelines-commentaries>

## Section 6: Lay summaries and patient information leaflets

This section is designed for patients and carers and for healthcare workers who wish to obtain a lay summary of this guideline. The section contains a one-page executive lay summary followed by a full lay guideline summary. The section also contains examples of patient information leaflets that can be used when initiating sodium-glucose co-transporter-2 (SGLT-2) inhibitors for people with diabetes and also for those without diabetes. It is anticipated that by providing a clear description of the contents of this guideline there will be greater understanding of the benefits and the risks of using SGLT-2 inhibitors for people with chronic kidney disease (CKD).

### 6.1 LAY EXECUTIVE SUMMARY

CKD is a significant medical problem affecting anything between 6 to 11% of the UK adult population. It is a disorder in which the kidneys are damaged causing a reduction in their ability to clean the blood. If the CKD is progressive (which means it slowly deteriorates over time) the person suffering this disorder is at risk of kidney failure and the need to start a treatment to replace their kidney function in the form of either dialysis or kidney transplant. Importantly, as well as the issue of suffering kidney failure, people with CKD have a much higher chance of suffering cardiovascular diseases in the form of heart attacks, heart failure, strokes and damage to the blood supply to the legs and feet.

The treatment of CKD has been centred around control of blood pressure, the reduction in other cardiovascular risk factors (for example, stopping smoking and managing cholesterol) and the use of a group of medications known as angiotensin-converting enzyme inhibitors (or ACE inhibitors - the names of which usually end with “-pril”) or angiotensin-II receptor blockers (ARBs - the names of which usually end with “-sartan”). However, even with the use of these interventions, people with CKD still suffer considerable harm related to their underlying kidney disorder.

The SGLT-2 inhibitors is the name given to a group of medications that were initially developed to treat people with diabetes by providing them with better control of their blood glucose (sugar) and can be recognised by the drug name ending in “-gliflozin”. As part of the developmental program for this group of medications, each of the individual SGLT-2 inhibitors underwent a large study to ensure that, not only are they effective in helping people with diabetes reduce blood glucose, but that they also did not cause any increased risk of cardiovascular disease. The findings from these large studies, which have been undertaken and reported over the last six years, has had a significant impact on the care of people with heart disease and CKD. This is because all of these medications have been shown to have unexpected beneficial effects in relation to reducing the rate of progression of CKD and reducing the risk of heart failure complications. In relation to CKD, this benefit was seen even though the study participants were already being treated with current best practice and even in this circumstance the SGLT-2 inhibitor provided very significant additional benefit.

As a result of these studies and the further specific studies directly examining the effects of SGLT-2 inhibitors in people with kidney disease and heart failure, it is recognised that these medications need to be offered to people who are likely to experience benefit from taking this medication. It is the purpose of this guideline to review the evidence related to the benefits and the potential adverse risks of SGLT-2 inhibitors, in order to provide clear recommendations as to which people with CKD are most likely to benefit from this medication, and in order to encourage the healthcare system to ensure that those individuals receive this beneficial treatment as speedily as possible.

All medical interventions can have side effects and for SGLT-2 inhibitors, we are clear as to the nature of the side effects and their frequency. These medications have a low risk of side effects but it is also possible to reduce that risk further by making careful choices about which individuals receive the medications and, most importantly, informing people prescribed SGLT-2 inhibitors of the side effects themselves and how to take

specific actions to reduce the risk of coming to any harm by taking these medications. It is to be remembered that people with CKD should only be offered an SGLT-2 inhibitor if the benefits significantly outweigh the risks. Therefore, this guideline also provides information around the side effects of SGLT-2 inhibitors and how those side-effect risks can be reduced.

## **6.2 FULL SUMMARY OF GUIDELINE**

### **6.2.1 Introduction**

Between 6 to 11% of the adult population of the United Kingdom is thought to have CKD. These individuals are not just at risk of progressive decline of kidney function resulting in them suffering symptoms related to poor kidney function and requiring them to be considered for end-stage kidney disease treatment (dialysis or transplant) but they also have a greatly increased risk of cardiovascular disease (heart attacks, heart failure, strokes and narrowing of the arteries to the legs termed peripheral vascular disease). This represents a significant burden for both the health economy of the United Kingdom and, more importantly, for the individuals themselves.

Treatment for CKD aims to halt or slow down progression of declining kidney function and reduce cardiovascular risk. These treatments have up until now been centred on a group of medications known as the inhibitors of the renin angiotensin system, which is a system that has a controlling influence on blood pressure and fluid status. In addition, control of blood pressure, blood glucose and blood lipids (or fats) remain key to reducing progression of CKD and the poor cardiovascular outcome. However, these treatments are only partially effective and there has been a pressing need to identify new treatments to help the large number of people with CKD avoid the requirement for dialysis or transplant, or from suffering cardiovascular harm.

SGLT-2 inhibitors are medications that were initially developed as a treatment for diabetes because they effectively reduce blood glucose (sugar). New research has found that these medications provide significant benefit to people with CKD both in terms of reducing decline in kidney function and reducing the poor cardiovascular outcomes people with CKD suffer.

The purpose of this guideline document is to produce practical advice for clinicians caring for people with kidney disease in relation to when and how to use SGLT-2 inhibitors.

It is the purpose of this section to provide lay individuals a greater understanding of the nature of SGLT-2 inhibitors, the benefits they offer, in which individuals they are most likely to be effective and to obtain a greater appreciation of the risks of these medications and how these risks can be reduced.

### **6.2.2 SGLT-2 inhibitors: what are they?**

The kidneys function to clean the blood and control the concentration of many constituents of the blood. They do this by “filtering” the blood through individual filtering units (called glomeruli, of which there are approximately 1 million within each kidney in healthy adults) and thereafter the filtered fluid or “filtrate” passes into small pipes or “tubules” within the kidneys where its content is adjusted. The filtrate eventually becomes the urine, which is passed from the kidneys to the bladder and removed when we pass urine.

Glucose is freely filtered from the blood but normally all of this filtered glucose is returned back into the blood within the early part of the tubule of the kidneys called the proximal tubule. This return is undertaken by co-transporter proteins called SGLT-2 which sit in the wall of the proximal tubule. Every person has a maximal amount of glucose that their kidney can reabsorb and in individuals who have high amounts of

filtered glucose (typically in people with diabetes) the SGLT-2 co-transporters become flooded and residual glucose is lost in the urine (and in fact it is the resulting sweet urine which gives diabetes mellitus its name).

SGLT-2 inhibitors are medicines that block the activity of the SGLT-2 co-transporter and by blocking this protein's actions, SGLT-2 inhibitors cause a loss of glucose into the urine and is the reason these medicines have been developed as a treatment to help reduce blood glucose in people with diabetes.

In addition to SGLT-2 co-transporters there are, within the body, a group of related proteins called SGLT-1 co-transporters. These proteins are found more predominantly in the gut where they are involved in the uptake of glucose from the food into the bloodstream. They are also found, albeit to a much lesser extent, in the kidney tubules where they make only a very minor contribution to total glucose reuptake in the kidneys.

### **6.2.3 Benefits of SGLT-2 inhibitors**

All new medications being introduced to treat diabetes are required to demonstrate that not only do they improve blood glucose control but they do not have an adverse effect on cardiovascular outcomes in people with diabetes. This is because there has been an example of a previous medication which provided significant benefit in relation to reducing blood glucose but at the same time was associated with an increased risk of heart attacks. Therefore, all new medications being introduced to treat diabetes are required to undergo what are termed cardiovascular outcome trials.

All the major SGLT-2 inhibitor medications have now reported on their cardiovascular outcomes and the findings from these studies has provided significant information in relation to additional benefits that these medications provide.

It was already known that these medications have benefits over and above their glucose reducing effect, which included a reduction in weight of around 2 to 4 kg and a small reduction in blood pressure. These additional effects were believed to result from the loss of salt in the urine (called the diuretic effect) and the loss of calories in the form of glucose within the urine. In addition to these effects, the cardiovascular outcome studies identified significant benefits in relation to reducing cardiovascular harm, most particularly in relation to reducing admission to hospital with heart failure and in reducing the progression of CKD.

### **6.2.4 How this guideline was developed**

This guideline has been developed by a writing group containing a broad range of healthcare clinicians with experience in kidney disease, diabetes and primary care who have worked together to review the evidence for the use of SGLT-2 inhibitors in people with kidney disease. In addition writing group has also included people with kidney disease to provide the patients' perspective. As a group, they have followed good practice in relation to reviewing the evidence and using that evidence to provide recommendations for the use of SGLT-2 inhibitors in people with CKD.

In generating the recommendations, the guideline writing committee gave the greatest priority to the results of trials that were most effective at discriminating both beneficial and adverse effects of SGLT-2 inhibitors. These were trials comparing people who were allocated to take SGLT-2 inhibitors at random (like a toss of a coin) to those who were allocated to take a dummy pill (known as the placebo group) and containing large (greater than 1000) numbers of participants.

From this evidence base, the guideline writing committee has developed summaries of evidence and proposed draft recommendations which were discussed at a consensus meeting of all members before final recommendations were made.

When making recommendations, the evidence that supported each recommendation was graded according to the UK Kidney Association's recommended grading system, which defines the level of evidence and the quality of evidence for each recommendation. Broadly, a grade 1 recommendation is a strong recommendation while a grade 2 recommendation is a weaker one. In addition, there is a letter designating the quality of the evidence that supports that recommendation.

Where the evidence to support a recommendation is strong (grade 1) we use the term "recommend" and where it is weaker (grade 2) we use the term "suggest".

We have also subdivided our recommendations into the following categories:

- a) recommendations for use which defines who should be offered SGLT-2 inhibitors
- b) recommendations for implementation which defines how SGLT-2 inhibitors should be used
- c) recommendations for clinical research which defines where there is ongoing clinical uncertainty
- d) recommendations for audit which defines how to demonstrate effective implementation of grade 1 recommendations

### **6.2.5 Benefits of SGLT-2 inhibitors: cardiovascular benefits**

The cardiovascular outcome trials identified the fact that SGLT-2 inhibitors had a small effect on reducing the incidence of heart attack which varied between the individual SGLT-2 inhibitors. However, all the trials demonstrated a significant reduction in heart failure hospitalizations that pointed to a significant benefit in people with heart failure. This benefit has now been confirmed in studies that have specifically looked at the use of SGLT-2 inhibitors in people with heart failure including people with and without diabetes.

### **6.2.6 Benefits of SGLT-2 inhibitors: kidney protection**

An unexpected and consistent finding from the cardiovascular outcome trials was that individuals treated with SGLT-2 inhibitors as opposed to placebo or dummy medications had improved kidney outcome in terms of a reduction in decline of kidney function, the need to commence treatment for end-stage kidney failure and death due to kidney causes.

These findings have been tested in further studies called CREDENCE and DAPA-CKD which have specifically looked at kidney outcomes in people with evidence of protein in the urine (protein in the urine signifies underlying kidney disease and is a key predictor for future loss of kidney function). In both of these trials, the reduction in risk of adverse kidney events compared to placebo was equivalent to that seen in the cardiovascular outcome trials, confirming benefits of SGLT-2 inhibitors in people with CKD.

### **6.2.7 Separation of glucose from cardiac and kidney benefit**

The benefits of SGLT-2 inhibitors in relation to the improvement in blood glucose control is known to be related to the glomerular filtration rate (GFR). This is a measure of global kidney filtering function and is the measure that progressively reduces as kidney function declines in CKD. A normal GFR should be approximately 90 mL/min/1.73m<sup>2</sup>, but there is a progressive normal decline with ageing. However, excessive decline down to single figures (i.e. less than 10 mL/min/1.73m<sup>2</sup>) is usually an indicator of the need to commence end-stage kidney failure treatment.

As the GFR declines so also does the ability of SGLT-2 inhibitors to improve glucose control in diabetes, such that by the time the GFR has reduced to  $45 \text{ mL/min/1.73m}^2$ , the glucose reducing effect of SGLT-2 inhibitors virtually disappears in people with diabetes treated with these agents. It is for this reason that these medications have not been recommended for use as a treatment for diabetes in people whose kidney function is already deranged because they have CKD.

In both the kidney specific outcome studies and studies looking at SGLT-2 inhibitors in people with heart failure, the benefits in relation to the cardiac and kidney outcomes did not appear to diminish as the kidney function declined, down to at least a GFR of about  $25\text{-}30 \text{ mL/min/1.73m}^2$ .

This separation of the glucose and cardiac and kidney protective effect was exemplified further by the fact that, in the DAPA-CKD study and the heart failure specific studies, SGLT-2 inhibitors were beneficial even in people without diabetes.

### **6.2.8 Identifying individuals where there is benefit in prescribing SGLT-2 inhibitors**

SGLT-2 inhibitors can only be recommended as a treatment if there is sufficient evidence to support that use and this is usually obtained from randomized controlled trials where participants in the trials are split randomly into those given the treatment and those given a dummy treatment. There are now a significant number of trials with SGLT-2 inhibitors that were designed first of all to assess the cardiovascular safety of these medications (cardiovascular outcome trials) as well as trials looking at these medications in people with heart failure and in people with kidney disease.

As these results have emerged, the licences (which determines how the treatment can be prescribed in the UK) for a number of SGLT-2 inhibitors have been broadened to allow the use of that specific SGLT-2 inhibitor for the purpose not just of glucose control, but also as protection against cardiovascular or kidney disease.

In assessing the evidence for benefit, one also needs to be clear about the outcomes that are being measured. For kidney disease there are many different potential outcomes that have been used in previous studies; however, not all of these clearly define outcomes that truly benefit people with CKD. Therefore, determination of benefit of SGLT-2 inhibitors for the purpose of generating recommendations in this guideline is based on real evidence for the reduction in progression of kidney disease which has been measured by the need to commence any form of kidney replacement therapy, death caused by kidney disease and significant reduction in decline in kidney function.

In the major cardiovascular outcome trials of all four of the SGLT-2 inhibitors, kidney effects were monitored and in all of these studies there was a decline in progression of kidney disease, need to commence kidney replacement therapy or death due to kidney disease. However, these effects were not the primary purpose of the studies and therefore there is a risk that the findings could have been identified by chance. Therefore, further studies have been undertaken that have looked primarily at the effect of SGLT-2 inhibitors in people with kidney disease. These studies include:

- 1) CREDENCE which tested the SGLT-2 inhibitor canagliflozin in people with type 2 diabetes and evidence of diabetic kidney disease in the form of some reduction in GFR and the presence of protein in the urine
- 2) DAPA-CKD which tested the SGLT-2 inhibitor dapagliflozin in people with evidence of kidney disease in the form of a reduction in GFR and presence of protein in the urine but, importantly, not just in people with diabetes as a cause for their kidney disease.

Further studies looking at the effect of specific SGLT-2 inhibitors are currently underway and in particular this includes the EMPA-KIDNEY study which will extend the findings of CREDENCE and DAPA-CKD by including people both with and without diabetes, down to a lower level of GFR and people with CKD with much lower, or indeed absent, levels of protein in the urine.

CREDENCE and DAPA-CKD have confirmed the safety findings from the cardiovascular outcome trials and demonstrated significant kidney benefits of SGLT-2 inhibitors in people with CKD. These benefits included clear reduction in progression of diabetic kidney disease by approximately 30 to 50%. Overall, they also reduced occurrences of heart attacks and deteriorations of heart failure in people with CKD. The evidence is strongest for people with diabetes and protein in the urine but DAPA-CKD provided evidence that this benefit also extends to people with CKD without a diagnosis of diabetes, but with some degree of protein in the urine.

Because of these findings this guideline recommends the initiation of SGLT-2 inhibitors in people with kidney disease caused both by type 2 diabetes and other causes down to an eGFR of 25 mL/min/1.73m<sup>2</sup>, if the level of protein in the urine exceeds a urine albumin to creatinine ratio (this is the common way to represent the degree of protein in the urine) of 25 mg/mmol. The guideline highlights that the evidence for this is strongest in people with type 2 diabetes. In addition, the guideline recommends initiation of SGLT-2 inhibitors in people with CKD and a history of heart failure.

Once initiated, this guideline recommends that the SGLT-2 inhibitor can be continued until the individual reaches end-stage kidney disease.

Practically, the SGLT-2 inhibitor that would be utilised would be dependent on the current licence for that individual SGLT-2 inhibitor and whether primary care (general practitioners) are able to prescribe that specific medicine.

### **6.2.9 Groups where there is uncertainty**

As described, it is only possible to recommend SGLT-2 inhibitor treatment for cardiac and kidney benefit in people who were represented in the studies of these medications, and in whom there is clear evidence of benefit.

There are a number of groups of people in whom it is not yet possible to be specific about the cardiac and kidney benefits of SGLT-2 inhibitors.

Currently, this includes people who have CKD caused by the genetically inherited condition called adult polycystic kidney disease and also in people who have specific inflammatory diseases that require the use of powerful medicines to suppress the immune system.

#### ***Type 1 Diabetes Mellitus***

There are two main types of diabetes which include type 1 diabetes (which occurs more usually at a younger age and in which there is loss of the ability to produce insulin) and the much more common type 2 diabetes. Type 2 diabetes usually occurs in the older age group and is related to the ability of insulin to be effective, with the most common reason for this being association with obesity.

Whilst there have been some studies of SGLT-2 inhibitors in type 1 diabetes, these have not been sufficient to make a clear recommendation on the use of SGLT-2 inhibitors in people with type 1 diabetes. There may be benefits in people with type 1 diabetes, but there is a risk of a condition called diabetic ketoacidosis which

is particularly high in people with type 1 diabetes. This means any potential benefits of SGLT-2 inhibitors may be finely balanced with potential risk of harm (more details below).

### ***Heart failure with preserved ejection fraction***

Heart failure has many different causes but broadly is divided into two main groups: those in which there is a reduction in the pumping ability of the heart, which is termed heart failure with reduced ejection fraction, and those where that pumping ability appears preserved but there are other factors that result in the failure of the heart to effectively pump blood around the circulation. This second group is termed heart failure with preserved ejection fraction.

Two large trials have shown SGLT-2 inhibitors provide significant benefit in people with heart failure and reduced ejection fraction, and one recent trial found benefit in heart failure with preserved ejection fraction. A further trial in this population is likely to report in 2022, and this guideline will be updated following the publication of this evidence.

### ***People with functioning kidney transplants***

Whilst it would be appealing to assume that the benefits that SGLT-2 inhibitors provide in relation to reduction in progression of CKD and protection against cardiovascular disease is present in all people with abnormal kidney function, kidney transplant recipients were not included in any of the trials. There is currently insufficient evidence at this time to recommend that people with a kidney transplant should be included in those initiated on SGLT-2 inhibitors. Whilst there are ongoing studies in this area, SGLT-2 inhibitors should only be offered to people with a kidney transplant after careful consideration and discussion between the kidney transplant team and the diabetes teams and with clear discussion undertaken with the individual with the kidney transplant.

#### **6.2.10 Side effects of SGLT-2 inhibitors and how to avoid them**

Every medication has potential to result in adverse events and it is important that these are appropriately understood in order for people to be advised appropriately about the risks of the medication and how it is possible for them to take steps to reduce any harm that could occur from taking a medication.

All people who are being prescribed new medications need information given to them that allows them to make an informed choice as to whether they wish to commence the treatment. This information needs to include a balance between both the risks of the medication and the potential benefit to them as an individual. Furthermore, the information needs to include advice on actions that would reduce the chance of harm coming to them by taking a particular medication.

SGLT-2 inhibitors have been found to have a number of adverse effects that people need to be informed about prior to initiation of this therapy. It is important to also appreciate that the likelihood of suffering an adverse effect may depend on the individual as well as the medication, and this would include factors such as whether they have diabetes, their age and their frailty.

### 6.2.11 Diabetes specific: diabetic ketoacidosis

SGLT-2 inhibition has an effect on the breakdown of carbohydrates and fats, which results in an excess of a group of substances known as ketones. These molecules are not dangerous of themselves, however, if the level of these ketones increases this can result in a dangerous situation in which the blood becomes very acidic which is termed ketoacidosis.

Ketoacidosis is a dangerous complication, seen most particularly in people with type 1 diabetes, but can occur in people with type 2 diabetes and there is evidence that SGLT-2 inhibitors increase the risk of this happening. Diabetic ketoacidosis usually occurs in conjunction with high levels of glucose, however, when it occurs in a person taking an SGLT-2 inhibitor, the excess glucose can be lost in the urine and this dangerous complication can occur in conjunction with normal levels of glucose which has the potential to confuse both the person with diabetes and the healthcare worker assessing the person.

The risk of diabetic ketoacidosis increases in the presence of infection or if the individual becomes dehydrated because of diarrhoea, vomiting or fasting. It also occurs in situations where there is not enough insulin, such as in people with type 2 diabetes who have low levels of their own insulin production and in situations when people who are treated with insulin have their insulin reduced, or even stopped.

A further factor that can be associated with an increased risk of diabetic ketoacidosis in people prescribed SGLT-2 inhibitors is the use of specific diets which are termed “very low carbohydrate” or “ketogenic” diets and which increase the blood levels of ketones (such as the Atkins diet).

Because of their greater risk of suffering diabetic ketoacidosis, people with type 1 diabetes should only be commenced on SGLT-2 inhibitors under strict direction of the diabetes team, and may be offered lower doses.

It is also recognised that there are a group of people with type 2 diabetes who are at greater risk of diabetic ketoacidosis because they have lower levels of insulin. One can identify this group of individuals by features associated with low insulin levels, of which the most important are the rapid requirement for insulin treatment following diagnosis (within one year) and the presence of type 2 diabetes and low body weight. It is recommended that for these people with type 2 diabetes who are at greater risk of diabetic ketoacidosis, SGLT-2 inhibitors should only be initiated after discussion with the diabetes team.

If an individual prescribed SGLT-2 inhibitors develops diabetic ketoacidosis, it is recommended that the SGLT-2 inhibitor should be stopped and that individual should be reviewed by a member of their clinical team to determine whether treatment could be re-initiated in the future. That decision will be dependent on the analysis of the reasons why the diabetic ketoacidosis occurred, and whether with changes to treatment, or better advice on management, the risk of future diabetic ketoacidosis can be significantly reduced. That decision should be discussed between the clinical team and that individual themselves.

Because of the risk of diabetic ketoacidosis, people started on SGLT-2 inhibitors need to be told about diabetic ketoacidosis and in particular the signs and symptoms of this disorder and the importance of seeking immediate medical advice if those symptoms develop.

Perhaps one of the most effective ways of preventing the occurrence of diabetic ketoacidosis is to use what are termed “sick day guidance”. This is where a medication, which ordinarily has a significant benefit to the individual, can cause an adverse effect if it is continued when they become unwell with features of a fever or inability to maintain their fluid status (such as vomiting or diarrhoea). In this instance, it is important to miss out the specific medication (such as the SGLT-2 inhibitors) if they become unwell or if they are hospitalized. The medication should be resumed once the illness has passed or the person has been discharged from hospital. If a person stops their SGLT-2 inhibitor because of ill health and there is no improvement beyond a period of 48 hours they should seek medical attention. It is for this reason that all people prescribed SGLT-2

inhibitors should be taught about sick day guidance to be used if they become unwell and that this advice is reiterated at every medication review.

Because of the relationship of diabetic ketoacidosis to specific diets and to situations where the individual is taking a reduced fluid intake such as when fasting, the individual should be advised not to follow these particular diets when on an SGLT-2 inhibitor and be given specific advice if they do choose to fast. This might include missing out the SGLT-2 inhibitors on fast days or testing for the presence of ketones if they become unwell.

### **6.2.12 Diabetes specific: Low blood glucose or hypoglycaemia**

SGLT-2 inhibitors have beneficial effects in improving blood glucose control, which is dependent on good kidney function. Hypoglycaemia is a situation where the person's blood glucose drops to a low level causing harm that varies from mild symptoms to profoundly significant symptoms including coma. Furthermore, severe hypoglycaemia can be associated with long-term damage affecting both the cardiovascular system and the brain. People who have suffered episodes of hypoglycaemia may have limitations on their ability to drive or to undertake certain occupational activities. Therefore, hypoglycaemia is a complication of diabetes that needs to be avoided and certainly minimised.

Whilst SGLT-2 inhibitors on their own do not produce hypoglycaemia, this can occur if they are used with a diabetes agent that has such a risk, such as insulin or the group of diabetes medications that work by directly stimulating insulin release (these are termed insulin secretagogues and include gliclazide, glimepiride, glipizide, repaglinide etc.).

In people treated for their diabetes with insulin or insulin secretagogues, consideration needs to be given as to whether to reduce the current diabetes treatment when commencing an SGLT-2 inhibitor. The decision on whether to make this change should be discussed by the clinician prescribing the SGLT-2 inhibitor and the individual who is receiving it. This decision should be based on a number of factors and should include an assessment of the underlying blood glucose control of that individual. For example, someone who has poor blood glucose control as assessed by their HbA1c (this is the blood test that is used to assess average blood glucose control over the preceding 8 to 12 weeks), may benefit from the addition of the SGLT-2 inhibitor without the need for any reduction in their insulin or insulin secretagogues dose. Conversely, an individual with better controlled HbA1c may need a reduction in the SGLT-2 inhibitor, insulin or insulin secretagogue dose. Also, as has been described, if the kidney function of that individual is poor ( $\text{GFR} < 45 \text{ mL/min/1.73m}^2$ ), then the blood glucose reducing effect of the SGLT-2 inhibitor will be significantly reduced and there may therefore be no reason to make that reduction in insulin or insulin secretagogue.

It is therefore recommended that where the person being prescribed the SGLT-2 inhibitor has diabetes and is on insulin or an insulin secretagogue, the dose of these medications should be reviewed together with their prescribing clinician. If they are on a sulphonylurea and their HbA1c is  $< 58 \text{ mmol/mol}$  and their  $\text{eGFR} > 45 \text{ mL/min/1.73m}^2$ , the insulin secretagogue dose should be reduced by approximately 50% and the insulin by approximately 20% in order to avoid the risk of hypoglycaemia.

Where the person with type 2 diabetes is being prescribed an SGLT-2 inhibitor and they are not on an insulin secretagogue or insulin then there is no need to adjust any other diabetes medications.

There is no evidence to suggest that there is a risk of low blood glucose in people prescribed SGLT-2 inhibitors who do not have type 2 diabetes.

### 6.2.13 Acute kidney injury

Because of their mechanism of action, there can be an initial small, reversible reduction in kidney function over the first few weeks after commencing an SGLT-2 inhibitor. This results from changes to the blood flow in the kidneys with a small reduction in the blood flow going through the filtering units (glomeruli). This effect is believed to be protective rather than an indicator of harm. In all the major cardiovascular outcome trials, there was an initial small fall in GFR (of the order of 2 to 5% but with wide variation within the individual studies) and thereafter stabilisation of the GFR in participants given an SGLT-2 inhibitor. In the placebo group, there was a slow progressive decline in GFR such that the kidney function of the placebo-treated participants was significantly lower than the SGLT-2 inhibitor treated participants at the end of the study.

Further reassurance of the lack of harm and indeed possible beneficial effect of SGLT-2 inhibitors in relation to acute kidney injury is the fact that in all the major cardiovascular outcome trials, kidney studies and heart failure studies, the incidence of acute kidney injury (this is where there is a significant drop in kidney function which is usually reversible) was always greater in the placebo-treated groups compared to the SGLT-2 inhibitor-treated groups. It may even be that SGLT-2 inhibitors protect against acute kidney injury.

It is important that this effect is properly understood so that people who are prescribed SGLT-2 inhibitors and who may gain significant benefit from these medications do not have them stopped because of changes in GFR if measured in the period following prescription of these agents.

It is therefore recommended that when a person is commenced on an SGLT-2 inhibitor, there is no need to check the kidney function in the early period following initiation of treatment, but this should be undertaken at the next usual review appointment for that individual. Furthermore, it is also recommended that if kidney function is assessed for another reason within the first few weeks following initiation of an SGLT-2 inhibitor, the result needs to be interpreted carefully and unwarranted discontinuation of treatment should not occur.

### 6.2.14 Dehydration issues

SGLT-2 inhibitors do cause an increase in urine output (diuretic effect), both because of the fact they result in loss of sodium (salt) in the urine but also because the extra glucose in the urine pulls in water to the urine. As a result, people started on these agents can experience an increased frequency of passing urine which is most prominent in the first few weeks after commencing the medication.

For the vast majority of people this is nothing more than a minor issue which reduces over time but there are occasional individuals who are at risk of dehydration when starting an SGLT-2 inhibitor. It is difficult to be certain how often this occurs because in all the trials that have been undertaken with SGLT-2 inhibitors there is variation in how this side effect is reported. In studies where there has been an increased frequency of dehydration issues reported, the increase has been small, affecting an extra 1-2 people out of 100. It is, however, most probable that it is only really relevant to individuals who are already taking "water-tablets" (diuretics) and particularly if they are taking these at high doses.

It is therefore recommended that if a person who is prescribed an SGLT-2 inhibitor is already on either diuretic or blood pressure medication, the prescriber should consider whether an early review to assess for dehydration or low blood pressure is undertaken and if either of these are identified, a reduction in the dose of either of these additional diuretic or blood pressure medications is required. Furthermore, if a person being commenced on an SGLT-2 inhibitor is already on a diuretic, they should be counselled on symptoms of dehydration or low blood pressure so they can seek medical attention if they develop such symptoms.

In addition it is important again to remind people being treated with SGLT-2 inhibitors to use good sick day guidance and omit SGLT-2 inhibitors if they are unwell.

### 6.2.15 Peripheral vascular disease

People with CKD, and especially those with diabetes, are at an increased risk of suffering disorders of their cardiovascular system which includes disorders that affect the blood supply to their legs, termed “peripheral vascular disease”.

In all the cardiovascular outcome trials for SGLT-2 inhibitors, issues relating to peripheral vascular disease were monitored and recorded. In one of the larger trials in people with type 2 diabetes (called CANVAS), the medication canagliflozin significantly increased the number of amputations undertaken in the group allocated to an SGLT-2 inhibitor compared to those allocated to placebo. This increased incidence of amputation (mainly of toes) was not identified in any of the other cardiovascular outcome trials which included large numbers of participants who were broadly similar to those recruited to CANVAS. Furthermore, in a study that looked at people with kidney disease and diabetes known as CREDENCE, and which also used canagliflozin, there was no increased risk of amputation despite the fact that this group of participants were at high risk of vascular disease.

Because of these findings a warning has been placed by the regulators in relation to using canagliflozin in people at high risk of amputation.

It is important to understand that any increased risk of amputation, if it exists, is significantly less than the benefits canagliflozin treatment would have in those individuals. It is for this reason that we recommend that when a person has evidence of active foot disease caused by problems with the blood supply, no SGLT-2 inhibitor should be started and if they have already been commenced on one of these agents then this should be withheld. However, because of the benefits that are likely to occur in these individuals it is also a recommendation that once the active foot disease has been effectively treated, discussion should occur with the individual in relation to the risks and benefits so that a decision can be made whether the resumption of an SGLT-2 inhibitor is in the person’s interests and in accordance with their wishes. Similarly, a discussion of this nature should be held prior to commencing an SGLT-2 inhibitor in a person with high risk of vascular disease.

We define active peripheral vascular disease as the presence of foot ulcers, what is termed intermittent claudication (which is when there is pain over the back of the calves associated with walking) or where there is other evidence of reduced blood supply to the legs and feet.

In order to reduce the chance of any harm occurring to a person prescribed SGLT-2 inhibitors, we recommend that all such individuals (and most particularly individuals with diabetes) should be given advice on good foot care and the importance of seeking early attention should any problems develop.

### 6.2.16 Bone Health

Within the CANVAS trial there was a small increase in fractures in the group allocated to canagliflozin. However, this has not been identified in any other cardiovascular outcome trial using an SGLT-2 inhibitor, nor in other studies using canagliflozin, such as CREDENCE. Therefore it is uncertain as to whether this is a real effect or just a result of the play of chance in that trial. People with CKD are at a greater risk of suffering from bone disorders and good practice already recommends that all these individuals should have measurements of good bone health monitored on a regular basis. It is our recommendation that any person with kidney disease who is commenced on an SGLT-2 inhibitor should receive the good care in relation to their bone health as recommended by national guidelines.

### **6.2.17 Fungal genital infections (i.e. thrush)**

Because the use of SGLT-2 inhibitors results in an increase in sugar in the urine, this can provide an environment in which certain fungal infections thrive and therefore an increase in these infections locally. These infections are termed genital infections and are typified by thrush, which is not an uncommon infection, particularly in women and particularly in people with diabetes.

All SGLT-2 inhibitors increase the risk of thrush. This is not a dangerous complication, but can cause irritation and needs to be managed appropriately. Symptoms involve irritation or itchiness and redness or inflammation in the genital area (vulva-vagina for women and tip of the penis in men (inflammation of which is known as balanitis)). It is most likely that the risk is greater if the person being treated has type 2 diabetes.

Before anyone starts an SGLT-2 inhibitor they need to be counselled on the risk of fungal genital infections such as thrush and on simple measures that they can implement to maintain good genital hygiene and thereby reduce the risk of thrush. They also need to be counselled on the symptoms of genital infections and how to seek help which can often be attained simply by attending a local pharmacist to obtain an antifungal cream.

This advice is most particularly important for men as they may not have as much knowledge of thrush as women.

If genital infections such as thrush occur while a person is using an SGLT-2 inhibitor they should be treated, but they do not necessarily need to stop the SGLT-2 inhibitor. Usually once treated the genital infection does not recur but if the individual suffers recurrent infections their GP can give them treatment to prevent infections which is either a cream or a tablet they take intermittently.

### **6.2.18 Fournier's gangrene**

Fournier's gangrene is a serious infection caused by bacteria infecting the skin in the genital area. It is exceedingly rare but theoretically it could be increased if the individual has an increased glucose concentration in the urine and it is recognised to occur, albeit very rarely, in people with diabetes. Occasional reports have been made of people suffering this complication while being treated with an SGLT-2 inhibitor and because of this the regulators have placed a warning of this complication for people using SGLT-2 inhibitors. It should be pointed out that no increased cases of Fournier's gangrene were identified in any of the cardiovascular outcome trials undertaken, which included large numbers of participants. However, even though we do not know whether SGLT-2 inhibitors truly increase the risk of this disorder, we recommend that all people started on an SGLT-2 inhibitor are counselled on the symptoms of Fournier's gangrene and advised to stop their SGLT-2 inhibitor and seek urgent medical attention if they develop such symptoms. The main symptom to be aware of is severe pain on pressing the skin over the groin area.

### **6.2.19 Urinary infections**

SGLT-2 inhibitors produce an increased amount of glucose in the urine, but despite this there is only a very small increased risk of urine infections. This may be because bacteria do not thrive in environments with high glucose or because there is an increase in urine output which works to help "flush away" bacteria in the urinary tract. There is a need to be alert to this, but it is unlikely that a person with a normal bladder and bladder function will have an increased risk of urine infection when using SGLT-2 inhibitors.

### **6.2.20 Special populations: Children, pregnancy and breastfeeding**

There is little experience in using SGLT-2 inhibitors in children and therefore it is not recommended that these medications are used in people under the age of 18.

There is some theoretical evidence that SGLT-2 inhibitors, at much higher doses and in animal models, can potentially result in malformations and therefore the use of these medications in pregnancy should be avoided. If a person who is being treated with SGLT-2 inhibitors wishes to consider pregnancy they should discuss this with their doctor and plan the pregnancy in advance with a plan to stop the SGLT-2 inhibitor prior to becoming pregnant, or if an unplanned pregnancy occurs.

Whilst there is no real evidence to suggest that SGLT-2 inhibitors is passed in the breastmilk in important quantities, it is not recommended that these agents should be used when breastfeeding.

## 6.3 EXAMPLE PATIENT INFORMATION SHEET FOR A PERSON BEING INITIATED ON AN SGLT-2 INHIBITOR WHO ALSO HAS DIABETES

# Getting the most from your sodium glucose co-transporter-2 inhibitors (SGLT-2i)

(for people with diabetes)

## Information for patients, relatives and carers

### **Introduction**

This leaflet has been designed to give you information about sodium glucose co-transporter-2 inhibitors (SGLT-2 inhibitors) and answers some of the questions that you or those who care for you may have about these medicines. It is not meant to replace the discussion between you and your medical team but aims to help you understand more about what is discussed. If you have any questions about the information below, please contact the person who provided you with this leaflet.

### **What are SGLT-2 inhibitors and who benefits from using them?**

You are being treated with one of the SGLT-2 inhibitor medicines, sometimes known as “gliflozins” or “flozins”. These include, canagliflozin (Invokana), dapagliflozin (Forxiga), empagliflozin (Jardiance) and ertugliflozin (Steglatro).

These medicines lower blood glucose (sugar) by increasing the amount of glucose in the urine, which is why these medicines are used for people who have diabetes. They have added benefits that include protecting the kidneys and heart, slowing the decline in kidney function and reducing the risk of heart failure and heart attacks in individuals at most risk.

### **Are there any side effects?**

Common:

- **Hypoglycaemia (low blood glucose)** – this usually only occurs if SGLT-2 inhibitors are used in combination with certain other diabetes medicines and your doctor may therefore need to reduce other diabetes medicines. However, never stop insulin altogether if you are already on this.
- **Dehydration** – Dehydration is when your body does not have as much water as it needs. These medicines increase the amount of urine that you pass so may cause dehydration. To prevent dehydration, drink fluids when you feel any dehydration symptoms and you should drink enough during the day so your urine is a pale clear colour (unless otherwise instructed by your doctor). It is also important to drink when there is a higher risk of dehydrating, for example, if you're vomiting, sweating or you have diarrhoea.
- **Fungal genital infections** – As these medicines increase the glucose in your urine, there is an increased risk of certain infections, such as thrush around the vagina and penis. However, this is easily treated (usually with a cream) and a pharmacist or your GP can give you advice if irritation or itching occurs in these areas. Washing your genital area with warm water, using non-perfumed soap and avoiding wearing tight underwear will reduce the risk of infection.

Uncommon:

- **An increase of acid in the blood** – SGLT-2 inhibitors may cause certain acids (ketones) to build up in the blood. This is called **diabetic ketoacidosis (DKA)**. This is a rare event but can happen **even when your blood glucose is normal**. Symptoms include nausea and vomiting, abdominal pain, rapid breathing, and dehydration e.g. dizziness and thirst. Sufferers' breath smells like pear-drops/nail varnish remover.

The risk of DKA is increased if you do not eat for long periods, become dehydrated, reduce your insulin dose too quickly, drink excessive alcohol or are unwell. **Please seek medical advice before starting any new diet** particularly very low carbohydrate diets (also called ketogenic diets) as these can increase the ketones in the blood.

DKA is a serious health condition. **If you believe you are developing symptoms of DKA then please seek urgent medical assessment** reporting your concern and the medication you are taking.

- **Foot disease leading to toe or other amputation** – if you have been told you have an “at risk foot” you should clarify with your doctor if you should start or remain on one of these medicines. If you have an active foot ulcer or problem with the blood supply in your leg you should stop these medicines.

Exceedingly rare:

- **“Fournier’s gangrene”** – this is an exceedingly rare infection in the groin area requiring urgent medical attention. The main symptom to be aware of is severe pain on pressing the skin over the groin area. If this develops, stop your SGLT-2 inhibitor and seek clinical advice.

### ***Should I stop taking these tablets if I become unwell?***

It is best practice to use **good sick day guidance** with these medications. You should miss them out if unwell especially in the presence of vomiting, diarrhoea or fever. You should also miss out your SGLT-2 inhibitor if you are fasting (e.g. before an elective surgical operation). You can restart them when you are better, however if you remain unwell (e.g. for longer than 48 hours), we advise you seek medical advice from your GP/Pharmacist/NHS 111.

#### **Sick day guidance for people with diabetes**

If you are unwell (vomiting, diarrhoea, fever, sweats and shaking), you should **temporarily** miss out the medicines listed below. If you are unsure or have any questions please seek medical advice.

- **blood pressure pills** – e.g. ramipril, lisinopril, losartan or other medicine ending with -sartan or -pril
- **diuretics** - (water tablets) e.g. furosemide, bumetanide, spironolactone
- **diabetes pills** -e.g. metformin, and your SGLT-2 inhibitor/‘gliflozin’. Do **not** stop taking your insulin

If you have diabetes, you must increase the number of times you check your blood glucose levels. If they run too high or low, please seek medical advice.

**Restart your medicines** as soon as you are well and eating normally. Please seek medical advice if you continue to feel unwell after 48 hours.

## 6.4 EXAMPLE PATIENT INFORMATION SHEET FOR A PATIENT BEING INITIATED ON AN SGLT-2 INHIBITOR WHO DOES NOT HAVE DIABETES

# Getting the most from your sodium glucose co-transporter-2 inhibitors (SGLT-2i)

(for people without diabetes)

## Information for patients, relatives and carers

### **Introduction**

This leaflet has been designed to give you information about sodium glucose co-transporter- 2 inhibitors (SGLT- 2 inhibitors) and answers some of the questions that you or those who care for you may have about these medicines. It is not meant to replace the discussion between you and your medical team but aims to help you understand more about what is discussed. If you have any questions about the information below, please contact the person who provided you with this leaflet.

### **What are SGLT-2 inhibitors and who benefits from using them?**

You are being treated with one of the SGLT-2 inhibitors medicines, sometimes known as “gliflozins” or “flozins”. These include, canagliflozin (Invokana), dapagliflozin (Forxiga), empagliflozin (Jardiance) and ertugliflozin (Steglatro).

These medicines were initially developed to treat people with diabetes as they lower blood glucose (sugar) by increasing the amount of glucose in the urine. They have been found to have additional benefits that include protecting the kidneys and heart, slowing the decline in kidney function and reducing the risk of heart failure and heart attacks in individuals at most risk.

### **Are there any side effects?**

Common:

- **Dehydration** – Dehydration is when your body does not have as much water as it needs. These medicines increase the amount of urine that you pass so may cause dehydration. To prevent dehydration, drink fluids when you feel any dehydration symptoms and you should drink enough during the day so your urine is a pale clear colour (unless otherwise instructed by your doctor). It is also important to drink when there is a higher risk of dehydrating, for example, if you are vomiting, sweating or you have diarrhoea.
- **Fungal genital infections** – As these medicines increase the glucose in your urine, there is an increased risk of certain infections, such as thrush around the vagina and penis. However, this is easily treated (usually with a cream) and a pharmacist or your GP can give you advice if irritation or itching occurs in these areas. Washing your genital area with warm water, using non-perfumed soap and avoiding wearing tight underwear will reduce the risk of infection.

### ***Uncommon side effects that are expected to be extremely rare in people without diabetes***

There are a series of side effects which may almost exclusively affect people with diabetes. These are uncommon or extremely rare, and are highly unlikely to affect people without diabetes:

- **An increase of acid in the blood** – SGLT-2 inhibitors may cause certain acids (ketones) to build up in the blood. This is called **ketoacidosis**. This is an event that occurs rarely in people without diabetes. The risk of ketoacidosis is increased if you do not eat for long periods, become dehydrated, drink excessive alcohol or are severely unwell. Please seek medical advice before starting any new diet particularly very low carbohydrate diets (also called ketogenic diets) as these can increase the ketones in the blood. Ketoacidosis presents with nausea and vomiting, abdominal pain, rapid breathing, and dehydration e.g. dizziness and thirst. Sufferers’ breath smells like pear-drops/nail varnish remover. Ketoacidosis requires urgent medical assessment.
- **Foot disease leading to toe or other amputation** – if you have been told you have an “at risk foot” because of poor blood supply you should clarify with your doctor if you should start or remain on one of these medicines. If you have an active foot ulcer or problem with the blood supply in your leg you should stop these medicines.
- **Hypoglycaemia (low blood glucose)** – this usually only occurs if SGLT-2 inhibitors are used in people with diabetes in combination with insulin.
- **“Fournier’s gangrene”** – this is an exceedingly rare infection in the groin area requiring urgent medical attention. The main symptom to be aware of is severe pain on pressing the skin over the groin area. If this develops, stop your SGLT-2 inhibitor and seek clinical advice.

### ***Should I stop taking these tablets if I become unwell?***

It is best practice to use **good sick day guidance** with these medications. You should miss them out if unwell especially in the presence of vomiting, diarrhoea or fever. You should also miss out your SGLT-2 inhibitor if you are fasting (e.g. before an elective surgical operation). You can restart them when you are better, however if you remain unwell (e.g. longer than 48 hours), we advise you seek medical advice from your GP/Pharmacist/NHS 111.

#### **Sick day guidance for people without diabetes**

If you are unwell (vomiting, diarrhoea, fever, sweats and shaking), you should **temporarily** miss out the medicines listed below. If you are unsure or have any questions please seek medical advice.

- **blood pressure pills** – e.g. ramipril, lisinopril, losartan or other medicines ending with -sartan or -pril
- **diuretics** - (water tablets) e.g. furosemide, bumetanide, spironolactone
- **your SGLT-2 inhibitor/“gliflozin”** – i.e. canagliflozin, dapagliflozin, empagliflozin or ertugliflozin being used to treat your kidney disease

**Restart your medicines** as soon as you are well and eating normally. Please seek medical advice if you continue to feel unwell after 48 hours.

<b>Version number</b>	<b>Date</b>	<b>Details</b>
-	21 Jul 2021	Draft for UKKA Clinical Practice Guideline Committee Review
-	10 Aug 2021	Draft for Public Consultation
-	21 Sept 2021	Draft for Clinical Practice Guideline Committee Review (containing revisions following Public Consultation, updates to NICE CKD guidance and publication of EMPEROR-PRESERVED results and the working group's meta-analysis)
1.0	18 October 2021	First released version