SGLT-2 INHIBITORS: A PERSPECTIVE ON SAFETY AND TOLERABILITY

KEY MESSAGES

- Dapagliflozin is a new sodium glucose co-transporter-2 (SGLT-2) inhibitor for the treatment of type 2 diabetes
- It improves glycaemic control and is associated with additional beneficial effects, including a modest reduction in blood pressure, weight loss, low risk of hypoglycaemia and reduction in cardiovascular events
- Adverse renal effects of dapagliflozin have not been demonstrated, but because pharmacokinetics are altered by renal function, dapagliflozin is contraindicated in patients with an estimated glomerular filtration rate <60ml/min
- Adverse events related to volume depletion are uncommon in general, but are more likely to occur in patients ≥65 years of age. If they do occur, most are related to hypovolaemia, are mild/moderate and do not require dose interruption or discontinuation
- Dapagliflozin is well tolerated in older individuals aged ≥75 years
- Type 2 diabetes is associated with an increased risk of non-sexually transmitted genital infections and SGLT-2 inhibitors increase this risk. Infections are usually responsive to the usual therapies. Patients should be warned about the risk and educated to be vigilant for symptoms, and to seek treatment if an infection occurs
- In patients with type 2 diabetes, diabetic ketoacidosis is a very rare adverse effect associated with SGLT-2 inhibitors. The risk can be minimised by careful patient selection and careful monitoring of patients at high risk.

The sodium glucose co-transporter-2 (SGLT-2) inhibitors (dapagliflozin, empagliflozin and canagliflozin) are a new class of drugs for the treatment of type 2 diabetes that has recently been introduced in South Africa. Inhibition of SGLT-2 increases renal glucose excretion in proportion to the amount of filtered glucose, which is, in turn, determined by the plasma glucose concentration and glomerular filtration rate (GFR). By blocking the action of SGLT-2, the SGLT-2 inhibitors promote glucose excretion and lower the renal threshold so that urinary glucose excretion occurs at a lower plasma glucose concentration.

Because the mechanism of action of the SGLT-2 inhibitors is independent of insulin and their effect diminishes as plasma glucose concentrations decrease, they are associated with a low risk of hypoglycaemia. Furthermore, caloric loss associated with increased glucose excretion leads to a reduction in body weight and fat mass, and because SGLT-2 inhibitors have a mild diuretic effect, they are associated with a modest reduction in blood pressure.1,2

Large randomised clinical trials and observational studies have shown that the SGLT-2 inhibitors are associated with a significant reduction in cardiovascular (CV) outcomes in patients with type 2 diabetes and this benefit is likely to be a class effect.3-8
Dapagliflozin
In October 2017, dapagliflozin was the first SGLT-2 inhibitor to become available in South Africa for the treatment of type 2 diabetes. Its efficacy and safety have been well established in clinical studies in combination with metformin, a sulphonylurea, thiazolidinedione, a dipeptidyl peptidase-4 (DPP-4) inhibitor (with and without metformin) and insulin. In these studies it was associated with significant reductions in HbA1c, and in fasting and postprandial glucose, an average of 2-4kg weight loss and a modest reduction in systolic blood pressure.9,10

Safety of SGLT-2 inhibitors
Because the SGLT-2 inhibitors are a new class of treatment with a novel mechanism of action, their safety is of specific interest to medical practitioners. In general they have been shown to be well tolerated, without major safety concerns. However some adverse events, especially those related to the mechanism of action, including genital and urinary tract infections (UTIs), and urinary frequency, may be common. In addition, concern over more serious adverse events emerging from early study results, some of which have not been confirmed by further studies and meta-analyses, nevertheless have resulted in the inclusion of warning and precautionary notes in the individual package inserts.1,10-18 The following is a brief overview of current understanding of the safety and tolerability of these drugs, with special emphasis on the safety of dapagliflozin.

Renal safety
SGLT-2 inhibition increases glucose excretion by reducing its reabsorption in the proximal convoluted tubule of the kidney. The glomerulus is not involved, therefore sparing it from damage related to increased glucose load in that part of the nephron. Clinical trials of dapagliflozin have not demonstrated any adverse effects on renal function. Similar to that seen in clinical trials with empagliflozin, dapagliflozin was associated with an initial decline in estimated GFR (eGFR) at week one (approximately -4ml/min), followed by a return towards baseline levels over 24 weeks that remained stable to week 102. Overall, over two years treatment with dapagliflozin, there was no evidence of new or worsening renal impairment, acute nephrotoxicity or progression of diabetic nephropathy.12,14,19 In a four-year comparison with glipizide, patients treated with dapagliflozin showed no consistent change in mean eGFR, and values were above baseline at final follow-up.10

The reversible decrease in eGFR may be a beneficial effect related to transient changes in tubular-glomerular feedback mechanisms (causing renal glomerular afferent vasoconstriction), renal haemodynamics and intraglomerular pressure, resulting from diuresis, restricted reabsorption of sodium and reduction in blood pressure.14,20 Indeed, in the EMPA-REG OUTCOME study, in comparison to placebo, empagliflozin was associated with a 39% reduction in incident or worsening nephropathy and slowed the expected natural progression of renal dysfunction.21

The pharmacokinetics of dapagliflozin are affected by renal function. Although drug exposure is increased in patients with impaired renal function, the beneficial effects decline with increasing renal impairment. The drug should not be initiated in patients with moderate and severe renal impairment with an eGFR <60ml/min, with end-stage renal failure or patients on dialysis.19

Volume depletion
Like the other SGLT-2 inhibitors, dapagliflozin causes glycosuria, which is associated with a mild osmotic diuretic effect that is limited to the kidney. It is therefore unlike other osmotic diuretics such as mannitol, which increases osmotic pressure in blood vessels and therefore exerts an effect throughout all body tissues. This
**Safety in older patients**

Type 2 diabetes is a common disease in older individuals, and the progressive decline in beta-cell function means that most elderly patients may require more complex treatment regimens. Furthermore, elderly patients are more likely to have comorbidities, multiple co-prescribed medications and other risk factors that affect both the course of the illness and drug pharmacokinetics, and consequently, decisions about appropriate treatment (Table 1).

A pooled analysis of phase IIb/III studies over up to 104 weeks has compared the safety of dapagliflozin in individuals <65 years, ≥65 years and ≥75 years.25 Dapagliflozin was well tolerated in older patients with no difference in incidence of adverse events across the age groups (including hypoglycaemia), except for adverse events related to volume reduction and renal function, which were more common among elderly individuals (Table 2). Most of the adverse events related to renal function were small transient increases in serum creatinine. The incidence of serious adverse events was

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**Table 1. Risk factors and comorbidities in elderly patients with type 2 diabetes**

<table>
<thead>
<tr>
<th>1. Co-existing illnesses</th>
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<tr>
<td>2. Multiple medications</td>
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<tr>
<td>3. Reduced insulin secretion and increased insulin resistance</td>
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<td>4. Increased risk for and severity of diabetes complications</td>
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<tr>
<td>5. Reduced lean mass (sarcopenia)</td>
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<td>6. Increased adipose tissue</td>
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<tr>
<td>7. Decreased physical activity</td>
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<td>8. Poor nutrition</td>
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<tr>
<td>9. Altered fluid status (e.g. due to medications (corticosteroids, diuretics), insufficient fluid intake)</td>
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<tr>
<td>10. Cognitive impairment, depression, dementia</td>
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<tr>
<td>11. Increased risk for hypoglycaemia</td>
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<tr>
<td>12. Increased risk for falls and fractures</td>
</tr>
<tr>
<td>13. Increased risk for hypotension and CV events</td>
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<tr>
<td>14. Poor vision and hearing</td>
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similar across age groups and was comparable with placebo. Dapagliflozin was not associated with an increased risk of fractures, falls or CV events.5,25

Because of the potential for weight loss, dehydration, hypotension, acute kidney injury and fungal genital infections, the 2017 SEMDSA guidelines for the treatment of type 2 diabetes recommend that SGLT-2 inhibitors be avoided in frail elderly individuals.

**Hypoglycaemia**

In patients with type 2 diabetes, hypoglycaemia adversely affects quality of life and adherence to treatment regimens, and is associated with an increased risk of CV events. Because the mechanism of action of the SGLT-2 inhibitors is independent of secretion or action of insulin and their effect diminishes as plasma glucose concentrations decrease, they are associated with a low risk of hypoglycaemia.1 In a pooled analysis of phase IIb/III studies over up to 104 weeks, the incidence of hypoglycaemia was 13.7% and 12.4% with dapagliflozin (n=2295, 958 patients years) and placebo (n=2360, 998 patients years), respectively.14 In a four-year study comparing dapagliflozin with glipizide in patients with type 2 diabetes, dapagliflozin was associated with a 10-fold lower incidence of hypoglycaemic events relative to placebo (5% vs 52%, respectively).26 The frequency of hypoglycaemia with dapagliflozin appears to be dependent on the background therapy to which it is added. No major episodes of hypoglycaemia occurred with dapagliflozin monotherapy. Severe hypoglycaemia with dapagliflozin is rare and was mainly observed in patients receiving concomitant treatment with a sulphonylurea or insulin.14,20,27

**UTIs and genital infections**

Due to elevated urinary glucose, increased bacterial growth and increased adherence of bacteria to the uroepithelium, patients with diabetes are at increased risk of UTIs and non-sexually transmitted genital infections (vulvovaginitis and balanitis). Because they increase renal glucose excretion, the SGLT-2 inhibitors may cause additional growth of commensal genital microorganisms and two of the most commonly reported adverse events in SGLT-2 inhibitor trials were UTIs and genital infections, both of which occurred significantly more commonly than with placebo.20,28

The increased risk of UTI with SGLT-2 inhibitors appears to be small. In a pooled

### Table 2. Incidence of adverse events with dapagliflozin among patients in different age groups

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Age &lt;65 years</th>
<th>Age ≥65 years</th>
<th>Age ≥75 years</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Dapagliflozin</td>
<td>Placebo</td>
<td>Dapagliflozin</td>
</tr>
<tr>
<td></td>
<td>(n=1406)</td>
<td>(n=1301)</td>
<td>(n=620)</td>
</tr>
<tr>
<td>All adverse events</td>
<td>73%</td>
<td>71%</td>
<td>77%</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>6%</td>
<td>5%</td>
<td>14%</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>11%</td>
<td>12%</td>
<td>20%</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>18%</td>
<td>13%</td>
<td>20%</td>
</tr>
<tr>
<td>UTI</td>
<td>9%</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Genital infection</td>
<td>8%</td>
<td>1%</td>
<td>7%</td>
</tr>
<tr>
<td>Volume reduction</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Renal function adverse event</td>
<td>3%</td>
<td>2%</td>
<td>14%</td>
</tr>
</tbody>
</table>
analysis of dapagliflozin trials the occurrence of UTI was 4.7% with dapagliflozin and 3.5% with placebo. UTIs were more common in women than in men and most were mild/moderate in intensity, responding well to initial antimicrobial treatment. To reduce the risk of UTI, patients should be advised to maintain adequate hydration and careful bathroom hygiene and to seek medical care if they experience symptoms.

However, the true significance of SGLT-2 inhibitor-associated UTIs is uncertain. Because of the mechanism of action, UTIs were closely monitored in clinical trials and, in addition to the increase in benign urinary symptoms that may occur with these drugs (e.g. increased urinary output), they may have been over-reported. It is interesting to note that a recent meta-analysis of SGLT-2 inhibitor studies failed to demonstrate any increase in risk of UTI associated with this class of medication.

Pyelonephritis is not increased with SGLT-2 inhibitor treatment.

Genital infections were more frequent with dapagliflozin than with placebo (5.5% vs 0.6%), with no clear dose relationship. They were more common in women (vulvovaginitis) than in men (balanitis), were mild to moderate in severity and responded to initial antimicrobial therapy. Patients with a history of recurrent genital yeast infections were more likely to be diagnosed with genital infection than those without. Most infections occurred early in the course of treatment and recurrence was uncommon. The frequency of genital infections was similar in clinical trials of empagliflozin and canagliflozin.

Malignancy

Meta-analyses of clinical studies have not demonstrated a significant increase in overall risk of cancer with SGLT-2 inhibitors. Early reports that dapagliflozin might be associated with an increased incidence of breast or bladder cancer have not been validated and recent data suggest that the imbalance in the occurrence of cancers observed in clinical studies might be due to early diagnosis of pre-existing neoplasms rather than a real increase in cancer incidence. As a precautionary measure, the European Medicines Agency and the 2017 SEMDSA recommend that dapagliflozin not be prescribed to patients with bladder cancer or in combination with pioglitazone, which has been linked to a small, but non-significant risk of bladder cancer.

Fractures and amputations

In the Canagliflozin Cardiovascular Assessment (CANVAS) programme, canagliflozin was associated with a small risk of both fractures and amputations (primarily at the level of the toe or metatarsal). These observations are confined to CANVAS and risk of fractures was not increased in a pooled analysis of non-CANVAS studies. Nevertheless, the US Food and Drug Administration (FDA) has issued safety alerts for both of these adverse events and requested that the prescribing information for canagliflozin be updated accordingly.

Diabetic ketoacidosis (DKA)

DKA is a sometimes life-threatening complication of diabetes. It occurs consequent to severe insulin deficiency, most commonly in poorly controlled type 1 diabetes, or in patients with type 2 diabetes who are subject to stressors, such as infection, injury or surgery. Although it is usually associated with marked hyperglycaemia and dehydration, less commonly it can occur with only moderately elevated or even normal levels of plasma glucose (euglycaemic DKA). The SGLT-2 inhibitors have been associated with uncommon cases of DKA, including euglycaemic DKA. It is possible that euglycaemic DKA may occur as a result of drug-induced glycosuria with consequent decline in both plasma glucose and circulating insulin. The low level of insulin promotes production of free fatty acids, which undergo beta-oxidation and conversion to ketone bodies in the liver.
Ketone production is also potentiated by an increase in glucagon secretion. Glycosuria prevents the plasma glucose from increasing to the excessive levels normally seen in DKA, which further aggravates low levels of insulin secretion. The clinical importance of euglycaemic DKA is that, because it is not necessarily associated with the typical clinical manifestations of DKA, such as dehydration induced by marked hyperglycaemia, diagnosis and treatment may be delayed, allowing progressive metabolic deterioration. Severe acidosis alone has the potential to become life-threatening. The risk of DKA with SGLT-2 inhibitors is greatest in patients with type 1 diabetes, in whom they should be avoided. Factors that might increase the risk of euglycaemic DKA in patients with type 2 diabetes are listed in Table 3.

In a recent review of patient outcomes from a large claims database in the USA, the incidence of DKA over 180 days follow-up among patients not receiving insulin was 2.5 and 1.0 per 1000 patient years for SGLT-2 inhibitors and DPP-4 inhibitors, respectively (odds ratio 2.5; 95% CI 1.1-5.5). In an analysis of the FDA Adverse Event Reporting System (FAERS) up until September 2016, in a heterogeneous group of patients including those with type 1 or type 2 diabetes, there were more than 2500 reports of DKA in which SGLT-2 inhibitors were listed as suspect or concomitant drugs. However, only 1.5% of cases were fatal. In phase IIb/III clinical trials with dapagliflozin the estimated incidence of DKA or metabolic acidosis was 0.03% and the estimated incidence of DKA alone was 0.02%. Patients for whom SGLT-2 inhibitors are prescribed and who have risk factors for DKA should be carefully monitored. Regardless of current plasma glucose levels, any patient who is being treated with an SGLT-2 inhibitor and who feels unwell (e.g. malaise, nausea, vomiting) should be investigated for ketonuria and ketonaemia.

Table 3. Risk factors for euglycaemic diabetic ketoacidosis in type 2 diabetes

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>Long-standing diabetes (severe beta-cell deficiency)</td>
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<tr>
<td>Reduced insulin doses (in insulin dependent diabetes)</td>
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<tr>
<td>Intercurrent illness</td>
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<tr>
<td>Reduced food and fluid intake (prolonged starvation; low carbohydrate diets)</td>
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<tr>
<td>After surgery</td>
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<tr>
<td>Alcohol</td>
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</table>

CV safety

The SGLT-2 inhibitors are associated with a modest reduction in blood pressure of around 3-5mmHg. In diabetic patients with hypertension, placebo-corrected changes in blood pressure with dapagliflozin were -3.6 and -1.2mmHg for systolic and diastolic blood pressure, respectively. These benefits are not associated with an increase in heart rate or an increase in orthostatic hypotension. In a large safety analysis of dapagliflozin studies, the incidence of syncope on treatment remained consistently lower than in the placebo group (≤0.2% vs ≤0.5% respectively) across all age groups, including among patients aged 75 years and older. In randomised placebo-controlled studies, treatment with both empagliflozin and canagliflozin was associated with a reduced incidence of major adverse CV events (MACE) and hospitalisation for heart failure in patients with type 2 diabetes at high risk for CV events who were already treated with standard care, including other glucose-lowering agents, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, antithrombotic agents and statins. Empagliflozin was also associated with a reduction in CV death. Large meta-analyses and observational studies have indicated that this beneficial class effect also extends to dapagliflozin. In an analysis of data from a large multinational observational study (CVD-REAL Nordic), CV outcomes were compared for new users of dapagliflozin (n=10 227) versus new users of DPP-4 inhibitors (n=30 681), among whom 23% had established CV disease at baseline. Treatment with dapagliflozin was associated with a significantly lower risk of MACE, hospitalisation for heart...
failure and all-cause mortality (21%, 38% and 41% lower risk, respectively). The CV safety of dapagliflozin is also the subject of a large ongoing randomised placebo-controlled trial, DECLARE. DECLARE will assess CV outcomes in a broad population of more than 17,000 patients with type 2 diabetes and established CV disease or multiple CV risk factors. Results are expected in 2019.

The exact mechanisms behind the beneficial CV effects of the SGLT-2 inhibitors are uncertain. However, possible contributory factors include the osmotic diuretic effect, improvement in glycaemic control and blood pressure, reduced blood volume and sodium retention, reduction in arterial stiffness and weight loss.

Conclusions

Rather than merely to achieve glycaemic targets, the aim of diabetes management is to reduce the burden of premature morbidity and mortality associated with the disease. With that in mind, the SGLT-2 inhibitors are an exciting new addition to the treatment options available to clinicians and their patients. In addition to helping achieve glycaemic targets, they have the potential to reduce both CV mortality and morbidity and improve quality of life in a diverse range of patients.

Overall, they are well tolerated with the incidence of most adverse events being comparable with placebo. More common adverse events, including genital infections, are easily managed and serious adverse events are rare. Careful patient selection and ongoing monitoring, as should be the usual standard of care for patients with type 2 diabetes, will help to ensure that patients receive the maximum benefit from this new class of treatments.

References

1. Vivian EM. Sodium-glucose co-transporter 2 (SGLT2) inhibitors: a growing class of antidiabetic agents. Drugs in Context 2014; 3: 212264. Published online. DOI: 10.7573/dic.212264


22. Johnson K. The Society for Endocrinology, Metabolism and Diabetes of the United Kingdom. 2017 SEMDSA Guidelines for the Management of Type 2 Diabetes. SEMDSA 2017; 21(1) Supplement 1: S1-S196.


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