Sodium-glucose co-transporter 2 inhibitors for type 2 diabetes mellitus: An overview for the primary care physician

Paresh Dandona | Ajay Chaudhuri

Department of Medicine, State University of New York at Buffalo, Buffalo, NY, USA

Correspondence
Paresh Dandona, Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, State University of New York at Buffalo, Buffalo, NY, USA.
Email: pdandona@kaleidahealth.org

Funding information
Boehringer Ingelheim Pharmaceuticals, Inc.

Summary
Aims: Sodium-glucose co-transporter type 2 (SGLT2) inhibitors are a new class of antihyperglycaemic agents in type 2 diabetes mellitus (T2DM). This review examines their mechanism of action and provides an overview of safety and efficacy from the main studies of SGLT2 inhibitors marketed in the United States and Europe, namely, canagliflozin, dapagliflozin and empagliflozin.

Methods: We searched the PubMed database to identify relevant publications on the mechanism of action of SGLT2 inhibitors and clinical trial reports.

Results: Clinical trials in patients with T2DM have shown significant improvements in glycaemic control vs placebo with canagliflozin, dapagliflozin and empagliflozin: patients were more likely to reach target glycated haemoglobin levels compared with patients receiving placebo. All SGLT2 inhibitors also led to modest reductions in body weight and blood pressure vs placebo. Generally, all agents were well tolerated, with the most common adverse events with this class being genital mycotic infections and urinary tract infections. Hypoglycaemia was reported at rates similar to those seen with placebo, except when SGLT2 inhibitors were given in combination with insulin or an insulin secretagogue. Long-term outcome data are available only for empagliflozin: in the EMPA-REG OUTCOME study, empagliflozin demonstrated reduced risk of the composite end-point of 3-point major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke), primarily because of a significant reduction in cardiovascular mortality.

Conclusions: SGLT2 inhibitors are an exciting addition to the list of available agents for T2DM, and may be suitable for various types of patients who need additional glycaemic control.

1 | INTRODUCTION

Diabetes mellitus (DM) is characterised by hyperglycaemia, and glycaemic control remains fundamental to the treatment of DM, especially for the prevention of microvascular complications. Since glycaemic control takes a long period of time to exert a beneficial effect on macrovascular complications, as shown by the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study, the search has to continue for drugs that will not only help glycaemic control but also reduce macrovascular complications. Over the past few years, however, a number of negative results in terms of cardiovascular (CV) outcomes from large clinical trials have shifted the focus to other CV risk factors such as hypertension and hyperlipidaemia, with emphasis on the control of these risk factors. The importance of independent beneficial drug effects on CV outcomes was brought back to centre stage with the dramatic results from the EMPA-REG OUTCOME study.
which showed reduced risk of major CV events as well as reduced risk of all-cause mortality with the glucose-lowering drug, empagliflozin. It is possible that other drugs in this class may also exert similar effects but such data for these drugs are currently not available.

Long-term glycaemic control is measured by the proportion (%) of haemoglobin that is glycated (HbA1c), and large-scale, randomised trials using various interventions in type 1 DM (T1DM) and type 2 DM (T2DM) have shown that every 1% decrease in HbA1c gives approximately 30% reduction in the risk of microvascular complications. Although lifestyle interventions, such as optimising nutrition and promoting physical activity, are crucial in improving glucose control and general health of individuals with T2DM, pharmacotherapy with glucose-lowering agents is necessary in the majority of these patients. Various approaches have been used, yet, despite the increasing number and availability of such agents over the past decade, glycaemic control remains suboptimal in a significant proportion of patients. For example, data from 2007 to 2010 US National Health and Nutrition Examination Survey revealed that only around half (52.5%) of approximately 1300 people with diabetes achieved the recommended target HbA1c of <7.0% (<53 mmol/mol). The same study reported that only 18.8% of people achieved the combined goals for control of HbA1c (<7.0%), blood pressure (BP, <130/80 mm Hg) and low-density lipoprotein cholesterol (LDL-C) (<100 mg/dL). In the face of such numbers, it may be tempting to feel that we cannot be expected to help all our patients achieve treatment targets, but the association with improved outcomes should compel us to treat intensively to target.

Given the progressive and variable nature of T2DM, pharmacotherapy to combat hyperglycaemia often requires the use of increasing doses of oral glucose-lowering agents, combination therapy and, ultimately, insulin to meet glycaemic goals. Consequently, more effective glucose-lowering agents are needed for the management of T2DM. The urgency of this need is rapidly increasing, since the global prevalence of DM is predicted to rise from 415 million (8.8%) in 2015 to 642 million (10.4%) by 2040, and T2DM accounts for 90%-95% of patients. These facts are relevant because although the proportion of patients with HbA1c below 7% has increased to more than 50% in the US, the overall number of uncontrolled diabetic patients has actually increased.

Glucose-lowering agents have targeted various body organs—including the pancreas, liver, muscle cells, adipose tissue and the gut—but, until now, the kidney has not been targeted despite its central role in glucose homeostasis. Targeting the kidney by induction of urinary glucose excretion (UGE, ie, glucosuria) via the inhibition of sodium-glucose co-transporter type 2 (SGLT2) is an entirely novel approach. This drug class has generated, in the short time since its introduction, considerable interest and debate. In many areas of clinical medicine, new medications remain in the realm of specialists until experience is gained but, as T2DM is frequently managed in the primary care setting, all primary care physicians will need a good understanding of this drug class. This review examines the literature reporting studies of SGLT2 inhibitors, and discusses key aspects and considerations of this unique therapeutic approach to the treatment of T2DM.

Review criteria

This non-systematic literature review was undertaken to evaluate recent developments in clinical trials with Sodium-glucose co-transporter type 2 (SGLT2) inhibitors, a novel class of glucose-lowering drugs for the treatment of type 2 diabetes mellitus (T2DM). The PubMed database was searched for clinical studies and narrative reviews, focusing on the SGLT2 inhibitors currently available in the US, namely canagliflozin, dapagliflozin and empagliflozin. Reference lists of retrieved articles were scanned for additional relevant publications.

Message for the clinic

Sodium-glucose co-transporter type 2 inhibitors alter clinical factors that are known to be associated with increased cardiovascular risk in diabetes, such as persistent hyperglycaemia, overweight and hypertension. Results from the EMPA-REG OUTCOME study indicate that SGLT2 inhibition can reduce cardiovascular mortality in high-risk patients with T2DM. Further ongoing cardiovascular outcome studies will provide additional insight into the potential of these drugs to influence long-term macrovascular outcomes in T2DM.

2 | METHODS

This non-systematic literature review was undertaken to provide an overview of SGLT2 inhibitors, with particular relevance to primary care. The PubMed database was used to search for clinical studies and narrative reviews, including the search term “SGLT2 inhibitor” and subsequently with the identified compounds available in the US (canagliflozin, dapagliflozin and empagliflozin). All publication types were considered, including case reports, since this class of agents is relatively recently available and case reports may therefore be relevant. In addition, reference lists of retrieved articles were scanned for relevant publications, and this included documents published by regulatory authorities. For meta-analyses, priority was given to more recent publications, but no specific time limit was set, again because this is a relatively recent class of agents. The review also includes practical considerations for clinical practice, which aims to provide a practical approach for use of SGLT2 inhibitors.

3 | ROLE OF THE KIDNEY IN GLUCOSE TRANSPORT

Plasma glucose is freely filtered in the kidney glomeruli, and the kidneys of healthy individuals will filter approximately 180 g of glucose per day. To prevent this valuable energy source from leaving the body in the urine, glucose is reabsorbed from the glomerular filtrate and returned to the circulation. Effectively, no glucose is excreted in the urine of a healthy individual. This extremely efficient renal glucose
transport system is carried out by two types of carrier protein: the active (energy-dependent) SGLTs and the facilitated (passive) glucose transporters (GLUTs).16–18

Reabsorption of glucose from the glomerular filtrate is mediated by two SGLT proteins (SGLT1 and SGLT2), both of which act independently of insulin. Reabsorption primarily occurs in the first section of the proximal renal tubule at the brush border of cells via the action of SGLT2, which removes the majority (~90%) of the filtered glucose, while the remainder (~10%) is removed further along the proximal tubule via the action of SGLT1. SGLT2 has a low affinity for glucose but a high capacity, whereas SGLT1 has a high affinity for glucose but a low capacity. Reabsorbed glucose is then released from proximal tubular cells at the basolateral membrane into the bloodstream via GLUT2 and to a lesser extent by GLUT1.16,17,19

At normal plasma glucose concentrations of approximately 100 mg/dL (5.5 mmol/L), all of the filtered glucose is reabsorbed and virtually none is excreted. As the plasma glucose concentration rises, the amount of glucose filtered by the kidney increases until a threshold is reached at which the renal glucose transport system is effectively saturated. This “saturation point” is called the transport maximum for glucose, or Tm glucose. In healthy, glucose-tolerant individuals, the Tm glucose is equivalent to a filtration rate of 260–350 mg/min. This occurs (ie, the threshold at which Tm glucose is reached) is approximately 200 mg/dL (11.0 mmol/L).20

When considering glucose handling by the kidney in people with T2DM, it may seem logical to anticipate increasing UGE in the presence of hyperglycaemia. However, this is not observed; instead, the kidneys continue to reabsorb glucose even when plasma glucose concentrations are high, with levels that usually exceed the Tm of healthy individuals. This is because mean Tm glucose could increase by up to 20% in patients with DM vs healthy individuals, implying that glucosuria occurs only at a further elevated plasma glucose threshold. One underlying explanation for this accelerated reabsorption of glucose emerged with data from in vitro studies that demonstrate up-regulation of SGLT2 and GLUT2 expression and activity in T2DM. Irrespective of the cause of the elevated Tm glucose and diminished UGE observed in T2DM, the consequence of this increased reabsorption of glucose is a continuous backflow of glucose from the kidneys into the circulation. This backflow will occur even in the presence of elevated blood glucose, thus potentiating hyperglycaemia and increasing the risk for diabetes-associated complications.

4 | SGLT2 INHIBITION

If SGLT2 activity works to conserve the body’s glucose stores and helps to maintain the plasma glucose concentration, it follows that inhibition of SGLT2 should have the converse effect. Consequently, SGLT2 inhibition could be expected to decrease the Tm glucose, instigating reduced glucose reabsorption from the glomerular filtrate and increased glucose excretion into the urine, and to cause glucosuria at a lower plasma glucose concentration. In an individual with T2DM, administering an agent that blocks SGLT2 action effectively should result in reduced hyperglycaemia by removing excess glucose from the body.

Why was SGLT2 selected as a therapeutic target instead of SGLT1? Firstly, SGLT2 enables reabsorption of the vast majority of glucose from the renal filtrate, so its inhibition should have a more significant effect on UGE. Secondly, although SGLT2 is predominantly expressed in the renal tubule, SGLT1 is also strongly expressed in the small intestine, where it has a key role in glucose/galactose absorption. Consequently, inhibition of SGLT1 prevents these sugars from being appropriately absorbed and may allow them to pass through to the large intestine: this has been shown to cause severe diarrhoea and dehydration. A dual inhibitor of SGLT1 and SGLT2 (sotagliflozin) is in development. Its potency for inhibition of SGLT2 is similar to that of existing SGLT2 inhibitors on the market but with greater potency for inhibition of SGLT1. The rationale for dual inhibition relates to the role of SGLT1 as the main transporter for the uptake of glucose from the gut; SGLT1 inhibition is expected to reduce postprandial glucose levels, and further research will determine whether this approach will have a place in the management of T2DM.

What characteristics might then be anticipated of pharmacological agents that inhibit SGLT2? To begin with, as the mechanism of action of SGLT2 (and SGLT1) is independent of insulin, compounds that inhibit SGLT2 should not be influenced by beta-cell mass/function or the degree of insulin resistance and may even have the potential to show efficacy as T2DM significantly progresses. This contrasts with the decline in glucose-lowering potential observed with other types of anti-diabetes agents that are dependent on beta-cell function, such as sulphonylureas or glinides. In addition, inhibition of SGLT2 should not increase the risk of hypoglycaemia, as SGLT2 inhibition does not affect endogenous glucose production in response to hypoglycaemia, and does not stimulate insulin release when glucose levels decline. Furthermore, the non-insulin-dependent mechanistic pathway suggests SGLT2 inhibitors could be given in combination with any of the existing therapeutic classes of glucose-lowering agents, including insulin. Another possible benefit is the potential for SGLT2 inhibitors to promote weight loss, partly because of the reduction in available calories caused by UGE.

However, unwanted issues with SGLT2 inhibition could also be hypothesised based on their mechanism of action. As in uncontrolled diabetes, the continual presence of glucose in the urine may increase the risk of urinary tract infections (UTIs) and/or urogenital infections. In addition, the increase in glucosuria may induce polyuria and nocturia. Furthermore, as SGLT2 inhibitors act on the renal tubule, it is theoretically possible that these agents may also affect bone metabolism, as this site is considered an important location for maintenance of calcium/phosphate homeostasis. Additionally, since there is 60% homology between SGLT2 and SGLT1, potential side effects may arise from any SGLT1 inhibition exhibited, such as severe diarrhoea (as described above). To overcome this, a candidate SGLT2 inhibitor would ideally be designed to be a potent inhibitor of SGLT2 and have a high degree of selectivity over SGLT1. In addition, it would also be orally
active to allow tablet/capsule formulation, alone and in combination with available oral anti-hyperglycaemic drugs.

5 | A BRIEF HISTORY

Years before renal glucose handling was fully characterised, early investigations were performed using phlorizin, a naturally occurring glucoside that was first isolated from apple tree bark in the early 1800s. Phlorizin was observed to cause glucosuria, weight loss and polyuria in dogs, and was ultimately found to be a non-selective inhibitor of SGLT. Pivotal research carried out in the mid-1980s, using a rodent model of diabetes, demonstrated that phlorizin induced glucosuria and reduced hyperglycaemia in an insulin-independent manner without causing hypoglycaemia, most likely because of inhibition of SGLT2. Unfortunately, phlorizin was unsuitable for clinical development as a glucose-lowering agent, as it also potently inhibited SGLT1 and had poor oral bioavailability. The potential was nonetheless clear, and phlorizin analogues have provided the foundation for subsequent generations of more selective SGLT2 inhibitor compounds.

As often observed in research, several initial SGLT2 inhibitor candidates, O-glucosides, had to be discontinued early in clinical development, such as T-1095 and sergliflozin, which were probably discontinued because of non-selective SGLT2 inhibition and bioavailability issues with the O-glucoside, respectively. However, the succeeding generation of C-glucosides has progressed through clinical research, and three drugs are available in the US and European Union: dapagliflozin, canagliflozin and empagliflozin. All are selective SGLT2 inhibitors, and are dosed orally (Table 1).

6 | CLINICAL EXPERIENCE

6.1 | Indications and dosing

Sodium-glucose co-transporter type 2 inhibitors are currently indicated for patients with T2DM and inadequate glycaemic control from diet and exercise. The recommended doses for dapagliflozin, canagliflozin and empagliflozin for the treatment of T2DM are shown in Table 1. SGLT2 inhibitors may offer additional options in T2DM as an oral therapy for patients with uncontrolled hyperglycaemia, but they are not indicated as weight-loss agents in their own right. At present, no SGLT2 inhibitor is approved for treatment of patients with T1DM, but the potential here is recognised, and SGLT2 inhibition has been evaluated in several pilot studies as adjunct to insulin therapy. Concerns have been raised about a possible link between SGLT2 inhibition and a risk of ketoacidosis, particularly in patients with T1DM; this risk would need to be balanced against the need for additional treatment options.

6.1.1 | Cardiovascular outcomes

The EMPA-REG OUTCOME study, published in September 2015, was the first dedicated CV outcome study to show that a glucose-lowering therapy was associated with a reduction in major adverse CV events (MACE) and in CV mortality in high-risk patients. In this double-blind study, patients with T2DM and at high risk of CV events were randomised to empagliflozin (10 and 25 mg dose groups) or placebo, on top of standard of care therapy. Of note, about half of all patients were receiving dual glucose-lowering therapy, approximately 48%
were receiving insulin, 80% were receiving angiotensin-converting enzyme (ACE) inhibitors/angiotensin-receptor blockers (ARBs) and approximately 80% were receiving lipid-lowering therapies (primarily with statins); altogether these data indicate a very high standard of care as background therapy in these patients. The primary outcome was a 3-point MACE composite of CV death, non-fatal myocardial infarction (excluding silent myocardial infarction) or non-fatal stroke.\(^1\) Significantly fewer patients in the pooled empagliflozin vs placebo group experienced a primary outcome event [10.5% vs 12.1%; hazard ratio (HR): 0.86; 95% CI: 0.74-0.99; \(P < .001\)]; however, no significant between-group differences were observed in the rates of myocardial infarction or stroke. Compared with placebo, empagliflozin therapy was associated with a 35% RRR in hospital admission for heart failure, and a 32% RRR in death from any cause. Additional analysis showed a 34% reduction in the composite outcome of hospitalisation for heart failure or CV death (HR: 0.66; 95% CI: 0.55-0.77; \(P < .001\)), regardless of the presence of heart failure at baseline.\(^46\) The mechanisms underlying the observed effects of empagliflozin are unclear at present but could result from the reduction in hyperglycaemia, BP and weight associated with empagliflozin therapy,\(^47\) in addition to a reduction of blood volume and sodium retention and a reduction in arterial stiffness.\(^48\)

---

**Figure 1** Summary of key efficacy data with SGLT2 inhibitors used as monotherapy. Mean reductions from baseline with (A) dapagliflozin, (B) canagliflozin, and (C) empagliflozin. Data are from the study of dapagliflozin monotherapy for 24 weeks (54), canagliflozin monotherapy for 26 weeks (56), and empagliflozin monotherapy for 24 weeks (55). Numbers of patients are the number of patients randomised to each treatment arm. HbA1c, glycated haemoglobin; SBP, systolic blood pressure. *Morning dosing. †Evening dosing.
Several other CV safety and outcome studies are ongoing with SGLT2 inhibitors. The initial phase of the Canagliflozin Cardiovascular Assessment Study (CANVAS) (ClinicalTrials.gov identifier: NCT01032629) has recruited 4330 patients with T2DM and elevated risk of CV disease and is expected to report in 2017. The Dapagliflozin Effect on Cardiovascular Events (DECLARE) (ClinicalTrials.gov identifier: NCT01730534) has completed recruitment of around 17 000 patients with T2DM and known CV disease (secondary prevention cohort) or at least two risk factors for CV disease (primary prevention cohort). Results are expected in 2019.

### 6.1.2 Renal outcomes

While CV outcomes are considered the most important complication of diabetes, microvascular complications, such as blindness and kidney disease, are also of critical importance. To date, clinical data are available only for empagliflozin from the EMPA-REG OUTCOME study discussed above. Initiation of renal-replacement therapy was relatively rare, but the risk was still significantly lower with empagliflozin, with the outcome reported in 0.6% of the placebo group and 0.3% of the pooled empagliflozin group. The composite renal microvascular outcome of incident or worsening nephropathy defined as progression to macroalbuminuria, doubling of serum creatinine accompanied by estimated glomerular filtration rate (eGFR) ≤45 mL/min/1.73 m², initiation of renal-replacement therapy, or death from renal disease occurred in 16.2% of patients in the empagliflozin group vs 23.6% of the placebo group (HR: 0.61; 95% CI: 0.55-0.69; P < .001). Empagliflozin also appeared to protect renal function from the natural progression expected in these patients. In the empagliflozin group, the eGFR initially dropped after starting treatment, then stabilised over the course of the study, and increased again after the end of treatment, whereas eGFR in the placebo group continued to decline. The results are particularly exciting given that the majority of patients in the study were receiving current standard of care with ACE inhibitors or ARBs.

For SGLT2 inhibitors other than empagliflozin, renal outcomes data are therefore awaited with interest and a dedicated study assessing canagliflozin in the prevention (or delay) of kidney failure in patients with nephropathy is underway (ClinicalTrials.gov identifier: NCT02065791). Similar patterns of eGFR effect—an initial drop followed by stabilisation—have been observed with dapagliflozin and canagliflozin. The observations on a reversible decrease in eGFR with SGLT2 inhibitor treatment suggest that the observed changes in renal function after SGLT2 inhibition may reflect changes in renal haemodynamics, and potentially also in intraglomerular pressure. This haemodynamic concept of SGLT2 in the kidneys is supported by data from an empagliflozin pilot study (25 mg once daily for 8 weeks) in patients with T1DM, in which the effect of SGLT2 inhibition on renal hyperfiltration was investigated. In T1DM subjects with renal hyperfiltration, short-term treatment with empagliflozin led to a significant reduction in hyperfiltration during clamped euglycaemic and hyperglycaemic conditions, probably by affecting tubular-glomerular feedback mechanisms. In contrast, renal haemodynamic parameters were unchanged in T1DM subjects with normal renal function. Differences in baseline renal haemodynamic function were considered mainly because of increased proximal tubular sodium-glucose co-transport, and SGLT2 inhibition resulted in an enhanced physiologic effect in T1DM patients with hyperfiltration.

### 6.2 Changes in glycaemic control

Glycaemic control remains the cornerstone of treatment for T2DM, since it is so closely linked to the risk of complications. A range of clinical trials have shown that canagliflozin, dapagliflozin and empagliflozin all have a favourable effect on HbA1c, with mean changes of around 0.5%–1.0%. Data from pivotal phase 3 studies involving monotherapy with dapagliflozin, canagliflozin and empagliflozin are presented in Figure 1. These agents have also been found to be effective and well tolerated when administered with other glucose-lowering therapies, including as add-on therapy to metformin, metformin plus sulphonylurea, pioglitazone or dipeptidyl peptidase-4 (DPP-4) inhibitor as well as in conjunction with insulin. Head-to-head studies have shown similar improvements in glycaemic control to sulphonylureas. SGLT2 inhibitors have also been evaluated in Asian patients with T2DM and shown to be well tolerated and effective in these patients at the same doses used in general clinical trial populations.

While mean HbA1c changes are essential information, in clinical practice, the proportion of patients achieving the target HbA1c of <7.0% also needs consideration, although it will depend to some extent on the baseline HbA1c. In a dapagliflozin monotherapy trial, HbA1c <7.0% occurred in 50.8%–51.6% of those receiving dapagliflozin 10 mg vs 31.6%–34.6% of those in the placebo group. Treatment with dapagliflozin 5 and 10 mg in combination with metformin led to a statistically significantly greater proportion of subjects achieving HbA1c <7.0% (37.5% and 40.6% vs 25.9% with placebo).

After canagliflozin monotherapy given for 26 weeks, 44.5% and 62.4% of subjects receiving 100 and 300 mg, respectively, achieved HbA1c <7.0% vs 20.6% of those receiving placebo. For canagliflozin used in active-controlled trials with metformin combination therapy, after 52 weeks HbA1c <7.0% occurred in 54% and 60% of subjects receiving 100 and 300 mg, respectively, vs 56% of those receiving the active comparator glimepiride.

For empagliflozin, HbA1c <7.0% was observed in 35.3% and 43.6% of subjects receiving empagliflozin 10 and 25 mg monotherapy for 24 weeks, respectively, vs 37.5% for the active comparator group (sitagliptin 100 mg) and 12.0% for those taking placebo. For treatment with empagliflozin in combination with metformin, HbA1c <7.0% occurred in 37.7% and 38.7% of empagliflozin 10 and 25 mg groups, respectively, vs 12.5% of the placebo group.

Sodium-glucose co-transporter type 2 inhibitors have reduced efficacy in patients with chronic kidney disease (CKD) because the drugs rely on renal function for their mechanism of action. Studies have nevertheless shown significant changes in patients with moderate CKD. It is recommended that renal function is assessed prior to commencing SGLT2 inhibitor therapy and periodically...
thereafter. The labelling information for patients with renal impairment for dapagliflozin, canagliflozin and empagliflozin is summarised in Table 1.

## 6.3 | Body weight

The UGE caused by SGLT2 inhibitors will lead to a loss of calories and studies have consistently shown weight loss, usually of 2-3 kg (Figure 1A-C). A small degree of weight loss may also result from mild osmotic diuresis, but body composition studies have shown that weight loss with SGLT2 inhibitors principally resulted from reduction in body fat mass.99

## 6.4 | Blood pressure

Reductions in BP have been observed consistently in SGLT2 inhibitor trials. As shown in Figure 1, mean reductions in systolic BP (SBP) with canagliflozin, dapagliflozin and empagliflozin have been around 3-5 mm Hg when the drugs are used as monotherapy, and similar reductions have been reported for pooled analyses in a range of combination therapies.37,48,81 A pooled analysis of 13 dapagliflozin studies evaluated the effect of treatment on BP in patients with T2DM with or without concurrent hypertension.82 In patients with concomitant hypertension, dapagliflozin was associated with a placebo-corrected change from baseline BP values of −3.6 and −1.2 mm Hg for SBP and DBP, respectively; for patients without hypertension, changes were −2.6 and −1.2 mm Hg, respectively. These benefits were achieved without an associated increase in heart rate and with a low risk of orthostatic reactions, with no increase in clinically registered orthostatic reactions for patients receiving dapagliflozin vs placebo.

A dedicated trial of SGLT2 inhibition in patients with T2DM and hypertension has demonstrated statistically significant and clinically meaningful treatment-related reductions in both office and ambulatory BP in patients receiving empagliflozin.83 After 12 weeks, patients achieved adjusted mean differences, vs placebo, in change from baseline mean 24-hour ambulatory SBP/DBP values of −3.44/−1.36 mm Hg with empagliflozin 10 mg and −36.3 μmol/L (−10.4%) with empagliflozin 10 mg and −36.3 μmol/L (−11.2%) with empagliflozin 25 mg vs an increase of 3.0 μmol/L (+0.9%) with placebo.89

## 6.5 | Safety and tolerability

### 6.5.1 | Ketoacidosis

The US Food and Drug Administration (FDA) has issued a drug safety communication about the risk of ketoacidosis following reports made to their Adverse Event Reporting System.90 Several of the case reports of ketoacidosis were atypical, with blood glucose levels only moderately raised, and the reported cases occurred in patients with T1DM and T2DM. All patients required hospitalisation or treatment in an emergency department. Subsequent to the FDA communication, published reports have suggested an association between SGLT2 inhibition and ketoacidosis,91,92 a rare event that is possibly triggered by factors such as major illness, reduced food and fluid intake and reduced insulin dose.90

### 6.5.2 | Urinary tract infections and genital infections

In general, in clinical development programmes SGLT2 inhibitors were well tolerated and showed an overall safety profile similar to placebo. The most commonly reported adverse events were an increased incidence of symptoms suggestive of genital infection and of UTI, which could both be attributed to elevated urinary glucose levels. In a systematic review, UTIs and genital tract infections were more common with SGLT2 inhibitors compared with placebo (odds ratio for UTIs: 1.34 (95% CI: 1.03-1.74) and for genital infections: 3.50 (95% CI: 2.46-4.99)).93

Across the pooled studies available, the incidence of genital infection was higher in women (vulvovaginitis) than in men (balanitis), as reported in the labelling information.36,38,41 Pooled analyses of safety data from studies of dapagliflozin, canagliflozin and empagliflozin reported that genital infections and UTIs occurred more frequently with each SGLT2 inhibitor vs placebo, although the difference in frequency vs placebo was much less for UTIs.

The pooled analysis of dapagliflozin examined data from 12 randomised placebo-controlled trials: diagnosed genital infection occurred in 4.1%-5.7% of dapagliflozin groups vs 0.9% of the placebo group.94
and diagnosed UTI occurred in 3.6%-5.7% of dapagliflozin groups vs 3.7% of the placebo group. Similarly for canagliflozin, a pooled analysis of four phase 3 studies reported UTI in 5.9% of patients receiving canagliflozin 100 mg, 4.3% receiving 300 mg vs in 4.0% of those receiving placebo, and genital mycotic infection in 10.4% of women and 4.2% of men receiving canagliflozin 100 mg, 11.4% of women and 3.7% of men receiving 300 mg vs 3.2% of women and 0.6% of men in the placebo group. While a pooled analysis of empagliflozin studies showed that the frequency of events consistent with genital infections was approximately 5% vs 1% for empagliflozin groups and placebo, respectively, the frequency of events consistent with UTI was similar, at 9.3%, 9.8% and 10.4% in the placebo, empagliflozin 10 mg and empagliflozin 25 mg groups, respectively.

Based on the mechanism of action of SGLT2 inhibitors, one would expect increased rates of UTIs and genital infection. Importantly, however, clinical experience with SGLT2 inhibitors across a wide range of investigational studies showed that these events could be effectively managed. The majority of patients receiving treatment with dapagliflozin, canagliflozin or empagliflozin who reported such an event experienced only a single occurrence, which was usually mild in intensity and responded to standard treatment. Furthermore, very few patients discontinued treatment as a result of such an event.

6.5.3 | Hypoglycaemia

Hypoglycaemia adversely affects quality of life in individuals with T2DM, and severe hypoglycaemia is associated with increased risk of subsequent mortality. As explained above, the insulin-independent mode of action of SGLT2 inhibitors should not lead to an increased risk of hypoglycaemia. This was confirmed by the recent systematic review of SGLT2 inhibitors, in which no increased risk of hypoglycaemia was observed (odds ratio vs placebo, 1.28 (95% CI: 0.99-1.65; I²=0%); odds ratio vs other anti-diabetes agents, 0.44 (95% CI: 0.35-0.54; I²=93%)). Furthermore, severe hypoglycaemia (defined as an episode requiring assistance from another person) was rare and was mainly observed in patients receiving concomitant sulphonylurea.

Based on studies to date, the frequency of hypoglycaemia with SGLT2 inhibitor therapy appears to be dependent upon the background therapy used. For example, with dapagliflozin used as monotherapy, no major episodes of hypoglycaemia occurred (defined as symptomatic episodes requiring external (third-party) assistance with a capillary or plasma glucose value <3 mmol/L (<54 mg/dL) and prompt recovery after glucose or glucagon administration). Differences among individual studies were only observed when dapagliflozin was combined with a sulphonylurea or insulin and were mainly seen as an increase in minor hypoglycaemic events (defined as either a symptomatic episode with a capillary or plasma glucose measurement <3.5 mmol/L (<63 mg/dL), regardless of the need for external assistance, or an asymptomatic capillary or plasma glucose measurement <3.5 mmol/L (<63 mg/dL) that does not qualify as a major episode). A pooled safety analysis of 12 placebo-controlled trials (n > 4000), which included sulphonylurea and insulin background therapy, reported that hypoglycaemia (not defined further) was more common with dapagliflozin (11.8%) vs placebo (7.0%); the authors noted this was primarily because of the results of studies using dapagliflozin with insulin or a sulphonylurea.

With canagliflozin, the risk of hypoglycaemia (defined as documented blood glucose ≤3.9 mmol/L (≤70 mg/dL)) and of severe hypoglycaemia (defined as requiring the assistance of another person, or resulting in the loss of consciousness or a seizure) was low among subjects receiving monotherapy, but increased when canagliflozin was used in combination with insulin or sulphonylureas. The prescribing information for canagliflozin recommends using a lower dose of insulin or insulin secretagogue to reduce the risk of hypoglycaemia when used in combination with canagliflozin.

With empagliflozin monotherapy, the rate of hypoglycaemia (defined as plasma glucose <3.9 mmol/L (≤70 mg/dL) and/or third-party assistance was required) was low and was similar to placebo. The frequency of confirmed hypoglycaemia was greater for empagliflozin vs placebo when used in combination with metformin plus sulphonylurea, but none of these events required assistance. A similar rate of hypoglycaemia was reported vs placebo when empagliflozin was added to multiple daily injections of insulin, with slightly higher rates when empagliflozin 25 mg was added to basal insulin. Accordingly, the prescribing information for empagliflozin also recommends considering a lower dose of insulin or insulin secretagogue to reduce the risk of hypoglycaemia when used in combination with empagliflozin.

6.5.4 | Bone safety

In a study carried out in patients with T2DM and moderate renal impairment, bone fractures were more common in patients receiving dapagliflozin than in those receiving placebo (7.7% vs 0% for dapagliflozin groups and placebo, respectively). However, in individuals with either normal renal function or mild renal impairment, there was no evidence that dapagliflozin induced bone demineralisation or increased fracture rates. Compared with placebo, no meaningful changes from baseline in markers of bone turnover or bone mineral density were identified over 102 weeks when dapagliflozin was added to metformin. For canagliflozin, a pooled analysis of nine trials reported apparent canagliflozin-associated increases in overall fractures (2.7%, 2.7% and 1.9% for 100 mg, 300 mg and control groups, respectively); this increase appeared to result mainly from an increase in the CANVAS study, for which only interim results are available at present. One of the studies included in the pooled analysis was a 26-week study in older patients (aged 55-80 years), and a 78-week extension of this trial showed small but significant reductions in total hip bone mineral density with canagliflozin vs placebo. Based on these results, canagliflozin labelling in the US has been updated with a warning to consider factors that contribute to fracture risk before starting treatment with canagliflozin.

For empagliflozin, a pooled analysis of more than 12 000 patients with T2DM (mean baseline age was 60 years) reported no increase in bone fractures with empagliflozin vs placebo, with bone fractures occurring in 1.7% and 1.3% of patients receiving empagliflozin 10 and 25 mg, respectively, and in...
1.8% of patients receiving placebo. When analysed by renal function subgroups, no imbalance was found between empagliflozin and placebo. In the longer term EMPA-REG OUTCOME study, in which the mean age at baseline was approximately 63 years, the proportion of patients with a fracture was similar for empagliflozin and placebo, with 3.9% of the placebo group, 3.9% of the empagliflozin 10 mg group and 3.7% of the empagliflozin 25 mg group reported to have one or more fracture adverse events during the study.89

### 6.5.5 Volume depletion

Osmotic diuresis induced by SGLT2 inhibitors could potentially pose a risk of hypovolaemia and associated hypotensive episodes in patients prone to these conditions. Volume depletion-related reactions, most commonly hypotension, occurred in 0.8% of subjects receiving dapagliflozin vs 0.4% of those receiving placebo; no events of dehydration or hypovolaemia were observed.75 Hypotension occurred more frequently in dapagliflozin-treated groups than placebo groups for subjects who were elderly, had moderate renal impairment or were treated with loop diuretics.75 As stated in the canagliflozin US Prescribing Information, the overall incidences of volume depletion adverse events using pooled data from eight clinical trials were 2.3% and 3.4% for canagliflozin 100 and 300 mg groups, respectively, vs 1.5% for comparator groups.36 Subgroups at increased risk from volume depletion adverse events with canagliflozin therapy included people aged 75 years or older, those with eGFR <60 mL/min/1.73 m², and those using loop diuretics.36 Empagliflozin was not associated with an increased frequency of volume depletion events vs placebo, except with the 25 mg dose of empagliflozin in patients aged 75 years or older, as reported in a pooled analysis of T2DM patients receiving either empagliflozin or placebo in phase 1, 2 and 3 trials (patients <50 years old: 0.4% and 1.2% vs 0.8% for empagliflozin 10 mg, 25 mg and placebo groups, respectively; patients ≥75 years old: 2.3% and 4.3% vs 2.1% for empagliflozin 10 mg, 25 mg and placebo groups, respectively).89

In terms of labelling information, dapagliflozin, canagliflozin or empagliflozin are not recommended in patients at risk of hypotension, such as those who are volume-depleted or who are receiving loop diuretics, and it is recommended that volume depletion should be assessed and corrected before initiating therapy.36,38,41 The EU summaries of product characteristics add that caution should be used with patients for whom a fall in BP could be hazardous, such as patients with known CV disease or a history of hypotension, or elderly patients. Monitoring of volume status should be undertaken in patients at risk of fluid loss (eg, with gastrointestinal conditions).37,39,40

### 6.5.6 Serum electrolytes

Hyperkalaemia can occur with canagliflozin therapy and is listed as a warning/precaution in the canagliflozin US Prescribing Information.36 Hyperkalaemia is more likely to develop in patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system.36 The canagliflozin Prescribing Information recommends that serum potassium levels are monitored periodically in patients with renal impairment and in patients predisposed to hyperkalaemia because of medications or other medical conditions.36 For this reason also, digoxin levels should be monitored with canagliflozin. No change from baseline in mean potassium occurred with dapagliflozin or placebo in a study of patients with T2DM and moderate renal impairment (defined as eGFR ≥30 to <59 mL/min/1.73 m²).77 No increase in mean potassium from baseline occurred with empagliflozin or placebo in patients with T2DM and stage 2 or stage 3 CKD (defined as eGFR ≥60 to <90 mL/min/1.73 m² and ≥30 to <60 mL/min/1.73 m², respectively).79

Dose-related increases in serum magnesium were observed within 6 weeks of canagliflozin initiation and remained elevated throughout treatment, per the US Prescribing Information.36 In a pool of four placebo-controlled trials, the mean change in serum magnesium was 8.1% and 9.3% with canagliflozin 100 and 300 mg, respectively, vs ~0.6% with placebo.36 In a phase 3 trial in patients with stage 3 CKD (albeit including a more restricted range than typically used to define stage 3 CKD of eGFR ≥30 to <50 mL/min/1.73 m²) increases in serum magnesium were 9.1% and 14.6% for canagliflozin 100 and 300 mg, respectively, vs no change (0%) with placebo—absolute values were not stated.79 The EU regulatory report for dapagliflozin stated that there were mean increases in serum magnesium in subjects with T2DM and moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m²) receiving dapagliflozin, but mean values remained within the normal range.75 Mean magnesium increased from baseline by 0.1 mmol/L with empagliflozin 25 mg vs no change with empagliflozin 10 mg or placebo in patients with stage 2 CKD (eGFR ≥60 to <90 mL/min/1.73 m²) and by 0.1 mmol/L with empagliflozin 25 mg vs no change with placebo in stage 3 CKD (≥30 to <60 mL/min/1.73 m²; in this study, there was no empagliflozin 10 mg group, as patients with stage 3 CKD were randomised to either empagliflozin 25 mg or placebo).79

### 6.5.7 Plasma lipids

Raised levels of LDL-C are independent predictors of CV risk, therefore, changes in lipid profiles reported during treatment with SGLT2 inhibition have caused some concern.104 Dose-related increases in LDL-C were observed with canagliflozin: pooled data from four 26-week placebo-controlled trials revealed the mean percentage increases from baseline in LDL-C for 100 and 300 mg canagliflozin relative to placebo were 4.5% and 8.0%, respectively.36 Monitoring of LDL-C and treatment per standard care is recommended after initiating canagliflozin.36 No clinically significant effect on lipid levels occurred in the individual dapagliflozin phase 3 trials (as monotherapy plus as add-on combination therapy) reviewed in a recent report,86 and overall small mean changes in LDL-C were observed in patients receiving dapagliflozin (ranging from ~0.5% to +9.5%).36 For empagliflozin, a pooled analysis of 17 randomised controlled trials and six extension studies reported small increases in LDL-C with placebo.
6.5.8 | Neoplasia

The relationship of SGLT2 inhibitors and neoplasia is also being examined, following a potential signal from dapagliflozin studies. A numerical excess of cases of breast cancer and bladder cancer was noted in the regulatory reports for dapagliflozin, although the incidence rates per 100 patient-years for tumours (identified using the standard MedDRA query “malignant or unspecified tumours”) were similar for dapagliflozin (1.4%) and placebo/comparator (1.3%). The European Medicines Agency assessment stated that a causal relationship was unlikely, and with such low numbers these results could have been found by chance, but further data are required before a signal can be ruled out. In the meantime, as a precautionary measure, dapagliflozin is not recommended in patients being treated with pioglitazone, as epidemiological data suggest a small increased risk of bladder cancer with pioglitazone. For canagliflozin, the incidence of breast or bladder tumours was low and occurred at a similar rate across treatment groups (breast cancer 0.38%-0.46% vs 0.4%; bladder cancer 0.06%-0.09% vs 0.11% for canagliflozin 100 and 300 mg groups vs non-canagliflozin groups, respectively). Similar findings were reported for renal cell cancer events (0.06%-0.09% vs 0.08% for canagliflozin vs non-canagliflozin groups, respectively). For empagliflozin, a European Medicines Agency Assessment Report noted that a risk of malignant melanoma and urinary tract malignancies cannot be ruled out but there are currently insufficient long-term data to determine the level of risk.

7 | CLINICAL PRACTICE CONSIDERATIONS

Sodium-glucose co-transporter type 2 inhibition represents a novel therapeutic approach that has generated considerable interest in the diabetes community. For the first time, a glucose-lowering mode of action is orchestrated by an insulin-independent mechanism targeting an organ that, although known to play a central role in glucose metabolism, had been widely neglected in drug development efforts for T2DM. Current randomised controlled trials have demonstrated that SGLT2 inhibitors improve glycaemic control in T2DM by reducing HbA1c, fasting plasma glucose and postprandial glucose levels. Additional effects include reductions in body weight and modest decreases in BP, attributes that could also benefit patients with T2DM.

Excitement about SGLT2 inhibitors increased when results of the EMPA-REG OUTCOME study were reported, showing reduced risk of major CV events or death from any cause with empagliflozin added to standard of care in patients with T2DM who were at increased CV risk. This may suggest that an SGLT2 inhibitor—presumably empagliflozin until equivalent evidence is available for the class—would be considered for all patients with T2DM and a history of CV disease. For most patients, however, metformin will remain the first-line treatment option: in the diabetes management algorithm issued jointly by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) in 2016, SGLT2 inhibitors are listed as a therapeutic alternative for patients with T2DM in whom metformin is not tolerated or otherwise contraindicated. The AACE/ACE algorithm also states that SGLT2 inhibitors could be used as add-on therapy to metformin, or in combination with two or three other agents, including insulin. The 2016 guidelines on glycaemic treatment from the American Diabetes Association include SGLT2 inhibitors as one of six therapeutic options for second-line therapy as add-on to metformin in patients with T2DM. The guidelines also note that SGLT2 inhibitors might be useful in patients with deteriorating glycaemic control by improving control and reducing the amount of insulin required. In primary care, we may be considering these agents for improving glycaemic control alongside benefits attributed to weight loss and BP reduction. Moreover, the oral, once-daily dosing of all three SGLT2 inhibitors described in this article supports convenience for patients, an attribute that may also have the potential to impact overall compliance and adherence. Nonetheless, although SGLT2 inhibitors reflect a novel and promising development, it will be the responsibility of the individual healthcare professional to weigh the benefits and risks of the different SGLT2 inhibitors for their patients. Based on individualised and informed treatment decision-making, physicians will need to carefully reflect on which patients are most appropriate for initiating these drugs. Evidence of their long-term safety and efficacy profiles is emerging from the results of trials of up to 4 years in duration, although information from postmarketing reports will also be of keen interest as these agents are used more widely in clinical practice.

7.1 | How will SGLT2 inhibitors fit into current treatment algorithms and practices?

For patients starting glucose-lowering therapy, metformin will be and remain the typical first-line agent; hence, SGLT2 inhibitors would most likely be considered among the options for add-on therapy in patients not achieving therapeutic targets with metformin with and without additional glucose-lowering therapies. They could of course also be considered as starting therapy for patients who are unable to tolerate metformin (eg, because of gastrointestinal side effects). In clinical trials, SGLT2 inhibitors have been successfully used as monotherapy and as add-on therapy with metformin alone or in combination with sulphonylureas, thiazolidinediones, DPP-4 inhibitors and insulin. Hence, SGLT2 inhibitors have proven to significantly improve glucose control either alone or in dual or triple combination with other commonly used oral glucose-lowering agents. In addition, their potential to be used in patients already on insulin regimens could be an alternative to increasing insulin doses and/or frequency of injections. This is further supported by the fact that SGLT2 inhibition is independent of insulin secretion/activity, and may therefore play a significant role along the entire course of type 2 diabetes, including in those patients with long-standing disease.
Sodium-glucose co-transporter type 2 inhibitors are generally well tolerated and trials have reported few serious adverse events to date. Hypoglycaemic episodes were mostly mild in severity and their frequency was comparable to that seen with placebo. However, when SGLT2 inhibitors are used with other agents known to increase hypoglycaemic risk, such as sulphonylureas and insulin, the risk of hypoglycaemia may increase and the prescribing information for SGLT2 inhibitors recommends appropriate dose reduction of those background therapies. Genital infections and UTI have been consistently reported with SGLT2 inhibitors and, although episodes were mostly mild and non-recurrent, caution is advised in patients with a history of such conditions.

Patients with T2DM who may benefit from SGLT2 inhibitor therapy would be those who need to improve glycaemic control (particularly those with concomitant obesity or overweight in whom weight gain often caused by other anti-diabetes therapies should be avoided), those who are unwilling or unable to commence injections and who would otherwise need to progress to insulin therapy and those for whom hypoglycaemia is a particular concern. Patients with advanced renal impairment may not be considered appropriate for SGLT2 treatment and guidance is provided by the respective prescribing information available. In patients prone to hypovolaemia, the risk and benefits of SGLT2 inhibitors should be cautiously evaluated. If such a treatment is desired, correction of the hypovolaemic status should be ensured before initiating the SGLT2 inhibitor, including in those patients receiving loop diuretics and those who are volume-depleted (for example, because of acute gastrointestinal illness).

Sodium-glucose co-transporter type 2 inhibitors alter clinical factors known to be associated with increased CV risk in diabetes, such as overweight and hypertension, and there is evidence from the EMPA-REG OUTCOME study that SGLT2 inhibition can reduce CV mortality in high CV risk patients.1 Several CV outcome studies are ongoing and will provide evidence regarding the CV safety of this drug class as well as whether the CV benefit seen with empagliflozin is shared by other members of the class.

ACKNOWLEDGEMENTS

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors received no direct compensation related to the development of the manuscript. Writing assistance was provided by Debra Brocksmith, MB ChB, PhD, of Envision Scientific Solutions, which was contracted and funded by Boehringer Ingelheim Pharmaceuticals, Inc. (BIP). BIP was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

DISCLOSURES

P. Danda has received consultancy fees, grants and speaker fees from Boehringer Ingelheim. A. Chaudhuri has received speaker fees from Boehringer Ingelheim, AstraZeneca and Janssen.

REFERENCES

1. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117-2128.
2. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med. 1993;329:304-309.
3. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977-986.
4. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995;28:103-117.
5. UK Prospective Diabetes Study UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837-853.
6. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352:854-865.
7. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321:405-412.
8. Stark Casagrande S, Fradkin JE, Saydah SH, et al. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988-2010. Diabetes Care 2013; 36: 2271-2279.
9. Khan H, Lasker SS, Chowdhury TA. Exploring reasons for very poor glycaemic control in patients with type 2 diabetes. Prim Care Diabetes. 2011;5:251-255.
10. Fox KM, Gerber RA, Bolinder B, et al. Prevalence of inadequate glycemic control among patients with type 2 diabetes in the United Kingdom general practice research database: a series of retrospective analyses of data from 1998 through 2002. Clin Ther. 2006;28:388-395.
11. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2016 executive summary. Endocr Pract. 2016;22:84-113.
12. International Diabetes Federation IDF Diabetes, 7 ed. Brussels: International Diabetes Federation, 2015. http://www.diabetesatlas.org. Accessed May 13, 2016.
13. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2013;36:S67-S74.
14. Bays H. From victim to ally: the kidney as an emerging target for the treatment of diabetes mellitus. Curr Med Res Opin. 2009;25:671-681.
15. Hirsch IB, Molitch ME. Clinical decisions. Glycemic management in a patient with type 2 diabetes. N Engl J Med. 2013;369:1370-1372.
16. Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. Physiol Rev. 2011;91:733-794.
17. Hediger MA, Rhoads DB. Molecular physiology of sodium-glucose cotransporters. Physiol Rev. 1994;74:993-1026.
18. Thorens B, Mueckler M. Glucose transporters in the 21st century. Am J Physiol Endocrinol Metab. 2010;298:E141-E145.
19. Dominguez JH, Camp K, Maianu L, Garvey WT. Glucose transporters of rat proximal tubule: differential expression and subcellular distribution. Am J Physiol. 1992;262:F807-F812.
20. Zelikovic I. Aminoaciduria and glycosuria. In: Avner ED, Harmon WE, Niaudet P, eds. Pediatric Nephrology, 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004:701-728.
21. Moe OW, Wright SH, Palacin M. Renal handling of organic solutes. In: Brenner BM, Rector FC, ed. Brenner and Rector’s the Kidney. Philadelphia, PA: Saunders Elsevier; 2008:214-247.

22. Mogensen CE. Maximum tubular reabsorption capacity for glucose and renal hemodynamics during rapid hypertonic glucose infusion in normal and diabetic subjects. Scand J Clin Lab Invest. 1971;28:101-109.

23. Rahmoun H, Thompson PW, Ward JM, et al. Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes. Diabetes. 2005;54:3427-3434.

24. Vestri S, Okamoto MM, de Freitas HS, et al. Changes in sodium or glucose filtration rate modulate expression of glucose transporters in renal proximal tubular cells of rat. J Membr Biol. 2001;182:105-112.

25. Abdul-Ghani MA, Norton L, Defronzo RA. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. Endocrine Rev. 2011;32:515-531.

26. Wright EM, Turk E, Martin MG. Molecular basis for glucose-galactose malabsorption. Cell Biochem Biophys. 2002;36:115-129.

27. Zambrowicz B, Ogbaa I, Frazier K, et al. Effects of LX4211, a dual sodium-dependent glucose cotransporters 1 and 2 inhibitor, on postprandial glucose, insulin, glucagon-like peptide 1, and peptide tyrosine tyrosine in a dose-ranging study in healthy subjects. Clin Ther. 2013;35:1162-1173.e8

28. McCrimmon RJ, Evans ML, Jacob RJ, et al. AICAR and phlorizin reverse the hypoglycemia-specific defect in glucagon secretion in the diabetic BB rat. Am J Physiol Endocrinol Metab. 2002;283:E1076-E1083.

29. Rossetti L, Smith D, Shulman GI, et al. Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. J Clin Invest. 1987;79:1510-1515.

30. Han S, Hagan DL, Taylor JR, et al. Dapagliflozin, a selective SGLT2 inhibitor, improves glucose homeostasis in normal and diabetic rats. Diabetes. 2008;57:1723-1729.

31. Ljunggren Ö, Bolinder J, Johannson L, et al. Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin. Diabetes Obes Metab. 2012;14:990-999.

32. Ehrenkranz JR, Lewis NG, Kahn CR, Roth J. Phlorizin: a review. Diabetes Metab Res Rev. 2005;21:31-38.

33. Rossetti L, Shulman GI, Zawalich W, DeFronzo RA. Effect of chronic hyperglycemia on in vivo insulin secretion in partially pancreatectomized rats. J Clin Invest. 1987;80:1037-1044.

34. Chao EC, Henry RR. SGLT2 inhibition—a novel strategy for diabetes treatment. Nat Rev Drug Discov. 2010;9:551-559.

35. Isaji M. SGLT2 inhibitors: molecular design and potential differences in effect. Kidney Int Suppl. 2011;120:S14-519.

36. Janssen Pharmaceuticals, Inc. INVOKANA (canagliflozin) tablets, for oral use. Revised March 2016. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204629s005lbl.pdf. Accessed March 23, 2016.

37. AstraZeneca AB. Summary of product characteristics: dapagliflozin. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002415/WC500184865.pdf. Accessed March 23, 2016.

38. AstraZeneca Pharmaceuticals LP. FARXIGA® (dapagliflozin) tablets, for oral use. Revised December 2015. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/202293s008lbl.pdf. Accessed March 23, 2016.

39. Janssen-Cilag International NV. Summary of product characteristics: canagliflozin. Updated 13 January 2016. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000269/WC500156456.pdf. Accessed March 23, 2016.

40. Boehringer Ingelheim International GmbH. Summary of product characteristics: empagliflozin. Updated December 7, 2015. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002677/WC500168592.pdf. Accessed March 23, 2016.

41. Boehringer Ingelheim Pharmaceuticals, Inc. JARDIANE® (empagliflozin) tablets, for oral use. Updated March 18, 2016. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204629s005lbl.pdf. Accessed March 23, 2016.

42. Henry RR, Thakkar P, Tong C, et al. Efficacy and safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. Diabetes Care. 2015;38:2258–2265.

43. Henry RR, Rosenstock J, Edelman S, et al. Exploring the potential of the SGLT2 inhibitor dapagliflozin in type 1 diabetes: a randomized, double-blind, placebo-controlled pilot study. Diabetes Care. 2015;38:412-419.

44. Piette TR, Favilla S, Elbirchan J, et al. Empagliflozin as adjunct to insulin in patients with type 1 diabetes: a 4-week, randomized, placebo-controlled trial (EASE-1). Diabetes Obes Metab. 2015;17:928-935.

45. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. Diabetes Care. 2015;38:1638-1642.

46. Fitchett D, Zinman B, Wanner C, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME(R) trial. Eur Heart J. 2016;37:1526-1534.

47. Cherney DZ, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation. 2014;129:587-597.

48. Chilton R, Tikkkanen I, cannons CP, et al. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. Diabetes Obes Metab. 2015;17:1180-1193.

49. Inzucchi SE, Zinman B, Wanner C, et al. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. Diab Vasc Dis Res. 2015;12:90-100.

50. Neal B, Perkovic V, de Zeeuw D, et al. Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS) – a randomized placebo-controlled trial. Am Heart J. 2013;166:217-223.e11

51. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2015;370:323-334.

52. Ptaszynska A, Johnsson KM, Parkih SJ, et al. Safety profile of dapagliflozin for type 2 diabetes: pooled analysis of clinical studies for overall safety and rare events. Drug Saf. 2014;37:815-829.

53. Heerspink HJ, Desai M, Jardine M, et al. SGLT2 inhibitors and renal glucose filtration rates: proposed pathways and review of ongoing outcome trials. J Am Soc Nephrol. 2017;28:368-375.

54. Ferrannini E, Ramos SJ, Salsali A, et al. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care. 2010;33:2217-2224.

55. Roden M, Weng J, Elbirchan J, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol. 2013;1:208-219.

56. Stenlöf K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab. 2013;15:372-382.

57. del Prato S, Nauck M, Durán-García S, et al. Long-term glycaemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in patients with type 2 diabetes: 4-year data. Diabetes Obes Metab. 2015;17:581-590.
58. Häring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care. 2014;37:1650-1659.

59. Riderstråle M, Andersen KR, Zeller C, et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endocrinol. 2014;2:691-700.

60. Schumm-Draeger PM, Burgess L, Korányi L, et al. Twice-daily dapagliflozin co-administered with metformin in type 2 diabetes: a 16-week randomized, placebo-controlled clinical trial. Diabetes Obes Metab. 2015;17:42-51.

61. Matthaei S, Bowering K, Rohwedder K, et al. Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: a 24-week randomized, double-blind clinical trial. Diabetes Care. 2015;38:365-372.

62. Kovacs CS, Seshiah V, Swallow R, et al. Empagliflozin improves glycemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. Diabetes Obes Metab. 2014;16:147-158.

63. Rosenstock J, Vico M, Wei L, et al. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA1c, body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care. 2012;35:1473-1478.

64. DeFronzo RA, Lewin A, Patel S, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care. 2015;38:384-393.

65. Jabbour SA, Hardy E, Sugg J, et al. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care. 2014;37:740-750.

66. Lewin A, DeFronzo RA, Patel S, et al. Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes. Diabetes Care. 2015;38:394-402.

67. Neal B, Perkovic V, de Zeeuw D, et al. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. Diabetes Care. 2015;38:403-411.

68. Rosenstock J, Jelaska A, Zeller C, et al. Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78-week randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2015;17:936-948.

69. Rosenstock J, Jelaska A, Frappin G, et al. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. Diabetes Care. 2014;37:1815-1823.

70. Nauck MA, del Prato S, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care. 2011;34:2015-2022.

71. Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet. 2013;382:941-950.

72. Ji L, Ma J, Li H, et al. Dapagliflozin as monotherapy in drug-naive Asian patients with type 2 diabetes mellitus: a randomized, blinded, prospective phase III study. Clin Ther. 2014;36:84-100.e9.

73. Kaku K, Maegawa H, Taniwaza Y, et al. Dapagliflozin as monotherapy or combination therapy in Japanese patients with type 2 diabetes: an open-label study. Diabetes Ther. 2014;5:415-433.

74. Nishimura R, Tanaka Y, Koivai K, et al. Effect of empagliflozin monotherapy on postprandial glucose and 24-hour glucose variability in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, 4-week study. Cardiovasc Diabetol. 2015;14:11.

75. European Medicines Agency. Forxiga (dapagliflozin). EMA assessment report. Procedure no. EMEA/H/C/002322. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002322/WC500136024.pdf. Accessed September 17, 2013.

76. Bailey CJ, Gross JL, Pieters A, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet. 2010;375:2223-2233.

77. Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney Int. 2014;85:962-971.

78. Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab. 2013;15:463-473.

79. Barnett AH, Mithal A, Manasse J, et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2014;2:369-384.

80. Bolinder J, Ljunggren Ö, Johansson L, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. Diabetes Obes Metab. 2014;16:159-169.

81. Weir MR, Januszewicz A, Gilbert RE, et al. Effect of canagliflozin on blood pressure and adverse events related to osteosclerotic diuresis and reduced intravascular volume in patients with type 2 diabetes mellitus. J Clin Hypertens. 2014;16:875-882.

82. Sjöström CD, Johansson P, Ptaszynska A, et al. Dapagliflozin lowers blood pressure in hypertensive and non-hypertensive patients with type 2 diabetes. Diab Vasc Dis Res. 2015;12:352-358.

83. Tikkanen I, Narko K, Zeller C, et al. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. Diabetes Care. 2015;38:420-428.

84. Amin NB, Wang X, Mitchell JR, et al. Blood pressure-lowering effect of the sodium glucose co-transporter-2 inhibitor ertugliflozin, assessed via ambulatory blood pressure monitoring in patients with type 2 diabetes and hypertension. Diabetes Obes Metab. 2015;17:805-808.

85. Kim SY, Guevara JP, Kim KM, et al. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. Arthritis Care Res. 2010;62:170-180.

86. Ptaszynska A, Hardy E, Johannson E, et al. Effects of dapagliflozin on cardiovascular risk factors. Postgrad Med. 2013;125:181-189.

87. Wilding JP, Charpentier G, Hollander P, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial. Int J Clin Pract. 2013;67:1267-1282.

88. Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. Diabetes Care. 2013;36:2508-2515.

89. Kohler S, Salsali A, Hantel S, et al. Safety and tolerability of empagliflozin in patients with type 2 diabetes. Clin Ther. 2016;38:1299-1313.

90. US Food and Drug Administration. FDA drug safety communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. Issued May 15, 2015. http://
91. Perkins BA, Cherney DZ, Partridge H, et al. Sodium-glucose cotransporter 2 inhibition and glycemic control in type 1 diabetes: results of an 8-week open-label proof-of-concept trial. Diabetes Care. 2014;37;1480-1483.

92. Taylor SI, Blau JE, Rother CI. SGLT2 inhibitors may predispose to ketoacidosis. J Clin Endocrinol Metab. 2015;100:2849-2852.

93. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013;159:262-274.

94. Johnsson KM, Ptaszynska A, Schmitz B, et al. Urinary tract infection in patients with diabetes treated with dapagliflozin. J Diabetes Complications. 2013;27:479-484.

95. Johnsson KM, Ptaszynska A, Schmitz B, et al. Urinary tract infections in patients with diabetes treated with dapagliflozin. J Diabetes Complications. 2013;27:473-478.

96. Nicolle LE, Capuano G, Fung A, Usiskin K. Urinary tract infection in randomized phase III studies of canagliflozin, a sodium glucose co-transporter 2 inhibitor. Postgrad Med. 2014;126:7-17.

97. Nyirjesy P, Sobel JD, Fung A, et al. Genital mycotic infections with canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. Curr Med Res Opin. 2014;30:1109-1119.

98. US Food and Drug Administration. Invokana (canagliflozin) tablets. NDA 204042. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM334550.pdf. Accessed 17 September 2013.

99. Barendse S, Singh H, Frier BM, Speight J. The impact of hypoglycemia on quality of life and related patient-reported outcomes in type 2 diabetes: a narrative review. Diabet Med. 2012;29:293-302.

100. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care. 2013;36:1384-1395.

101. Häring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care. 2013;36:3396-3404.

102. Watts NB, Bilezikian JP, Usiskin K, et al. Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2016;101:157-166.

103. Bilezikian JP, Watts NB, Usiskin K, et al. Evaluation of bone mineral density and bone biomarkers in patients with type 2 diabetes treated with canagliflozin. J Clin Endocrinol Metab. 2016;101:44-51.

104. Rodriguez-Gutiérrez R, Gonzalez-Saldivar G. Canagliflozin. Cleve Clin J Med. 2014;81:87-88.

105. US Food and Drug Administration. Dapagliflozin tablets, 5 and 10 mg. NDA202293. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm262994.pdf. Accessed September 17, 2013.

106. European Medicines Agency. Assessment Report: Jardiance (empagliflozin). March 20, 2014. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002677/WC500168594.pdf. Accessed March 17, 2016.

107. American Diabetes Association. Approaches to glycemic treatment. Sec. 7. In Standards of Medical Care in Diabetes – 2016. Diabetes Care. 2016;39:S52-S59.

108. Grempler R, Thomas L, Eckhardt M, et al. Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors. Diabetes Obes Metab. 2012;14:83-90.

109. Kasichayanula S, Liu X, Lacreta F, et al. Clinical pharmacokinetics and pharmacodynamics of dapagliflozin, a selective inhibitor of sodium-glucose co-transporter type 2. Clin Pharmacokinet. 2014;53:17-27.

110. Francke S, Mamidi RN, Solanki B, et al. In vitro metabolism of canagliflozin in human liver, kidney, intestine microsomes, and recombinant uridine diphosphate glucuronosyltransferases (UGT) and the effect of genetic variability of UGT enzymes on the pharmacokinetics of canagliflozin in humans. J Clin Pharmacol. 2015;55:1061-1072.

111. Lamos EM, Younk LM, Davis SN. Canagliflozin, an inhibitor of sodium-glucose cotransporter 2, for the treatment of type 2 diabetes mellitus. Expert Opin Drug Metab Toxicol. 2013;9:763-775.

112. Chen LZ, Jungnik A, Mao Y, et al. Biotransformation and mass balance of the SGLT2 inhibitor empagliflozin in healthy volunteers. Xenobiotica. 2015;45:520-529.

How to cite this article: Dandonia P, Chaudhuri A. Sodium glucose co-transporter 2 inhibitors for type 2 diabetes mellitus: an overview for the primary care physician. Int J Clin Pract. 2017;71:e12937. https://doi.org/10.1111/ijcp.12937