Current Opinion in Cardiology
2020, 35 : 2 178-186

REVIEW

Sodium-glucose cotransporter 2 inhibitors and type 2 diabetes: clinical pearls for in-hospital initiation, in-hospital management, and postdischarge

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Purpose of review
The aim of this article is to provide practical recommendations on safe initiation of sodium-glucose cotransporter 2 (SGLT2) inhibitors to in-patients as well as management of those who are already on SGLT2 inhibitors.

Recent findings
Robust data from stable outpatient cohorts indicate that the SGLT2 inhibitors are associated with clinically meaningful reductions in major adverse cardiovascular events, lower rates of hospitalization for heart failure, and a reduction in major kidney outcomes There is however a lack of information on how to initiate and manage SGLT2 inhibitors in an acute in-patient setting.

Summary
SGLT2 inhibitors may be cautiously appropriate for in-patients if all the criteria for safe use are met but good clinical judgment must prevail. Temporary withholding of SGLT2 inhibitors is appropriate in hospitalized patients during a period of stress and/or insulinopenia.

Keywords
diabetes, in-hospital initiation, in-hospital management, postdischarge, sodium-glucose cotransporter 2 inhibitors

INTRODUCTION

Since 2015, three cardiovascular outcome trials [1,2,3▪▪] and one renal outcome trial [4▪▪] of type 2 diabetes cohorts have provided robust evidence demonstrating that the sodium-glucose cotransporter 2 (SGLT2) inhibitors canagliflozin, dapagliflozin, and empagliflozin, when added to standard-of-care diabetes therapies, are associated with clinically meaningful reductions in major adverse cardiovascular events, lower rates of hospitalization for heart failure (HHF) and a reduction in major kidney outcomes. In short duration (24–52 weeks) trials with participants who had type 1 diabetes, SGLT2 inhibition was associated with improved glycated hemoglobin (A1C) levels and time in range without an increase in hypoglycemia as well as weight loss [5–8]. A recent trial that enrolled individuals with heart failure and reduced ejection fraction (HFrEF) showed lower risk of worsening heart failure and cardiovascular death with dapagliflozin in both the absence and presence of a history of type 2 diabetes [9▪▪]. Given that longer term studies with type 1 diabetes mellitus cohorts are necessary and more trials with SGLT2 inhibitors in people with heart failure are ongoing, it is likely that SGLT2 inhibitors will, for now, be primarily initiated in people who already have a confirmed type 2 diabetes mellitus diagnosis.

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Curr Opin Cardiol 2020, 35:178–186
DOI:10.1097/HCO.0000000000000704

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KEY POINTS

- SGLT2 inhibitors have been associated with clinically meaningful cardiorenal benefits in people with type 2 diabetes.
- Physicians working in the emergency department should familiarize themselves with the diagnostic features of SGLT2 inhibitor-associated diabetic ketoacidosis, which may be euglycemic.
- Initiation of SGLT2 inhibitors in the acute setting requires consideration of the individual's renal, metabolic, and hemodynamic status.
- Concomitant medications that have been associated with hypoglycemia and volume-depletion should be reviewed and adjusted, if required, prior to starting SGLT2 inhibitor therapy.
- SGLT2 inhibitor regimens in patients with diabetes should be halted three days prior to major surgeries and only resumed after carbohydrate intake and fluid balance have stabilized.
- SGLT2 inhibitor initiation should be accompanied by education on sick day management, and signs and symptoms of diabetic ketoacidosis as well as appropriate follow-up visits to monitor blood pressure, renal function, and glycemia.

Despite their broad clinical advantages, including cardiorenal benefits, A1C lowering, weight loss, and very low risk of hypoglycemia [1,2,3▪▪,4▪▪,9▪▪], in-hospital initiation or ongoing use of SGLT2 inhibitors requires a comprehensive understanding of the nuances around the safe use of this class of antihyperglycemic agents. Recognizing that not all physicians and their allied health colleagues routinely prescribe SGLT2 inhibitors or encounter individuals who are taking SGLT2 inhibitors in the hospital setting, the overarching goal of this manuscript was to synthesize a document with practical recommendations on how to safely initiate SGLT2 inhibitors to in-patients as well as manage those who are already on SGLT2 inhibitors. SGLT2 inhibitor-related trials, and case and safety reports that were published in PubMed, presented at professional conferences or in the public domain from January 1st, 1996 up to June 13th, 2019 were reviewed by the group independently and collectively. The recommendations within this document arose from discussions at an expert forum attended by the authors (one anesthesiologist/intensivist, one bariatric specialist, one cardiologist, one cardiac surgeon, and three endocrinologists) on June 14th, 2019 and are unanimously endorsed by the group.

What emergency department physicians should consider in individuals using sodium-glucose cotransporter 2 inhibitors

Diabetic ketoacidosis (DKA) is one of the most common diabetic decompensation emergencies. This potentially fatal condition, with reported mortality rates of 0.65–3.3%, stems from a complex disordered metabolic state that is characterized by the triad of hyperglycemia, metabolic acidosis, and ketonemia. The presentation of DKA is commonly triggered by inadequate insulin therapy and/or precipitating stressors, such as a cardiovascular event, trauma, or an infection [10].

DKA occurs commonly in individuals with type 1 diabetes mellitus with incidence estimates of between 4.6 and 8.0 per 1000 patient-years [11]. By comparison, DKA is rarer among people with type 2 diabetes mellitus where reported incidences range from 0.32 to 2.0 per 1000 patient-years [12]. Of note, persons with ketone-prone diabetes appear to be predisposed to DKA [13]. SGLT2 inhibitor-associated DKA is rare and estimated to occur in 0.1% or less of people with type 2 diabetes who are being treated with these agents [14].

The symptoms of DKA that present in the emergency department are often quite nonspecific (weakness, nausea, vomiting, abdominal pain, polyuria, polydipsia, shortness of breath, confusion) [15]. Emergency department personnel should therefore suspect DKA if the following are met at presentation [10]:

(1) a pH of 7.3 or less
(2) a bicarbonate concentration of 15 mmol/l or less
(3) an anion gap of more than 12 mmol/l
(4) positive serum or urine ketones (note however that serum ketone monitoring which measures β-hydroxybutyrate is more sensitive and specific for DKA than urine ketone monitoring which detects the less stable ketone acetoacetate [16])
(5) a plasma glucose level of at least 14 mmol/l (but may be lower with SGLT2 inhibitor treatment, i.e., euglycemic DKA, see below)
(6) the presence of a precipitating factor (acute illness, major surgical procedures including bariatric surgery, excessive exercise, low carbohydrate diet, excessive alcohol intake) [14]

Emergency department physicians and their colleagues should also be aware that several conditions can make DKA challenging to diagnose. These include the following [10]:

(1) a rise in bicarbonate levels (e.g., from vomiting) that produces a mixed acid–base disorder and a pH that is not as low as that observed in typical DKA

(2) enhanced renal glycosuria resulting in normal or only mildly increased blood glucose (e.g., pregnancy or use of SGLT2 inhibitors)
(3) significant osmotic diuresis that causes loss of ketones and creates a normal or only mildly elevated anion gap
(4) high levels of β-hydroxybutyrate which may not be detected by some serum ketone assays

It is important for physicians in the emergency department and allied health personnel to recognize that DKA can present in the absence of elevated plasma glucose levels. By way of their mechanism of action, SGLT2 inhibitors can modify the typical rise in plasma glucose levels that are associated with DKA and provide a milieu for 'euglycemic DKA' where plasma glucose levels are lower than the expected more than 14 mmol/l. Accordingly, sole reliance on plasma glucose levels in individuals taking SGLT2 inhibitors may result in DKA cases being overlooked. Proactive measurements of serum ketone levels, bicarbonate concentrations and the anion gap are warranted in these cases. If the patient is determined to not be in DKA, it may still be prudent to hold the SGLT2 inhibitor during an acute illness. If DKA is diagnosed, the patient should be admitted and treated with an insulin infusion and intravenous fluids with adequate carbohydrate. The patient should be closely monitored and only discharged after all DKA-associated metabolic and clinical derangements have been corrected. This is especially important as case reports suggest that SGLT2 inhibitor-associated DKA may result in prolonged ketonemia for up to 12 days or glycosuria for up to nine days after discontinuation of the SGLT2 inhibitor [17,18].

Hemodynamic and renal considerations when initiating sodium-glucose cotransporter 2 inhibitors in-hospital

Given the site and mechanism of action of SGLT2 inhibitors, the potential risk of experiencing urinary tract infections (UTIs), hypotension, and acute kidney injury (AKI) must be considered prior to initiating SGLT2 inhibitor therapy. Of note, the United States Food and Drug Administration (FDA) issued a safety update in 2015 suggesting an elevated risk of UTI and DKA with SGLT2 inhibitor use [19]. This was followed, a year later, by an FDA warning suggesting that the SGLT2 inhibitors, canagliflozin and dapagliflozin, may predispose users to AKI [20]. It should be noted that FDA warnings are based on case reports that do not prove causality, and that data from the randomized trials that have reported to date do not support the concept that these agents increase the risk of UTIs or AKI. A systematic review and metaanalysis of 112 randomized cohorts found that UTIs were the most frequently reported adverse outcome in SGLT2 inhibitor trials, although there was no increase in risk of UTIs with the SGLT2 inhibitors as a class relative to placebo [21▪]. Furthermore, UTIs were not increased with SGLT2 inhibitor therapies in the large outcome trials [1,2,3▪▪,4▪▪,9▪▪]. Despite these findings, good clinical judgment suggests that patients at high risk for UTI are not ideal candidates for SGLT2 inhibitor treatment. Four placebo-controlled outcome trials (three cardiovascular, one renal) have collectively demonstrated lower progression of diabetic kidney disease which likely resulted, at least in part, from the attenuation of estimated glomerular filtration rate (eGFR) decline [1,2,3▪▪,4▪▪]. In these same trials, the incidence of AKI was either neutral or reduced with SGLT2 inhibitor therapy [1,2,3▪▪,4▪▪]. Three independent metaanalyses conducted with outpatient populations support the notion that SGLT2 inhibitors might actually protect against AKI, but the mechanism remains uncertain [21▪,22▪,23▪]. Although there may be clinical concern that individuals with renal impairment who are at a greater risk of AKI may be more likely to develop AKI with SGLT2 inhibitor therapy, the large cardiovascular outcome trials have demonstrated either a reduction [24] or no change [25] in AKI with SGLT2 inhibitor therapy in patients with renal impairment (eGFR 30–< 60 ml/min/1.73 m^2). Notably, the Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) trial demonstrated a neutral effect with canagliflozin in patients with an eGFR in the 30–90-ml/min/1.73 m^2 range at baseline (4). Despite the data suggesting a neutral effect or potentially even protection against AKI with SGLT2 inhibitors, clinical practice guidelines still appropriately suggest withholding these agents during acute illnesses with reduced oral intake and potential for volume depletion [26].

SGLT2 inhibitors have also been associated in clinical trials with small but clinically meaningful lowering of both systolic and diastolic blood pressure. Importantly, these potential benefits occurred regardless of whether there was a history of hypertension [27] and also when there was moderate decline in kidney function (eGFR 30–60 ml/min/1.73 m^2) [4▪▪,28▪]. Because of osmotic diuresis and natriuresis, SGLT2 inhibition can be associated with a reduced plasma volume and volume-related adverse effects (e.g., hypotension). In a metaanalysis of 16 405 individuals from randomized controlled trials, volume depletion-related side-effects in the SGLT2 inhibitor-treated group were 1.28-fold greater compared with the control group [29]. Interestingly, volume-related adverse effects were increased in only one of the five large

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outcome trials with SGLT2 inhibitors [1,2,3▪▪,4▪▪,9▪▪]. Accordingly, clinicians must use clinical judgment when prescribing SGLT2 inhibitors. Risk of volume-related adverse effects is especially important to consider in those with low systolic blood pressure, the elderly or frail individuals, those with moderate renal impairment or individuals who are being treated with diuretics, renin–angiotensin system (RAS) blockers or other antihypertensive agents.

Inasmuch as in-patients are generally sicker, may be hemodynamically unstable, and therefore more likely to have fluctuating renal function compared with outpatients, a series of factors and potential actions must be considered prior to suggesting SGLT2 inhibitor therapy despite the potential benefits that have been observed in clinical trials (see Fig. 1). In cases where (declining) renal function is a concern, it would be worthwhile including a nephrologist in the circle of care.

Using sodium-glucose cotransporter 2 inhibitors safely for in-patients after an acute cardiovascular event

The outcome trials have revealed much information on the cardiovascular and renal benefits of SGLT2 inhibitors in stable outpatient settings [1,2,3▪▪,4▪▪]. There remains, however, a paucity of evidence-based data to support the use of SGLT2 inhibitors for cardiovascular patients in the acute setting. That said, SGLT2 inhibitors are not contraindicated in acute care and could therefore be considered for use in the in-hospital setting following a cardiovascular event (e.g., stroke, HHF, myocardial infarction or acute coronary syndrome, major adverse limb events in individuals with type 2 diabetes mellitus). However, prior to initiating SGLT2 inhibitor therapy in an in-patient who has recently experienced a cardiovascular event, it would be prudent to ensure that the individual satisfies three critical criteria (Fig. 2). First, her/his vital signs should be stable. This would encompass a steady systolic blood pressure of over 100 mmHg (an arbitrary threshold that should be interpreted in the context of the baseline blood pressure and good clinical judgement) and clinical euvolemia or hypervolemia. Second, renal function should be stable (see Fig. 2 for the eGFRs and the appropriate dosages at which SGLT2 inhibitors may be initiated) with no expected change in factors, such as medications, that may affect the renal system (e.g., diuretics and RAS blockers). Third, these individuals should not be scheduled for investigations such as contrast computed tomography and coronary angiography that require the use of contrast agents. In most cases, stability over 48 h would provide reassurance that an untoward hemodynamic, metabolic, or renal effect of SGLT2 inhibition can be avoided. However, it cannot be overemphasized that the 48-h window as well as the suggested algorithm (Fig. 2) must be undertaken

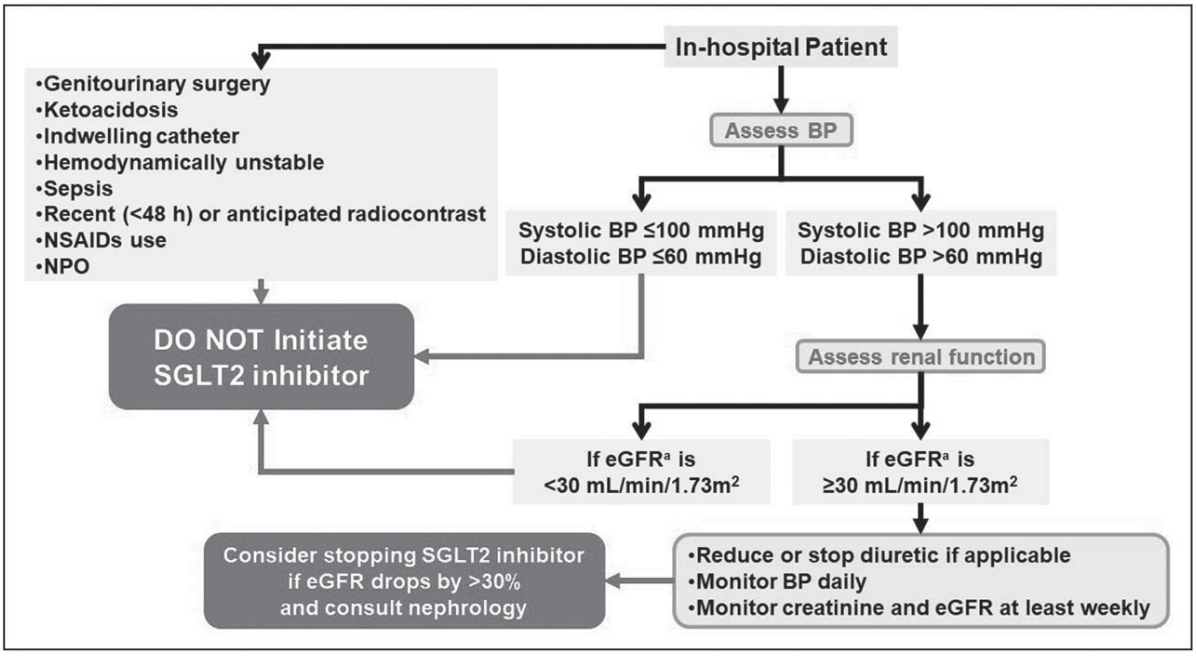

FIGURE 1. Renal and hemodynamic considerations for in-hospital initiation of SGLT2 inhibitors. *BP*, Blood pressure; *eGFR*, estimated glomerular filtrated rate; *NPO*, *nil per os* (nothing by mouth); *NSAIDs*, nonsteroidal antiinflammatory drugs. [a]Refer to local prescribing recommendations for eGFR considerations.

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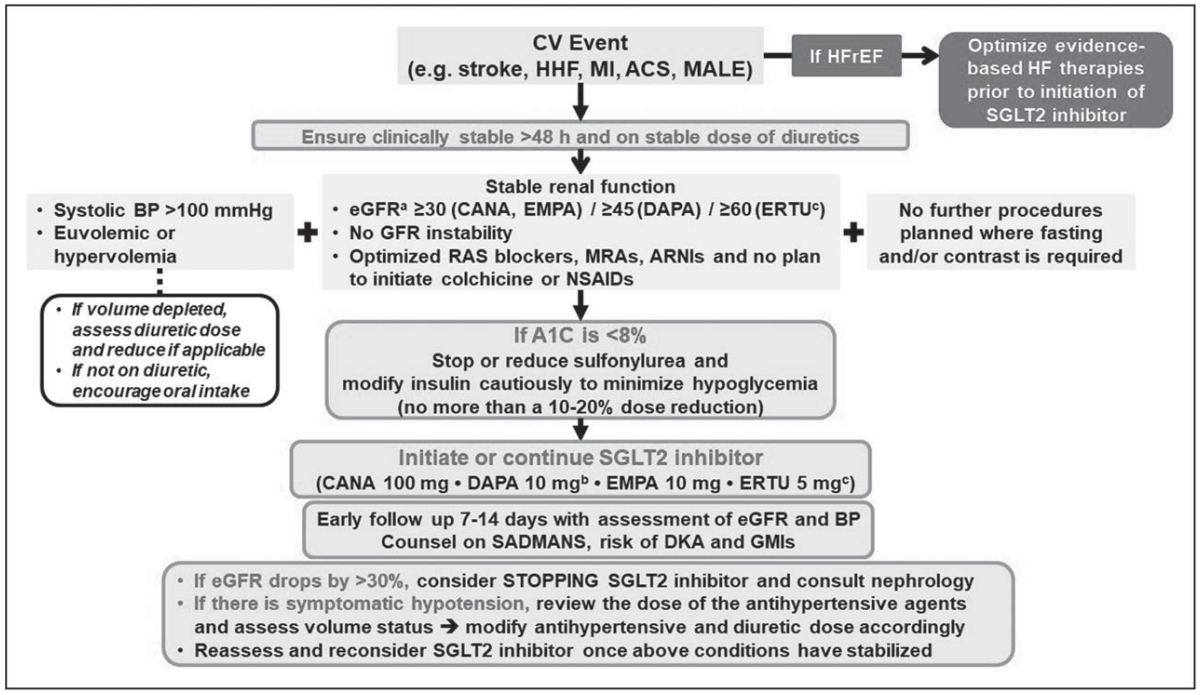

FIGURE 2. Considerations for managing in-patients on SGLT2 inhibitors who have recently had a cardiovascular event. *ACS*, Acute coronary syndrome; *ARNIs*, angiotensin receptor-neprilysin inhibitors; *BP*, blood pressure; *CANA*, canagliflozin; *CV*, cardiovascular; *DAPA*, dapagliflozin; *DKA*, diabetic ketoacidosis, *eGFR*, estimated glomerular filtrated rate; *EMPA*, empagliflozin; *ERTU*, ertugliflozin; *GMIs*, genital mycotic infections; *HF*, heart failure; *HFrEF*, heart failure with reduced ejection fraction; *HHF*, hospitalization for heart failure; *MALE*, major adverse limb events (amputation or limb ischemia); *MI*, myocardial infarction; *MRAs*, mineralocorticoid receptor antagonists; *NSAIDs*, nonsteroidal antiinflammatory drugs; *RAS*, renin–angiotensin system; *SADMANS*, a pneumonic developed by Diabetes Canada to underscore the need to hold medications (sulfonylureas, angiotensin-converting enzyme inhibitors, diuretics, and direct renin inhibitors, metformin, angiotensin receptor blockers, NSAIDs, SGLT2 inhibitors) that are likely to produce adverse drug responses during sick days. [a]Measured in ml/min/1.73 m^2; [b]may need to be adjusted according to local product monograph; [c]cardiovascular outcome trial results with ERTU are pending [26].

alongside good clinical judgment until more experience is gained with these agents. The RAS blockers perhaps provide an appropriate analogy as they were initially only used in the outpatient setting but with increased experience, they have proven safety and efficacy for early initiation in the in-patient setting.

SGLT2 inhibitor therapy may be started while the patient is in-hospital, at discharge or two to four weeks postdischarge depending on the individual circumstances and physician–patient conversation. Regardless of when the SGLT2 inhibitor is (re)introduced, the existing antihyperglycemic and antihypertensive regimens should first be reviewed and modified as clinically indicated. SGLT2 inhibitors, on their own, do not cause hypoglycemia, but the combination of an SGLT2 inhibitor with insulin or a sulfonylurea may trigger hypoglycemic episodes [30]. In such cases, proactive cautious reduction of the insulin dose (no more than a 10–20% reduction) or sulfonylurea dose would be appropriate. If hypotension is a concern, reduction of background diuretics or RAS blockers may be indicated. It is essential that if the physician–patient conversation results in consideration of SGLT2 inhibitor therapy, the initiation of the new regimen should be done in conjunction with education on the possible side-effects, appropriate lifestyle modification and a discussion on how to manage the medication on sick days [26,31]. Given the very limited data on in-hospital initiation of SGLT2 inhibitors, earlier than normal postdischarge follow-up to assess renal function, blood pressure, and overall well-being and to reinforce education strategies would not be unreasonable (see the 'Practical tips for postdischarge use of sodium-glucose cotransporter 2 inhibitors' section).

Perioperative management of sodium-glucose cotransporter 2 inhibitors – when to stop and re-start

People who live with diabetes are more likely than those without diabetes to require surgery and are also at a heightened risk of experiencing postoperative surgical complications [32]. The three

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primary concerns in surgical patients with diabetes and who are taking SGLT2 inhibitors are DKA, hypovolemia, and AKI. As all invasive surgical procedures can impose significant physiological stress which may in turn precipitate and exacerbate DKA as well as hypovolemia, it is imperative that perioperative clinicians who manage such individuals should be knowledgeable and vigilant about the possibility of DKA, which may be euglycemic, and thus be under or misdiagnosed if elevated glucose levels are relied upon to make a diagnosis (see above) [33▪].

The perioperative setting, given the related stress and likely reduced caloric and oral intake, can perpetuate a ketone-rich and hypovolemic milieu that predisposes to the development of SGLT2 inhibitor-associated DKA [14]. This is of particular concern in candidates for bariatric surgery who are typically requested to follow a low to very low-calorie diet for as long as two to three weeks before the surgery [34,35], or with other nonbariatric surgical patients where weight loss is desired to facilitate surgery. Indeed, a recent systematic review of SGLT2 inhibitor-associated perioperative DKA uncovered 47 cases of DKA: 42 of which were euglycemic DKA, including 12 bariatric cases with 10 of these precipitated by the very low-calorie diets [33▪]. These findings suggest that SGLT2 inhibitors should be withheld at the time of initiation of prebariatric surgery very low-calorie diets and that SGLT2 inhibitors should not be initiated or continued in any patient following very low-calorie diets (less than 900 kcal/day) or low-carbohydrate diets as a nonsurgical weight loss intervention, especially if the diet composes of less than 40 g carbohydrates/day. Although there are currently no specific recommendations regarding perioperative management of SGLT2 inhibitors in surgery, the available evidence suggests that SGLT2 inhibitors may be safely continued for minor surgeries [33▪] but should be held for at least 72 h prior to elective surgeries requiring anesthesia, analgesia, or sedation [14].

If an individual requires urgent or emergent surgery, it is recommended that the SGLT2 inhibitor be withheld immediately and surgery avoided for three days if possible, with efforts to maintain adequate hydration, carbohydrate intake, and glycemia. Monitoring for possible DKA should be considered until the patient is stable and asymptomatic postoperatively (serum electrolytes, anion-gap, and pH, β-hydroxybutyrate if indicated) and if previously on insulin, it should be continued pre and postoperatively with cautious adjustments (to avoid triggering DKA from insulin deficiency). If DKA develops despite heightened vigilance, endocrinology should be involved, and the usual protocol of volume resuscitation, electrolyte correction, and insulin infusion with dextrose be implemented.

Postsurgery feeding and rehydration are critical during the recovery phase. It would be prudent for SGLT2 inhibitor therapy to only be reintroduced after the nutritional and fluid balance are stabilized without ongoing hypovolemia, ketosis, or catabolism. This will on average take three to five days postoperatively although individuals who have undergone bariatric surgery will be subjected to a protracted recovery window (4–6 weeks) because they typically experience restricted caloric intake because of the resection of a significant portion of their stomach and may be at continued increased risk of volume contraction as they habituate to their oral intake.

Surgical patients should also be monitored perioperatively for the possibility of AKI. The resumption of SGLT2 inhibitor use should be delayed if renal function is unstable, if the current diuretic and antihypertensive regimens are being adjusted or if hemodynamic instability is occurring.

The key recommendations for managing surgical in-patients who are on SGLT2 inhibitors are summarized in Table 1.

Practical tips for postdischarge use of sodium-glucose cotransporter 2 inhibitors

SGLT2 inhibitors are often held once an individual is admitted to the hospital. This is a logical decision as the cause for admission could predispose the individual to DKA. Indeed, among those taking insulin, the risk of developing DKA may be compounded by the fact that in-patients often eat less because of what is ailing them or because they are

Table 1. Recommendations for managing surgical in-patients who have recently been treated with SGLT2 inhibitors

1	Individuals undergoing minor surgery may continue with their SGLT2 inhibitor regimen
2	SGLT2 inhibitor therapy should be withheld at least 72 h prior to all major surgeries, and plasma glucose levels closely monitored perioperatively
3	There should be vigilant postoperative monitoring for DKA even with normal plasma glucose levels and especially if signs or symptoms of DKA develop
4	SGLT2 inhibitor therapy should only be restarted after the nutritional and fluid balance are stabilized without hypovolemia, ketosis, or catabolism (approximately 3–5 days for most people; up to 4–6 weeks for those who have undergone bariatric surgery)
5	SGLT2 inhibitor therapy should only be restarted in individuals if their antihypertensive/diuretic therapy is stable and there is no ongoing hemodynamic or renal function instability

DKA, Diabetic ketoacidosis; *SGLT2*, sodium-glucose cotransporter 2.

Table 2. Questions to consider prior to initiating SGLT2 inhibitor therapy prior to or postdischarge and assessments to be conducted at follow-up

Question	Groups of interest
Why was the patient admitted and what was the course in-hospital?	Do not initiate in those with hemodynamic instability, dehydration, urinary tract infections, urosepsis, labile blood pressure, or hypotension until these conditions have resolved
What other medical issues does the patient have?	Caution in the elderly and those with a history of falls, lower eGFRs, and frailty
What other medications is the individual taking and do they need to be adjusted?	Particular attention should be paid to those who are taking antihypertensive agents/diuretics and antihyperglycemic agents that can cause hypoglycemia
Are there important indications of this patient to be taking SGLT2 inhibitors?	Recommended in those with type 2 diabetes and established clinical cardiovascular disease, heart failure, or diabetic nephropathy
Follow-up assessments	
Renal function (creatinine, eGFR)	
Blood pressure (supine and upright)	
A1C	
Serum electrolytes, pH, β-hydroxybutyrate if signs or symptoms of DKA	

DKA, Diabetic ketoacidosis; *eGFR*, estimated glomerular filtration rate; *SGLT2*, sodium-glucose cotransporter 2.

required to fast for procedures thereby necessitating a down-titration of the insulin dose. If the patient's vital status is deemed to have stabilized, it may be appropriate to restart the SGLT2 inhibitor prior to discharge or at outpatient follow-up after several critical questions have been considered (Table 2).

There are currently no validated recommendations on how to manage and monitor people who are initiated on SGLT2 inhibitors in-hospital or are restarted on SGLT2 inhibitors upon or after they are discharged from the hospital. Individuals who are taking antihyperglycemic agents that have been associated with hypoglycemia (insulin and/or sulfonylureas) should have their glucose-lowering regimens reviewed and adjusted as necessary [30] and instructed to monitor their glucose levels regularly. The reader is referred to two excellent resources that provide guidance on how to adjust antihyperglycemic agents or antihypertensive/diuretic therapies that may increase the risk of side-effects when combined with SGLT2 inhibitors [15,36]. SGLT2 inhibitor users should be educated on sick day

Table 3. Summary of the potential benefits/advantages and potential side-effects of using SGLT2 inhibitors and potential actions to minimize risks

Potential benefits	Potential side-effects	Response to potential side-effects
Glucose control (without hypoglycemia)	Genital mycotic infections	Treat in the standard fashion and continue using SGLT2 inhibitor
Weight loss	Urinary tract infections	Treat in the standard fashion and continue using SGLT2 inhibitor
Blood pressure reduction	Volume depletion-related adverse events	Keep well hydrated and consider reducing or stopping diuretics/RAS blockers if hypotension is a concern
Improved renal outcomes	Acute kidney injury	Stop SGLT2 inhibitor for sick days
Reduced cardiovascular mortality and fewer hospitalizations heart failure	Hypoglycemia (if treated with sulfonylurea and/or insulin)	Consider decreasing or stopping sulfonylurea or cautiously reducing insulin dose (no more than a 10–20% reduction) if hypoglycemia is an issue and especially if A1C < 8.0%
Lower risk of MACE	Diabetic ketoacidosis (rare and may be euglycemic)	To avoid the risk of diabetic ketoacidosis, stop SGLT2 inhibitor for sick days or prior to major surgery, avoid very low-carbohydrate diets, caution with alcohol excess or extreme exercise, and avoid excessive insulin dose reduction
Oral tablet	Bone fractures (canagliflozin)	Consider factors that contribute to fracture risk (osteoporosis, falls)
	Rare amputations (canagliflozin)	Reinforce proper foot care

MACE, major adverse cardiovascular events; *SGLT2*, sodium-glucose cotransporter 2.
Adapted from Scheen AJ. 2016 [37].

management [26], the symptoms of DKA and when to seek medical attention, as well as other potential side-effects and how to manage them. It would be rational to reassess renal function and blood pressure within two weeks following discharge from the hospital and review any potential SGLT2 inhibitor-associated side-effects.

CONCLUSION

The body of evidence that supports the use of SGLT2 inhibitors in stable outpatients with type 2 diabetes is solid and growing, with demonstrated cardiorenal benefits, A1C lowering, weight loss, and rare hypoglycemia. There are compelling reasons for consideration of SGLT2 inhibitor initiation in hospitalized patients but at the same time, there are no official recommendations on when SGLT2 inhibitors may be considered in the acute setting. Given the current scarcity of information, SGLT2 inhibitors may be cautiously initiated if the in-patient fulfills all the criteria for safe use but good clinical judgment must always prevail. Table 3 summarizes the potential benefits and side-effects that in-patients may experience following initiation of SGLT2 inhibitor therapy and practical management strategies regarding side-effects. Ongoing research of SGLT2 inhibitor use in hospitalized patients will help to inform proper utilization of this important class of antihyperglycemic agents.

Acknowledgements

Hwee Teoh, Ph.D. of HTaq Biomedical Editorial and Education Services Inc. is acknowledged for writing and editorial support in the preparation of this manuscript.

Financial support and sponsorship

The conduct of the expert forum was supported by unrestricted grants from AstraZeneca (Canada), the Boehringer Ingelheim-Eli Lilly Diabetes Alliance (Canada), Janssen (Canada) and Merck (Canada). The development of this document was funded through unrestricted grants from AstraZeneca (Canada), the Boehringer Ingelheim-Eli Lilly Diabetes Alliance (Canada) and Janssen (Canada). The opinions expressed herein are those of the authors and do not necessarily reflect the views of the funders. The funders were not involved in the development, preparation, review or approval of the manuscript nor in the decision of submitting the manuscript for publication or the target journal.

Conflicts of interest

C.D.M. holds a Merit Award from the Department of Anesthesia at the University of Toronto and reports receiving honoraria from Amgen, Boehringer Ingelheim, and OctaPharma.
A.A. reports research support from Allergan and Sanofi; serving on advisory panels for and receiving speaker honoraria from Boehringer Ingelheim, Dexcom, Medtronic, Novo Nordisk, and Sanofi.
K.A.C. has received research grants to his institution from AstraZeneca and Boehringer Ingelheim, received support for travel to scientific meeting from Boehringer Ingelheim and honoraria for speaking engagements and ad hoc participation in advisory boards from AstraZeneca, Boehringer Ingelheim, and Janssen. K.A.C. is listed as an inventor on a patent application by Boehringer Ingelheim on the use of DPP-4 inhibitors in heart failure.
J.D.G. reports serving on advisory panels for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi; serving on speaker bureaus for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi.
S.A.G. has no conflicts of interest to report.
S.V. holds a Tier 1 Canada Research Chair in Cardiovascular Surgery; and reports receiving research grants and/or speaking honoraria from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Janssen, Merck, Novartis, Novo Nordisk, Sanofi, and Sun Pharmaceuticals. He is also the President of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization.
R.M.G. reports research support from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, Medtronic, Merck, Novartis, Novo Nordisk, Roche, Sanofi, and Takeda; serving on advisory panels for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Roche, Sanofi, and Takeda; speaker bureaus for Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, and Servier; consulting for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk, and Takeda.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

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