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Re-examining the widespread policy of stopping SGLT2 inhibitors during acute illness: A perspective based on the updated evidence

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Abstract

Sodium Glucose Co-Transporter-2 (SGLT2) inhibitors are now seen as an integral part of therapy in type 2 diabetes to not only control blood glucose but to improve cardiovascular and kidney outcomes. Diabetic Ketoacidosis (DKA) is an uncommon but a serious complication of type 2 diabetes which has a high case fatality rate. The absolute risk of DKA in large, prospective randomized clinical trials (RCTs) in people with type 2 diabetes using SGLT2 inhibitors has been very low, although the relative risk is higher in those assigned to SGLT2i compared with placebo. In those without diabetes prescribed SGLT2 inhibitors for heart failure or chronic kidney disease, the risk of DKA is similar to placebo. Over the course of the COVID-19 pandemic, cases of DKA have also been reported in cases of COVID-19 hospitalizations. Consensus guidelines have recommended that SGLT2 inhibitors should be avoided in cases of serious illness and suggest they are not recommended for routine in-hospital use. However, recent data suggest potential beneficial effects of SGLT2 inhibitors in the setting of acute illness with COVID-19 with no increase in adverse events and low rates of DKA which were non-severe. Given the low rates of DKA in cardiovascular outcome trials and in hospitalised type 2 diabetes patients, the potential for SGLT2 inhibitors not being re-initiated following discharge and their cardiovascular and kidney benefits, we believe the practice of routine "sick day" guidance should be re-examined based on current evidence with a call for further research in this area. Further high quality trials of initiation of SGLT2 inhibitors in people admitted to hospital with cardiovascular disease or kidney disease and trials of continuation of SGLT2 inhibitors in people with careful monitoring of DKA should be conducted. These should be further supplemented with large observational studies.

Background

Sodium Glucose Co-Transporter-2 (SGLT2) inhibitors, are a class of antihyperglycemic drugs that block the sodium-glucose cotransporter in the proximal tubule of the kidney, increasing urinary excretion of glucose as well as sodium. Recent cardiovascular outcome trials (CVOT) have examined the effects of SGLT2 inhibitors on major adverse cardiovascular events (MACE) and heart failure endpoints in people with type 2 diabetes at high cardiovascular risk. Despite within-class differences on 3-point MACE, all of these agents consistently showed a reduction of heart failure hospitalisation and recent studies have also shown that they are beneficial in those with heart failure and/or chronic kidney disease, irrespective of the ejection fraction or coexistence of diabetes.(1, 2) Thus, SGLT2 inhibitors are now seen as an integral part of therapy in type 2 diabetes to not only control blood glucose but to improve cardiovascular and kidney outcomes.

Diabetic Ketoacidosis (DKA) is an uncommon but serious complication of type 2 diabetes which has a high case fatality rate. In 2015, the US Food and Drug Administration (FDA) published a safety update about the association between use of SGLT2 and risk of DKA(3). This risk was first identified during off-label use of this medication class in patients with type 1 diabetes, who are at greater risk for DKA. The presentation and progression of DKA in any patient can be rapid with patients needing hospitalisation with loss of consciousness within 24 hours. It may also prove to be fatal. In type 2 diabetes, risk factors for DKA include acute illness, changes or omissions of insulin dose, surgery and other stressors, glucocorticoids, alcohol consumption, or reductions in calorie intake. (4) Recent studies have also shown that COVID-19 in people with diabetes is associated with higher risk of DKA(5). However, the overall risk of DKA in people admitted with COVID-19 is low and has not been reported in people without diabetes. This was also recently confirmed in the Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19) Trial.(6)

In view of previous data from CVOTs and the safety data from the DARE-19 trial, in this *Personal View*, we propose that the consensus recommendations of discontinuing SGLT2 inhibitors in people with acute illness, both in ambulatory settings and among those hospitalised, should be reconsidered so that appropriate patients may continue to benefit from the cardiovascular and kidney benefits of these therapies.

SGLT2 inhibitors and cardiovascular outcome trials (CVOTS)

The results of recent CVOTs have led to major changes in guideline recommendations for patients with type 2 diabetes. The EASD / ADA Consensus Report recommends SGLT2 inhibitors for patients at high cardiovascular risk independent of baseline HbA1c or HbA1c target to reduce cardiovascular risk in patients with type 2 diabetes.(7) Similarly, cardiology guidelines such as the European Society of Cardiology (ESC) guidelines on "Diabetes, Pre- diabetes and cardiovascular disease from 2019 (8) as well consensus statements from the American Heart Association (AHA) and American College of Cardiology (ACC)(9, 10) guidelines recommend SGLT2 inhibitors in patients to reduce cardiovascular morbidity at high / very high risk. Recently National Institute for Health and Care Excellence (NICE) has also recently updated their 2015 guidelines on management of type 2 diabetes in adults with the new recommendations on earlier use of SGLT2 inhibitors in people at high risk of cardiovascular disease, heart failure or chronic kidney disease.(11)

SGLT2 inhibitors have now also become broadly accepted as foundational treatment in heart failure joining the existing treatment options of β-blockers, renin-angiotensin system inhibitors (angiotensin converting enzyme inhibitors or angiotensin receptor blockers or angiotensin receptor neprilysin inhibitors), sacubitril/valsartan and mineralocorticoid receptor antagonists. Together, the DAPA-HF and EMPEROR-Reduced trials collectively showed that SGLT2 inhibitors reduced hospitalisations, reduced cardiovascular death and improved kidney outcomes.(12) These benefits were also observed irrespective of the presence of diabetes and SGLT2 inhibitors received (a Class I, Level A recommendation for the treatment of HFrEF in the European society of Cardiology 2021 guidelines). The evidence of benefit of SGLT2 inhibitors has recently been extended to patients with heart failure with preserved ejection fraction, as seen in EMPEROR-Preserved(13), the PRESERVED-HF Trial (14) and in the EMPagliflozin 10 mg Compared to Placebo, Initiated in Patients Hospitalised for acUte Heart faiLure (de Novo or Decompensated Chronic HF) Who Have Been StabilisEd (EMPULSE) (15) trial, regardless of the ejection fraction.

Glucose lowering therapies and COVID-19

Cardiometabolic diseases are an important risk factor for severe COVID-19 and mortality and the risk of acute cardiorenal complications are also high in people admitted to hospital with COVID-19. A recent meta-analysis of 44 studies with 14,866 patients showed that acute cardiac injury occurred in 15 % of patients (95 % confidence interval 5-38 %), venous-thromboembolism in 15 %, (95 % CI, 0-100 %) and acute kidney injury in 6 % (95% CI, 1-41%).(16) The safety of glucose lowering therapies in people with type 2 diabetes has therefore been questioned during the COVID-19 pandemic. The main entry receptor for SARS-CoV-2 is the angiotensin-converting enzyme 2 (ACE2).(17) In view of these concerns, early expert consensus recommendation suggested that SGLT2 inhibitors are safe for use in routine clinical practice during the pandemic but to avoid metformin and SGLT2 inhibitors in people admitted to hospital with COVID- 19 because of their possible risks of lactic acidosis and DKA respectively.(18-21). These recommendations, however, were based mainly on consensus opinions without any evidence from randomised controlled trials.

Despite the recommendations published during the pandemic, the absolute benefits of SGLT2 inhibitors particularly for cardiovascular and kidney outcomes is greatest in higher risk patients with a more favourable benefit risk balance.(22) SGLT2 inhibitors have beneficial effects on weight, glycaemic control and cardiovascular events including cardiovascular death and renal outcomes, which are associated within increased prevalence of COVID-19.(23) There are a number of other mechanisms by which SGLT2 inhibitors might potentially be beneficial such as improvements in oxidative stress, insulin resistance and low grade inflammation.(24, 25)

Over the course of the pandemic a few observational studies have evaluated the association of COVID-19 related outcomes in people prescribed SGLT2 inhibitors using routinely collected administrative data with majority having limitations due to observational nature of the studies. Initially there were case reports suggesting COVID-19 was associated euglycemic diabetic ketoacidosis in people with type 2 diabetes prescribed SGLT2 inhibitors. (26, 27) A nationwide registry study from Denmark examined the impact of glucose lowering therapies on risk of hospital admission and severe outcomes in people with COVID-19.(28) They examined the impact of GLP-1 receptor agonists and DPP4 inhibitors with SGLT2 inhibitor users on the risk of hospital admission and severe outcomes. The study found that current users of GLP-1 receptor agonists had an adjusted risk ratio of 0.89(95 % CI, 0.34-2.33) and users of DPP4 inhibitors have

an adjusted risk ratio of 2.42(95 % CI, 0.99-5.890 for 30 days mortality compared to those who were SGLT2 inhibitors users.(28)

Another recent observational database study reported that both GLP1-RA and SGLT2i use were associated with lower 60-day mortality compared with DPP4i use (OR 0.54 [95% CI 0.37–0.80] and 0.66 [0.50–0.86], respectively).(29) Use of both medications was also associated with decreased total mortality, emergency room visits, and hospitalisations. The largest study to evaluate the risk of COVID-19 related mortality in people with type 2 diabetes used a nationwide database of nearly 3 million people in England. (30) The adjusted hazard ratio for mortality for people on SGLT2 inhibitors prior to admission was 0.82 (95 % CI, 0.74-0.91). (30) The authors concluded that overall differences in risks and benefits for all glucose lowering therapies including SGLT2 inhibitors was small, and likely to be confounded by indication.(30)

SGLT2 inhibitors and DKA

DKA is most frequently encountered in those with type 1 diabetes but can also occur in patients with type 2 diabetes, typically during an acute illness, such as sepsis, myocardial infarction or stroke.(31) It represents a state of relative or severe insulin deficiency in conjunction with high levels of counter-regulatory hormones that promote significant hyperglycemia, increased lipolysis, and the production of ketone bodies by the liver (Figure). Classically patients with DKA have extremely high blood glucose concentrations (often above 500 mg/dl, 27.8 mmol/L). Water and electrolyte impbalaces and DKA are often encoutred in patients on SGLT2 inhibitors. Though patients with DKA during treatment with an SGLT2 inhibitor may present with near-normal or only mildly elevated blood glucose levels (<250mg/dl (13.9 mmol/L)), as a result of ongoing urinary glucose losses despite volume contraction.(32) In early reported case series of SGLT2i associated DKA, the absence of significant hyperglycaemia was felt to have delayed the recognition of this condition.(32) Diagnostic criteria for DKA include plasma glucose >250 mg/dl (13.9 mmol/L), arterial blood pH< 7.30, serum bicarbonate <18 MEq/L, elevated anion gap, and positive urinary (> 2+) or serum ketones. The UK Joint British Diabetes Societies (JBDS) inpatient care guidelines diagnostic criteria include presence of blood glucose of >11mmol/l, capillary ketone concentration of >3mmol/l or significant ketonuria ($\geq$2+) on standard urine sticks and bicarbonate concentration of <15mmol/L and/or venous pH <7.3.(33)

The degree of acidosis in DKA can be profound, sometimes resulting in blood pH <7.0. Volume contraction can also be significant, owing to the osmotic diuresis induced by hyperglycaemia. This may

be accompanied by acute kidney injury. The severity of acidaemia and hypovolaemia and the accompanying electrolyte derangements are also associated with complications of DKA, including cardiac dysrhythmias and mortality.(34)

The incidence of DKA in large, prospective randomized clinical trials (RCTs) using SGLT2 inhibitors has been very low, although the rate is higher in those assigned to SGLT2i compared to placebo (Table) (2, 13, 22, 35-42). However, the diagnostic criteria for DKA did vary among these trials. Risk factors noted with SGLT2 inhibitor-associated DKA include previously unrecognized latent autoimmune diabetes of adulthood (LADA), post-operative state, and a recent decrease in the dose of or the discontinuation of insulin.(43) Inpatient admission is also a reported risk for SGLT2 inhibitor associated DKA. In a retrospective multicentre cohort study from Australia, the risk of DKA in patients with type 2 diabetes during inpatient admission was small but higher in SGLT2 inhibitor vs non-SGLT2 inhibitor users, with planned fasting and surgery being identified as potential risk factors.(44)

The occurrence of diabetic ketoacidosis in studies of patients with established heart failure has been very low, with only 3 cases among 2368 patients (0.1%) receiving dapagliflozin in DAPA-HF,(22) and no cases of diabetic ketoacidosis in EMPEROR-Reduced(2), and 4 of 2996 patients (0.1%) receiving empagliflozin (compared to 5 cases among 2989 patients [0.2%] receiving placebo) in EMPEROR-Preserved(13). All 3 cases of diabetic ketoacidosis in DAPA-HF occurred in patients with a history of type 2 diabetes, with no occurrences among patients without diabetes.(45) More recently, the effects of sotagliflozin, a dual inhibitor of SGLT 1 and 2, was studied in the Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure trial (SOLOIST-WHF).(42) Importantly, patients in SOLIST-WHF uniformly had a history of type 2 diabetes and were enrolled during or shortly following worsening of existing heart failure requiring intravenous diuretic therapy. This usually occurred in a hospital setting; thus constituting a population with more impaired New York Heart Association functional class, lower median estimated glomerular filtration rate, and higher median natriuretic peptide levels compared to DAPA-HF. Among this cohort, DKA occurred in 2 of 605 (0.3%) patients receiving sotagliflozin – comparable to the event rate in patients receiving placebo (4 of 611 patients [0.7%]).(42) Furthermore, SOLOIST proved that initiation of SGLT2 inhibition in the inpatient setting with heart failure was safe and well tolerated. This provides further evidence that inpatient use of SGLT2 inhibitors in hospitalized patients not in intensive care units is safe.(46)

DKA in people with diabetes and COVID-19

Not surprisingly, cases of DKA have been reported in the setting of COVID-19 hospitalizations.(47-50) Infections in general are common precipitant of DKA and any viral (or bacterial) infection can be a precipitant in predisposed individuals.(34) It has also been postulated that the virus may have potential direct toxic effects on pancreatic islets, further enhancing DKA risk.(51) Moreover, COVID-19 infections are associated with a marked inflammatory state and patients are frequently treated with glucocorticoids, both of which can contribute. In one survey involving 210 cases of DKA occurring in patients with COVID-19,(48) mortality and acute kidney injury was higher when compared to a contemporaneous group of patients with DKA but without COVID-19 infection. In addition, COVID-19 patients required higher insulin doses, longer duration of insulin infusion, and experienced slower resolution of DKA. In a systematic literature review and meta-analysis from January 2020 to January 2021 in patients with confirmed COVID-19 infection, previous SGLT2 inhibitor use was significantly associated with euglycemic DKA ($p=0.004$), but negatively associated with acute kidney injury ($p=0.023$).(52)

Consensus recommendations on SGLT2i during acute illness and during COVID-19 hospitalization

In general, the appropriate use of non-insulin glucose lowering therapies in the inpatient setting and during acute illness has not been studied systematically.(53) Additionally few studies have explored transition of diabetes care from home to hospital setting and later discharge.(54) The American Diabetes Association's Standards of Medical Care in Diabetes – 2021 (55) suggests that SGLT inhibitors "should be avoided in cases of severe illness, in patients with ketonemia or ketonuria, and during prolonged fasting and surgical procedures." They further posit that "Until safety and effectiveness are established, SGLT2 inhibitors are not recommended for routine in-hospital use." This recommendation was first introduced in the American Diabetes Association's Standards in 2017(56) and has continued in the recommendations since. We are not aware of other guidelines that address the SGLT2 inhibitor in the inpatient setting.

Treatment recommendations prior to surgery recommend that SGLT2 inhibitors should be discontinued 3 days prior to surgery to avoid the potential risk of euglycemic DKA.(57) The US Food and Drug Administration has also issued recommendations for each SGLT2 inhibitor, suggesting they be stopped at least 3 days before scheduled surgical procedures. The current perioperative diabetes guidance published from The Centre of Perioperative Care in the UK suggests that they should be stopped one day before an

elective surgery.(58) The concern regarding the use of SGLT2 inhibitor in the setting of acute illness and hospitalization is related to the potential for DKA, as reviewed previously. These logical recommendations stem from the recognition that stress hormones and the fasting state can increase lipolysis and ketone production, and this risk may be exaggerated in the setting of prevalent SGLT2 inhibitor therapy. Indeed, ketosis events in T1D SGLT2 inhibitor clinical trials has prevented approval of these agents for this subset of the population of patients with diabetes. The European Medical Agency in 2016 recommended that SGL2 inhibitors should be stopped immediately if DKA is suspected or confirmed and should not be re-started unless another cause for the ketoacidosis is identified and resolved.(59) In the UK, the JBDS inpatient care guidelines also recommend that SGLT2 inhibitors should be stopped in people who have DKA.(33)

Initiation of SGLT2 inhibitors people admitted to hospital

There have been few inpatient trials of SGLT2 inhibitor including SOLOIST discussed previously. Damman and colleagues reported the results of an 80-patient study in which patients with acute decompensated heart failure within 24 hours of presentation were randomized to empagliflozin 10 mg/d or matched placebo in 5 hospitals in the Netherlands. (60)Though there were no significant effects on the primary inpatient endpoints, there was a reduction in the combined endpoint of worsening heart failure, rehospitalisation for heart failure and death at 60 days, which occurred in 4 patients (10%) in the empagliflozin group vs. 13 patients (33%) in the placebo group (P = 0.014). Importantly there were no significant safety findings and the single case of DKA occurred in a placebo treated patient. A smaller study in Japan similarly suggested no new safety signals. (61)

Due to the potential beneficial effects of SGLT2 inhibitors during acute illness, such as COVID-19, as well as concerns about the safety of these agents in this patient population due to the potential risk of DKA, hypovolemia and acute kidney injury, it was imperative to evaluate these issues in a randomized clinical trial setting. Accordingly, the effectiveness and safety of SGLT2 inhibitor dapagliflozin was investigated in the Dapagliflozin in Respiratory Failure in Patients with Covid-19 (DARE-19) trial. This randomized 1250 patients with cardiometabolic risk factors (Type 2 diabetes, hypertension, ASCVD, heart failure or CKD) who were hospitalized with COVID-19 across 7 countries and 95 sites to either dapagliflozin 10 mg daily or placebo for 30 days.(62) Treatment was continued even if a patients' clinical status deteriorated at the point of requiring ICU level care, and regardless of hospital discharge. In addition, safety was closely monitored, in particular DKA and acute kidney injury. Specifically, due to

potential concerns regarding the risk of DKA in patients treated with dapagliflozin, a proactive surveillance program was used in the trial, with mandatory daily monitoring of acid-base status among those with Type 2 diabetes. If there was an abnormal increase in anion gap and/or reduced bicarbonate levels, measurement of blood levels of ketones, lactate, and analysis of pH were to be performed, and dapagliflozin was to be temporarily discontinued, if DKA was suspected. If a diagnosis of DKA was confirmed, treatment with SGLT2 inhibitors was to be discontinued.

Numerically fewer patients treated with dapagliflozin experienced the primary composite endpoint of respiratory, cardiovascular or kidney failure, or death from any cause at 30 days (HR 0.80, 95% CI 0.58-1.10); although this did not achieve statistical significance, the trial only accrued 156 of the initially planned 380 events (due to a large decline in mortality during the course of the trial) and therefore did not have sufficient power. Importantly, the results were directionally favourable to dapagliflozin across each component of this composite outcome, including all-cause mortality (HR 0.77, 95% CI 0.52 – 1.16).(6)

In DARE-19, dapagliflozin was well tolerated, with fewer serious adverse events than placebo. In total, 65 patients (10·6%) in the dapagliflozin group, and 82 (13·3%) in the placebo group were reported to have serious adverse events. Safety events of acute kidney injury were reported in 21 (3·4%) patients in the dapagliflozin group, and 34 (5·5%) in the placebo group. Diabetic ketoacidosis was reported in two patients in the dapagliflozin group both of whom had type 2 diabetes at baseline; these events were non-severe and resolved after study medication discontinuation.(6)

In view of the results of DARE-19 Trial, with suggestion of a possible therapeutic benefit for prevention of organ failure and death, the potential role of SGLT2 inhibitors in the treatment of COVID-19 continues to be investigated. Specifically, the investigators in the United Kingdom recently announced the addition of empagliflozin treatment arm in the RECOVERY platform trial, with patients being actively recruited(63) and the National Institutes of Health have added SGLT2 inhibitor domain to the Activ4a pragmatic trial platform which is evaluating promising treatments in patients hospitalized with Covid-19. Subsequently the Empagliflozin in patients hospitalised for acute heart failure(EMPULSE) trial has been published. In this double blind trial 530 patients with acute de novo or decompensated chronic heart failure were randomly assigned to empagliflozin 10 mg daily or placebo.(64) Initiation of empagliflozin resulted in a statistically significant and clinically meaningful benefit in 90 days after randomisation with reduction in all cause deaths, hospitalisation for heart failure and improvements in quality of life (using Kansas city Cardiomyopathy questionnaire) (HR 1.36,95% CI 1.09-1.68). Interstingly there were no cases of DKA in the empagliflozin arm.

Proposed management of patients admitted to hospital on SGLT2i

Upon introduction of SGLT2 inhibitors in clinical practice in people with T2 diabetes, caution was advised in using SGLT2i among the elderly, those on diuretic therapy, and those with kidney disease. Furthermore, most guidelines still recommend caution in using SGLT2 inhibitors in these groups and for them to be stopped in people acutely ill including in those hospitalised with COVID-19. However, there is now overwhelming evidence of the benefits of SGLT2 inhibitors on cardiovascular, heart failure and kidney outcomes, with benefits extending to essentially all subgroups of patients, including the elderly, those on diuretics and those with impaired kidney function - all groups that consistently derive greater absolute benefit with SGLT2 inhibitors in randomised trials in the outpatient setting. In addition, the hospitalisation period represents a unique opportunity to optimise cardiovascular care. A key concern is the potential for these cardiovascular and kidney protective therapies not being initiated during hospitalization, at the time or following discharge from hospital. One US study of patients with Type 2 diabetes hospitalized following a myocardial infarction showed that around half the patients following discharge from hospital may not have had their glucose lowering therapy commenced post-discharge.(65) Discontinuation of glucose lowering therapies is common in older patients admitted with acute myocardial infarction and is associated with higher mortality (66). There are no data for people on SGLT2 inhibitors admitted with COVID-19 but discontinuation rates are likely to be high.

In randomised controlled trials, SGLT2 inhibitors are associated with a significantly increased risk of DKA versus control, however in absolute terms, this only translates to a rate of approximately 1 per 1000 person-years.(67) The risks of continuing SGLT2 inhibitors appear exceedingly low in people with type 2 diabetes, whereas the risks of stopping these therapies are unknown. Wisdom of routine “sick day” guidance pertaining to these medications in both primary and hospitalised patients should therefore be re-examined as it has not necessarily fully evidence based. The DARE-19 trial demonstrated numerically better outcomes and low risk in people commenced on dapagliflozin in an acute setting, and raises a hypothesis that SGLT2 inhibitors may afford organ protection in other types of acute illness. The EMPULSE study also demonstrated significantly better outcomes in people admitted with heart failure and randomized to empagliflozin without a signal for DKA. This hypothesis needs further evaluation in future trials of SGLT2 inhibitors not being stopped in people admitted to hospital.

Based on the available evidence, SGLT2 inhibitors should not be routinely discontinued in all stable patients admitted with acute illness, including Covid-19. Continuation of SGLT2 inhibitor treatment in

these individuals should, instead, be considered, with close monitoring of volume and acid-base status (68). (Figure 2) Specifically, during acute illness not directly stemming from use of the medications (e.g., urinary tract infection), patients may be instructed to monitor ketones with self-monitored ketone testing and to stop SGLT2 inhibitors if ketones are detected and to inform their health care professional. Further high quality trials of initiation of SGLT2 inhibitors in people admitted to hospital with cardiovascular disease or kidney disease, and trials of continutation of SGLT2 inhibitors in people with careful monitoring of DKA should be conducted. These should be further supplemented with large observational studies.

In summary, new data suggest that prevailing guidelines concerning use of SGL2 inhibitors during acute illness and hospilisation need to be re-examined with additional research. We may be doing more harm than good in stopping this potentially valuable therapy during a time in which patients may continue to benefit from them.

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Figure 1. Mechanism of DKA associated with SGLT2 inhibitors

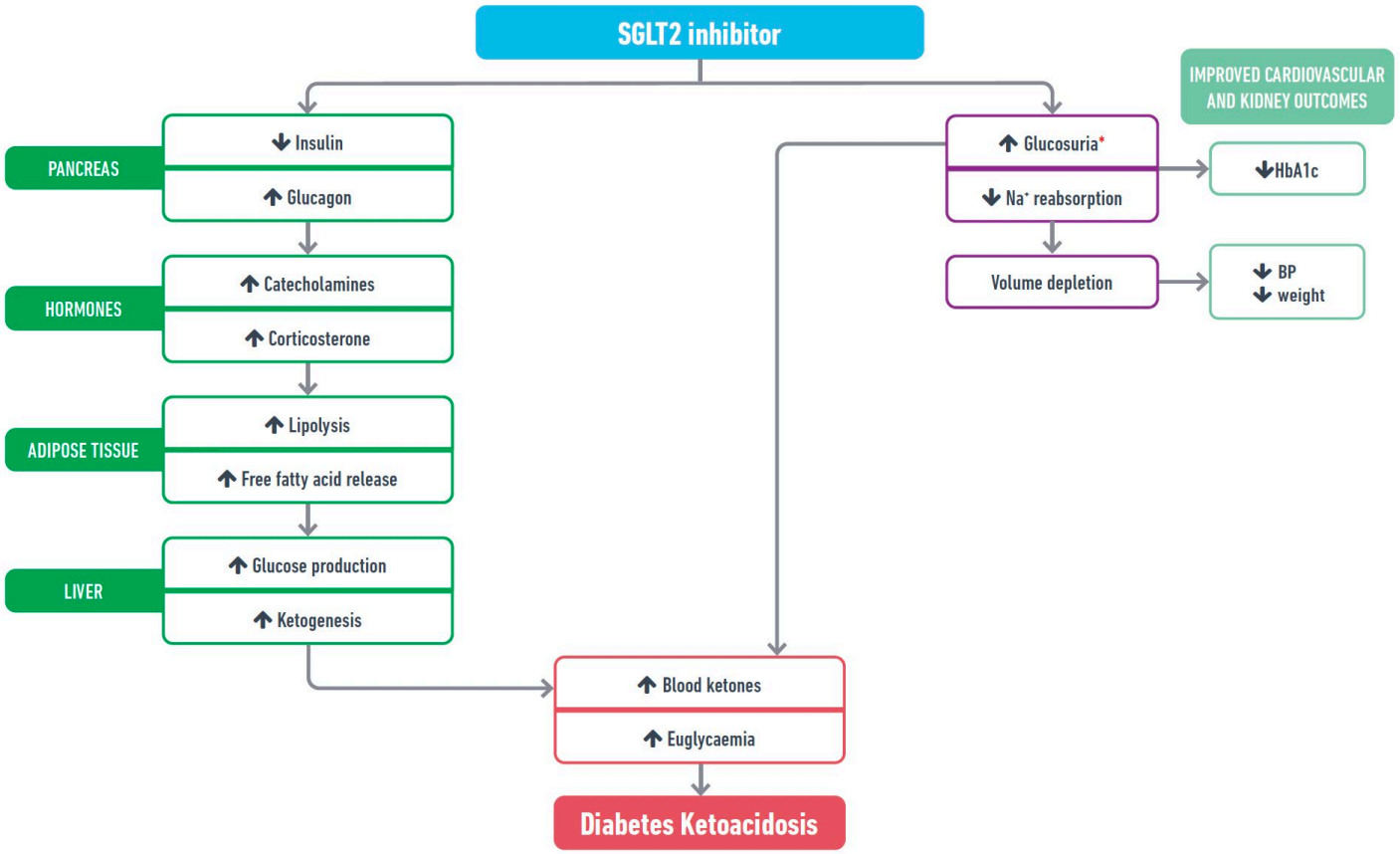
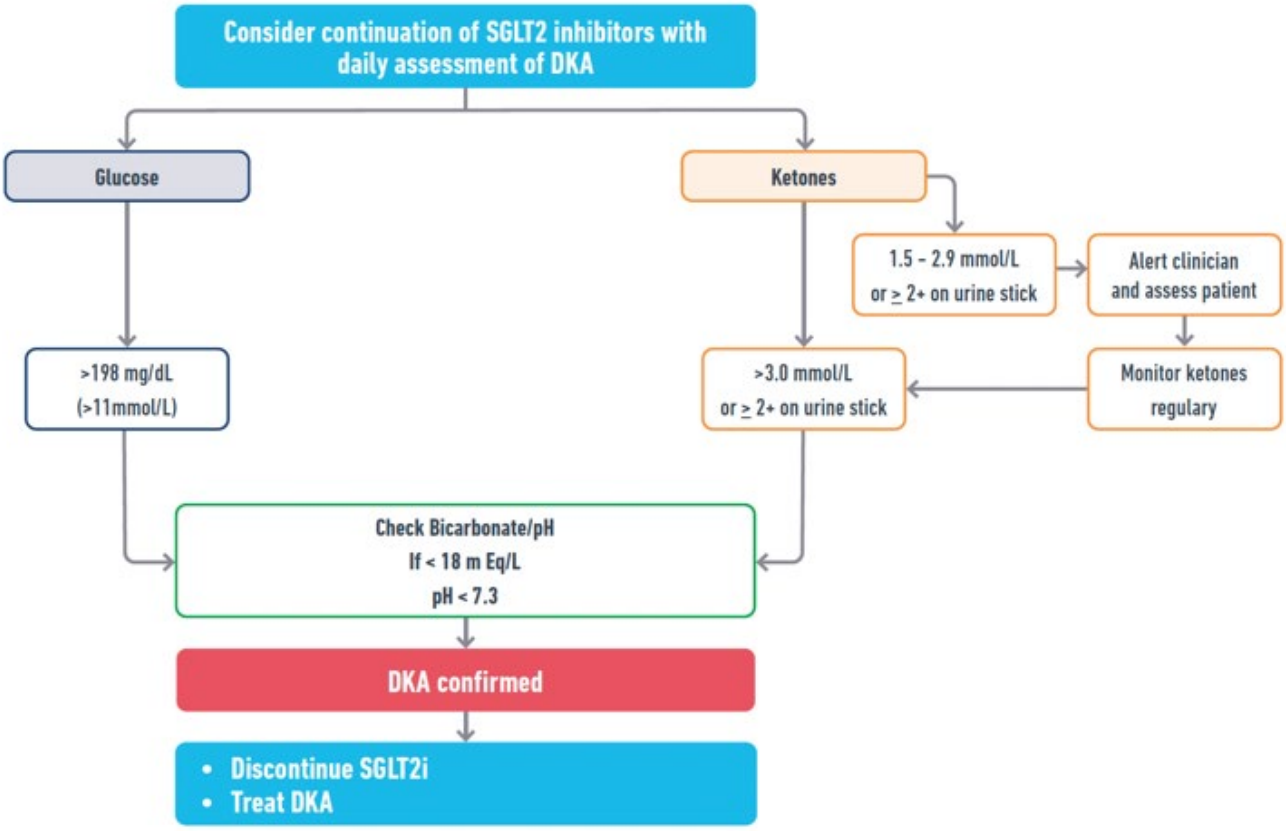


Table. Number and percentage of patients randomized to SGLT2i vs. placebo who developed DKA in recent large cardiovascular, renal, or heart failure outcome trials

Trial name (SGLT2i, publication year)	Population Descriptor	Median Follow-Up	SGLT2i group	Placebo group
EMPA-REG OUTCOME (empagliflozin, 2015)(35)	T2DM and established ASCVD	3.1 years	4/4687 (0.1%)	1/2333 (<0.1%)
CANVAS (canagliflozin, 2017)(36)	T2DM with established ASCVD or with CV risk factors	3.6 years (mean)	0.6/1000-patient-years*	0.3/1000 patient-year*
DECLARE (dapagliflozin, 2019)(37)	T2DM with established ASCVD or with CV risk factors	4.2 years	27/8574 (0.3%)	12/8569 (0.1%)
VERTIS CV (ertugliflozin, 2020)(39)	T2DM and established ASCVD	3.0 years	19/5493 (0.3%)	2/2745 (0.1%)
SCORED (sotagliflozin, 2021)(41)	T2DM, CKD (eGFR 25-60 ml/min/1.73 m^2) and CV risk factors	1.3 years^	30/5291 (0.6%)	14/5286 (0.3%)
CREDENCE (canagliflozin, 2019)(38)	T2DM and CKD (eGFR 30 to <90 ml/min/1.73 m^2 and albuminuria)	2.6 years	11/2200 (0.5%)	1/2197 (<0.1%)
DAPA-CKD (dapagliflozin, 2020)(40)	CKD (eGFR 25-75 ml/min/1.73 m^2 and albuminuria)	2.4 years	0/2149 (0%)	2/2149 (<0.1%)
DAPA-HF (dapagliflozin, 2019)(22)	Ejection fraction $\leq$ 40% and NYHA functional class II-IV	1.5 years	3/2368 (0.1%)	0/2371 (0%)
EMPEROR-Reduced (empagliflozin, 2020)(2)	Ejection fraction $\leq$ 40% and NYHA functional class II-IV	1.3 years	0/1863 (0%)	0/1863 (0%)
SOLOIST-WHF (sotagliflozin, 2021)(42)	T2DM, hospitalized for signs/symptoms of HF requiring IV diuretic treatment	0.75 years^	2/605 (0.3%)	4/611 (0.7%)
EMPEROR-Preserved (empagliflozin, 2021)	Class II-IV heart failure with an ejection fraction of > 40%	2.18 years	4/2996 (0.1%)	5/2989 (0.2%)
EMPULSE(64)	Patients admitted with heart failure regardless of ejection fraction	90 days	0/265	0/265

*Number and % not available ^trial ended early due to loss of funding from sponsor. CV, cardiovascular; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HF, heart failure

Figure 2. Proposed management of patients admitted to hospital on SGLT2 inhibitors



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