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Re-examining the widespread policy of stopping sodium-glucose cotransporter-2 inhibitors during acute illness: A perspective based on the updated evidence

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Abstract

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are now seen as an integral part of therapy in type 2 diabetes to control not only 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. The absolute risk of DKA in large, prospective randomized clinical trials in people with type 2 diabetes using SGLT2 inhibitors has been low, although the relative risk is higher in those assigned to SGLT2 inhibitors compared with placebo. In those without diabetes but 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 hospitalized patients with type 2 diabetes, 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. Furthermore, 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.

KEYWORDS
diabetes complications, type 2 diabetes, SGLT2 inhibitor, diabetic, retinopathy

1 | BACKGROUND

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a class of anti-hyperglycaemic 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 (CVOTs) have examined the effects of SGLT2 inhibitors on major adverse cardiovascular events and heart failure endpoints in people with type 2 diabetes at high cardiovascular risk. Despite within-class differences on 3-point major adverse cardiovascular events, all of these agents consistently showed a reduction of heart failure hospitalization and recent studies have 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 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 hospitalization with loss of consciousness within 24 h. 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 hospitalized, should be reconsidered so that appropriate patients may continue to benefit from the cardiovascular and kidney benefits of these therapies.

2 | SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS AND CARDIOVASCULAR OUTCOME TRIALS

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 glycated haemoglobin or glycated haemoglobin 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 hospitalizations, 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 heart failure with reduced ejection fraction 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 heart failure) who have been StabilisEd (EMPULSE)[15] trial, regardless of the ejection fraction.

3 | GLUCOSE-LOWERING THERAPIES AND COVID-19

Cardiometabolic diseases are an important risk factor for severe COVID-19 and mortality and the risks of acute cardiorenal complications are high in people admitted to hospital with COVID-19. A recent meta-analysis of 44 studies with 14 866 patients showed that an 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.[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 randomized controlled trials.

Despite the recommendations published during the pandemic, the absolute benefits of SGLT2 inhibitors particularly for cardiovascular and

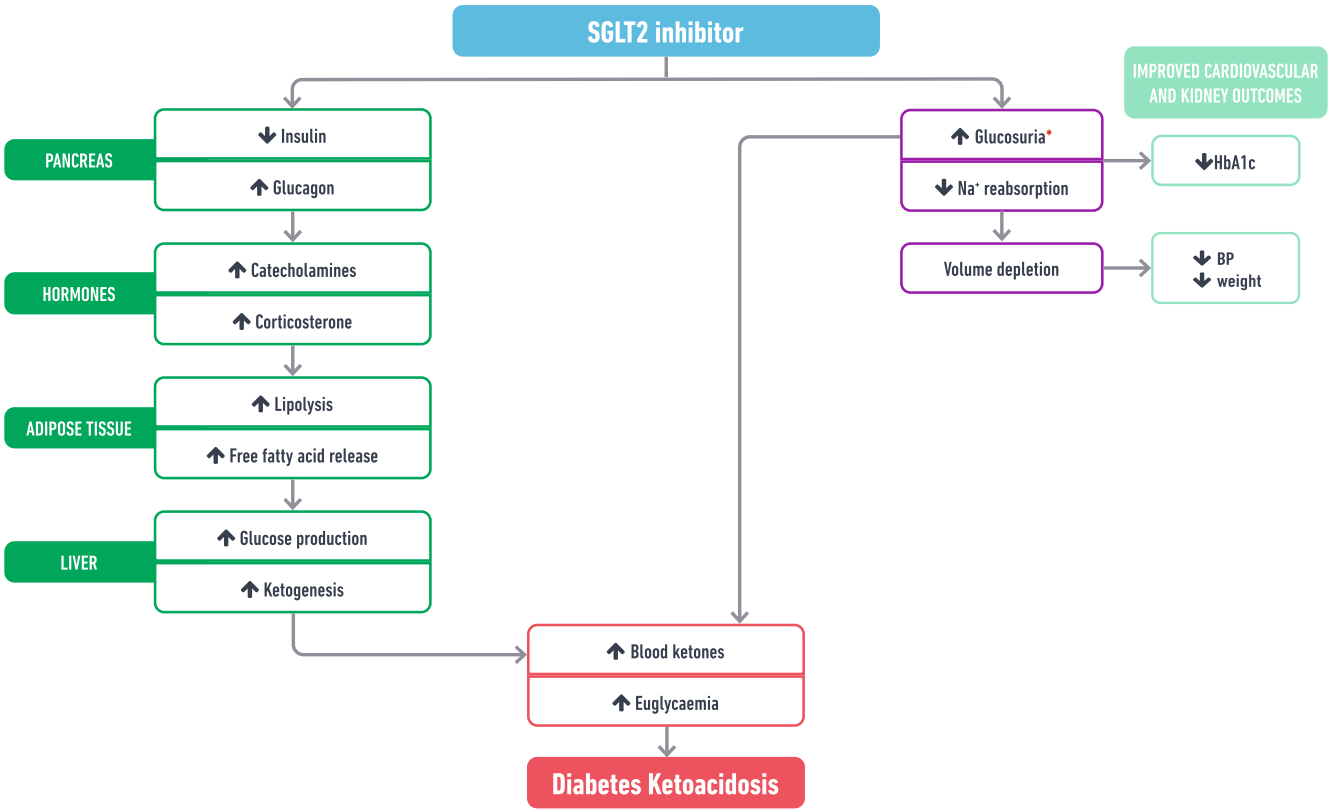

FIGURE 1 Mechanism of diabetic ketoacidosis associated with SGLT2 inhibitors. BP, blood pressure; HbA1c, glycated haemoglobin; SGLT2, sodium-glucose cotransporter-2

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 the majority having limitations because of the observational nature of the studies. Initially, there were case reports suggesting COVID-19 was associated with euglycaemic DKA 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 the risk of hospital admission and severe outcomes in people with COVID-19.[28] They examined the impact of glucagon-like peptide (GLP)-1 receptor agonists and dipeptidyl peptidase (DPP)4 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 with those who were SGLT2 inhibitors users.[28]

Another recent observational database study reported that both GLP1 receptor agonists and SGLT2 inhibitor use were associated with lower 60-day mortality compared with DPP4 inhibitor 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 hospitalizations. 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 (HR) for mortality for people on SGLT2 inhibitors before 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 would probably be confounded by indication.[30]

4 | SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS AND DIABETIC KETOACIDOSIS

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 hyperglycaemia, increased lipolysis and the production of ketone bodies by the liver (Figure 1). Classically, patients with DKA have high blood glucose concentrations (often >500 mg/dl, 27.8 mmol/L).

TABLE 1 Patients randomized to SGLT2is versus 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
Cardiovascular outcomes trials				
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[a]	0.3/1000 patient-years[a]
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[b]	30/5291 (0.6%)	14/5286 (0.3%)
Renal outcomes trials				
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%)
Heart failure outcomes trials				
DAPA-HF (dapagliflozin, 2019)[22]	Ejection fraction ≤40% and NYHA functional class II-IV	1.5 years	3/2368 (0.1%)	0/2371 (0%)
EMPEROR-reduced (empagliflozin, 2020)[2]	Ejection fraction ≤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 y[b]	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

[a]Number and % not available.
[b]Trial ended early because of loss of funding from sponsor.
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; IV, intravenous; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T2DM, type 2 diabetes.

Water and electrolyte imbalances and DKA are often encountered in patients using SGLT2 inhibitors. Patients with DKA during treatment with an SGLT2 inhibitor may present with near-normal or only mildly elevated blood glucose levels [<250 mg/dl (13.9 mmol/L)], because of ongoing urinary glucose losses despite volume contraction.[32] In early reported case series of SGLT2 inhibitor-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 inpatient care guidelines for diagnostic criteria include presence of blood glucose of >11 mmol/L, capillary ketone concentration of >3 mmol/L or significant ketonuria (≥2+) on standard urine sticks and bicarbonate concentration of <15 mmol/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 using SGLT2 inhibitors has been very low, although the rate is higher in those assigned to SGLT2 inhibitors compared with placebo (Table 1).[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, postoperative 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 versus non-SGLT2 inhibitor users, with planned fasting and surgery being identified as potential risk factors.[44]

The occurrence of DKA in studies of patients with established heart failure has been low, with only three cases among 2368 patients (0.1%) receiving dapagliflozin in the DAPA-HF trial,[22] and no cases of DKA in the EMPEROR-Reduced trial,[2] and four of 2996 patients (0.1%) receiving empagliflozin [compared with five cases among 2989 patients (0.2%) receiving placebo] in the EMPEROR-Preserved trial.[13] All three cases of DKA in the DAPA-HF trial 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 SGLT1 and -2, were studied in the Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial.[42] Importantly, patients in the SOLIST-WHF trial 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 with the DAPA-HF trial. Among this cohort, DKA occurred in two of 605 (0.3%) patients receiving sotagliflozin—comparable with the event rate in patients receiving placebo [four of 611 patients (0.7%)].[42] Furthermore, the 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]

5 | DIABETIC KETOACIDOSIS 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 precipitants 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 with a contemporaneous group of patients with DKA but without COVID-19 infection. In addition, patients with COVID-19 required higher insulin doses, longer duration of insulin infusion, and they experienced a 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 euglycaemic DKA ($p = .004$), but negatively associated with acute kidney injury ($p = .023$).[52]

6 | CONSENSUS RECOMMENDATIONS ON SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS 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] In addition, few studies have explored the 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 advice before surgery recommends that SGLT2 inhibitors should be discontinued 3 days before surgery to avoid the potential risk of euglycaemic 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 1 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 type 1 diabetes SGLT2 inhibitor clinical trials have 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 restarted unless another cause for the ketoacidosis is identified and resolved.[59] In the UK, the UK Joint British Diabetes Societies inpatient care guidelines also recommend that SGLT2 inhibitors should be stopped in people who have DKA.[33]

7 | INITIATION OF SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS IN PEOPLE ADMITTED TO HOSPITAL

There have been few inpatient trials of SGLT2 inhibitors, 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 h of presentation were randomized to empagliflozin 10 mg/day or matched placebo, in five hospitals in the Netherlands.[60] Although there were no significant effects on the

primary inpatient endpoints, there was a reduction in the combined endpoint of worsening heart failure, rehospitalization for heart failure, and death at 60 days, which occurred in four patients (10%) in the empagliflozin group versus 13 patients (33%) in the placebo group ($p = .014$). 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]

Because of 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 because of the potential risk of DKA, hypovolaemia 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 DARE-19 trial. This randomized 1250 patients with cardiometabolic risk factors (type 2 diabetes, hypertension, atherosclerotic cardiovascular disease, heart failure or chronic kidney disease) who were hospitalized with COVID-19 across seven 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, because of the potential concerns regarding the risk of DKA in patients treated with dapagliflozin, a proactive surveillance programme 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 (because of 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. DKA 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 discontinuation of study medication.[6]

In view of the results of the 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 the SGLT2 inhibitor domain to the Activ4a pragmatic trial platform, which is evaluating promising treatments in patients hospitalized with COVID-19. Subsequently, the 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 randomization with reduction in all-cause deaths, hospitalization for heart failure and improvements in quality of life (using the Kansas City cardiomyopathy questionnaire) (HR 1.36.95% CI 1.09-1.68). Interestingly, there were no cases of DKA in the empagliflozin arm.

8 | PROPOSED MANAGEMENT OF PATIENTS ADMITTED TO HOSPITAL ON SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS

Upon introduction of SGLT2 inhibitors in clinical practice in people with type 2 diabetes, caution was advised in using SGLT2 inhibitors 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 that were acutely ill, including in those hospitalized 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 all subgroups of patients, including the elderly, those on diuretics and those with impaired kidney function, i.e. all groups that consistently derive greater absolute benefit with SGLT2 inhibitors in randomized trials in the outpatient setting. In addition, the hospitalization period represents a unique opportunity to optimize 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 about 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 will probably be high.

In randomized 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 to be low in people with type 2 diabetes, whereas the risks of stopping these therapies are unknown. The wisdom of routine 'sick day' guidance pertaining to these medications in both primary and

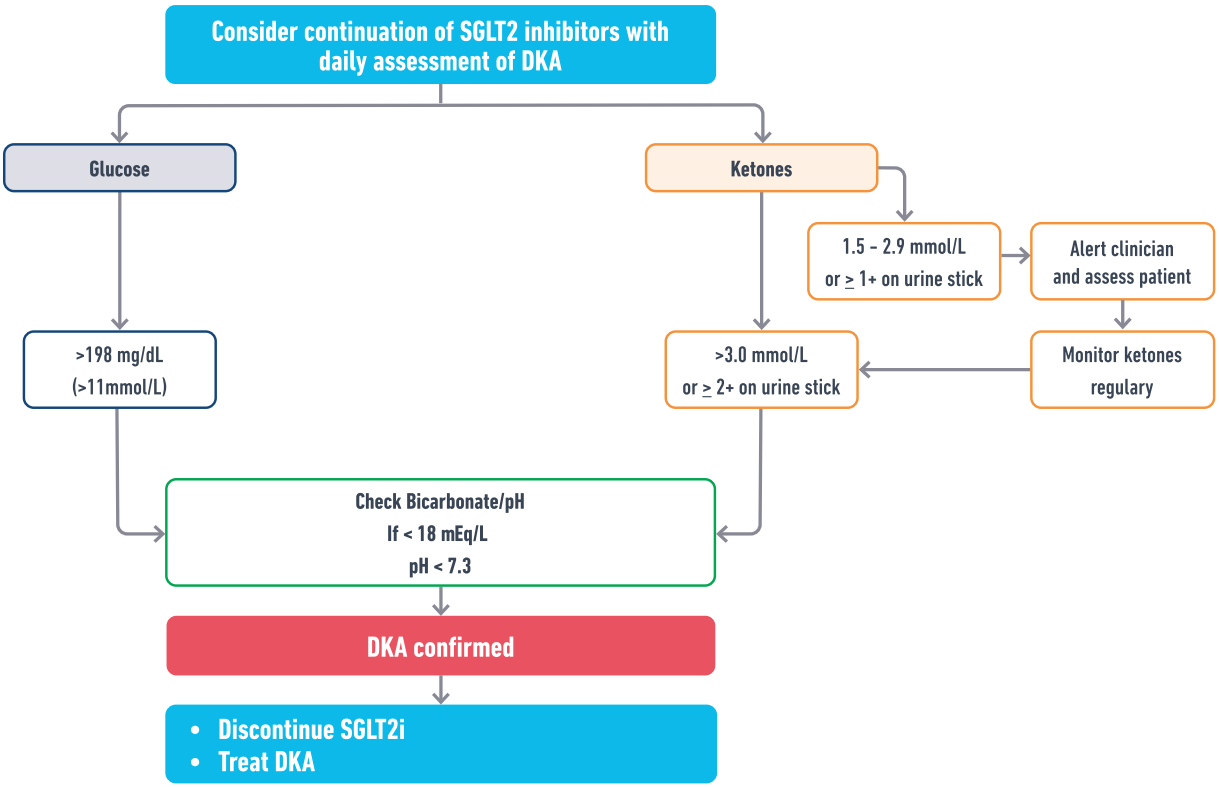

FIGURE 2 Proposed management of patients admitted to hospital on SGLT2i. DKA, diabetic ketoacidosis; SGLT2i, sodium-glucose cotransporter-2 inhibitors

hospitalized patients should therefore be re-examined as it is not necessarily fully evidence based. The DARE-19 trial showed numerically better outcomes and low risk in people commenced on dapagliflozin in an acute setting, which raises an hypothesis that SGLT2 inhibitors may afford organ protection in other types of acute illness. The EMPULSE study also showed 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 the 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.

In conclusion, new data suggest that prevailing guidelines concerning the use of SGL2 inhibitors during acute illness and hospitalizations 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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CONFLICT OF INTEREST

Kamlesh Khunti has acted as a consultant, speaker or received grants for investigator-initiated studies for Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, and Merck Sharp & Dohme, Boehringer Ingelheim, Bayer, Berlin-Chemie AG/Menarini Group, Janssen and Napp. Vanita R. Aroda has served as a consultant for Applied Therapeutics, Fractyl, Novo Nordisk, Pfizer and Sanofi; has a spouse employed at Janssen; and has received research support (through institution) for clinical trial investigator and/or clinical trial leadership roles from Applied Therapeutics, Eli Lilly, Fractyl, Novo Nordisk and Sanofi. Silvio E. Inzucchi has acted as a consultant or been on clinical trial steering/publications committees for Astra Zeneca, Boehringer Ingelheim, Merck, Pfizer, Novo Nordisk, vTv Therapeutics, Esperion and Abbott. He has given lectures supported by Astra Zeneca and Boehringer Ingelheim. Nikolaus Marx has received support for clinical trial leadership from Boehringer Ingelheim and Novo Nordisk; served

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Heerspink has had grant funding from AstraZeneca, Boehringer Ingeleheim, Janssen and Novo Nordisk; and received consulting fees from AstraZeneca, AbbVie, Boehringer Ingelheim, CSL Behring, Bayer, Chinook, Gilead, Goldfinch, Merck, NovoNordisk, Janssen, Mitsubishi Tanabe and Travere paid to his institute. Deepak L. Bhatt discloses the following relationships: Advisory Board for Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Janssen, Level Ex, Medscape Cardiology, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences and Stasys; Board of Directors for the Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Inaugural Chair for American Heart Association Quality Oversight Committee; Data Monitoring Committees for the Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo) and Novartis, Population Health Research Institute; Honoraria from American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Chair for ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation) and Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); other posts include *Clinical Cardiology* (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); research funding from Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company and 89Bio; received royalties from Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); site co-investigator for Abbott, Biotronik, Boston Scientific, CSI, St Jude Medical (now Abbott), Philips and Svelte; trustee for the American College of Cardiology; unfunded research for FlowCo, Merck and Takeda. 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DATA AVAILABILITY STATEMENT

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