Could Dapagliflozin Attenuate COVID-19 Progression in High-Risk Patients With or Without Diabetes? Behind DARE-19 Concept

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See accompanying Commentary by Rizvi et al on pages 1–2.

Abstract: Epidemiological studies indicate that diabetes is the second most common comorbidity in COVID-19 (coronavirus disease 2019). Dapagliflozin, a sodium-glucose co-transporter 2 inhibitor, exerts direct cardioprotective and nephroprotective effects. DARE-19 (Dapagliflozin in Respiratory Failure in Patients With COVID-19), an ongoing clinical trial, is designed to investigate the impact of dapagliflozin on COVID-19 progression. This article discusses the potential favorable impact of dapagliflozin on COVID-19 and its complications.

Key Words: COVID-19, SARS-CoV-2, diabetes, dapagliflozin, SGLT2i, DARE-19

(*J Cardiovasc Pharmacol*™ 2021;78:12–19)

INTRODUCTION

In December 2019, a sequence of pneumonia cases of unknown cause was documented in Wuhan, Hubei, China.[1] Respiratory track samples revealed a novel coronavirus as the causative factor, named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] Diabetes is the second most common comorbidity in COVID-19 (coronavirus disease 2019).[2] Severe COVID-19 frequently occurs in patients with comorbidities, such as cardiovascular disease, diabetes, hypertension, chronic lung disease, chronic kidney disease, obesity, and cancer.[2,3]

Individuals with diabetes and COVID-19 experience worse outcomes.[4–8] Indeed, data from a Chinese retrospective study showed that patients with diabetes and COVID-19 had more severe pneumonia and greater mortality compared with those without (16.5% vs. 0%).[9] Evidence from a survey in England showed that of patients dying from COVID-19 (n = 23,804), 32% had type 2 diabetes.[10]

Several scientific societies have issued recommendations on the administration of antidiabetic medications during COVID-19 pandemic.[11–14] It has been demonstrated that COVID-19 increases the risk of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state.[15] Euglycemic DKA is a rare side effect associated with sodium-glucose co-transporter 2 inhibitors (SGLT2i).[16,17] For this reason, specialists recommend that SGLT2i should be discontinued in patients with severe COVID-19 to reduce the risk of DKA.[18] However, discontinuing SGLT2i is not recommended for outpatients in the absence of serious COVID-19.[19,20]

In this setting, a randomized, double-blind, placebo-controlled, phase 3 Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19) study is evaluating the effect of dapagliflozin 10 mg versus placebo in reducing COVID-19 disease progression, complications, and all-cause mortality.[21] Study population includes hospitalized patients with mild–moderate manifestations of COVID-19 and a history of at least one of the following: hypertension, type 2 diabetes, atherosclerotic cardiovascular disease, heart failure (HF), or chronic kidney disease (CKD) stage 3–4 (estimated glomerular filtration rate between 25 and 60 mL/min/1.73 m^2). Therefore, both patients with and without diabetes are included. Cases of severe COVID-19 are excluded from the trial because of increased DKA risk.[16] In addition, a randomized open-label trial, the TACTIC-E (mulTi-Arm Therapeutic Study in Pre-ICu Patients Admitted With COVID-19—Experimental Drugs and Mechanisms), is assessing the effect of a novel immunomodulatory agent, EDP1815, and a combination of dapagliflozin 10 mg and ambrisentan 5 mg as potential treatments for COVID-19.[22] In this article, we aim to summarize the potential favorable impact of dapagliflozin on COVID-19 progression and associated systemic complications.

ROLE OF SGLT2i

SGLT2i block glucose and sodium reabsorption in the proximal renal tubule and consequently decrease glucose in patients with diabetes, reduce blood pressure and body weight, and have beneficial effects on HF and CKD.[23–25] SGLT2i may exhibit multiple pleiotropic properties,

Received for publication January 24, 2021; accepted February 20, 2021.

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E. Hatziagelaki has participated in educational, research, and advisory activities sponsored by MSD, Eli Lilly, Bristol/AstraZeneca, Novo Nordisk, Menarini, Win Medica, Boehringer-Ingelheim, Sanofi, Novartis, and Elpen; E. Liberopoulos has participated in educational, research, and advisory activities sponsored by Astra-Zeneca, MSD, Lilly, Bayer, Amgen, Sanofi, Boehringer-Ingelheim, Novartis, Novo Nordisk, and Servier. The remaining authors report no conflicts of interest.

G. Anastasiou: Conceptualization, Methodology, Investigation, and Writing—original draft. E. Hatziagelaki: Writing—review and editing. E. Liberopoulos: Visualization, Conceptualization, Methodology, Investigation, Supervision, Project administration, and Writing—Review and editing.

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including mitigation of inflammation and oxidative stress, improved myocardial and endothelial function, enhanced oxygen delivery, and increased diuresis.[23,26,27]

Potential Role of SGLT2i on COVID-19

(1) It has been reported that low cytosolic pH increases the probability of COVID-19 infection by affecting the angiotensin-converting enzyme 2 (ACE2)[28] and that ACE2 activity is increased in an acidic environment[29] (Fig. 1). Hydroxychloroquine may inhibit SARS-CoV-2 that attach to ACE2 by increasing the cytosolic pH.[30,31] Angiotensin (Ang) II promotes Na^+ reabsorption and H^+ secretion through (Na^+)/hydrogen (H^+) membrane antiporter and therefore increases cytosolic pH.[32] Aging, itself and by decreasing Ang II, and hypertension reduce cytosolic pH, and thus makes the virus binding to ACE2 easier.[33–35] Furthermore, smoking and obesity may increase the probability of COVID-19 because of hypercapnia-mediated reduction of cytosolic pH.[36] These data suggest that low cytosolic pH facilitates the binding of SARS-CoV-2 with ACE2 and subsequently may increase viral load.

Severe virus infections, including COVID-19, may cause cytokine-mediated tissue damage and lactate dehydrogenase (LDH) release.[37] Indeed, elevated LDH levels have been associated with worse prognosis in COVID-19.[38] LDH is a cytosolic enzyme that increases in serum as infected cells break down. LDH induces lactate formation increases from pyruvate under anaerobic conditions.[39] SARS-CoV-2 pulmonary infection results in high hypoxic environment due to tissue deoxygenation and increased lactate production.[40] Na^+/H^+ exchanger (NHE) and lactate/H^+ symporter play an important role in regulating intracellular pH.[41] On elevated lactate levels in the extracellular area, the lactate/H^+ symporter co-transports lactate and H^+ intracellularly.[41] This triggers NHE activation that extracts one H^+ from the intracellular to the extracellular area and transports Na^+, water, and Ca^{2+} inside the cell.[41] As a consequence, the cell swells and dies.[41]

Dapagliflozin has been reported to reduce lactate levels by various mechanisms, ie, reduction of oxygen consumption in tissues.[42,43] This lactate decrease in the extracellular area lowers the activation of lactate/H^+ symporter and subsequently the cytosolic pH is maintained. In addition, dapagliflozin inhibits NHE and the subsequent flow of Na^+ and Ca^{2+}, preventing the cells from swelling and death.[44]

(2) SARS-CoV-2 enters into target cells after binding to ACE2.[45] SGLT2i seem to upregulate ACE2 receptors on the cells.[46,47] ACE2 increases the Ang 1–7 level. It has been proposed that increased Ang 1–7, a potent vasodilator, exerts

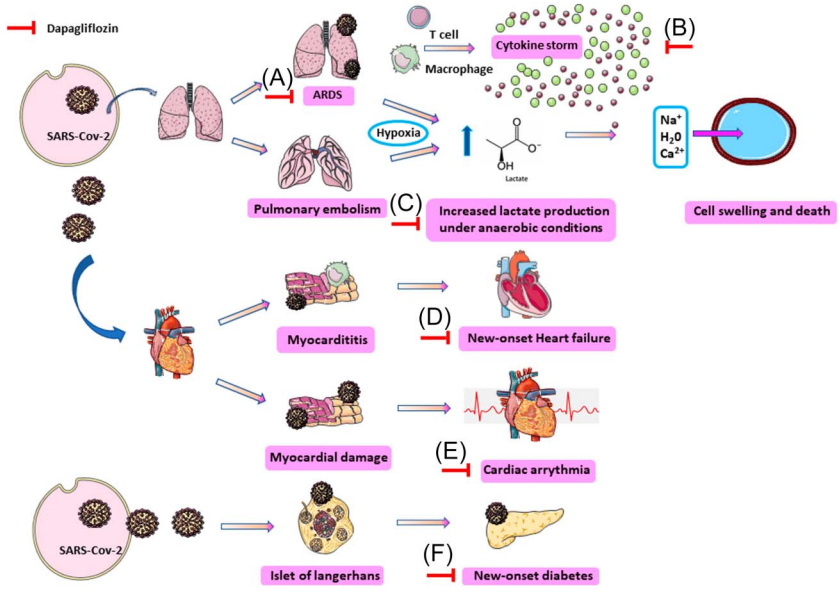

FIGURE 1. Potential beneficial role of SGLT2i in COVID-19 short-term and long-term complications. (A) SGLT2i seem to upregulate ACE2 receptors on the cells and thus increase the Ang 1–7 level that exert protective effect against ARDS caused by COVID-19; (B) SGLT2i reduce proinflammatory cytokines including those of COVID-19 cytokine storm, ie, IL-6, IL-10, and TNF-a; (C) ARDS and PE caused by COVID-19 lead to tissue hypoxia and subsequently increased lactate production. SGLT2i reduce lactate production and lactate/H^+-symporter and NHE antiporter activity, and thus decrease Na^+, water, and Ca^{2+} influx intracellularly through NHE and subsequent cell swelling and death; (D) anti-inflammatory properties of SGLT2i could likely alleviate myocarditis progression but no evidence exists to support this hypothesis. SGLT2i could potentially decrease the odds of new-onset HF caused by COVID-19 with the following mechanisms: (1) osmotic diuresis and natriuresis that decreases cardiac overload, (2) reduction of sarcoplasmic Ca^{2+} leak and thus increased myocardium contractility, (3) dampening of SNS, (4) reduction of oxidative stress and inflammation, (5) increased O_2 delivery by triggering EPO secretion, (6) increased cardiac efficiency, and (7) blood pressure, HbA1c, body weight, and vascular stiffness decreasing; (E) SGLT2i decrease the arrhythmogenic risk caused by COVID-19 as they (1) mitigate inflammation and oxidative stress, (2) improve myocardial efficiency, (3) improve oxygen delivery, (4) increase reabsorption of magnesium and potassium from the tubular fluid, (5) improve cardiac metabolism, (6) exert sympathoinhibitory effect, and (7) reduce cardiac fibrosis and left ventricular hypertrophy, which provide a substrate for arrhythmia development; (F) SARS-CoV-2 can infect and damage the pancreatic alpha and beta cells, whereas the cytokine storm can aggravate this impairment and lead to new-onset diabetes. Dapagliflozin reduced the incidence of new-onset diabetes in participants with HFrEF without diabetes at baseline. ACE2, angiotensin-converting enzyme 2; Ang 1–7, angiotensin 1-7; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; EPO, erythropoietin; HbA1c, hemoglobin A1c; HFrEF, heart failure with reduced ejection fraction; IL-10, interleukin-10; IL-6, interleukin-6; Na^+ HF, heart failure; NHE, Na^+/H^+ exchanger; PE, pulmonary embolism; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SGLT2i, sodium-glucose co-transporter 2 inhibitors; SNS, sympathetic nervous system; TNF-a, tumor necrosis factor-a.

protective effects against acute respiratory distress syndrome (ARDS) related to COVID-19.[48] Indeed, animal experimental studies have shown that Ang 1–7 can significantly improve vascular endothelial function.[49] Conversely, increased ACE2 can also trigger cardiac arrhythmias and myocarditis by increasing the cellular intrusion of SARS-CoV-2 into the heart tissue.[50]

In this context, a recent retrospective observational study (n = 717 hospitalized patients with COVID-19) showed that SGLT2i were significantly associated with a lower risk of mechanical ventilation [adjusted Relative risk (RR) = 0.03; 95% confidence interval (CI): 0.00–0.70] in patients with diabetes.[51] However, another study in Spain (n = 2666 patients with type 2 diabetes admitted for COVID-19) showed that none of the at-home glucose-lowering drugs analyzed (metformin, DPP4i, insulin, metformin plus DPP4i, metformin plus SGLT2i, and metformin plus insulin) were significantly associated with in-hospital deaths; the composite outcome of the need for intensive care unit, mechanical ventilation, or in-hospital death; in-hospital complications; or a long-time hospital stay.[52]

Another question is whether increased ACE2 levels from SGLT2i might contribute in increased susceptibility to COVID-19.[53] In a propensity score–matched cohort study with active comparators and a negative control outcome in a large UK-based primary care data set, participants prescribed SGLT2i (n = 9948) were compared with those prescribed dipeptidyl peptidase-4 inhibitors (DPP4i) (n = 14,917). The incidence rate of confirmed or clinically suspected COVID-19 was not significantly different between users of SGLT2i and users of DPP4i (adjusted HR 0.92, 95% CI 0.66–1.29).[54] It was concluded that clinicians may safely use SGLT2i in the everyday care of people with diabetes during the COVID-19 pandemic.

COVID-19 CLINICAL SPECTRUM AND THE ROLE OF DAPAGLIFLOZIN

COVID-19, New-Onset Diabetes and Dapagliflozin

New-onset diabetes has been observed in patients with COVID-19[55] (Fig. 1). In a population of 453 patients with COVID-19, 94 developed new-onset diabetes [defined as initial recognized fasting plasma glucose ≥7 mmol/L and HbA1c ≥48 mmol/mol (6.5%) at hospital admission].[56] One study showed that SARS-CoV-2 can infect and damage the pancreatic alpha and beta cells, whereas the cytokine storm can aggravate this impairment.[57] These data support that COVID-19 can lead to new-onset diabetes. Conversely, in a prespecified exploratory analysis from DAPA-HF trial (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure), dapagliflozin reduced by 32% [HR = 0.68 (95% CI, 0.50–0.94); $P = 0.019$] the incidence of new-onset diabetes in participants without diabetes at baseline (n = 2605).[58] Decreasing the risk of new-onset diabetes may be of benefit in patients with COVID-19 without diabetes at the time of infection.

COVID-19, Immune Response Alterations and Dapagliflozin

Hyperglycemia is the principal reason of attenuated innate immunity; it decreases neutrophil chemotaxis, phagocytosis, and adherence to endothelium.[59] This makes the first-line defense against SARS-CoV-2 inadequate and cells become more vulnerable to SARS-CoV-2–related inflammatory response.[60] In general, better diabetes control is associated with more efficient immune response.[61]

Diabetes is associated with low-grade chronic inflammation due to increased secretion of cytokines and adipose tissue hormones, such as leptin, tumor necrosis factor-a (TNF-a), and interleukin-6 (IL-6).[62–64] As a result, if individuals with diabetes get infected by SARS-CoV-2, the underlying chronic inflammatory state may enhance the cytokine storm associated with COVID-19, ie, an increased secretion of IL-6, IL-10, and TNF-a, with potential organ damage.[9] SGLT2i decrease proinflammatory cytokines, including those involved in cytokine storm of COVID-19.[65]

In addition, diabetes is considered as a hypercoagulable state because of increased platelet aggregation and stimulation and increased levels of clotting factors and fibrinolysis inhibitors as well as endothelium dysfunction.[66,67] COVID-19 has been linked with thrombotic and coagulation abnormalities, which can clinically be manifested as pulmonary embolism and deep vein thrombosis.[68–70] Furthermore, in severe SARS-CoV-2 infection, histopathological studies demonstrated direct viral infection of endothelial cells, endotheliitis with inflammation response and secondary endothelial dysfunction, and microthrombi formation.[71–73] However, SLGT2i have been demonstrated to improve endothelial function.[74,75] Interestingly, empagliflozin and dapagliflozin reduced in vitro platelet activation, potentially through NHE inhibition and thus may prevent thrombosis.[76] However, in a meta-analysis of 29 randomized controlled trials (RCTs) (n = 56,035 patients with type 2 diabetes), no significant association between SGLT2i and risk of deep vein thrombosis, pulmonary embolism, and venous thromboembolism was found.[77] It remains uncertain how SGLT2i affect thromboembolic events, and multiple mechanistic studies are ongoing to elucidate their impact on vascular system.

COVID-19, Cardiovascular System and Dapagliflozin

A recent study demonstrated that the coexistence of cardiovascular disease and diabetes further increased COVID-19 mortality risk.[10] One multihospital cohort study in New York City demonstrated that of hospitalized patients with COVID-19 (n = 2736), 36% had myocardial injury.[78] Cardiovascular presentation of COVID-19 includes myocarditis, cardiac arrhythmias, acute coronary syndrome, and death.[79,80] Whether the cardiac damage is provoked directly by the virus or is associated with the immunologic response remains a testable hypothesis.[81]

COVID-19, Myocarditis, Heart Failure, and Dapagliflozin

COVID-19 myocarditis is associated with cytokine storm and probably SARS-CoV-2 entry into cardiomyocytes by binding to ACE2.[82] Anti-inflammatory properties of

SGLT2i could likely alleviate myocarditis progression, but until now no evidence exists to support this hypothesis.[83]

Interestingly, Puntmann et al[84] demonstrated that of patients recently recovered from COVID-19 (n = 100), 78% had demonstrable cardiac injury, 60% had active myocardial inflammation in cardiovascular magnetic resonance imaging, and 76% had detectable high-sensitivity troponin after 71 days from COVID-19 diagnosis. Indeed, recently recovered patients had lower left ventricular ejection fraction, higher left ventricle volumes, higher left ventricle mass, and late gadolinium enhancement compared with controls.[84] In the same line, postmortem pathological findings of deceased individuals demonstrated (1) increased activity of 6 proinflammatory genes in heart tissue with SARS-CoV-2 infection compared with hearts with no SARS-CoV-2, (2) detection of virus in the heart of 24 patients (61.5%), and (3) active viral replication in interstitial cells or macrophages.[85] Furthermore, COVID-19–related myocarditis and cytokine storm may increase the odds for HF.[86] These findings indicate that COVID-19, even if resolved, might lead to long-term residual left ventricular dysfunction and inflammation and thus evolve to new-onset HF.[84–87]

To this end, SGLT2i could play a crucial role in preventing HF progression in these patients. DAPA-HF trial (n = 4744) demonstrated that among patients with HF and a reduced ejection fraction, dapagliflozin reduced the risk of worsening HF or death from cardiovascular causes versus placebo, regardless of the presence or absence of diabetes.[24] Especially, dapagliflozin compared with placebo reduced the risk of worsening HF or cardiovascular death by 27% [hazard ratio (HR), 0.73 (95% CI, 0.60–0.88)] in patients without diabetes and by 25% in patients with diabetes [HR, 0.75 (95% CI, 0.63–0.90)].[88] These data support a potential beneficial role of SGLT2i in HF of patients with COVID-19 without diabetes as well. Possible underlying mechanisms include (1) osmotic diuresis and natriuresis that lower cardiac overload,[89] (2) reduction of sarcoplasmic Ca^{2+} leak that increases cardiac contractility,[90] (3) dampening the sympathetic nervous system,[91] (4) reduction of inflammation and oxidative stress,[74,92–94] (5) increased oxygen delivery to the heart through triggering renal erythropoietin secretion,[94,95] (6) increased cardiac efficiency,[96–99] and (7) blood pressure, body weight, A1c, and vascular stiffness reduction.[100,101]

COVID-19, Arrythmias and Dapagliflozin

COVID-19 has been implicated in cardiac arrhythmias, especially in critically ill patients.[102,103] These include supraventricular tachycardia,[104] atrial fibrillation (AF),[103] atrial flutter (AFL),[105] complete heart block,[105,106] cardiac arrest,[103] polymorphic ventricular tachycardia,[103] multifocal ventricular tachycardia,[106] and sinus tachycardia.[107] Interestingly, in a study of 137 patients with COVID-19 in tertiary hospitals in China, almost 7.3% reported palpitations as one of the presenting symptoms[108]. In another study, 16.7% of patients with COVID-19 were documented to have arrhythmias, commonly in the intensive care unit setting (44.4%)[109]. Sustained episodes of ventricular tachycardia/ventricular fibrillation occurred in 5.9% of 187 hospitalized patients with COVID-19.[79] Possible mechanisms for arrhythmogenesis in COVID-19 include (1) myocarditis,[102,110] (2) hypoxia induced from direct viral injury on pulmonary system,[102,111] (3) myocardial ischemia,[86] (4) myocardial strain due to pulmonary hypertension, (5) increased IL-6 and IL-1β that are potentially proarrhythmic factors,[102] (6) electrolyte decompensation and intravascular volume disturbance from diarrhea, vomiting, and/or renal injury, and (8) drug side effects.[112]

In the DECLARE TIMI 58 trial, dapagliflozin reduced the risk of new AF/AFL events by 19% (HR: 0.81, 95% CI 0.68–0.95, $P = 0.009$), the risk of atrial tachycardia by 20% (HR: 0.80, 95% CI 0.68–0.94), the risk of supraventricular tachyarrhythmia/tachycardia by 17% (HR: 0.83, 95% CI 0.71–0.97), and the total number of AF/AFL events by 17% (HR: 0.77, 95% CI 0.64–0.92) in high-risk patients with type 2 diabetes.[113] Similarly, one real-world study demonstrated that SGLT2i administration was associated with a lower risk of new-onset arrhythmias in patients with type 2 diabetes compared with those not receiving SGLT2i.[114] SGLT2i may (1) mitigate inflammation and oxidative stress, (2) improve myocardial efficiency, and (3) improve oxygen delivery, all of which may be important in preventing AF/AFL.[23,26,27] The EMPA-HEART CardioLink-6 trial, a 6-month double-blind, randomized, placebo-controlled trial in patients with type 2 diabetes and coronary artery disease demonstrated that left ventricular mass index was reduced by 2.6 g/m^2 with empagliflozin and by 0.01 g/m^2 with placebo from baseline to the 6-month visit ($P = 0.01$).[115] In this context, the Losartan Intervention for Endpoint Reduction in Hypertension trial has shown that left ventricular mass regression is independently associated with a reduction in new heart failure and new AF.[116] Moreover, dapagliflozin may exert antiarrhythmic effects through (1) increasing reabsorption of magnesium and potassium from the tubular fluid,[100] (2) improving cardiac metabolism,[100] (3) exerting sympathoinhibitory effect,[117,118] and (4) reducing cardiac fibrosis and left ventricular hypertrophy, which provide a substrate for arrhythmia development.[119,120]

COVID-19, Renal System and Dapagliflozin

Acute kidney injury (AKI) has been observed in hospitalized patients with COVID-19 with a prevalence as high as 46%.[121] In a retrospective observational study in New York (n = 5449), 1993 (36.6%) patients with COVID-19 developed AKI.[122] Another study reported that of 62 hospitalized patients COVID-19 not on dialysis, 10% required kidney replacement therapies.[123] The exact underlying mechanism is not well understood. COVID-19 is proposed to cause AKI with the following mechanisms: (1) direct viral infection of the endothelial cells of the glomerular capillary loop,[124] (2) direct tubular or glomerular injury,[57,125,126] (3) acute ischemic tubular necrosis induced by systemic collapse and/or COVID-19–related prothrombotic state, and (4) inflammatory syndrome-mediated renal injury.[127] In one of the largest autopsy studies on 26 patients with COVID-19 in China, renal tissue biopsies of 3 patients had glomerular thrombi, 3 pigmented tubular casts, and 7 viral-like particles under electron microscopy.[125]

SGLT2i have well-recognized nephroprotective properties that might play a key role in COVID-19–related AKI.[128–130] RCTs have demonstrated that SGLT2i administration do not increase AKI risk.[131–134] Actually, dapagliflozin was associated with significantly lower AKI risk (HR 0.69, 95% CI 0.55–

0.87).[132] A recently published study (n = 39,094) demonstrated that SGLT2i initiation was associated with a 21% reduction in the 90-day risk of AKI compared with DPP4i (weighted risk ratio: 0.79, 95% CI 0.64–0.98).[135] A meta-analysis of 3 large RCTs of cardiovascular outcomes with SGLT2i demonstrated that AKI was reduced by 34% with SGLT2i administration (HR: 0.66, 95% confidence interval 0.54–0.80) compared with placebo.[131] A systematic review and meta-analysis of RCTs (n = 38,723) reported that SGLT2i use was associated with a 25% reduction of AKI versus placebo.[136] These data suggest a beneficial role of SGLT2i on AKI and hopefully in the setting of COVID-19–related AKI.

In the cardiovascular and renal outcomes trials of SGLT2i, renoprotective properties of SGLT2i seem to extend beyond glycemic control.[76,134] Notably, SGLT2i have been proposed to favor renal function by activating tubuloglomerular feedback and reducing intrarenal hypoxia.[137,138] Two large cardiovascular and renal outcomes trials, EMPA-KIDNEY and DAPA-CKD, were designed to demonstrate the potential benefit of SGLT2i in CKD.[139,140] EMPA-KIDNEY, a randomized double-blind trial, investigates the effect of empagliflozin on kidney disease progression or cardiovascular death versus placebo on top of standard of care in patients (n = 6000) with preexisting CKD with and without type 2 diabetes.[139] DAPA-CKD, a phase III randomized double-blind trial, demonstrated that dapagliflozin compared with placebo significantly reduced time to first occurrence of a composite renal end point (estimated glomerular filtration rate decline >50%, end-stage renal disease or renal death) or cardiovascular death in patients (n = 4304) with CKD stages 2–4 regardless of diabetes status.[25] These glucose-independent, salutary effects of SGLT2i on CKD might favor renal function in patients with COVID-19 with or without diabetes.

SGLT2i AND ADVERSE EVENTS DURING COVID-19

SGLT2i are associated with adverse events, including DKA, hypovolemia, and low blood pressure, as well as genital mycotic infections that can be exacerbated by COVID-19.[141]

COVID-19, DKA and Dapagliflozin

DKA has been reported more frequently among patients with COVID-19 with diabetes.[142] Infection-related conditions potentially contribute to the development of DKA, including starvation, dehydration due to high fever, vomiting and/or diarrhea, and release of insulin-antagonistic hormones, such as catecholamines and cortisol. In addition, volume depletion and low blood pressure can be amplified by SGLT2i.[132–134] As a result, DKA risk among SGLT2i-treated patients might be high in severe COVID-19.[143] In this regard, a number of SGLT2i-related cases of euglycemic DKA in patients with COVID-19 have been reported.[144–146]

COVID-19, Dapagliflozin and Low Pressure

COVID-19 is associated with respiratory failure, shock, multiorgan failure, and tend to decrease blood pressure due to natriuresis.[147,148] Thus, SGLT2i administration could aggravate shock caused by severe COVID-19.

COVID-19, Dapagliflozin and Urogenital System Mycotic Infections

SGLT2i have been linked with a higher incidence of urogenital fungal infections.[23,149,150] Antibiotics, and dexamethasone, commonly used in patients with COVID-19 are known to also predispose to fungal infections.[151]

COVID-19, Dapagliflozin and Drug Interactions

As of October 3, 2020, no meaningful interactions for empagliflozin or dapagliflozin were documented, whereas canagliflozin may potentially interact with lopinavir-ritonavir (Kaletra) requiring efficient drug-dosing modifications (https://www.covid19-druginteractions.org/).

CONCLUSIONS

SGLT2i could play a key role in reducing COVID-19 progression and prevent its short-term and long-term complications, mainly by offering cardioprotection and nephroprotection. SGLT2i seem to upregulate ACE2 receptors and thus increase the Ang 1–7, which exert protective effects against ARDS related to COVID-19. Furthermore, SGLT2i may reduce proinflammatory cytokines, including those of COVID-19 cytokine storm, ie, IL-6, IL-10, and TNF-a. Interestingly, SGLT2i could reduce the risk of new-onset diabetes observed in COVID-19. In addition, they could alleviate myocarditis, arrhythmogenesis, HF progression, and kidney injury in these patients. DARE-19 will show if this hypothesis is true.

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