Learnings from Throwing Paint at the Wall for COVID-19 with an SGLT2 Inhibitor

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The coronavirus disease 2019 (COVID-19) pandemic has truly been a surreal experience. Many aspects of ordinary life changed quickly and dramatically. We witnessed major supply shortages of everyday items within a suddenly masked and at-home society, and major disruptions of health care systems accompanied by widening health, social, and economic disparities. In a desperate attempt to address this emergent crisis, the early phase of the pandemic was characterized by numerous rapid-fire reports about COVID-19 complications and treatments largely based on anecdotes, conjecture, and uncontrolled case series (1–3). Although understandable given the calamitous circumstances, many of these reports were erroneous or frankly dangerous. What really was the biologic rationale for giving hydroxychloroquine or ivermectin for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection? Conversely, why were so many people opposed to vaccines made by scientists for a public health emergency with desperate attempts to try (e.g., hydroxychloroquine, ivermectin) or, contrarily, avoid (e.g., vaccines) almost anything if a story could be concocted for it.

During the same era, sodium-glucose cotransporter 2 (SGLT2) inhibitors were emerging as new “wonder drugs” that provided unprecedented benefits for a triangle of “cardio-renal-metabolic” conditions, including atherosclerotic cardiovascular disease, heart failure, CKD, and AKI, all the while lowering hyperglycemia and body weight (4,5). And, in persons with CKD, one trial showed reduction in all-cause mortality, driven, at least in part, by fewer deaths due to infection (6). SGLT2 inhibitors are indeed much more than glucose-lowering drugs! So, why not try an SGLT2 inhibitor to mitigate COVID-19 risks in patients with cardiometabolic risk factors? That is just what was done in the Dapagliflozin in Patients with Cardiometabolic Risk Factors Hospitalised with COVID-19 (DARE-19) trial, on the basis of a hypothesis that this class of therapeutic agents may have organ (heart, lung, kidney)-protective effects extending to severe COVID-19 in hospitalized patients (7). Among numerous proposed mechanisms, off-target benefits of SGLT2 inhibitors have been purported as anti-inflammatory effects, such as inhibition of the NLR-family pyrin domain-containing protein 3 inflammasome and reduced oxidative stress, along with salutary effects to increase oxygen carrying capacity via higher hemoglobin levels, and a mild ketosis that may augment myocardial energetics with $\beta$-hydroxybutyrate as a preferred fuel source (8). In the DARE-19 clinical trial, persons hospitalized with SARS-CoV-2 infection who had one or more cardiometabolic risk factors (hypertension, type 2 diabetes, atherosclerotic cardiovascular disease, heart failure, or an eGFR of $25–59$ $\text{ml/min per 1.73 m}^2$) were randomized 1:1 to dapagliflozin or placebo on top of the local standard of care. The coprimary outcomes were a prevention (heart, lung, kidney dysfunction, or death) and a recovery (all-mentioned organ dysfunction during hospitalization plus 30-day survival, oxygen requirements, and hospital discharge) outcome. As for a variety of interventions that seemed plausible at the time, DARE-19 was a negative trial for all of these outcomes, individually and collectively.

In this issue of CJASN, the main DARE-19 outcomes were analyzed by eGFR status at baseline ($\geq 60$ or $<60$ $\text{ml/min per 1.73 m}^2$) along with a longitudinal analysis of eGFR by dapagliflozin use. The main DARE-19 outcomes were corroborated, irrespective of baseline kidney function, including $231$ of $1250$ patients ($18\%$) with low eGFR ($<60$ $\text{ml/min per 1.73 m}^2$) during hospitalization for COVID-19 (9). Nevertheless, DARE-19 was a positive trial from the perspective of the safety of using an SGLT2 inhibitor while experiencing acute illness in patients with either preserved or reduced kidney function. The risk of AKI was notably not increased, whereas the magnitude of risk was numerically lower (hazard ratio, $0.70$; $95\%$ confidence interval, $0.42$ to $1.17$), corresponding to a relative risk reduction of $30\%$. Moreover, the inpatient AKI definition was stringent, a doubling of serum creatinine corresponding to the Kidney Disease Improving Global Outcomes criteria of stage 2. Therefore, smaller, acute decreases in kidney function would not have been counted and may have contributed to underpowering the analysis for detecting a difference in the risk of AKI. The slightly lower eGFR after dapagliflozin initiation (mean of approximately
3–5 mL/min per 1.73 m² during hospitalization is expected, on the basis of the mechanism of action for the drug to reduce glomerular hyperfiltration, and did not associate with AKI or other adverse events. No episodes of diabetic ketoacidosis were observed in the group treated with dapagliflozin who had low eGFR, and only two of 487 cases occurred in those with an eGFR of ≥60 mL/min per 1.73 m².

These safety observations raise important questions about whether SGLT2 inhibitors need to be stopped during acute illness in all persons. Although DARE-19 may have been underpowered to assess risk of AKI in hospitalized patients with COVID-19, the signal was in the right direction and in line with the 25% lower risk of AKI seen in studies of nonhospitalized persons with diabetes, cardiovascular disease, or CKD (4). Indeed, the DARE-19 study population had a high level of acuity, yet fared well on an SGLT2 inhibitor. These findings are worthy of further inquiry, including studies to determine if SGLT2 inhibitors can be safely used to prevent AKI during acute illness of various types or with high-risk procedures, such as cardiac surgery or intravascular administration of iodinated contrast. Hospitalization might also represent a golden moment for implementation of an SGLT2 inhibitor in appropriate patients, especially those with CKD or heart failure (10). This could be a key strategy to improve the dismal low implementation rates of SGLT2 inhibitors for kidney and heart protection in suitable patients.

Now is the time to stop throwing paint at the wall, both for treating COVID-19 and for using SGLT2 inhibitors to treat disparate kinds of maladies. We need solid science and data-driven approaches for COVID-19, recognizing its effects across countless domains of clinical care and research. Factually based understanding for how to detect and treat the SARS-CoV-2 virus, and its emerging variants, is essential to winding down the present pandemic and preventing the next one. The same can be said for the importance of understanding mechanisms of action for SGLT2 inhibitors to guide therapeutic application and address drug safety. A logical next step will be research on proper use of these agents during acute illness and high-risk procedures, while also recognizing this as a potential opportunity for therapeutic implementation of SGLT2 inhibitors for kidney and heart diseases.

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Author Contributions
K.R. Tuttle conceptualized the study, wrote the original draft, and was responsible for project administration.

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