Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Looking deeper into the findings of DARE-19: Failure or an open door to future success?

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Since November 2019, when the first outbreak started in Wuhan, Hubei, China, the world has been experiencing the dramatic impact of the COVID-19 pandemic on every aspect of social and economic life. Despite the timely development of effective vaccines against SARS-CoV-2, the disease continues to represent a huge burden on health care systems globally. Although numerous anti-inflammatory and anti-viral agents have been tested in COVID-19 so far, only a few of them have provided clear clinical benefits; thus, the need for developing effective and safe therapeutic options against SARS-CoV-2 remains an ongoing challenge. Sodium-glucose co-transporter 2 inhibitors (SGLT2i) emerged as drugs for the management of hyperglycemia in people with type 2 diabetes (T2D). However, they soon proved to manifest remarkable cardiorenal benefits irrespectively of diabetes status and a broad spectrum of off-target effects, leading to the extension of their licensed use in heart failure (HF) and chronic kidney disease, apart from diabetes.

SGLT2i are known to ameliorate systemic inflammation by down-regulating the production and expression of proinflammatory cytokines, such as interleukin-1, 6, and tumor necrosis factor-α [1], whose up-regulation has been positively associated with the severity and mortality of the disease. They also improve tissue hypoxia by increasing erythropoietin and hematocrit levels and attenuate endothelial dysfunction, which both are important pathogenic mechanisms in COVID-19 [2]. In addition, organ failure caused by SARS-CoV-2, including heart and kidney injury, seems to share common pathogenetic pathways with diabetes complications [3]. In this context, DARE-19 is a recently completed randomized trial which investigated the effect of the SGLT2i dapagliflozin versus placebo on the risk for organ failure or death or improving recovery among adults with cardiometabolic risk factors hospitalized with COVID-19 [4]. The primary composite outcome of organ dysfunction or death was observed in 70 participants (11.2%) in the dapagliflozin group and 86 (13.8%) in the placebo group (hazard ratio [HR] 0.80, 95% CI 0.58–1.10; p = 0.17). 547 individuals (87.5%) treated with dapagliflozin and 532 (85.1%) who received placebo experienced clinical status improvement; however, the difference did not reach statistical significance (win ratio 1.09, 95% CI 0.97–1.22; p = 0.14).

A deeper look into the results of DARE-19 reveals some interesting insights. Although the trial failed to demonstrate that dapagliflozin is superior to placebo in improving COVID-19 related outcomes, numerically fewer participants in the intervention arm manifested organ failure or death events compared to the placebo group. The same was applicable for each component of the composite endpoint, separately. Considering the pathophysiological relevance between the pleiotropic actions of gliflozins and the mechanisms resulting in organ damage in COVID-19, it could be argued that statistical significance would have been achieved if the sample size of the trial was bigger and the follow-up period longer. Although this sounds largely speculative, it is worth considering that the study took place in the course of an evolving pandemic, during which the number of people experiencing the endpoints of death or organ failure presented a continuously falling trend, as a result of a progressive improvement in the management of people with COVID-19. For instance, the mortality rate in the United States declined from approximately 25% in April 2020 to about 5% in August of the same year [5], thus, making it difficult to properly design and evaluate study endpoints, as well as to calculate the exact number of events required for statistical certainty.

In any case, DARE-19 findings put on the table the hypothesis that SGLT2i might confer protection against organ damage in various settings of acute illness, apart from COVID-19. Despite promising mechanisms of action, the vast majority of drug candidates in the field of sepsis have failed to prove meaningful clinical benefits over the past two decades [6]. In a recent work, Maayah and colleagues [7] demonstrated that empagliflozin has the potential to ameliorate systemic and renal inflammation, protect against acute kidney injury and improve survival in a mouse model of septic shock. Taken together, these data indicate a potential place of SGLT2i in future trials evaluating novel treatments for septic patients requiring intensive-care therapy [6,7]. In this context, the RECOVERY trial has recently made an amendment to the protocol and will explore empagliflozin as a possible treatment for COVID-19.

For many years, the use of SGLT2i in the acute (inpatient) setting seemed to be prohibitive, mainly due to the risk of euglycemic diabetic ketoacidosis (DKA), which is a serious side effect of these drugs. In DARE-19 however, severe adverse events were numerically fewer in the dapagliflozin than in the placebo group (65 vs 82, respectively). Regarding specifically DKA, there were only two cases in individuals with T2D receiving dapagliflozin. Both cases were identified through the daily monitoring of the acid-base balance as per study protocol and characterized as non-severe, whereas rapidly resolved when patients

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received appropriate treatment. Consequently, maybe the strongest message coming from DARE-19 is that the use of these agents in individuals with acute illness implicates a low risk of DKA, provided that patients are closely monitored.

Why is the above ascertainment of potential clinical importance? A significant amount of evidence coming from animal studies suggests that gliflozins have the potential to reduce mortality rates when administered in the acute phase of cardiovascular (CV) episodes, through several mechanisms, such as the suppression of sympathetic activity, reduction of oxidative stress, enhancement of autophagy and promotion of cardiac remodeling [1–3]. Moreover, very recent data support the efficacy of sotagliflozin in improving HF outcomes among people who have started the treatment prior to hospital discharge, encouraging an "earlier, better" approach to therapy with SGLT2i, particularly in those at the highest category of CV risk [2].

In conclusion, the findings of DARE-19, although not reaching statistical significance, should not be necessarily seen as a failure of SGLT2i to conquer another summit. They added value to the safety profile of these drugs, suggesting a low risk of adverse events even in the acute setting, when properly used. They could also represent an open door to the future potential of the class to prevent organ damage and reduce CV events in hospitalized patients, irrespectively of diabetes status and COVID-19. Of course, this remains to be further tested in appropriately designed and powered clinical studies. At the end of the day and according to A. Huffington's famous quote: "Failure is not the opposite of success; it's part of success."

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Not applicable.

Research involving human participants and/or animals

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Theocharis Koufakis** has received honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Pharmaserve Lilly and Novo Nordisk, for advisory boards from Novo Nordisk, and has participated in sponsored studies by Eli-Lilly. **Giuseppe Maltese** has received honoraria for lectures from AstraZeneca and Novo Nordisk. **Kalliopi Kotsa** has received honoraria for lectures/advisory boards and research support from Astra Zeneca, Boehringer Ingelheim, Pharmaserve Lilly, Sanofi-Aventis, ELPEN, MSD, and Novo Nordisk. Other authors report no conflict of interest.

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