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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COVID-19 and sulfonylureas: A reminder of the pleiotropic actions of an old class of drugs just before their swansong

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To the editor,

Sulfonylureas (SUs) have been used for the treatment of hyperglycemia for more than 60 years and are currently the second most commonly prescribed antidiabetic agents worldwide after metformin [1]. Their low cost, the strong glucose-lowering action, and the vast clinical experience with their use have always been attractive features for physicians, health care systems, and scientific societies when discussing the therapeutic strategy for type 2 diabetes (T2D). On the other hand, important concerns over their use, related to the risk of hypoglycemia and weight gain, but primarily to their cardiovascular (CV) safety, never allowed SUs to be considered ideal glucose-lowering drugs [2]. Although some recent large trials have been reassuring, showing a neutral effect of the newer SUs on CV outcomes [3], hypoglycemia *per se* is known to have a deleterious impact on CV health [4].

During the last few years, humanity has lived in the shadow of the COVID-19 pandemic. Suboptimal glycemic control has been associated with an increased risk of mortality and poor outcomes in infected patients [5]. Surprisingly, despite the established association between COVID-19 and CV complications [6], a recently published, large meta-analysis including data from 3,061,584 individuals [7] demonstrated a neutral effect of therapy with SUs prior to infection on COVID-19-related mortality. The findings were adjusted for several confounders such as age, race, body weight, presence of hypertension, and chronic kidney disease. Two previous meta-analyses had shown that SUs could be associated with a reduced mortality risk in patients with T2D who have COVID-19 [8,9]. The results should be interpreted with caution due to the observational nature of most relevant studies. However, these findings unavoidably bring in mind some older works showing that SUs might possess important anti-inflammatory properties.

Compared to insulin-treated patients, people with T2D receiving glimepiride were found to have lower levels of markers of systemic inflammation, including Tumor Necrosis Factor, Interleukin (Il)-6, and C-Reactive Protein (CRP) [10]. In a study comparing metformin monotherapy with glyburide, only the latter was able to promote a significant decrease in CRP levels within a short period of time (3 months) [11]. Cytokine storm release is known to be associated with rapid clinical deterioration in patients with COVID-19 [12]. Glyburide has been shown to downregulate the expression of the pro-inflammatory cytokines IL-1β and IL-18 and reduce mRNA expression in macrophages isolated from wounds [13]. In addition, it has been demonstrated to inhibit the NLRP-3 inflammasome in a model of diabetes-induced fracture healing [14]. Taken together, these indicative data imply that the adverse relationship observed between SU treatment and mortality in people with COVID-19 could be mediated by the anti-inflammatory properties of this drug category.

The cost of antidiabetic treatment remains an issue in many places around the world. However, considering that the growing burden of diabetes on societies is mainly driven by its complications [15], it becomes increasingly evident that sooner or later we will have to bid adieu to SUs. The spotlights of medical research are reasonably on the pleiotropic properties of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists and soon on more treatments to come, such as the dual GLP-1/glucose-dependent insulinotropic polypeptide receptor agonists. In the era of spectacular benefits of the new glucose-lowering agents in terms of alleviating cardiorenal risk, there is no space for debates on the CV safety of antidiabetic drugs. However, the COVID-19 pandemic reminded us of the largely unexplored pleiotropic actions of an old therapeutic class that probably deserved a closer look.

Declaration of competing interest

TK 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 and Novo Nordisk. **DSP** declares associations with the following companies: Abbott, Alkaloid, AstraZeneca, Boehringer-Ingelheim, Berlin-Chemie, Eli Lilly, Galenika, Krka, Merck, Novo Nordisk, PharmaSwiss, Sanofi-Aventis, Servier, and Worwag Pharma. **KK** has received honoraria for lectures/advisory boards and research support from Astra Zeneca, Boehringer Ingelheim, Pharmaserve Lilly, Sanofi-Aventis, ELPEN, MSD, and Novo Nordisk. **SM** declares no conflict of interest.

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Authors' contributions

TK reviewed the literature and wrote the first version of the manuscript. **DSP**, **SM**, and **KK** reviewed the literature and edited the manuscript. All authors have read and approved the final version of the manuscript.

Research involving human participants and/or animals

Not applicable.

Ethics approval and consent to participate

Not applicable.

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