Diabetes Ther (2020) 11:3007–3009
https://doi.org/10.1007/s13300-020-00943-6

LETTER

A Response To: Sodium–Glucose Cotransporter 2 Inhibitors and Major COVID-19 Outcomes: Promising Mechanisms, Conflicting Data, and Intriguing Clinical Decisions

Antonio C. Bossi · Franco Forloni · Paolo L. Colombelli

Received: September 30, 2020 / Accepted: October 3, 2020 / Published online: October 14, 2020

Keywords: Pleiotropic effects of SGLT2-i; SGLT2-i in COVID-19; Sodium–glucose cotransporter 2 inhibitors (SGLT2-i)

DIGITAL FEATURES

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Sir,

The observations provided in the letter "Sodium–glucose cotransporter 2 inhibitors [SGLT2-i] and major COVID-19 outcomes: promising mechanisms, conflicting data, and intriguing clinical decisions" [1] are completely agreeable. The authors recall the potential pleiotropic effects of these drugs, providing potential benefits that go beyond the improvement of glucose control in patients with type 2 diabetes (and in subjects with type 1 diabetes), underlying the cardiovascular and renal advantages even in subjects without diabetes. Other potential therapeutic activities of SGLT2-i have been tested in hypertension (thanks to their peculiar natriuretic activity, different from that obtained by classical diuretics) [2]; obesity and NAFLD (non-alcoholic fatty liver disease), considering their induced weight loss and their activity on visceral adipose tissue which lead to a reduction in hepatic steatosis [3, 4]; gout (thanks to the increased urate excretion) [5]; SIADH (syndrome of inappropriate ADH secretion), by means of their potential effect on free-water clearance in addition to fluid restriction [6]; and PCOS (polycystic ovarian syndrome) owing to their action on hyperglycemia and overweight [7].

It should be of interest to emphasize some more activities exerted by the drugs of this class on respiratory function. For instance, patients suffering from obstructive sleep apnea syndrome (OSAS) may benefit from the weight loss obtained with SGLT2-i [8]. Furthermore, empagliflozin was able to lower mortality in experimental pulmonary hypertension. This result was partially explained by the observed reduced pulmonary remodelling [9]. Interestingly, SGLT2 was recognized as a potential marker of indeterminate lung nodules: its activity may help in identifying metabolically active lung premalignancy and early-stage lung adenocarcinoma [10]. As a matter of fact, SGLT2 is expressed early in lung carcinogenesis: its activity could be observed in patients by means of positron emission tomography (PET) with a

A. C. Bossi (✉) · F. Forloni
Endocrine Unit-Diabetes Regional Center, Treviglio, BG, Italy
e-mail: antonio_bossi@asst-bgovest.it; acbossi@gmail.com

P. L. Colombelli
Internal Medicine Division, ASST Bergamo Ovest, Treviglio, BG, Italy

specific tracer (Me4FDG: methyl-4[^{18}F]-4-deoxyglucose). SGLT2-i suppress growth of early stage lung adenocarcinoma and may afford an extended survival in animal models. These observations shed some more light on the so-called pleiotropic activity of this class of drugs, although more data are warranted to better understand their therapeutic possibilities both in pulmonary diseases and in respiratory failure in patients with COVID-19. Concerning this latter point, the outcomes of the Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19) trial (ClinicalTrials.gov identifier NCT04350593) should provide more evidence.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure. Antonio C. Bossi, Franco Forloni and Paolo L. Colombelli have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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