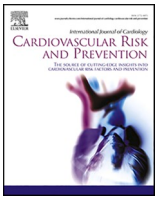
International Journal of Cardiology Cardiovascular Risk and Prevention 10 (2021) 200100

Contents lists available at ScienceDirect

International Journal of Cardiology
Cardiovascular Risk and Prevention

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-cardiovascular-risk-and-prevention



Do clinical trial data suggest a role for SGLT2-inhibitors in primary prevention of heart failure and chronic kidney disease?

ARTICLE INFO

SGLT2 inhibitors
Heart failure
Diastolic left ventricular dysfunction
Chronic kidney disease
Prevention

Randomized clinical trials (RCTs) consolidated and enlarged the indications of sodium-dependent glucose cotransporter-2 inhibitors (SGLT2-Is), a drug class originally conceived to improve glycemic control in type-2 diabetic (T2DM) patients. The EMPEROR-Reduced trial (NCT03057977) enrolled patients with heart failure (HF) with reduced ejection fraction and demonstrated that compared to placebo, empaglifozin decreased hospitalized HF by 30 % and chronic kidney disease (CKD) by 50 %; combined with the dapaglifozin results in DAPA-HF (NCT03036124), the pooled estimates of risk reduction were 31 % and 38 %, respectively [1]. The DAPA-CKD trial (NCT03036150) demonstrated relative risk reductions by 44 % for CKD and by 29 % for cardiovascular death combined with HF. In EMPEROR-Reduced and DAPA-CKD, the beneficial effects of SGLT2-I treatment were similar in patients with and without T2DM. Based on DAPA-HF, the FDA approved dapaglifozin for treating adult HF patients with reduced ejection fraction, irrespective of the presence of T2DM, and more recently started evaluation of empaglifozin in the same indication.

Ambulatory monitoring is state-of-the-art in blood pressure (BP) measurement. In 2238 T2DM patients enrolled in seven RCTs, SGLT2-Is decreased 24-h systolic/diastolic BP by 4.4/1.9 mm Hg (95% confidence interval, 3.4–5.5/1.2–2.6 mm Hg) compared with placebo [2]. In EMPEROR-Reduced, the placebo-corrected decrease in systolic office BP on empaglifozin was only −0.7 mm Hg (−1.8 to 0.4 mm Hg). However, the −0.7 mm Hg estimate might be explained by the low initial systolic BP level in HF patients on multiple medications and by the undefined clinical methods of office BP assessment. We updated our systematic review of the placebo-controlled SGLT2-I outcome trials [2]. Across the now seven SGLT2-Is RCTs, including 51,501 patients with a median follow-up ranging from 1.3 to 4.2 years, the summative hazard ratios were 0.82 (95 % confidence interval, 0.76–0.88) for major cardiovascular events, 0.69 (0.64–0.75) for HF, 0.83 (0.77–0.90) for total mortality, and 0.60 (0.56–0.65) for worsening CKD. The aggregate effect sizes on systolic office BP, body weight, and HbA1c (unavailable from DAPA-CKD) were −2.3 mm Hg, −1.1 kg, and −0.23 %, respectively (all $P < 0.001$). Ongoing placebo-controlled RCTs in HF patients with reduced or preserved ejection fraction, with or without T2DM, are further exploring the benefits of SGLT2-Is in terms of hard outcomes, such as in EMPEROR-Preserved (NCT03057951) and DELIVER (NCT03619213) or in terms of left ventricular remodeling or function. Given that there is no specific therapy for HF with preserved ejection fraction [3], the results of EMPEROR-Preserved and DELIVER are eagerly awaited and expected to be published soon.

The blood glucose and BP lowering effects of SGLT2-Is are entirely self-contained. Indeed, approximately half of the frail DAPA-HF and EMPEROR-Reduced patients were nondiabetic and had a normal BP. Thus, the key message emerging from the RCTs reviewed above is that SGLT2-Is have advantageous effects over and beyond their antidiabetic activity and their BP- and weight-lowering effects [2]. The critical question in the management of cardiovascular risk by SGLT2-Is should now shift from their value in established disease to the primary prevention in asymptomatic stage-A HF or stage-2 CKD patients, often associated with hypertension [4]. Proving that SGLT2-Is would be effective in primary prevention without major adverse events, would be a game changer. Their application in the earliest asymptomatic phases of disease would be highly valuable for people at risk and their caregivers, who for the first time would be able to offer a novel treatment modality to patients at risk. Furthermore, applying SGLT2-Is in primary prevention would also be profitable for payers by mitigating the huge healthcare costs related to HF, currently far exceeding those of cancer; expressed per-capita, this is also the case for the burden of end-stage CKD on healthcare. It took over two decades for RCTs of statins to move from secondary to primary prevention [5] and for guidelines to include high cardiovascular risk, irrespective of the serum cholesterol level, among the compelling indications for this lipid-lowering drug class. The numbers of patients to treat for 1 year to prevent one major coronary event was 310 in the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial [5] and 338 in our meta-analysis. We hope that based on the experience with statins lessons have been learnt and that researchers and industry will join forces to mount RCTs of SGLT2-Is focusing on true primary prevention of HF and

https://doi.org/10.1016/j.ijcrp.2021.200100

Available online 25 September 2021

CKD in individuals with or without T2DM.

Acknowledgements

The Research Institute Alliance for the Promotion of Preventive Medicine, Mechelen (URL: www.appremed.org) received a non-binding grant from OMRON Healthcare Co. Ltd., Kyoto, Japan.

References

[1] F. Zannad, J.P. Ferreira, S.J. Pocock, S.D. Anker, J. Butler, G. Filippatos, M. Brueckmann, A.P. Ofstad, E. Pfarr, F. Jamal, M. Packer, SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HT trials, Lancet 396 (2020) 819–829.

[2] C. Yan, L. Thijs, Y. Cao, S. Trenson, Z.Y. Zhang, S. Janssens, J.A. Staessen, Y.M. Feng, Opportunities of antidiabetic drug in cardiovascular medicine: a meta-analysis and perspectives for trial design, Hypertension 76 (2020) 420–431.

[3] W.J. Paulus, van Ballegoij JJM, Treatment of heart failure with normal ejection fraction: an inconvenient truth!, J. Am. Coll. Cardiol 55 (2010) 526–537.

[4] Z.Y. Zhang, E. Nkuipou-Kenfack, W.Y. Yang, F.F. Wei, N. Cauwenberghs, L. Thijs, Q. F. Huang, Y.M. Feng, J.P. Schanstra, T. Kuznetsova, J.U. Voigt, P. Verhamme, H. Mischak, J.A. Staessen, Epidemiologic observations guiding clinical application of a urinary peptidomic marker of diastolic left ventricular dysfunction, J. Am. Soc. Hypertens 12 (2018) 438–447.

[5] B.M.Y. Cheung, I.J. Lauder, C.P. Lau, C.R. Kumana, Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes, Br. J. Clin. Pharmacossl 57 (2004) 640–651.

Jan A. Staessen*
Research Institute Alliance for the Promotion of Preventive Medicine, Belgium
Biomedical Science Group, Faculty of Medicine, University of Leuven, Leuven, Belgium

Stefan Janssens
Division of Cardiology, University Hospitals Leuven, Leuven, Belgium

Frans Van de Werf
Biomedical Science Group, Faculty of Medicine, University of Leuven, Leuven, Belgium

* Corresponding author. Alliance for the Promotion of Preventive Medicine, Leopoldstraat 59, BE -2800, Mechelen, Belgium.
E-mail addresses: jan.staessen@appremed.org, jan.staessen@med.kuleuven.be (J.A. Staessen).