ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy (2021) **7**, e9–e10
doi:10.1093/ehjcvp/pvab012

PHARMAPULSE

Sodium–glucose co-transporter 2 inhibitors in heart failure

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Online publish-ahead-of-print 9 February 2021

During the past 2 decades, significant advances in drug treatment have improved the prognosis of patients with heart failure with reduced ejection fraction.

More recently, the SGLT2i has demonstrated an un-expected significant and consistent effect in patients with HFrEF. The serendipity of these drugs started with the evidence of the effect of canagliflozin, dapagliflozin, and empagliflozin in reducing hospitalizations for heart failure in patients with diabetes mellitus (DM) where these drugs were tested to prove their safety. Meta-analyses of the cardiovascular outcome studies in diabetic patients consistently demonstrated that SGLT2 inhibitors, as a class, reduced the risk of hHF by 31–32% in patients with DM, and that event reductions were similar in comparable patient populations.[1] *Post hoc* analyses of the studies in DM provided more insights on the effect of SGLT2 inhibitors in HFrEF. An analysis of the CANVAS programme found that canagliflozin reduced the overall risk of HFrEF hospitalization or death (hazard ratio: 0.69; 95% confidence interval: 0.48–1.00]. A *post hoc* analysis of DECLARE-TIMI 58 suggested a 45% risk reduction for CV death and a 51% risk reduction in all-cause death in patients with a history of HFrEF receiving dapagliflozin.

Boosted by these results trials with SGLT2i were rolled out in patients with HFrEF. The DAPA-HF was the first of these studies to investigate the treatment of HF in patients with HFrEF with and without T2DM.[2] The study demonstrated a 26% reduction in the primary endpoint of cardiovascular death and hospitalizations for HFrEF, a 30% reduction in hospitalizations for HFrEF, and an 18% reduction in death from CV causes. This effect was similar in patients with and without DM. The EMPEROR-Reduced study with empagliflozin demonstrated a 25% reduction in the composite endpoint of hospitalizations for HFrEF and cardiovascular mortality.[3] This effect was primarily driven by a 30% reduced rates of hospitalizations for HFrEF.

More recently, the results of the SOLOIST-WHF trial with the dual SGLT1/SGLT2 inhibitor sotagliflozin in diabetic patients with heart failure have been reported.[4] The study was stopped early because of lack of funding and its primary endpoint had been revised by the steering committee to increase the power of the trial before the analysis of the results. Nevertheless, a robust 33% reduction in the revised primary endpoint and a 32% reduction in the original primary endpoint of cardiovascular mortality and hospitalizations for HF were reported.

All the above studies also demonstrated a significant reduction in the rate of renal disease progression even in patients with severely reduced eGFR. Thereby suggesting that these drugs can be safely used even in patients with severely impaired renal function.

The results from the available studies with SGLT2i in HFrEF suggest a completely new approach to HF management. They strongly support the rationale for the use of SGLT2 inhibitors in patients with HFrEF, which must impact future clinical practice. These results establish a new standard of care in HFrEF consisting of SGLT2i be used from the beginning, together with neuro-hormonal inhibition to reduce mortality and morbidity and to slow the progression of the disease.

Acknowledgements

G.R. and C.V. have been supported by a grant from Ricerca Corrente Ministero della Salute.

Conflict of interest: G.S. reports grants and personal fees from Vifor; grants and non-financial support from Boehringer Ingelheim; personal fees from Societa' Prodotti Antibiotici; grants and personal fees from AstraZeneca; personal fees from Roche and Servier; grants from Novartis; personal fees from GENESIS, Cytokinetics, and Medtronic; and grants from Boston Scientific, outside the submitted work.

References

1. Rosano G, Quek D, Martínez F. Sodium-glucose co-transporter 2 inhibitors in heart failure: recent data and implications for practice. *Card Fail Rev* 2020;**6**:e31.
2. McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Bengtsson O, Ponikowski P, Sabatine MS, Sjöstrand M, Solomon SD, McMurray JJ, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Ponikowski P, Sabatine MS, Sjöstrand M, Solomon SD, Diez M, Nicolau J, Katova T, O'Meara E, Howlett J, Verma S, Ge J, Belohlavek J, Schou M, Böhm M, Merkely B, Chopra V, Kitakaze M, de Boer RA, Drozdz J, Tereshchenko S, Dukat A, Ljungman C, Chiang C-E, Petrie M, Desai A, Anand I, Pham VN, Pfeffer MA, Pocock S, Swedberg K, Rouleau JL, Chaturvedi N, Ivanovich P, Levey AS, Christ-Schmidt H, Held C, Varenhorst C, Christersson C, Mann J, Holmgren P, Hallberg T, Langkilde A, Sjöstrand M, Denison H, Reicher B, Bengtsson O, Fox Y, Forsby M, Alenhag E-L, Nilsson A, Kazanowska K, Olofsson EL, Karup C,

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Ekedahl-Berggren M, Klockargård A-L, Kempe K, Selvén M; on behalf of the DAPA-HF Committees and Investigators. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur J Heart Fail* 2019;**21**:665–675.

3. Packer M, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, Kimura K, Zeller C, George J, Brueckmann M, Anker SD, Zannad F, Packer M, Anker SD, Butler J, Filippatos G, Zannad F, George J, Brueckmann M, Perrone S, Nicholls S, Janssens S, Bocchi E, Giannetti N, Verma S, Jian Z, Spinar J, Seronde M-F, Böhm M, Merkely B, Chopra V, Senni M, Taddei S, Tsutsui H, Choi D-J, Chuquiure E, La Rocca HPB, Ponikowski P, Juanatey JRG, Squire I, Butler J, Januzzi J, Pina I, Pocock SJ, Carson P, Doehner W, Miller A, Haas M, Pehrson S, Komajda M, Anand I, Teerlink J, Rabinstein A, Steiner T, Kamel H, Tsivgoulis G, Lewis J, Freston J, Kaplowitz N, Mann J, Petrie M, Bernstein R, Cheung A, Green J, Januzzi J, Kaul S, Ping CLS, Lip G, Marx N, McCullough P, Mehta C, Ponikowski P, Rosenstock J, Sattar N, Scirica B, Tsutsui H, Verma S, Wanner C, Welty FK, Parhofer KG, Clayton T, Pedersen TR, Lees KR, Konstam MA, Greenberg B, Palmer M; EMPEROR-Reduced Trial Committees and Investigators. Evaluation of the effect of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality of patients with chronic heart failure and a reduced ejection fraction: rationale for and design of the EMPEROR-Reduced trial. *Eur J Heart Fail* 2019;**21**:1270–1278.
4. Docherty KF, McMurray JJV. SOLOIST-WHF and updated meta-analysis: sodium-glucose co-transporter 2 inhibitors should be initiated in patients hospitalized with worsening heart failure. *Eur J Heart Fail* 2020; doi:10.1002/ejhf.2075. Epub ahead of print.