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EDITORIAL

New treatment options to reduce heart failure hospitalization

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Results of two new meta-analyses appearing in the December issue of 2020 in ESC Heart Failure support the application of sodium–glucose co-transporter-2 (SGLT2) inhibitors[1] and intravenous iron[2] to reduce hospitalization in chronic heart failure (HF).

Sodium–glucose co-transporter-2 inhibitors were originally introduced for the treatment of type 2 diabetes mellitus (T2DM). SGLT2 inhibitors, also known as gliflozins, inhibit insulin-independent glucose reabsorption in the kidney and therefore lower the level of blood glucose.[3] In addition to the antidiabetic effects, gliflozins have been initially associated with cardiovascular (CV) benefits in T2DM patients and later in CV patients even in the absence of T2DM.[4] SGLT2 inhibitors possess metabolic and antihypertensive effects, thereby providing a rationale for their use in CV diseases.[5] Most notably, gliflozins reduced the risk of HF hospitalization in T2DM patients with CV disease or at high risk of CV disease, although the exact mechanism remained elusive.[6–8] It seems to be straightforward to link reductions in CV risks with the primary receptor target in the proximal tubules of the kidney. Accordingly, gliflozin-induced hypoglycaemic and insulin-reducing effects were initially considered for the metabolic and antihypertensive effects, whereby increased urinary glucose loss reduces circulating plasma volume (due to osmotic diuresis) and leads to optimized metabolic and loading conditions for the heart.[9] Nevertheless, additional apparently independent benign effects were also noted. These included improvements in endothelial and vascular functions, an increase in HDL-cholesterol level, and reductions in triglyceride level, visceral fat deposition, albuminuria, oxidative stress, sympathetic activity, and uric acid level.[10] All of these changes are desired during CV disorders, albeit the molecular mechanisms are still not entirely clear. Of note, SGLT2 inhibition associated with a number of preferred changes in kidney function and thus implicated renoprotective effects in the context of cardiorenal interactions. A shift towards ketogenic cardiac metabolism, reduction in tissue fibrosis, and a direct influence on myocardial Na^+/H^+ exchange can be involved, too.[10] Recent analyses of the available preclinical and clinical information stress the significance of glucose-independent (and consequently T2DM-independent) effects of SGLT2 inhibitors.[11] Clearly, more studies are required to complete this stimulating puzzle and thus to clarify how SGLT2 inhibitors, primarily designed as antidiabetic drugs, protect the heart.

Irrespective to the somewhat elusive nature of the mechanisms, clinical trials are gaining momentum to prove the efficacy of SGLT2 inhibitors in CV medicine. Presented in this issue, Butler *et al*. report a state-of-the-art meta-analysis on the safety and efficacy of SGLT2 inhibitors in patients with HF.[1] Their results include all HF patients having been reported by clinical trials (reaching a patient number of almost 17 000). They aimed to refine the focus on the clinical applicability of SGLT2 inhibitors in HF and defined cohorts according to the types of HF: patients with reduced ejection fraction (HFrEF) or with preserved ejection fraction (HFpEF) and general HF patients. The presented results support highly significant improvements (i.e. up to 30% reduction in CV hazard ratios) for SGLT2 inhibitors in patients with HFrEF (independently of the potentially co-existing T2DM) and illustrate a moderate benefit for HFpEF patients.

Iron deficiency (ID) can develop even in the absence of anaemia (with a prevalence as high as 50%) in HF patients and it is thought to contribute to increased morbidity and mortality.[12] Several factors and conditions co-existing with HF increase the propensity for ID.[13] Iron, as an essential micronutrient, is required for the metabolism in every cell of the human body, and ID is considered as a contributor of the deteriorating CV function during HF and as a marker of poor prognosis.[14] Accordingly, current guidelines included clinical recommendations for iron supplementations.[15] Iron supplementation characteristically involves intravenous administration of ferric carboxymaltose (FCM), because oral iron therapy is proved to be less efficacious and difficult to tolerate. The clinical effects of intravenous iron have been

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previously studied in randomized clinical trials.[14,16–19] Results of these clinical investigations evidenced improved functional characteristics for HF patients.

Khan *et al*. aimed to correct the limitations of previous clinical studies by a meta-analysis. Their results, presented in this issue,[2] shed a new light on the clinical efficacy of iron supplementation. The number of their total cohort (reaching almost 2000 individuals) allowed the recognition of significantly reduced risks of the composite endpoint of time to first HF hospitalization or CV death. FCM also significantly reduced the risk of recurrent HF hospitalizations and recurrent CV hospitalizations, nevertheless, in the absence of significant risk reductions of all-cause or CV mortality. Collectively, these findings support FCM administration as a pharmacological therapy in HF.

Conflict of interest

Zoltán Papp has received a speaker honorarium from Drug Company Orion. Attila Tóth declares that he has no conflict of interest.

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References

1. Butler, Usman MS, Khan MS, Greene SJ, Friede T, Vaduganathan M, Filippatos GS, Coats AJS, Anker SD. Efficacy and safety of SGLT2 inhibitors in heart failure: a systematic review and meta-analysis. *ESC Heart Failure*.
2. Khan S, Usman MS, von Haehling S, Doehner W, Coats AJS. Ferric carboxymaltose for the treatment of iron deficient heart failure patients: a systematic review and meta-analysis. *ESC Heart Failure*.
3. Shubrook JH, Bokaie BB, Adkins SE. Empagliflozin in the treatment of type 2 diabetes: evidence to date. *Drug Des Devel Ther* 2015; **9**: 5793–5803.
4. Usman MS, Siddiqi TJ, Memon MM, Khan MS, Rawasia WF, Talha Ayub M, Sreenivasan J, Golzar Y. Sodium-glucose co-transporter 2 inhibitors and cardiovascular outcomes: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2018; **25**: 495–502.
5. Haas B, Eckstein N, Pfeifer V, Mayer P, Hass MD. Efficacy, safety and regulatory status of SGLT2 inhibitors: focus on canagliflozin. *Nutr Diabetes* 2014; **4**: e143.
6. Seferović PM, Petrie MC, Filippatos GS, Anker SD, Rosano G, Bauersachs J, Paulus WJ, Komajda M, Cosentino F, de Boer RA, Farmakis D, Doehner W, Lambrinou E, Lopatin Y, Piepoli MF, Theodorakis MJ, Wiggers H, Lekakis J, Mebazaa A, Mamas MA, Tschöpe C, Hoes AW, Seferović JP, Logue J, McDonagh T, Riley JP, Milinković I, Polovina M, van Veldhuisen DJ, Lainscak M, Maggioni AP, Ruschitzka F, McMurray JJV. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018; **20**: 853–872.
7. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; **373**: 2117–2128.
8. Mahaffey KW, Neal B, Perkovic V, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Fabbrini E, Sun T, Li Q, Desai M, Matthews DR. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS program (Canagliflozin Cardiovascular Assessment Study). *Circulation* 2018; **137**: 323–334.
9. Verma S, McMurray JJV, Cherney DZI. The metabolodiuretic promise of sodium-dependent glucose cotransporter 2 inhibition: the search for the sweet spot in heart failure. *JAMA Cardiol* 2017; **2**: 939–940.
10. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia* 2018; **61**: 2108–2117.
11. Heerspink HJL, Kosiborod M, Inzucchi SE, Cherney DZI. Renoprotective effects of sodium-glucose cotransporter-2 inhibitors. *Kidney Int* 2018; **94**: 26–39.
12. Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, Borodulin-Nadzieja L, Banasiak W, Polonski L, Filippatos G, McMurray JJ, Anker SD, Ponikowski P. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J* 2010; **31**: 1872–1880.
13. von Haehling S, Ebner N, Evertz R, Ponikowski P, Anker SD. Iron deficiency in heart failure: an overview. *JACC Heart Fail* 2019; **7**: 36–46.
14. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Lüscher TF, Bart B, Banasiak W, Niegowska J, Kirwan BA, Mori C, von Eisenhart Rothe B, Pocock SJ, Poole-Wilson PA, Ponikowski P. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009; **361**: 2436–2448.
15. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.
16. Zhou X, Xu W, Xu Y, Qian Z. Iron supplementation improves cardiovascular outcomes in patients with heart failure. *Am J Med* 2019; **132**: 955–963.
17. Filippatos G, Farmakis D, Colet JC, Dickstein K, Lüscher TF, Willenheimer R, Parissis J, Gaudesius G, Mori C, von Eisenhart Rothe B, Greenlaw N, Ford I, Ponikowski P, Anker SD. Intravenous ferric carboxymaltose in iron-deficient chronic heart failure patients with and without anaemia: a subanalysis of the FAIR-HF trial. *Eur J Heart Fail* 2013; **15**: 1267–1276.
18. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filippatos G, Ruschitzka F, Anker SD. Beneficial effects of long-term intravenous iron therapy with

ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J* 2015; **36**: 657–668.
19. Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J, Fabien V, Filippatos G, Göhring UM, Keren A, Khintibidze I, Kragten H, Martinez FA, Metra M, Milicic D, Nicolau JC, Ohlsson M, Parkhomenko A, Pascual-Figal DA, Ruschitzka F, Sim D, Skouri H, van der Meer P, Lewis BS, Comin-Colet J, von Haehling S, Cohen-Solal A, Danchin N, Doehner W, Dargie HJ, Motro M, Butler J, Friede T, Jensen KH, Pocock S, Jankowska EA. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet* 2020.