

# Heart failure drug treatment: the fantastic four

Johann Bauersachs  \*

Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany

**This editorial refers to ‘Influence of neprilysin inhibition on the efficacy and safety of empagliflozin in patients with chronic heart failure and a reduced ejection fraction: the EMPEROR-Reduced Trial’, by M. Packer et al., doi:10.1093/eurheartj/ehaa968.**

Heart failure with reduced ejection fraction (HFrEF) requires a multi-modal treatment with combination of several drugs as the cornerstone for symptomatic and prognostic improvement in all patients.<sup>1,2</sup> Drug therapies such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor/neprilysin inhibitors (ARNIs; sacubitril/valsartan), beta-blockers, and mineralocorticoid receptor antagonists (MRAs) provide incremental benefit with marked reduction in all-cause mortality, cardiovascular mortality, all-cause hospitalizations, and hospitalizations for heart failure.<sup>3</sup> Recently, the sodium–glucose co-transporter 2 (SGLT2) inhibitors dapagliflozin (DAPA-HF) and empagliflozin (EMPEROR-Reduced) showed a highly significant and clinically relevant reduction in mortality and heart failure hospitalizations, and improvement of quality of life when added to current standard drugs in patients with HFrEF.<sup>4,5</sup> Importantly, outcomes were ameliorated to a similar extent in patients with and without diabetes.

The question remained, however, of whether the nominally ‘standard’ heart failure drug treatment in the SGLT2 inhibitor trials corresponded to a ‘real’ modern guideline-directed medical therapy. While in both DAPA-HF and EMPEROR-Reduced the majority of patients received a combination of ACE inhibition, beta-blockade, and an MRA, only 10.7% of patients enrolled in DAPA-HF were treated with sacubitril/valsartan at baseline.<sup>4</sup> The benefit of dapagliflozin on the primary endpoint of cardiovascular death or worsening heart failure and the secondary endpoints was identical in patients treated with or without sacubitril/valsartan.<sup>6</sup>

In the current issue of the *European Heart Journal*, Packer et al.<sup>7</sup> provide a detailed analysis of the influence of ARNI pre-treatment on the effects of SGLT2 inhibition with empagliflozin in patients with

HFrEF included in EMPEROR-Reduced. In this trial, 19.5% of the patients received sacubitril/valsartan at baseline. The remarkable reduction of the primary endpoint (cardiovascular death or first heart failure hospitalization) and secondary endpoint of total heart failure hospitalizations was similar in patients with and without ARNI at baseline. Also the secondary renal endpoint (slope of the change in estimated glomerular filtration rate supported by an analysis of a composite of serious adverse renal outcomes) was markedly reduced in patients treated both with and without sacubitril/valsartan. In particular, the hazard ratios for all the primary and key secondary endpoints all tended to be even smaller in patients on an ARNI vs. the patients without an ARNI. The current analysis goes far beyond the initial report<sup>5</sup> and includes corrections for important covariates and baseline differences. Patients taking a neprilysin inhibitor at baseline, for example, had slightly lower blood pressure, and were more likely to be treated with implantable cardioverter-defibrillator and/or cardiac resynchronization therapy.<sup>7</sup> Side effects were similar in patients taking or not taking an ARNI; symptomatic hypotension non-significantly tended to be more frequent in patients on sacubitril/valsartan.

Thus, the detailed analyses from two large outcome trials in HFrEF with SGLT2 inhibitors<sup>6,7</sup> now substantiate the first crude data already reported in the original publications<sup>4,5</sup> as well as in the meta-analysis of DAPA-HF and EMPEROR-Reduced showing that patients treated with an ARNI derive at least the same benefit from additional SGLT2 inhibitor treatment as patients not on an ARNI.<sup>8</sup>

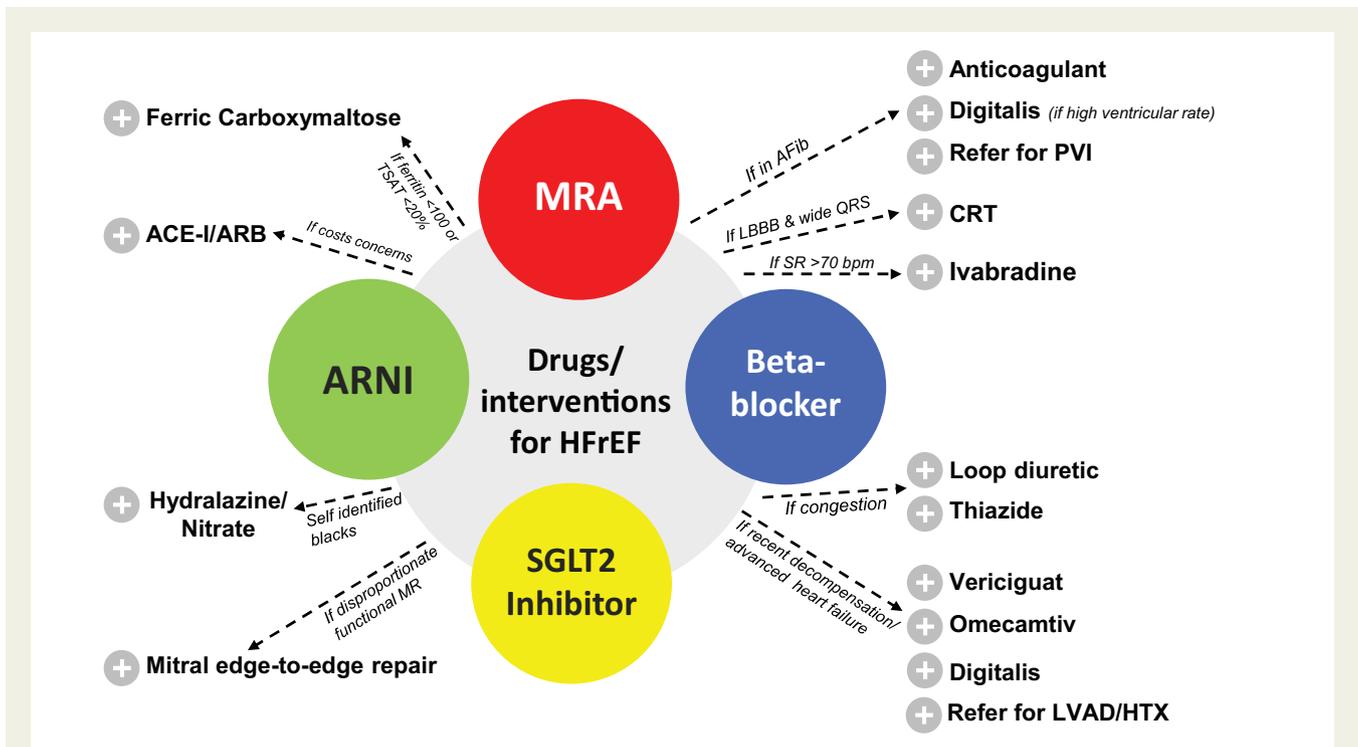
Taken together, these results derived from a considerable number of patients with ARNI pre-treatment now provide fundamental evidence that physicians caring for patients with HFrEF should not consider prescribing either an ARNI or an SGLT2 inhibitor, but rather both therapeutic principles in combination as default strategy. Thus, in clinical practice, patients without contraindications appear to gain most benefit from combined treatment with the ‘fantastic four’: an ARNI, a beta-blocker, an MRA, and an SGLT2 inhibitor (*Figure 1*). According to an elegant analysis by Vaduganathan et al. (2020) this

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

\* Corresponding author. Department of Cardiology and Angiology, Hannover Medical School, Carl-Neuberg-Str., D-130625 Hannover, Germany. Tel: +49 511 532 3841, Fax: +49 511 532 5412, Email: [bauersachs.johann@mh-hannover.de](mailto:bauersachs.johann@mh-hannover.de)

© The Author(s) 2021. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com)



**Figure 1** Drug, interventional, and device treatment for heart failure with reduced ejection fraction (HFrEF). ACE-I, angiotensin-converting enzyme inhibitor; Afib, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; CRT, cardiac resynchronization therapy; HTX, heart transplantation; LBBB, left bundle branch block; LVAD, left ventricular assist device; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; PVI, pulmonary vein isolation; SGLT2, sodium-glucose co-transporter 2; SR, sinus rhythm; TSAT, transferrin saturation.

four-drug strategy in a 55-year-old HFrEF patient provides an additional gain of 8.3 years free from cardiovascular death or first heart failure hospital admission, and 6.3 additional years of survival compared with the often used conventional combination of an ACE inhibitor and beta-blocker. Also, older patients derive substantial benefit.<sup>9</sup> The additive effect of SGLT2 inhibition on top of an already optimized background triple neurohormonal blockade including an ARNI is supported by a recent analysis from DAPA-HF: the beneficial effect of dapagliflozin was also consistent in patients on a beta-blocker, MRA, and ARNI: the hazard ratio for the primary endpoint was 0.70 as compared with 0.74 in patients without an ARNI.<sup>10</sup>

Physicians treating HFrEF patients are now in a comfortable situation. We do have four standard drugs to offer to our patients as default strategy with remarkable improvement of survival, hospitalization rates, symptoms, and quality of life. In addition, we can offer a bunch of additional drugs as well as a variety of interventional and device therapies for personalized treatment of specific patient populations with evidence-based benefits (Figure 1).

Where to go from here? An important question relates to the timing of drug initiation. While traditionally additional drugs were only started in stable outpatients with HFrEF, the PIONEER-HF trial nicely showed that sacubitril/valsartan started early after a decompensation was associated with a significantly stronger reduction of N-terminal-pro-brain natriuretic peptide (NT-proBNP) values and of the exploratory composite endpoint of death, heart failure rehospitalization, transplant listing, and ventricular assist device implantation

already after 8 weeks.<sup>11</sup> In the absence of newer European guidelines, the Clinical Practice Update of the ESC Heart Failure Association (HFA) stated that initiation of sacubitril/valsartan rather than an ACE inhibitor may be considered for patients hospitalized with new-onset heart failure or decompensated chronic heart failure to reduce the short-term risk of adverse events and to simplify management.<sup>12</sup>

In a recent update from the Heart Failure Association on SGLT2 inhibitors in heart failure, dapagliflozin or empagliflozin are recommended to reduce the risk of heart failure hospitalization and cardiovascular death in HFrEF patients already receiving guideline-directed medical therapy, regardless of the presence of type 2 diabetes mellitus.<sup>13</sup> Also in the SGLT2 inhibitor trials, the treatment effect emerged quickly, with the curves diverging within the first month.<sup>4,5</sup> Such early effects have similarly been observed with the SGLT2 inhibitor sotagliflozin in the SOLOIST-WHF trial that randomized patients with type 2 diabetes after a recent hospitalization for worsening heart failure.<sup>14</sup> Substantial benefit occurred early after randomization regarding the primary endpoint of cardiovascular deaths, total hospitalizations, and urgent visits for heart failure.

In summary, the totality of evidence now suggests that patients with HFrEF should be treated early with a combination of the four drugs: an ARNI, beta-blocker, MRA, and SGLT2 inhibitor in order to benefit from substantial and sustained reductions of mortality, heart failure hospitalizations, and symptoms.<sup>15,16</sup> The important task is now to ensure access to this evidence-based therapy for all HFrEF patients.

**Conflict of interest:** J.B. reports honoraria for lectures and/or consulting from Novartis, BMS, Pfizer, Vifor, Bayer, Servier, Daichii Sankyo, CVRx, MSD, Boehringer Ingelheim, AstraZeneca, Cardior, Abiomed, Abbott, and Medtronic; and research support from Zoll, CVRx, Vifor, and Abiomed.

## References

- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, 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). *Eur J Heart Fail* 2016;**18**:891–975.
- Berliner D, Hänselmann A, Bauersachs J. The treatment of heart failure with reduced ejection fraction. *Dtsch Arztebl Int* 2020;**117**:376–386.
- Komajda M, Böhm M, Borer JS, Ford I, Tavazzi L, Pannaux M, Swedberg K. Incremental benefit of drug therapies for chronic heart failure with reduced ejection fraction: a network meta-analysis. *Eur J Heart Fail* 2018;**20**:1315–1322.
- McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008.
- Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F; EMPEROR Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;**383**:1413–1424.
- Solomon SD, Jhund PS, Claggett BL, Dewan P, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Inzucchi SE, Desai AS, Bengtsson O, Lindholm D, Sjostrand M, Langkilde AM, McMurray JJV. Effect of dapagliflozin in patients with HFrEF treated with sacubitril/valsartan: the DAPA-HF trial. *JACC Heart Fail* 2020;**8**:811–818.
- Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, Brunner-La Rocca HP, Janssens S, Tsutsui H, Zhang J, Brueckmann M, Jamal W, Cotton D, Iwata T, Schnee J, Zannad F; for the EMPEROR-Reduced Trial Committees and Investigators. Influence of neprilysin inhibition on the efficacy and safety of empagliflozin in patients with chronic heart failure and a reduced ejection fraction: the EMPEROR-Reduced Trial. *Eur Heart J* 2020;doi:10.1093/eurheartj/ehaa968.
- Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, Brueckmann M, Ofstad AP, Pfarr E, Jamal W, Packer M. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* 2020;**396**:819–829.
- Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, Packer M, Fonarow GC, McMurray JJV, Solomon SD. Estimating life-time benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet* 2020;**396**:121–128.
- Docherty KF, Jhund PS, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, DeMets DL, Sabatine MS, Bengtsson O, Sjöstrand M, Langkilde AM, Desai AS, Diez M, Howlett JG, Katova T, Ljungman CEA, O'Meara E, Petrie MC, Schou M, Verma S, Vinh PN, Solomon SD, McMurray JJV. Effects of dapagliflozin in DAPA-HF according to background heart failure therapy. *Eur Heart J* 2020;**41**:2379–2392.
- Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, Rocha R, Braunwald E; PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med* 2019;**380**:539–548.
- Seferović PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, de Boer RA, Drexel H, Ben Gal T, Hill L, Jaarsma T, Jankowska EA, Anker MS, Lainscak M, Lewis BS, McDonagh T, Metra M, Milicic D, Mullens W, Piepoli MF, Rosano G, Ruschitzka F, Volterrani M, Voors AA, Filippatos G, Coats AJS. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:1169–1186.
- Seferović PM, Frangasso G, Petrie M, Mullens W, Ferrari R, Thum T, Bauersachs J, Anker SD, Ray R, Çavuşoğlu Y, Polovina M, Metra M, Ambrosio G, Prasad K, Seferović J, Jhund PS, Dattilo G, Čelutkienė J, Piepoli M, Moura B, Chioncel O, Ben Gal T, Heymans S, Jaarsma T, Hill L, Lopatin Y, Lyon AR, Ponikowski P, Lainščak M, Jankowska E, Mueller C, Cosentino F, Lund LH, Filippatos GS, Ruschitzka F, Coats AJS, Rosano GMC. Heart Failure Association of the European Society of Cardiology update on sodium–glucose co-transporter 2 inhibitors in heart failure (an update on the sodium–glucose co-transporter 2 inhibitors in heart failure: beyond glycaemic control. A position paper of the Heart Failure Association of the European Society of Cardiology). *Eur J Heart Fail* 2020;doi: 10.1002/ehjhf.2026.
- Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Voors AA, Metra M, Lund LH, Komajda M, Testani JM, Wilcox CS, Ponikowski P, Lopes RD, Verma S, Lapuerta P, Pitt B; SOLOIST-WHF Trial Investigators. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2020;doi: 10.1056/NEJMoa2030183.
- Butler J, Zannad F, Filippatos G, Anker SD, Packer M. Totality of evidence in trials of sodium–glucose co-transporter-2 inhibitors in the patients with heart failure with reduced ejection fraction: implications for clinical practice. *Eur Heart J* 2020;**41**:3398–3401.
- Bassi NS, Ziaei B, Yancy CW, Fonarow GC. Association of optimal implementation of sodium–glucose cotransporter 2 inhibitor therapy with outcome for patients with heart failure. *JAMA Cardiol* 2020;**5**:1–5.