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Letter

Are post-hoc analyses on subgroups sufficient to support new treatment algorithms of heart failure? The case of SGLT2 inhibitors associated with sacubitril/valsartan

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Short Title: Combination of SGLT2 inhibitors and sacubitril/valsartan

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Abstract

The use of sodium glucose cotransporter 2 inhibitors (SGLT2i) in heart failure (HF) with reduced ejection fraction (HFrEF) has been strongly supported by the results of recent randomized clinical trials. Upon this evidence, international recommendations and consensus documents propose the inclusion of SGLT2i among the first-line classes for HFrEF management.

Subsequent analyses of treatment subgroups have been performed to investigate the effects of SGLT2i in patients treated with first line classes including sacubitril/valsartan (Sac/Val), showing a consistent reduction of cardiovascular (CV) outcomes with a good safety profile of SGLT2i in combination with the other classes. Accordingly, SGLT2i are recommended also in combination with Sac/Val.

This association, however, may require caution before being translated into guideline directed medical therapy (GDMT) in clinical practice, since the proportion of patients receiving Sac/Val and SGLT2i in the available studies was poorly represented. In order to support an effective and safe sequencing or a simultaneous initiation of these two drug classes, pragmatic and real world clinical studies would be helpful.

The development of sodium glucose cotransporter 2 inhibitors (SGLT2i) and their clinical use in heart failure (HF) with reduced ejection fraction (HFrEF) also in diabetic patients has been strongly supported following the publication of two successful large randomized controlled trials. The DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) [1] and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction) [2] trials, which compared dapagliflozin and empagliflozin, respectively, with placebo on top of standard-of-care therapy, showed significant reductions of primary endpoint event rates in HFrEF treated with SGLT2i. Upon this evidence, recent international recommendations and consensus documents propose the inclusion of SGLT2i among the first-line classes for HFrEF management [3]. Subsequent analyses of treatment subgroups have been performed to assess whether the benefits of SGLT2i on cardiovascular (CV) outcomes are uniform and are confirmed when combined with other disease modifying drugs. In particular, analyses have been attempted to investigate the effects of SGLT2i in patients treated with sacubitril/valsartan (Sac/Val) [4].

In a recent article based on a prespecified subgroup analysis (one of twelve) of the EMPEROR-Reduced [5], Packer and colleagues reported that the favorable effects of empagliflozin in patients with HFrEF were preserved in the subgroup of patients treated with Sac/Val. For most endpoints (including the primary endpoint of CV mortality and HF hospitalizations), the magnitude of the effect of empagliflozin in patients receiving Sac/Val tended to be numerically larger than in those not receiving Sac/Val, although the interaction P-values were not statistically significant [1]. However, only 727 subjects were treated with Sac/Val, representing the 19.5% of the overall study population. Among them, 340 received both empagliflozin and Sac/Val [1]. On the other hand, patients treated with RAS blockers, beta-blockers and MRA were well represented, being 71%, 95% and 70% of the study population, respectively.

A similar finding was described by Solomon et al. [6] in the subgroup analysis of DAPA-HF. Again, there was consistency of treatment benefit with dapagliflozin in favor of a reduction of the composite primary end-point in the Sac/Val subgroup which was not different from what was observed in the non-Sac/Val group. Again, 508 subjects (10.7% of the entire study population) were treated with Sac/Val in DAPA-HF, of these only 250 received both dapagliflozin and Sac/Val. A much larger proportion of patients was treated with diuretics (93%), RAS blockers (85%), beta-blockers (96%) and MRA (71%) [2,7]. Similarly, in the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure) trial [8] patients receiving

background therapy with Sac/Val were under-represented, accounting for only 15% (92 patients) of the active treatment group.

Based upon the subgroup analyses of the EMPEROR-Reduced and DAPA-HF trials, a recently published meta-analysis not surprisingly confirmed the benefits of SGLT2i in patients treated or untreated with Sac/Val [9], a finding confirmed by retrospective studies in patients with HFrEF and diabetes mellitus [10,11].

The association of Sac/Val and SGLT2i in HFrEF appears to be safe, since a hypothesized adverse effect of a synergistic blood pressure reduction, mostly linked to increased diuresis, is not supported by subgroup post hoc analyses of EMPEROR-Reduced [5] and DAPA-HF [6].

In light of the abovementioned reports, SGLT2i are currently recommended also in combination with Sac/Val [3,12-14]. These results [4-6,8], however, may require caution before being translated in clinical practice.

In fact, while the effects of SGLT2i in patients with HFrEF have been demonstrated in randomized clinical trials on top of GDMT with renin-angiotensin-system (RAS) blockers, beta-blockers, mineralocorticoid receptor antagonists (MRA) or loop diuretics [1,2], the proportion of patients receiving Sac/Val were poorly represented and this may unfortunately undermine definite recommendations.

In addition studies with Sac/Val did not report the use of SGLT2i [15-18].

Even though Sac/Val and SGLT2i may have a synergistic action on diuresis/natriuresis, inhibition of the sympathetic nervous system and prevention of adverse cardiac remodeling, with potential additive beneficial effects, there are no preclinical studies investigating this combination.

In order to support an effective and safe sequencing or as some propose simultaneous initiation of the four classes as a new standard of care for HFrEF, pragmatic and real world clinical studies would best evaluate the combination of these two drug classes. This virtuous effort would represent, in our view, a key step to further support the paradigm of simultaneous initiation of Sac/Val and SGLT2i in the management of HFrEF.

Statements

Conflict of Interest Statement

Massimo Volpe reports personal fees for speaker bureau and/or consulting in Advisory Board from Amgen, Astra Zeneca, Daiichi-Sankyo, Menarini Int, MSD, Novartis Pharma, Novo Nordisk outside the submitted work.

Giovanna Gallo was sub-investigator of the EMPEROR-Reduced and EMPEROR-Preserved trials sponsored by Boehringer Ingelheim and of the PARAGON-HF trial sponsored by Novartis.

Shelley Zieroth reports personal fees for speaker bureau and/or consulting in Advisory Board from Abbott, Akcea, Astra Zeneca, Amgen, Alnylam, Bayer, Boehringer Ingelheim, Eli-Lilly, HLS Therapeutics, Janssen, Merck, Novartis, Novo Nordisk, Otsuka, Pfizer, Servier, Vifor. She also is national lead, steering committee member or site investigator for clinical trials sponsored by Astra Zeneca, Bayer, Boehringer Ingelheim, Eidos, Novartis outside the submitted work. She is one of the Journal's Editorial Board Member.

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Author Contributions

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References

- 1) McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al; DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019 Nov 21;381(21):1995-2008.
- 2) Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al; EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med*. 2020 Oct 8;383(15):1413-1424.
- 3) McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021 Aug 27;ehab368.
- 4) Volpe M, Bauersachs J, Bayés-Genís A, Butler J, Cohen-Solal A, Gallo G et al. Sacubitril/valsartan for the management of heart failure: A perspective viewpoint on current evidence. *Int J Cardiol*. 2021 Mar 15;327:138-145.
- 5) Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, et al; 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*. 2021 Feb 11;42(6):671-680.
- 6) Solomon SD, Jhund PS, Claggett BL, Dewan P, Køber L, Kosiborod MN, et al. Effect of Dapagliflozin in Patients With HFrEF Treated With Sacubitril/Valsartan: The DAPA-HF Trial. *JACC Heart Fail*. 2020 Oct;8(10):811-818.
- 7) Docherty KF, Jhund PS, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Effects of dapagliflozin in DAPA-HF according to background heart failure therapy. *Eur Heart J*. 2020 Jul 1;41(25):2379-2392.
- 8) Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al; SOLOIST-WHF Trial Investigators. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med*. 2021 Jan 14;384(2):117-128.
- 9) Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet*. 2020 Sep 19;396(10254):819-829
- 10) Hsiao FC, Lin CP, Tung YC, Chang, PC, McMurray JJV, Chu PH. Combining sodium-glucose cotransporter 2 inhibitors and angiotensin receptor-neprilysin inhibitors in heart failure patients with reduced ejection fraction and diabetes mellitus: A multi-institutional study. *Int J Cardiol*. 2021 May 1;330:91-97
- 11) Jiménez-Blanco Bravo M, Valle A, Ordás JG, Díaz SDP, Pereda DC, Climent HM, et al. Safety and Efficacy of the Combination of Sacubitril/Valsartan and SGLT2i in HFrEF patients (SECSI Registry). *J Cardiovasc Pharmacol*. 2021 Jul 19. doi: 10.1097/FJC.0000000000001111
- 12) Ahmad T, Desai NR. Quadruple Therapy Is the New Standard of Care for HFrEF. *JACC Heart Fail*. 2020 Oct;8(10):819-821
- 13) Bauersachs J. Heart failure drug treatment: the fantastic four. *Eur Heart J*. 2021 Feb 11;42(6):681-683
- 14) McMurray JJV, Packer M. How Should We Sequence the Treatments for Heart Failure and a Reduced Ejection Fraction?: A Redefinition of Evidence-Based Medicine. *Circulation*. 2021 Mar 2;143(9):875-877.
- 15) McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014 Sep 11;371(11):993-1004.
- 16) Januzzi JL Jr, Prescott MF, Butler J, Felker GM, Maisel AS, McCague K, et al; PROVE-HF Investigators. Association of Change in N-Terminal Pro-B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment With Cardiac Structure and Function in Patients With Heart Failure With Reduced Ejection Fraction. *JAMA*. 2019 Sep 17;322(11):1-11.
- 17) Wachter R, Senni M, Belohlavek J, Straburzynska-Migaj E, Witte KK, Kobalava Z, et al; TRANSITION Investigators. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. *Eur J Heart Fail*. 2019 Aug;21(8):998-1007.
- 18) Senni M, McMurray JJ, Wachter R, McIntyre HF, Reyes A, Majercak I, et al. Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens. *Eur J Heart Fail*. 2016 Sep;18(9):1193-202

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