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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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 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 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 2 drug classes, pragmatic and real-world clinical studies would be helpful.

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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 have been strongly supported following the publication of 2 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 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 (1 of 12) of the EMPEROR-Reduced [5], Packer and colleagues reported that the favorable effects of em-

pagliflozin in patients with HFrEF were preserved in the subgroup of patients treated with Sac/Val. For most endpoints (including the primary endpoint of cardiovascular mortality and HF hospitalizations), the magnitude of the effect of empagliflozin in patients receiving Sac/Val tended to be numerically larger than that 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 renin-angiotensin-system (RAS) blockers, β -blockers, and mineralocorticoid receptor antagonists (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 endpoint 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%), β -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 underrepresented, accounting for only 15% (92 patients) of the active treatment group.

Based on 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 guideline-directed medical therapy with RAS blockers, β -blockers, MRA, or loop diuretics [1, 2],

the proportion of patients receiving Sac/Val was 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 4 classes as a new standard of care for HFrEF, pragmatic and real-world clinical studies would best evaluate the combination of these 2 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.

Conflict of Interest Statement

Massimo Volpe reports personal fees for speaker bureau and/or consulting in Advisory Board from Amgen, Thousand Oaks, CA, USA; AstraZeneca, Cambridge, UK; Daiichi-Sankyo, Tokyo, Japan; Menarini Int, Florence, Italy; MSD, Kenilworth, NJ, USA; Novartis Pharma, Basel, Switzerland; and Novo Nordisk, Plainsboro, NJ, USA, outside the submitted work. Giovanna Gallo was sub-investigator of the EMPEROR-Reduced and EMPEROR-Preserved trials sponsored by Boehringer Ingelheim, Ingelheim, Germany, and of the PARAGON-HF trial sponsored by Novartis, Basel, Switzerland. Shelley Zieroth reports personal fees for speaker bureau and/or consulting in Advisory Board from Abbott, Lake Bluff, IL, USA; Akcea, Boston, MA, USA; AstraZeneca, Amgen, and Alnylam, Cambridge, MA, USA; Bayer, Leverkusen, Germany; Boehringer Ingelheim, Eli-Lilly, Indianapolis, IN, USA; HLS Therapeutics, Etobicoke, ON, USA; Janssen, Beerse, Belgium; Merck, Darmstadt, Germany; Novartis; Novo Nordisk; Otsuka, Tokyo, Japan; Pfizer, New York, NY, USA; Servier, Suresnes, France; and Vifor, St. Gallen, Switzerland. She also is national lead, steering committee member, or site investigator for clinical trials sponsored by AstraZeneca, Bayer, Boehringer Ingelheim, and Eidos, San Francisco, CA, USA; and 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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