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Low Blood Pressure and Managing Drugs in HF: Where Do SGLT2 Inhibitors Stand?

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Effective novel interventions continue to be of benefit in heart failure with reduced ejection fraction (HFrEF)¹. However, a major limitation in the implementation of optimized treatment for HFrEF is low blood pressure as most HF drugs can induce hypotension, thus incurring symptoms and/or concerns for potential complications. As recently highlighted^{2,3}, the proportion of HF patients actually receiving the target dose (or receiving at least 50% of the target dose) is low overall, partly due to hypotension^{2,4}.

In this month's issue of the *Journal of the American College of Cardiology*, Michael Bohme and colleagues provide very insightful evidence on blood pressure in the setting of Sodium Glucose cotransporter type 2 (SGLT2) inhibitors treatment from the EMPEROR-HF trial⁵. Briefly, they show that patients with a systolic blood pressure (SBP) <110 mmHg (approximately ¼ patients in the EMPEROR-HF trial) experienced a similar risk of hypotension (including symptomatic hypotension) and an at-least similar treatment benefit for the primary outcome than patients with higher SBP (p for interaction 0.83 – assessed on a relative scale). The authors additionally showed that, when corrected for placebo, a slight early increase in SBP occurred in patients in the SBP <110 mmHg group during the early phase of the trial. This rather surprising result is likely the consequence of the (all too often forgotten) “regression to the mean phenomenon”, although it may also be related to the intrinsic early cardiovascular benefit from SGLT2 inhibitors. It should be emphasized that these results from the EMPEROR-HF trial parallel the findings published from the DAPA-HF trial⁶ in which the placebo-

corrected reduction in SBP within the first weeks of dapagliflozin initiation was less than 3 mmHg, while the benefit from SGLT2 inhibitors was similar across all BP groups (p for interaction 0.78 – assessed on a relative scale). Importantly, since low BP is a strong risk marker of outcome, the absolute treatment effect of SGLT2 inhibitors was numerically higher in this subgroup.

Taken together, these data suggest that SGLT2 inhibitors are rather neutral from a BP standpoint. Discontinuing SGLT2 inhibitors in patients with hypotension, even symptomatic hypotension occurring after SGLT2 inhibitor initiation, should probably be perceived as questionable. Indeed, hypotension rates in patients randomized to placebo or SGLT2 inhibitors were actually similar in the EMPEROR-HF trial, which strongly argue against the parenthood of SGLT2 inhibitors in the genesis of hypotension. In addition, given that patients with low blood pressure are intrinsically more at risk of events and experience a strong benefit from SGLT2, discontinuing SGLT2 inhibitor treatment could potentially be detrimental.

The above results in SGLT2 inhibitor trials echo the very good blood pressure-related safety profile of mineralocorticoids receptor antagonists (MRA) treatment recently reported in the EMPHASIS trial⁷ in which the placebo-corrected reduction in SBP at 6 months of eplerenone initiation was less than 3 mmHg, and the benefit from MRA was similar across all BP groups (p for interaction 0.95 – assessed on a relative scale). From a broader perspective, amongst the 4 pillars of HFrEF treatment (ACE inhibitors/ARN inhibitors; beta-blockers; MRA; SGLT2 inhibitors), we can individualize 2 pillars for which low BP is a struggle (ACE inhibitors/ARN inhibitors; beta-blockers) whereas the 2 other pillars (MRA; SGLT2 inhibitors) do not cause significant blood-related issues. This key facet should be kept in mind while treating patients with HFrEF !

With the increasing complexity of pharmacological HF management entailing the aforementioned 4 pillars of treatment, the day-to-day management of HF drug polypharmacy may represent an increasingly difficult challenge, primarily because of the frequent/repeated occurrence of worsening renal function and low blood pressure. The practical management of these hurdles currently remains poorly studied/documentated. A practical pharmacological management algorithm was published under the umbrella of the French Heart Failure group last year, intended to assist physicians in optimizing HF drug management in patients with worsening renal function and/or hyperkalemia⁸.

Likewise, we similarly published a practical algorithm in 2020 for managing low blood pressure in HFrEF, based on the experience of our group of HF experts⁹. The main phases of this algorithm are: (1) a careful assessment of BP to ascertain that symptoms are related to low BP, (2) the discontinuation or reduction of non-HFrEF BP lowering therapy, (3) decreasing diuretics when feasible and (4) modifications in HF medications adapted to the clinical profile of the patient (eGFR<30 ml/min, K>5.0 mEq/l, HR<60 bpm, history of severe arrhythmia, or none of the above).

Where do SGLT2 inhibitors fit into this algorithm? In the accompanying Figure, a tentative modification of the algorithm including SGLT2 inhibitors is provided. In fact, following the publication of the analysis centered on blood pressure from the EMPEROR trial, SGLT2 inhibitors should probably be perceived as blood pressure issue-free, and be the last HF treatment to be suspended in patients facing symptomatic hypotension. Consequently, we only included a brief mention related to SGLT inhibitors in this revised algorithm, suggesting that they should generally be maintained. Indeed, it is rather the occurrence of adverse effects truly related to SGLT2 inhibitors that should prompt its discontinuation, such as recurrent genital infection or acidocetosis in diabetic patients.

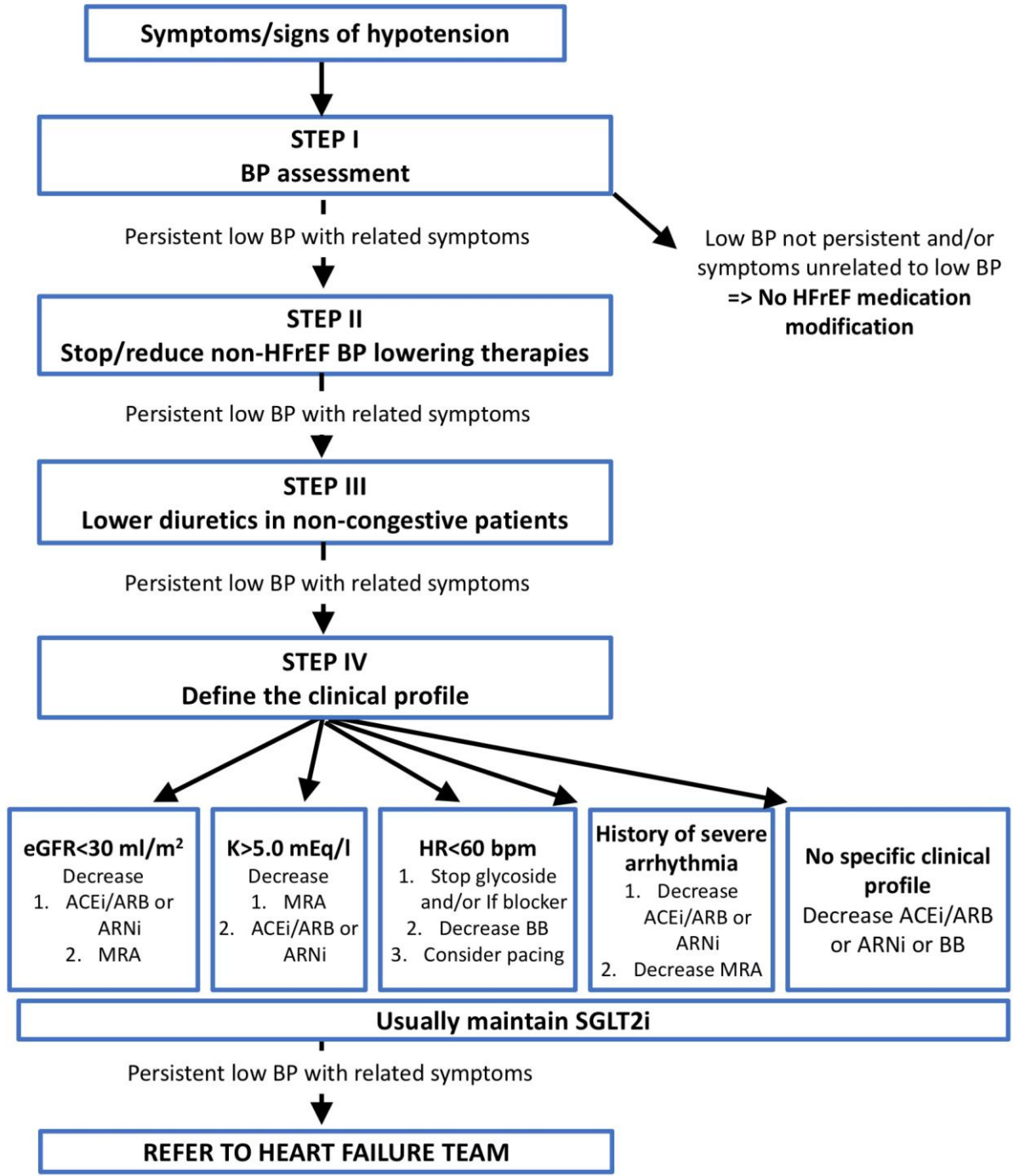
It is genuinely hoped that the article published in this month's issue of *JACC* will reassure physicians regarding good blood pressure tolerability of SGLT2 inhibitors. Importantly, this proven hemodynamic tolerability, along with a considerable renal protective effect, should probably prompt an early/initial initiation of SGLT2 inhibitors in patients with HFrEF, along with other pharmacological pillars of HF treatment. We believe that a voluntarist approach, favoring the implementation of the major therapeutic advances obtained in the field of HF in the past decade, can actually change the face of HF in the next decade.

Figure legend

Revised algorithm to manage low blood pressure in patients with HFrEF including SGLT2 inhibitors. Adapted from Cautela et al.⁹

Legend: HFrEF, Heart failure with reduced ejection fraction; BP, blood pressure; eGFR, estimated glomerular filtration rate; angiotensin-converting enzyme inhibitors, ACEi; Angiotensin II receptor blockers, ARB; Angiotensin receptor neprilysin inhibitor, ARNi; Mineralocorticoids receptor antagonists, MRA; Sodium Glucose cotransporter type 2 inhibitors, SGLT2i.

Decision tree for the management of low blood pressure in HFrEF



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