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Effect of Empagliflozin in Preventing Progression of Renal Dysfunction in Diabetic Patients With Compensated Heart Failure — Reply —

We appreciate the comments of Imamura regarding our recent publication in *Circulation Reports*,[1] which evaluated the efficacy of empagliflozin in patients with compensated heart failure (HF).

Because various beneficial and pleiotropic effects of sodium-glucose cotransporter 2 (SGLT2) have been reported recently,[2] conventional sequencing treatment for HF has been reconsidered in the guidelines. Conventional sequencing for HF treatments was performed in a step-by-step manner: Step 1, angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB); Step 2, β-blocker; Step 3, mineralocorticoid receptor blocker (MRB); Step 4, sacubitril/valsartan (angiotensin receptor-neprilysin inhibitor [ARNI]); and Step 5, SGLT2 inhibitor. Up-titration to target doses at each step was recommended; thus, 6 months or more is typically required. New sequencing treatment was suggested in 2021, in which the recommended steps were SLTT2 inhibitor/β-blocker treatment was as Step 1, ARNI as Step 2, and MRB as Step 3.[3] All 3 steps should be achieved within 4 weeks, with uptitration to the target doses performed thereafter.

Based on substantial evidence to support the effects of SGLT2 in HF, the importance of SGLT2 inhibitors in HF treatment is growing day by day, and they may become the mainstay of HF treatment in the near future. Although the beneficial effects of the administration of SGLT2 inhibitors on plasma B-type natriuretic peptide (BNP) concentrations and the estimated glomerular filtration rate (eGFR) were already suggested by a multicenter study,[4] the present study did not reveal any significant differences for these 2 parameters.[1] We performed statistical analyses to investigate the relationship between the administration of SGLT2 inhibitors, changes in BNP/eGFR (ΔBNP/ΔeGFR) from the start date to 3 and 6 months (calculated as follows: ΔBNP/ΔeGFR = BNP/eGFR on Day 1 − BNP/eGFR at 3 and 6 months), and Δ%BNP/Δ%eGFR (the percentage change in BNP/eGFR from the start date to 3 and 6 months; Δ%BNP/Δ%eGFR = BNP/eGFR on Day 1 ÷ BNP/eGFR at 3 and 6 months). Unfortunately, a Mann-Whitney analysis revealed no significant differences in the ΔBNP, ΔeGFR, Δ%BNP and Δ%eGFR values between the empagliflozin and non-empagliflozin groups. In addition, an inter-group trend analysis of the values at the start date and at 3 and 6 months in the empagliflozin group was performed using the Jonckheere-Terpstra test. However, no significant differences were identified.

As Imamura pointed out, our study included a small number of patients, the cohort was relatively less sick, and the observation period was short. This may be the reason why statistically significant differences were not observed in the BNP and eGFR values. Because beneficial effects in the heart and kidney have been demonstrated in various large multicenter cohorts,[4,5] these issues were one of the major limitations of our study. Furthermore, 16 patients in our study underwent combination therapy with ACEI/ARB and empagliflozin during 6 month follow-up, but none of the patients was treated with ARNI. Urinary acetyl-β-D-glucosaminidase excretion was significantly (P=0.046) decreased from the start date to 6 months in the combination therapy (ACE-I/ARB and empagliflozin) cohort (n=16; from a median [interquartile range] of 5.5 [2.3–13.0] to 3.3 [2.1–5.2] IU/L). Early simultaneous administration of ACEI/ARB and empagliflozin may prevent renal dysfunction, particularly renal tubular injury in HF patients. This finding is consistent with the recommended new sequencing treatment strategy in 2021.[3] An investigation of the efficacy of combination therapy is an important future task in the new era of HF management.

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Disclosures

The authors declare no conflict of interest in association with the present study.

IRB Information

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