Renal function dynamics following co-administration of sacubitril/valsartan and empaglioflozin in patients with heart failure and type 2 diabetes

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Abstract

Aims  The aim of this study was to evaluate the safety profile in terms of changes in renal function after co-treatment with sacubitril/valsartan and empaglioflozin in patients with type 2 diabetes (T2D) and heart failure with reduced ejection fraction (HFrEF).

Methods and results  This multicentre observational analysis included 108 patients with T2D and HFrEF treated with both agents: baseline sacubitril/valsartan (Group A; n = 43), baseline empaglioflozin (Group B; n = 42), or both agents initiated simultaneously (Group C; n = 23). The primary endpoint was estimated glomerular filtration rate (eGFR) dynamics across treatment groups. A binary characterization of worsening renal function (WRF)/improved renal function (IRF) was included in the primary endpoint. WRF and IRF were defined as an increase/decrease in serum creatinine ≥ 0.3 mg/dl or GFR ≥ 20%. Changes in quantitative variables were evaluated using joint modelling of survival and longitudinal data (JM). Rates and their treatment differences were determined by Poisson regression. The mean left ventricle ejection fraction and eGFR were 32 ± 6% and 70 ± 28 mL/min/1.73 m², respectively. At a median follow-up of 1.01 years (inter-quartile range 0.71–1.50), 377 outpatient visits were recorded. Although there were differences in GFR trajectories over time within each treatment, they did not achieve statistical significance (omnibus P = 0.154). However, when these differences were contrasted among groups, there was a significant decrease in GFR in Group A as compared with Group B (P = 0.002). The contrast between Groups C and B was not significant (P = 0.430). These differences were also reflected when the rates for WRF and IRF were contrasted among treatments.

Conclusions  The co-administration of sacubitril/valsartan and empaglioflozin in patients with HFrEF and concomitant T2D appears to be safe in terms of renal function.

Keywords  Heart failure with reduced ejection fraction (HFrEF); Type 2 diabetes mellitus; Sacubitril/valsartan; SGLT2i; Renal function; Renal safety profile

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Introduction

The angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan has become fundamental in the treatment of heart failure (HF) with reduced ejection fraction (HFrEF).¹ Sodium-glucose co-transporter-2 inhibitors (SGLT2is) have also shown promise in patients with HFrEF with and without type 2 diabetes (T2D).² Sacubitril/valsartan and SGLT2is result

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in a superior renal function profile at long-term follow-up as compared with enalapril and placebo, respectively.\(^2\)\(^\text{-}^\text{6}\) However, both treatments may cause short-term renal dysfunction.\(^5\)\(^\text{-}^\text{7}\)

Renal function after concomitant administration of sacubitril/valsartan and SGLT2i in patients with HFrEF and T2D is currently uncertain. Here, we evaluated renal function dynamics during concomitant treatment with sacubitril/valsartan and empagliflozin in addition to contemporary treatment in a cohort of consecutive ambulatory patients with HFrEF and T2D.

### Methods

#### Study design and patients

This is a consecutive multicentre observational study of 108 patients with chronic HFrEF and T2D who received empagliflozin and sacubitril/valsartan in addition to standard treatment. Only patients receiving sacubitril/valsartan and empagliflozin, according to the European Medicines Agency approved indication and current guidelines, were included in this analysis. All patients were treated with renin–angiotensin system (RAS) inhibitors before starting sacubitril/valsartan. Patients were included from 1 March 2017 to 1 December 2018, from four dedicated HF clinics at tertiary hospitals in Spain. The timing for initiation, combination, and up-titration of these two drugs was left to the discretion of the patient’s physician by following established recommendations. At the baseline visit, 43 patients were already being treated with sacubitril/valsartan and empagliflozin (Group A), 42 were already being treated with empagliflozin and sacubitril/valsartan (Group B), and 23 patients were prescribed both drugs simultaneously (Group C). All patients were treated with both empagliflozin and sacubitril/valsartan after the baseline visit.

#### Clinical monitoring

Ambulatory follow-up was performed in the HF units of each centre. At each clinical visit (baseline and follow-up), we recorded demographic information, medical history [New York Heart Association (NYHA) class], vital signs (systolic blood pressures and heart rate), 12-lead electrocardiogram results, standard laboratory data, and concomitant changes in HF therapy. Standard laboratory data included serum creatinine, estimated glomerular filtration rate (eGFR) as determined by CKD-EPI, haemoglobin, sodium, and potassium at all visits.

### Endpoints

The primary endpoint of the study was the safety profile in terms of changes in renal function as represented by the eGFR after co-treatment with sacubitril/valsartan and empagliflozin. A binary characterization of worsening renal function (WRF)/improved renal function (IRF) was included in the primary endpoint. WRF was defined as an increased serum creatinine \(\geq 0.3 \text{ mg/dL} \) or decreased GFR \(\geq 20\%\). IRF was defined as a decrease in creatinine \(\geq 0.3\) or an increase in GFR \(\geq 20\%\). A sensitivity analysis evaluating the trajectory of creatinine clearance (Cockcroft–Gault formula) were also analysed.

### Statistical analysis

Continuous variables were expressed as means (±1 SD) or medians [inter-quartile range (IQR)] and discrete variables as percentages. Comparisons of means, medians, and frequencies among treatment groups were carried out with one-way ANOVA, Kruskal–Wallis test, and \(\chi^2\), respectively.

Because the treatment groups of interest were assembled after the baseline visit, most of the analyses included the data beginning at the first follow-up visit; data on variables measured at baseline were used as covariates in the regression models. Changes in quantitative variables were evaluated using linear mixed regression, with random slopes on participant ID, random coefficient on continuous follow-up time, and unstructured covariance. These models included as fixed effects the interaction of treatment group with time (modelled as 4 df RCS), the baseline value of the longitudinal outcome tested, and the following baseline variables (age, eGFR, length of prior exposure to each treatment, left ventricular ejection fraction, serum sodium, and treatment with beta-blockers and aldosterone receptor blockers). In addition, furosemide-equivalent dose (VED) and sacubitril/valsartan and empagliflozin doses were added as time-specific covariates (time varying). For binary WRF/IRF, incidence rates and the treatment ratio were estimated by Poisson regression analysis. Stata 15.1 (Stata Statistical Software, Release 15 [2017]; StataCorp LP, College Station, TX, USA) was used for the analyses.

### Results

The mean age of the total cohort at baseline was 69 ± 9 years (range 73–80 years); 75% of patients were male, 63.9% had ischaemic heart disease, 58.7% had a history of a previous admission for acute HF, and 71.3% of patients were NYHA II. The mean left ventricular ejection fraction, eGFR, creatinine, BUN, and systolic blood pressure was 52 ± 6%,
Clinical features of heart failure

Detailed baseline characteristics for all patients are presented in Table 1. No significant differences were found across treatment groups. The time on treatment (length of exposure) with sacubitril/valsartan (Group A) and empagliflozin (Group B) was 133 (60–253) and 100 days (47–210), respectively.

### Treatment titration during follow-up and adverse events

This study included 120.8 person-years of follow-up or a total of 382 patient-visits. At a median follow-up of 1.01 years (IQR 0.71–1.50), there was a median of three visits per patient (range 2–15). After baseline, the first, second, and third visits occurred at a median of 38.5 (IQR 23–119), 143 (IQR 68–232), and 245 days (IQR 146–313), respectively.

Table 1 Baseline characteristics across treatment groups

| Characteristic                      | None (n = 23) | Empagliflozin first (n = 42) | Sacubitril/valsartan first (n = 43) | Total (n = 108) | P-value |
|-------------------------------------|--------------|------------------------------|------------------------------------|-----------------|---------|
| Age, years                          | 69 ± 10      | 70 ± 9                       | 68 ± 9                             | 69 ± 9          | 0.599   |
| Male sex, n (%)                     | 18 (78.3)    | 30 (71.4)                    | 33 (76.7)                          | 81 (75.0)       | 0.784   |
| Clinical features of heart failure  |              |                              |                                    |                 |         |
| Ischaemic aetiology, n (%)          | 14 (60.9)    | 26 (61.9)                    | 29 (67.4)                          | 69 (63.9)       | 0.820   |
| Left ventricular ejection fraction, % | 31 ± 6       | 32 ± 6                       | 32 ± 6                             | 32 ± 6          | 0.887   |
| NT-proBNP, pg/mL*                   | 2145 (1483;4609) | 2117 (662;4731)             | 1600 (628;3136)                    | 1795 (715;4234) | 0.283   |
| CA125, U/mL*                        | 44 (14;114)  | 38 (14;92)                   | 44 (21;66)                         | 42 (15;84)      | 0.875   |
| NYHA functional class, n (%)        |              |                              |                                    |                 | 0.699   |
| I                                   | 0 (0.0)      | 2 (4.8)                      | 3 (7.0)                            | 5 (4.6)         |         |
| II                                  | 16 (69.6)    | 30 (71.4)                    | 31 (72.1)                          | 77 (71.3)       |         |
| III                                 | 7 (30.4)     | 9 (21.4)                     | 9 (20.9)                           | 25 (23.1)       |         |
| IV                                  | 0 (0.0)      | 1 (2.4)                      | 0 (0.0)                            | 1 (0.9)         |         |
| Heart rate, mmHg                    | 68 ± 10      | 73 ± 15                      | 76 ± 14                            | 73 ± 14         | 0.102   |
| Systolic blood pressure, mmHg       | 127 ± 23     | 128 ± 22                     | 129 ± 18                           | 128 ± 21        | 0.946   |
| Creatinine, mg/dL                   | 1.25 ± 0.51  | 1.18 ± 0.39                  | 1.13 ± 0.39                        | 1.18 ± 0.42     | 0.540   |
| Estimated GFR, ml/min/1.73 m²       | 64.4 ± 20.6  | 68.3 ± 27.9                  | 74.1 ± 31.0                        | 69.8 ± 27.9     | 0.374   |
| Medical history, n (%)              |              |                              |                                    |                 |         |
| Hypertension                        | 21 (91.3)    | 33 (78.6)                    | 36 (83.7)                          | 90 (83.3)       | 0.418   |
| Ischaemic heart disease             | 14 (60.9)    | 25 (59.5)                    | 30 (69.8)                          | 69 (63.9)       | 0.582   |
| Atrial fibrillation                 | 8 (34.8)     | 17 (40.5)                    | 16 (37.2)                          | 41 (38.0)       | 0.895   |
| Prior admission for AHF, n (%)      | 13 (56.5)    | 17 (40.5)                    | 14 (32.6)                          | 44 (40.7)       | 0.168   |
| Background therapy, n (%)           |              |                              |                                    |                 |         |
| Mineralocorticoid receptor antagonist| 18 (78.3)    | 33 (78.6)                    | 35 (81.4)                          | 86 (79.6)       | 0.933   |
| Betablocker                          | 22 (95.7)    | 42 (100.0)                   | 40 (93.0)                          | 104 (96.3)      | 0.231   |
| Ibradine                            | 9 (39.1)     | 12 (28.6)                    | 7 (16.3)                           | 28 (25.9)       | 0.115   |
| Implantable cardioverter-defibrillator | 3 (13.0) | 7 (16.7)                     | 12 (27.9)                          | 22 (20.4)       | 0.270   |
| Cardiac resynchronization therapy    | 2 (8.7)      | 5 (11.9)                     | 3 (7.0)                            | 10 (9.3)        | 0.732   |
| Loop diuretics                      | 20 (87.0)    | 37 (88.1)                    | 30 (69.8)                          | 87 (80.6)       | 0.070   |
| Thiadiazide                         | 2 (8.7)      | 3 (7.1)                      | 5 (11.6)                           | 10 (9.3)        | 0.771   |
| Metformin                           | 19 (82.6)    | 22 (52.4)                    | 31 (72.1)                          | 72 (66.7)       | 0.029   |

GFR was estimated using the Modification of Diet in Renal Disease Study (MDRD) formula. Continuous variables are expressed as mean ± standard deviation, unless otherwise specified.

AHF, acute heart failure; CA125, antigen carbohydrate 125; GFR, glomerular filtration rate; NT-proBNP, amino-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.

Values expressed as median (inter-quartile range).
Sacubitril/valsartan was withdrawn in one patient owing to symptomatic hypotension. Empagliflozin was stopped in seven patients, mainly owing to urinary/genital tract infection (n = 4). In the other three cases treated with empagliflozin, the reason for withdrawal was not recorded.

When modelled over time, the FED decreased in all groups (mainly during the first 6 months), without significant differential effect across treatment groups (Figure S2). Neither loop diuretics nor thiazides were prescribed in 21 patients at follow-up. In 22 patients (20.4%), loop diuretic doses were down-titrated at least once (12.8%, 21.7%, and 30.4% for Groups A, B, and C, respectively; P = 0.239).

During the entire follow-up, six deaths (5.6%), nine (8.3%) admissions for acute HF, and seven visits to the emergency room (6.5%) were recorded. No differences were found among the treatment groups (Table S1).

Changes in renal function

Overall trajectory by treatment group

The slope of the GFR trajectories for Groups A and B showed a bimodal response with an early increase (first 6 months) and a later plateau or decrease. The slope for the Group B trajectory was statistically significant different from 0 (flat slope). Group C, on the other hand, showed a consistent increase over the entire follow-up (Figure J). Analysis of differences between groups (using Group B as a reference) over the continuum of the follow-up showed a significant decrease in eGFR for Group A (Figure 2A). The overall trajectory comparing Group B vs. C showed no significant differences (Figure 2B). Similar trajectories among treatments groups were found when creatinine clearance was evaluated (Figure S3). Likewise, we did not find significant changes in blood urea nitrogen and serum sodium Figures S4 and S5).

Worsening and improved renal function

During the entire follow-up, 45 and 38 episodes of WRF and IRF were recorded in 33 (30.6%) and 23 (21.3%) patients, respectively. Mean crude rates for WRF and IRF are presented in Figure 3A and B, respectively. Overall, patients belonging to Group A had the highest rates of WRF. Conversely, Group B had the lowest and

Figure 1 Continuous changes in eGFR across treatment groups. Group A: patients on stable sacubitril/valsartan treatment in which empagliflozin was initiated. Group B: patients on stable empagliflozin treatment in which sacubitril/valsartan was initiated. Group C: naïve patients in which sacubitril/valsartan and empagliflozin were initiated simultaneously. eGFR, glomerular filtration rate (mL/min/1.73 m²). eGFR was determined by CKD-EPI formula.
highest rates for WRF and IRF, respectively. Intermediate rates were found in Group C. No patients met the WRF criteria.

Compared with Group B, and assuming a constant effect over the follow-up, patients in the Group A showed a significant increase in the risk of WRF (IRR = 2.36, 95% CI: 1.03–

**Figure 2** Changes in renal function compared between groups. Group A: patients on stable sacubitril/valsartan treatment in which empagliflozin was initiated. Group B: patients on stable empagliflozin treatment in which sacubitril/valsartan was initiated. Group C: naïve patients in which sacubitril/valsartan and empagliflozin were initiated simultaneously. Group B was used as a reference.

**Figure 3** Renal function trajectories across treatment groups. (A) Worsening renal function (WRF) rate. (B) Improved renal function (IRF) rate. Group A: patients on stable sacubitril/valsartan treatment in which empagliflozin was initiated. Group B: patients on stable empagliflozin treatment in which sacubitril/valsartan was initiated. Group C: naïve patients in which sacubitril/valsartan and empagliflozin were initiated simultaneously.
5.43; \( P = 0.043 \)). No significant differences were found for Group C (IRR = 2.02, 95% CI: 0.88–4.67; \( P = 0.097 \)). Likewise, and compared with Group B, patients belonging to Group A showed a lower risk of IRF (IRR = 0.20, 95% CI: 0.05–0.83; \( P = 0.027 \)) without differences for Group C (IRR = 0.86, 95% CI: 0.32–2.28; \( P = 0.767 \)).

Discussion

In this observational multicentre registry, we found that co-administration of sacubitril/valsartan and empagliflozin in patients with chronic HFrEF, T2D, and normal or mildly reduced renal function (eGFR > 60 mL/min/1.73 m\(^2\)) did not translate into significant and clinically relevant changes in eGFR. None of the patients in this cohort had a >50% decrease in eGFR during the follow-up. When examined continuously using smaller changes in renal function parameters (increase/decrease in creatinine \( \geq 0.3 \) or decrease/increase in GFR \( \geq 20\% \)), we found that the higher risk of WRF was attributable to empagliflozin initiation in those already being treated with sacubitril/valsartan. Conversely, initiation of sacubitril/valsartan in those already being treated with empagliflozin was associated with IRF. An intermediate risk of WRF was found when both treatments were initiated simultaneously.

These findings suggest that the combined ARNI-SGLT2 inhibition appears to have a similar renal safety profile (at mid-term) as previously reported when both treatments are used separately.\(^3\,4,6,8\) Our results are somehow reassuring considering that these two treatments seem to have independent and additive benefits when used in combination. Notably, the present findings do not apply to other HF scenarios (e.g. patients with more than mild renal dysfunction, no T2D, and acute HF syndromes) in which we should likely be more conservative and vigilant.

Combined administration of empagliflozin and sacubitril/valsartan: friend or foe for the kidney

Given the observational nature of this study, we can only speculate how empagliflozin and sacubitril/valsartan exerted their effects on kidney function (Figure 4). Both
SGLT2 and nephrilysin receptors are abundantly expressed in the kidneys.

Several explanations are possible for the early slight decrease in eGFR after empagliflozin initiation in patients already being treated with ARNI. First, it may be related to an adenosine-mediated increase in afferent pre-glomerular arteriolar resistance with a coinciding decrease in intraglomerular pressure. Second, recent findings suggest a predominant vasodilatory effect of SGLT2is on efferent arterioles mediated by adenosine A2 receptor activation when the potential for pre-glomerular vasoconstriction has already been achieved. The authors observed that eGFR was accompanied by stable, or even reduced, pre-glomerular vascular resistance, suggesting that post-glomerular vasodilation explains the acute decrease in eGFR after SGLT2i initiation.

Third, in addition to the aforementioned glomerular haemodynamic effects, a reduction in proximal tubular sodium reabsorption together with enhanced tubular flow secondary to osmotic diuresis may increase substrate availability in the distal nephron. Accordingly, SGLT2is may work synergistically with more distal diuretics, potentiating diuresis and natriuresis. This aspect is relevant, as 80% of patients were receiving loop diuretics at baseline. An alternative explanation could be related to plasma volume contraction rather than ‘true’ WRF; we observed FED reductions in all groups, mainly during the first 6 months of follow-up.

In contrast, eGFR slightly improved when sacubitril/valsartan was added to patients who were already treated with empagliflozin. Natriuretic peptides (NPs) are known to reduce pre-glomerular vascular resistance and may also increase the filtration surface area by relaxing glomerular mesangial cells. However, the renal effects of these peptides are markedly attenuated in HF because renal nephrilysin activity and protein expression levels are upregulated in this syndrome. Accordingly, nephrilysin inhibition by sacubitril/valsartan may boost the effects of NPs on glomerular haemodynamic. The immediate increase in urinary albumin/creatinine ratio observed in PARADIGM-HF after initiation of sacubitril/valsartan, with normalization to pre-screening values following discontinuation, clearly suggests a haemodynamic effect. Therefore, the observed improvement in eGFR in our cohort after the introduction of sacubitril/valsartan suggests that it may counteract the vasoconstrictive action of empagliflozin on the pre-glomerular arteriole. In addition, sacubitril/valsartan promptly reduces cardiac filling pressures and promotes left ventricular reverse remodelling, which may also have contributed to enhanced renal blood flow.

Limitations
As an observational study, causality cannot be inferred. Additional limitations of this study are the limited sample size, which is prone to bias because of unmeasured confounding, and eGFR may not be the most accurate and sensitive parameter for detecting early renal function changes. Additionally, the cohort was primarily composed of ambulatory patients with chronic HFrEF, concomitant T2D, and normal or mildly reduced renal function. Therefore, it is unclear how the results will apply to the broader HF population, those without T2D, and patients with higher degrees of renal impairment. Finally, we did not measure other surrogates of renal haemodynamic and urine parameters that may be useful to explain these results. Therefore, all the conclusions are merely speculative and only allow us to generate hypothesis about the underlying mechanism behind these findings.

Conclusions
The co-administration of sacubitril/valsartan and empagliflozin in ambulatory patients with chronic HFrEF, T2D, and normal or mildly reduced renal function appears to be safe in terms of renal function. A better renal function profile emerged when sacubitril/valsartan was added to empagliflozin. Further studies are needed to unravel the potential synergistic effect of both treatments in terms of cardiorenal outcomes.

Conflict of Interest
The authors have no other funding, financial relationships, or conflicts of interest to disclose relative to this work.

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Supporting information
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Sacubitril valsartan dose pattern at follow-up. Group A: patients on stable sacubitril/valsartan treatment in which empagliflozin was initiated. Group B: patients on stable empagliflozin treatment in which sacubitril/valsartan was initiated. Group C: naïve patients in which sacubitril/valsartan and empagliflozin were initiated simultaneously.

Figure S2. Furosemide-equivalent dose pattern during the first 6-months in the whole sample (A), without significant differential
effect across treatment groups (B). Group A: patients on stable sacubitril/valsartan treatment in which empagliflozin was initiated. Group B: patients on stable empagliflozin treatment in which sacubitril/valsartan was initiated. Group C: naïve patients in which sacubitril/valsartan and empagliflozin were initiated simultaneously. Table S1. Adverse events across treatment groups

**Figure S3.** Predicted Cockcroft-Gault formula trajectories. Group A: patients on stable sacubitril/valsartan treatment in which empagliflozin was initiated. Group B: patients on stable empagliflozin treatment in which sacubitril/valsartan was initiated. Group C: naïve patients in which sacubitril/valsartan and empagliflozin were initiated simultaneously.

**Figure S4.** Continuous changes in BUN across treatment groups. Group A: patients on stable sacubitril/valsartan treatment in which empagliflozin was initiated. Group B: patients on stable empagliflozin treatment in which sacubitril/valsartan was initiated. Group C: naïve patients in which sacubitril/valsartan and empagliflozin were initiated simultaneously. Group C: naïve patients in which sacubitril/valsartan and empagliflozin were initiated simultaneously.

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