ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 3792–3800
Published online 22 September 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12965

ORIGINAL RESEARCH ARTICLE

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

Rafael de la Espriella[1], Antoni Bayés-Genís[2,3], Herminio Morillas[4], Rafael Bravo[5], Verónica Vidal[6], Eduardo Núñez[1], Enrique Santas[1], Gema Miñana[1], Juan Sanchis[1,2], Lorenzo Fácila[6], Francisco Torres[4], Jose Luis Górriz[7], Alfonso Valle[4] and Julio Núñez[1,2]*

[1]*Cardiology Department, Hospital Clínico Universitario de Valencia, INCLIVA, Departamento de Medicina, Universitat de València, Valencia, Spain;* [2]*CIBER in Cardiovascular Diseases (CIBERCV), Madrid, Spain;* [3]*Heart Institute, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, and Department of Medicine, Universitat Autonoma de Barcelona, Barcelona, Spain;* [4]*Cardiology Department, Hospital de Dénia-MarinaSalud, Dénia, Spain;* [5]*Cardiology Department, Hospital Costa del Sol, Marbella, Spain;* [6]*Cardiology Department, Hospital General de Valencia, Valencia, Spain;* [7]*Nephrology Department, Hospital Clínico Universitario de Valencia, INCLIVA, Departamento de Medicina, Universitat de València, Valencia, Spain*

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 empagliflozin 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 empagliflozin (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 $\geq$ 0.3 mg/dL or GFR $\geq$ 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 m^2, 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 empagliflozin 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

Received: 9 February 2020; Revised: 5 June 2020; Accepted: 6 August 2020
**Correspondence to: Julio Núñez, Cardiology Department, Hospital Clínico Universitario de Valencia, Av. Blasco Ibáñez 17, 46010 Valencia, Spain. Tel: +34652856689; Fax: +34963862658. Email: yulnunez@gmail.com*

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

in a superior renal function profile at long-term follow-up as compared with enalapril and placebo, respectively.[3–6] However, both treatments may cause short-term renal dysfunction.[5,7]

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 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 χ^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 (FED) 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 32 ± 6%,

70 ± 28 mL/min/1.73 m^2, 1.18 ± 0.42 mg/dL, 26.5 ± 13 mg/dL, and 128 ± 21 mmHg, respectively. The median NT-proBNP was 1795 pg/mL (IQR 715–4234). At baseline, most of the patients were receiving loop diuretics (80.6%), beta-blockers (96.3%), and mineralocorticoid receptor antagonists (79.6%). 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.

Sacubitril/valsartan was up-titrated in 27 patients during the follow-up. After up-titration, the follow-up visit occurred at a median of 66 (IQR 30–163) days. The proportion of patients taking medium (100 mg b.i.d.) and higher doses (200 mg b.i.d.) of sacubitril/valsartan increased during follow-up (P = 0.001) without differences among groups (P = 0.112; *Figure S1*). No differences were found for doses of empagliflozin during the follow-up in the whole sample (mean dose = 10 mg q.d.; P = 0.379) and across treatment groups (interaction P-value = 0.896).

During follow-up, WRF occurred in six (22.2%) patients in whom sacubitril/valsartan was up-titrated and in 26 (32.1%) in whom it was not (P = 0.330). No patient experienced an eGFR decrease ≥50%, development of end-stage renal disease, or death due to renal failure.

Sacubitril/valsartan was down-titrated in three (2.8%) patients. The reason for down-titration was symptomatic hypotension in two (1.8%) patients and WRF in one patient (0.9%). However, the drug was not withdrawn in any of these patients.

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 m^2	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
Beta-blocker	22 (95.7)	42 (100.0)	40 (93.0)	104 (96.3)	0.231
Ivabradine	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
Thiazides	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).

DOI: 10.1002/ehf2.12965

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

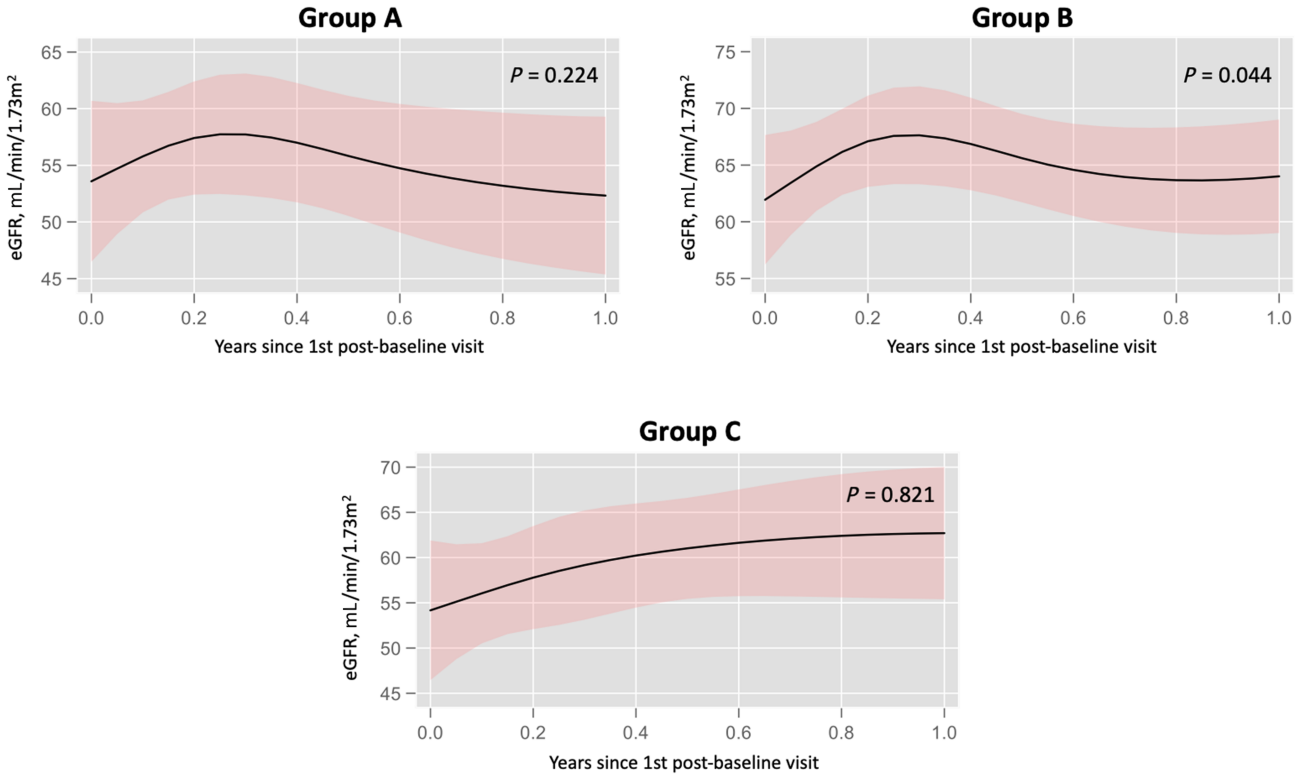
Overall trajectory by treatment group

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 1*). 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

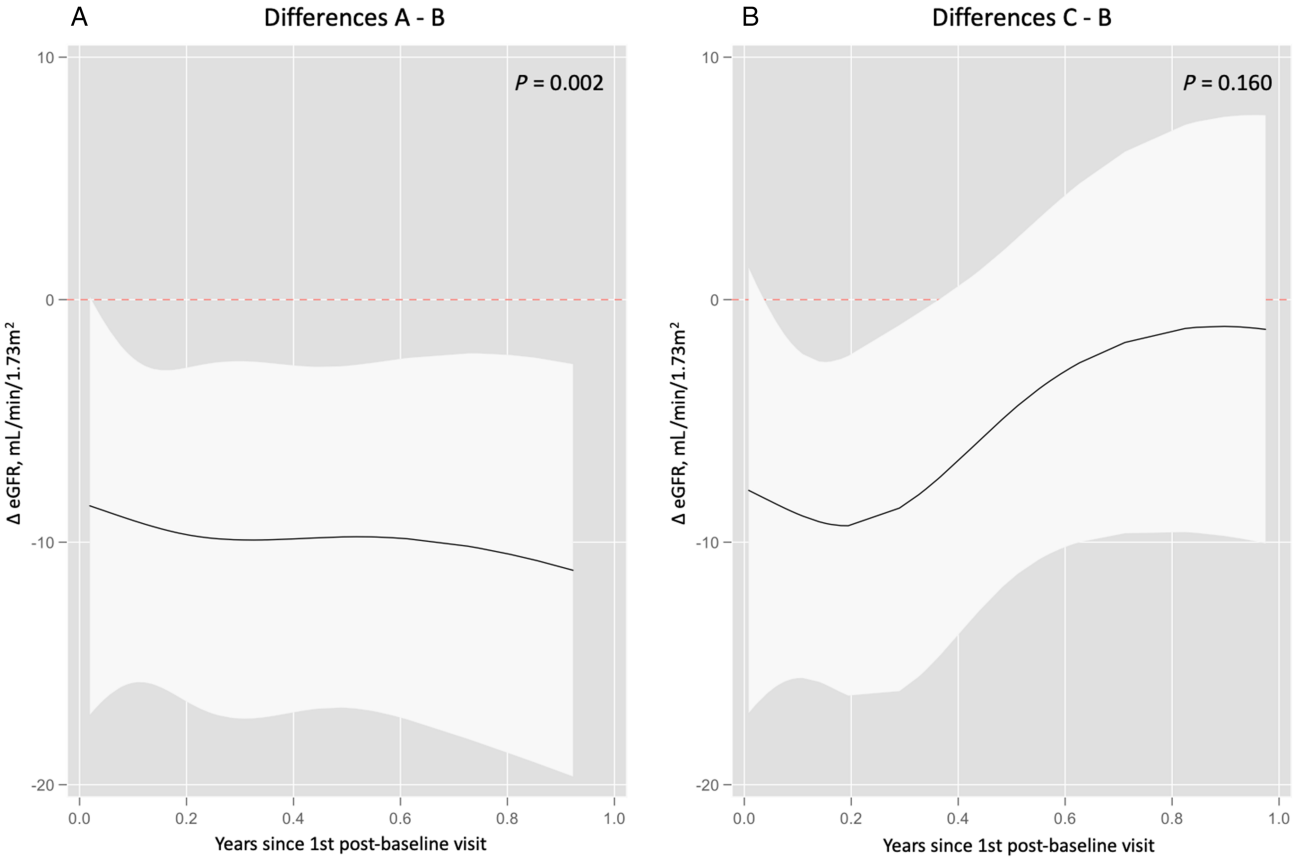
During the entire follow-up, 45 and 38 episodes of WRF and IRF were recorded in 33 (30.6%) and 23 (21.3%) patients, respectively. Mean crude rates for WRF and IRF are presented in *Figure 3A and B*, respectively. Overall, patients belonging to Group A had the highest rates of WRF_1. Conversely, Group 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 m^2). eGFR was determined by CKD-EPI formula.



DOI: 10.1002/ehf2.12965

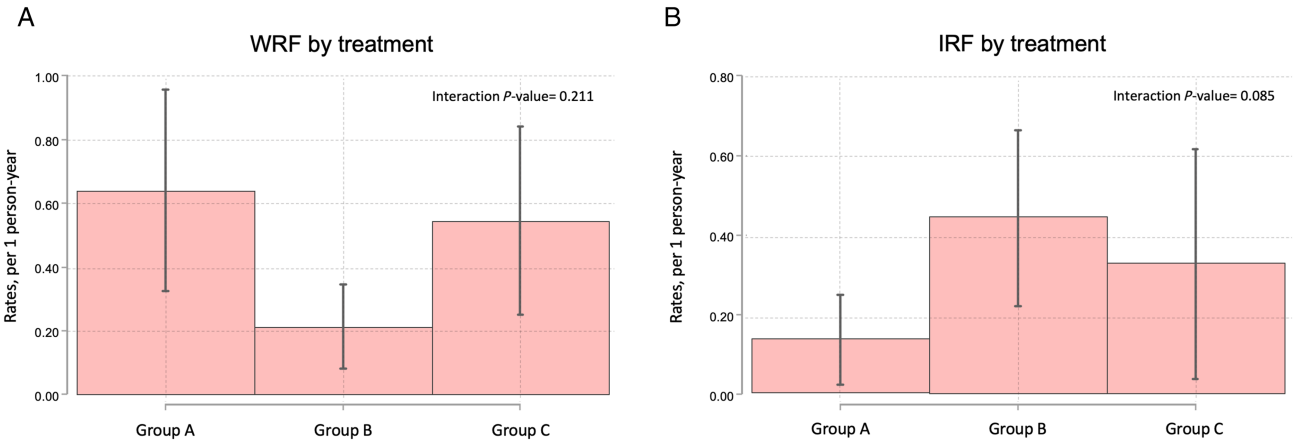
Figure 2 Changes in renal function compared between groups. Group A: patients on stable sacubitril/valsartan treatment in which empagliflozin was initiated. Group B: patients on stable empagliflozin treatment in which sacubitril/valsartan was initiated. Group C: naïve patients in which sacubitril/valsartan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



highest rates for WRF and IRF, respectively. Intermediate rates were found in Group C. No patients met the WRF_2 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 WRF1 (IRR = 2.36, 95% CI: 1.03–

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.



DOI: 10.1002/ehf2.12965

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

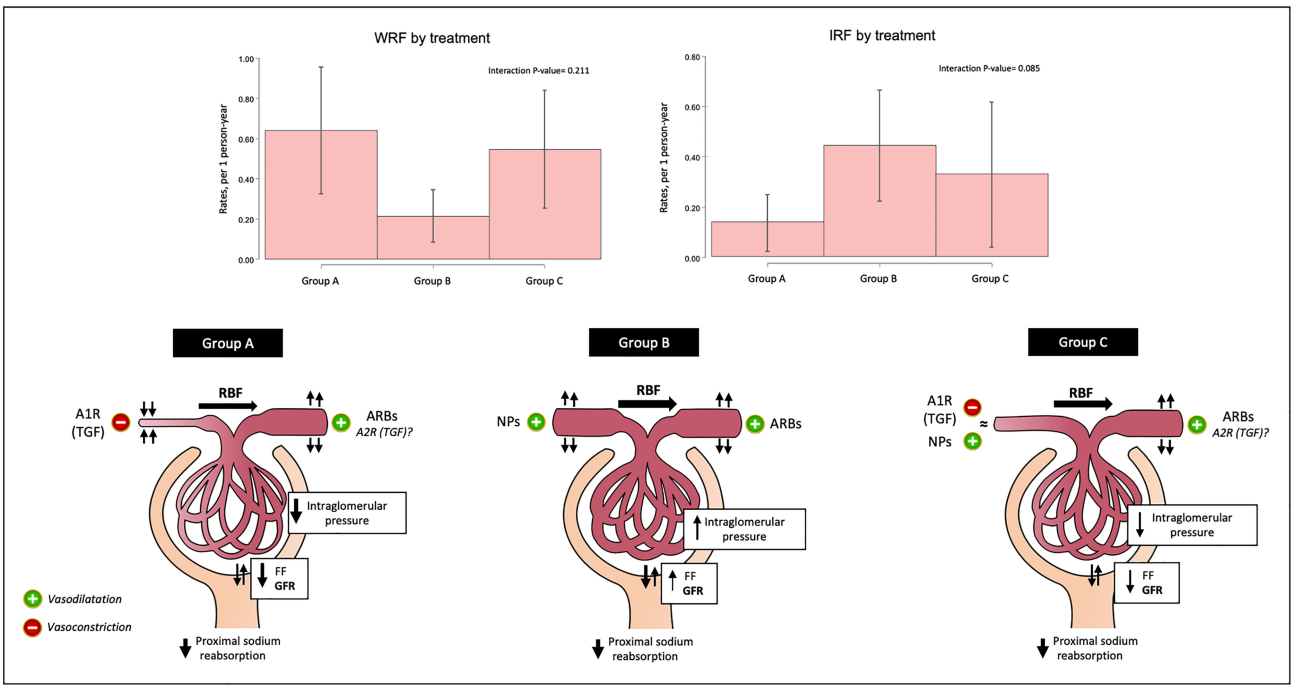
In this observational multicentre registry, we found that co-administration of sacubitril/valsartan and empagliflozin in patients with chronic HFrEF, T2D, and normal or mildly reduced renal function (eGFR $>$ 60 mL/min/1.73 m^2) did not translate into significant and clinically relevant changes in eGFR. 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

Figure 4 Hypothesized renal haemodynamic effects of co-administration of SGLT2i and sacubitril/valsartan in patients with HFrEF and T2D. Group A: patients on stable sacubitril/valsartan treatment in which empagliflozin was initiated. SGLT2i causes pre-glomerular vasoconstriction via TGF activation with a coinciding drop in intra-glomerular pressures. A post-glomerular vasodilatation effect via adenosine A2 receptor activation has also been suggested. Group B: patients on stable empagliflozin treatment in which sacubitril/valsartan was initiated. NPs decrease pre-glomerular vascular resistance and may counteract the vasoconstrictive action of SGLT2 inhibition on the pre-glomerular arteriole. Group C: naïve patients in which sacubitril/valsartan and empagliflozin were initiated simultaneously. An intermediate effect on afferent arteriole tone could be expected by the concomitant administration of both treatments. A1R, adenosine type 1 receptor; A2R, adenosine type 1 receptor; ARBs, angiotensin receptor blockers; FF, filtration fraction; GFR, glomerular filtration rate; IRF, improved renal function; NPs, natriuretic peptides; RBF, renal blood flow; TGF, tubuloglomerular feedback; WRF, worsening renal function.



SGLT2 and neprilysin 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 intra-glomerular pressure.[9,10] 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.[11] 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.[11] 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.[12,13] Accordingly, SGLT2is may work synergistically with more distal diuretics, potentiating diuresis and natriuresis.[14] 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[15,16]; 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.[17] However, the renal effects of these peptides are markedly attenuated in HF because renal neprilysin activity and protein expression levels are upregulated in this syndrome.[18] Accordingly, neprilysin 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.[3] 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,[7,19] 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[16,20] 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.

Funding

This work was supported in part by grants from CentrodeInvestigación Biomédica en Red Enfermedades Cardiovasculares (CIBER CV) (grant numbers 16/11/00420 and 16/11/00403).

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 differenetial*

effect acroos teratment 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 Cockroft-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. BUN, blood urea nitrogen*

Figure S5. *Continuous changes in serum sodium 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.*

References

1. Burnett H, Earley A, Voors AA, Senni M, McMurray JJV, Deschaseaux C, Cope S. Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection fraction: a network meta-analysis. *Circ Heart Fail* 2017; **10**: e003529.
2. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang C-E, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets D, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM, DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; **381**: 1995–2008.
3. Damman K, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP, Prescott MF, Shi VC, Rouleau JL, Swedberg K, Zile MR, Packer M, Desai AS, Solomon SD, McMurray JJV. Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. *JACC Heart Failure* 2018; **6**: 489–498.
4. Packer M, Claggett B, Lefkowitz MP, McMurray JJV, Rouleau JL, Solomon SD, Zile MR. Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin–angiotensin system: a secondary analysis of the PARADIGM-HF trial. *Lancet Diab Endocrinol* 2018; **6**: 547–554.
5. Butler J, Zannad F, Fitchett D, Zinman B, Koitka-Weber A, von Eynatten M, Zwiener I, George J, Brueckmann M, Cheung AK, Wanner C. Empagliflozin improves kidney outcomes in patients with or without heart failure: insights from the EMPA-REG OUTCOME Trial. *Circ Heart Fail* 2019; **12**: e005875.
6. Kluger AY, Tecson KM, Lee AY, Lerma EV, Rangaswami J, Lepor NE, Cobble ME, McCullough PA. Class effects of SGLT2 inhibitors on cardiorenal outcomes. *Cardiovasc Diabetol* 2019; **18**: 99.
7. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, Rocha R, Braunwald E. Angiotensin–neprilysin inhibition in acute decompensated heart failure. *N Engl J Med* 2019; **380**: 539–548.
8. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019; **393**: 31–39.
9. Kidokoro K, Cherney DZI, Bozovic A, Nagasu H, Satoh M, Kanda E, Sasaki T, Kashihara N. Evaluation of glomerular hemodynamic function by empagliflozin in diabetic mice using in vivo imaging. *Circulation* 2019; **140**: 303–315.
10. Kuriyama S. Protection of the kidney with sodium–glucose cotransporter 2 inhibitors: potential mechanisms raised by the large-scaled randomized control trials. *Clin Exp Nephrol* 2019; **23**: 304–312.
11. van Bommel EJM, Muskiet MHA, van Baar MJB, Tonneijck L, Smits MM, Emanuel AL, Bozovic A, Danser AHJ, Geurts F, Hoorn EJ, Touw DJ, Larsen EL, Poulsen HE, Kramer MHH, Nieuwdorp M, Joles JA, van Raalte DH. The renal hemodynamic effects of the SGLT2 inhibitor dapagliflozin are caused by post-glomerular vasodilatation rather than pre-glomerular vasoconstriction in metformin-treated patients with type 2 diabetes in the randomized, double-blind RED trial. *Kidney Int* 2019: S0085253819309913.
12. Mullens W, Damman K, Harjola V-P, Mebazaa A, Brunner-La Rocca H-P, Martens P, Testani JM, Tang WHW, Orso F, Rossignol P, Metra M, Filippatos G, Seferovic PM, Ruschitzka F, Coats AJ. The use of diuretics in heart failure with congestion—a position statement from the Heart Failure Association of the European Society of Cardiology: Diuretics in heart failure. *Eur J Heart Fail* 2019; **21**: 137–155.
13. Wanner C. EMPA-REG OUTCOME: the nephrologist's point of view. *Am J Med* 2017; **130**: S63–S72.
14. Mullens W, Verbrugge FH, Nijst P, Martens P, Tartaglia K, Theunissen E, Bruckers L, Droogne W, Troisfontaines P, Damman K, Lassus J, Mebazaa A, Filippatos G, Ruschitzka F, Dupont M. Rationale and design of the ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial: acetazolamide in decompensated heart failure with volume overload. *Eur J Heart Fail* 2018; **20**: 1591–1600.
15. Sokolski M, Zymliński R, Biegus J, Siwołowski P, Nawrocka-Millward S, Todd J, Yerramilli MR, Estis J, Jankowska EA, Banasiak W, Ponikowski P. Urinary levels of novel kidney biomarkers and risk of true worsening renal function and mortality in patients with acute heart failure: kidney biomarkers and risk of true worsening renal function and mortality in AHF. *Eur J Heart Fail* 2017; **19**: 760–767.
16. Ahmad T, Jackson K, Rao VS, Tang WHW, Brisco-Bacik MA, Chen HH, Felker GM, Hernandez AF, O'Connor CM, Sabbisetti VS, Bonventre JV, Wilson FP, Coca SG, Testani JM. Worsening renal function in patients with acute heart failure undergoing aggressive diuresis is not associated with tubular injury. *Circulation* 2018; **137**: 2016–2028.
17. Brenner BM, Ballermann BJ, Gunning ME, Zeidel ML. Diverse biological actions of atrial natriuretic peptide. *Physiol Rev* 1990; **70**: 665–699.

18. Knecht M, Pagel I, Langenickel T, Philipp S, Scheuermann-Freestone M, Willnow T, Bruemmer D, Graf K, Dietz R, Willenbrock R. Increased expression of renal neutral endopeptidase in severe heart failure. *Life Sci* 2002; **71**: 2701–2712.
19. Januzzi JL, Prescott MF, Butler J, Felker GM, Maisel AS, McCague K, Camacho A, Piña IL, Rocha RA, Shah AM, Williamson KM, Solomon SD, for the 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; **322**: 1085.
20. Metra M, Cotter G, Senger S, Edwards C, Cleland JG, Ponikowski P, Cursack GC, Milo O, Teerlink JR, Givertz MM, O'Connor CM, Dittrich HC, Bloomfield DM, Voors AA, Davison BA. Prognostic significance of creatinine increases during an acute heart failure admission in patients with and without residual congestion: a post hoc analysis of the PROTECT data. *Circ Heart Fail* 2018; **11**: e004644.