ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 4404–4407
Published online 11 September 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12988

SHORT COMMUNICATION

The role of sacubitril/valsartan in the management of cardiac resynchronization therapy non-responders: a retrospective analysis

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Abstract

Aims Optimal medical therapy after cardiac resynchronization therapy (CRT) implantation is important in heart failure (HF) with reduced ejection fraction (HFrEF) patients. Although sacubitril/valsartan (SV) is a mainstay in the treatment of HFrEF, its efficacy in the management of CRT non-responders has not been emphasized. We aimed to investigate the efficacy of SV in CRT non-responders.

Methods and results We analysed 175 HFrEF patients who received CRT implantation between January 2010 and January 2019. CRT responder was defined as a decrease in left ventricular (LV) end-systolic volume $>$ 15% on echocardiography 6 months after implantation. Medical records were retrospectively reviewed. Patients underwent follow-up for HF rehospitalization, heart transplantation (HT), implantation of a LV assistant device (LVAD), cardiac death, and all-cause death. Among the study population, 164 patients were evaluated for CRT response; 54 (33%) were CRT non-responders. Four patients (6%) who received SV before CRT implantation were excluded, leaving 50 patients for analysis. Twenty-two non-responders (44%) received SV. There was no significant difference in baseline characteristics between SV users and non-users (n = 28). During follow-up, SV users had significantly lower incidence of all-cause death [1 (5%) vs. 10 (36%), P = 0.022] and tended to have lower HF rehospitalization [6 (27%) vs. 16 (57%), P = 0.068] and cardiac death (including HT and LVAD implant) [2 (9%) vs. 10 (36%), P = 0.064]. Kaplan–Meier survival analysis revealed that SV use was associated with a lower risk of cardiac death (including HT and LVAD implant) (log-rank P = 0.029).

Conclusions SV treatment was related to a lower incidence of cardiac death including HT and LVAD implant in CRT non-responders. The optimization of HF management, including SV, should be considered in CRT non-responders.

Keywords Cardiac resynchronization therapy; Heart failure with reduced ejection fraction; Sacubitril/valsartan

Received: 29 May 2020; Revised: 4 August 2020; Accepted: 13 August 2020
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Introduction

Implantation of cardiac resynchronization therapy (CRT) devices has been known to improve desynchronized left ventricular (LV) dysfunction and clinical prognosis in patients with heart failure (HF) with reduced ejection fraction (HFrEF).[1] Nevertheless, according to the international CRT registry, there are still about 20% of patients who did not respond to CRT therapy and had higher clinical event rates compared to CRT responders.[2] A recent descriptive post hoc analysis revealed that almost half of the non-responders did not receive any additional management of HF including medication optimization.[2,3]

Aims

Sacubitril/valsartan (SV) is one of the main therapies in current guideline-directed medical treatment (GDMT) for HFrEF.[4] Therefore, the importance of SV in the management

of CRT non-responders cannot be overemphasized. In the present study, we aimed to investigate the efficacy of SV on clinical outcomes in CRT non-responders.

Methods

We retrospectively investigated 175 HFrEF patients who received CRT implantation between January 2010 and January 2019 in a single tertiary university hospital. CRT implantation was performed using guidelines for HF management: LV ejection fraction (LVEF) $\leq$ 35%, QRS duration $\geq$ 130 ms, and New York Heart Association functional class II or III despite optimal medical therapy for $\geq$3 months.[4] Patients lost to follow-up, those who died within 6 months after CRT implantation, and those in whom the CRT device was removed within 6 months were excluded. After CRT implantation, patients were followed up at the clinic every 3 months. CRT interrogation and optimization based on intracardiac electrogram were performed at every visit to achieve optimal biventricular pacing rate. CRT response was defined as a decrease in the LV end-systolic volume $>$ 15% on echocardiography 6 months after CRT implantation.[5] Patients defined as non-responders were analysed and followed up using the same methods. An echocardiographic CRT response observed after $>$6 months after CRT implantation was defined as a delayed CRT response. Medication records were collected for each patient at implantation and during the follow-up period. Patients who started SV treatment after CRT implantation were defined as SV group, and patients who never received SV were defined as the control group. Patients underwent follow-up for appropriate implantable cardioverter-defibrillator (ICD) therapy, HF rehospitalization, cardiac death, and all-cause death. Clinical endpoint was a composite of cardiac death, heart transplantation (HT), and implantation of a LV assistant device (LVAD). This investigation conforms with the principles outlined in the *Declaration of Helsinki*. The study design was approved by the Institutional Review Board of the Yonsei University Health System (1–2013-0061), and all patients provided written informed consent.

Statistical methods

Data are presented as mean ± standard deviation or frequency. Comparisons between the groups were made with the Student *t*-test or Wilcoxon rank-sum test. The occurrence of each event was analysed and compared using χ^2 test. Cumulative probability of events was analysed using Kaplan–Meier method, and log-rank test was used to compare the probability of event curves between groups.

Table 1 Baseline characteristics

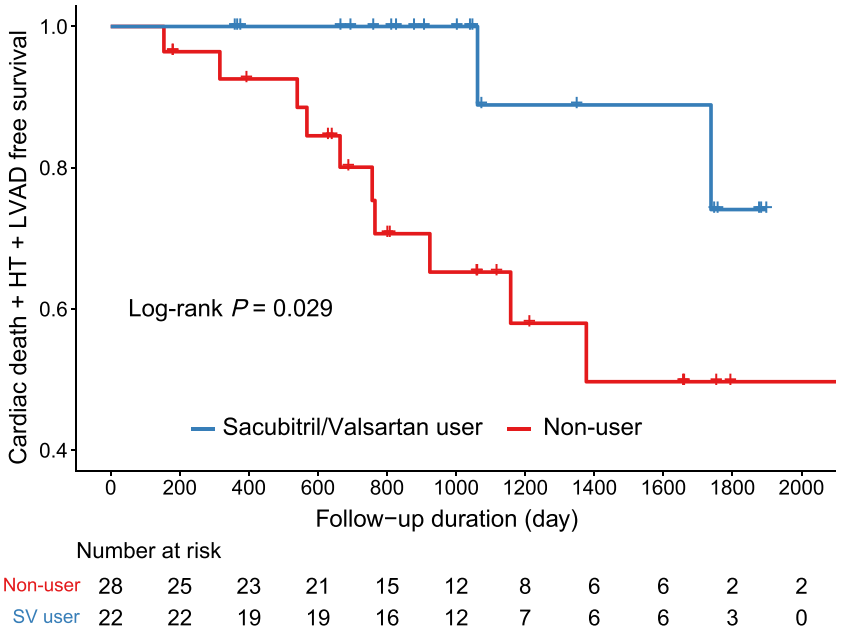
	Non-user (n = 28)	Sacubitril/valsartan user (n = 22)	Total (n = 50)	P-value
Age, year	65 (59–68)	67 (56–71)	66 (57–69)	0.378
Male sex	17 (61)	16 (73)	33 (66)	0.556
BSA, m^2	1.7 ± 0.2	1.7 ± 0.2	1.7 ± 0.2	0.407
BMI, kg/m^2	22.4 (20.4–23.7)	23.2 (21.4–25.8)	22.7 (21.0–25.3)	0.171
Systolic BP, mmHg	104 ± 16	109 ± 15	106 ± 16	0.260
Diastolic BP, mmHg	64 ± 9	67 ± 11	66 ± 10	0.331
NYHA (III/IV)	22 (77)	13 (59)	35 (70)	0.238
Hypertension	12 (43)	11 (50)	23 (46)	0.828
Diabetes	16 (57)	9 (41)	25 (50)	0.393
CKD	6 (21)	4 (18)	10 (20)	>0.999
Stroke	4 (14)	6 (27)	10 (20)	0.433
Atrial fibrillation	10 (36)	9 (41)	19 (38)	0.935
Aetiology				>0.999
Ischaemic CMP	8 (29)	7 (32)	15 (30)	
Non-ischaemic CMP	20 (71)	15 (68)	35 (70)	
Left bundle branch block	10 (36)	9 (41)	19 (38)	0.935
QRS duration, ms	168 ± 24	159 ± 23	164 ± 24	0.204
QRS $\geq$ 150 ms	22 (79)	14 (64)	36 (72)	0.395
BiV pacing, %	98.0 (95.3–99.3)	97.2 (96.0–98.8)	97.5 (96.0–99.0)	0.304
BiV pacing $\geq$ 98%	11 (44)	9 (41)	20 (43)	>0.999
Haemoglobin, g/mL	12.5 ± 1.7	12.8 ± 2.1	12.6 ± 1.9	0.662
eGFR, mL/min/1.73 m^2	65.9 ± 23.1	68.7 ± 21.6	67.2 ± 22.3	0.663
NT-proBNP, pg/mL	5491 ± 8060	4558 ± 4579	5080 ± 6709	0.609
Log NT-proBNP	3.4 ± 0.6	3.4 ± 0.6	3.4 ± 0.6	0.857
ACEi/ARBs	26 (93)	22 (100)	48 (96)	0.581
Beta-blockers	22 (79)	20 (91)	42 (84)	0.428
MRAs	21 (75)	18 (82)	39 (78)	0.815
Loop diuretics	28 (100)	21 (96)	49 (98)	0.903
Ivabradines	6 (21)	5 (23)	11 (22)	>0.999

Data are presented as mean ± standard deviation (SD) when variables follow a normal distribution, median value (inter-quartile range, IQR) when not normally distributed, or absolute numbers (%).
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BiV, biventricular; BMI, body mass index; BP, blood pressure; BSA, body surface area; CKD, chronic kidney disease; CMP, cardiomyopathy; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association.

Results

Of 164 CRT patients, 54 (33%) were CRT non-responders and four (6%) who were administered SV before implantation were excluded, leaving 50 patients for analysis (median 66 years, 66% male). Patients were divided into groups according to SV use after CRT implantation. There was no significant difference in baseline characteristics between SV

Figure 1 Kaplan–Meier survival curves according to sacubitril/valsartan (SV) treatment for cardiac death, heart transplantation (HT), and left ventricular assist device (LVAD) implantation.



users (n = 22) and non-users (n = 28) (*Table* 1). All patients in the SV user group switched from angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) to SV (starting dose: 90 ± 64 mg/day, final dose: 136 ± 107 mg/day). Most non-users (26 of 28, 93%) received ACEi or ARB. Seven per cent of non-users could not tolerate ACEi or ARB owing to hypotension. The most common reason for non-use of SV was the lack of insurance coverage before 2017. In addition, one patient with end-stage renal disease did not meet the indications for SV use, and we did not use SV for patients whose LVEF was recovered (>40%) at follow-up, even if they were defined as a non-responder at the first evaluation.

During follow-up (median, 30 months; inter-quartile range, 22 to 45 months), nine patients (18%) died from end-stage HF, two (4%) died from non-cardiac disease, one (2%) had HT, and two (4%) underwent LVAD implantation. Follow-up duration was not significantly different between SV users and non-users (median, 26 vs. 33 months, P = 0.308). The prevalence of delayed CRT response [7 (32%) vs. 7 (25%), P = 0.829], appropriate ICD shock [1 (5%) vs. 2 (10%), $P > 0.999$], and new-onset atrial fibrillation [2 (9%) vs. 2 (7%), $P > 0.999$] was not significantly different. However, SV users had a significantly lower incidence of all-cause death [1 (5%) vs. 10 (36%), P = 0.022] and tended to have lower HF rehospitalization [6 (27%) vs. 16 (57%), P = 0.068] and lower cardiac death including HT and LVAD implant [2 (9%) vs. 10 (36%), P = 0.064] than SV non-users. Kaplan–Meier survival analysis revealed that SV use was associated with a lower risk of cardiac death including HT and LVAD implant (log-rank P = 0.029) (*Figure* 1).

Conclusions

The present study evaluated the impact of SV on clinical outcomes in CRT non-responders. Although CRT can improve prognosis, CRT non-responders remain at risk of adverse cardiac events.[6] On applying the current guidelines, up to 38% of patients who underwent CRT were potentially indicated for further optimization of GDMT, and most patients (86%) were eligible for SV.[3] SV is recommended as a replacement for ACEi/ARB in symptomatic HFrEF patients.[4] However, there have been no data regarding the optimization of GDMT with SV after CRT implantation, especially in CRT non-responders. In our results, we showed that SV treatment was associated with a lower risk of a composite of cardiac death, HT, and LVAD implantation in CRT non-responders. Although device therapy can result in mechanistic synchronization, further neurohormonal modulation should be considered to improve outcomes. In this regard, we suggest that, with the combined inhibition of the renin–angiotensin system and neprilysin, SV use can provide additional clinical benefits in CRT non-responders.[7]

Our study had several limitations. This was a retrospective non-randomized study with a small sample size. The time period between CRT response determination and SV initiation was various among the SV users (median, 4.5 months). In the SV non-user group, most patients could not take SV because they had undergone CRT implantation before 2017, when the national insurance coverage began. Therefore, patients who underwent CRT implantation late 2017 onwards were able to start SV just after the implantation or evaluation for CRT

response; those who received CRT implantation before late 2017 did not start SV until much later. The follow-up period was <1000 days in patients who started SV since late 2017. This may have caused the difference in dropout rates between SV users and non-users, as observed in the Kaplan–Meier analysis. However, the follow-up period was not significantly different between SV users and non-users. Despite the limitations of our study, our data may help address a need in CRT non-responders. If confirmed by future prospective, randomized studies, SV may be considered for CRT non-responders.

Conflict of Interest

None declared.

Funding

This work was partly supported by Institute of Information & communications Technology Planning & Evaluation (IITP) grant funded by the Korea government (MSIT) (2019-0-01750) and partly supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2020R1I1A1A01074368).

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