Effectiveness of sacubitril/valsartan for patients with cancer therapy-related cardiac dysfunction: A systematic review of descriptive studies

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Received August 5, 2022; Accepted January 11, 2023

DOI: 10.3892/ol.2023.13694

Abstract. The present review assessed the effectiveness of sacubitril/valsartan in patients with cancer therapy-related cardiac dysfunction (CTRCD). Studies that included patients with CTRCD treated with sacubitril/valsartan were retrieved from the Medline, Embase, Cochrane Library and ClinicalTrials databases. Only descriptive studies on sacubitril/valsartan for patients with CTRCD were included in this review; therefore, all variables were qualitatively analyzed. A total of five studies comprising 109 patients were included. The duration from anticancer therapy to heart failure (HF) or from HF to the use of sacubitril/valsartan exhibited interindividual variations. In patients with CTRCD who were treated with sacubitril/valsartan, the left ventricular ejection fraction improved, N-terminal pro-B-type natriuretic peptide levels decreased and exercise tolerance improved, as indicated by the change in the New York Heart Association functional class. These clinical, echocardiographic and biochemical improvements were found for different dosages or treatment durations of sacubitril/valsartan. No difference was found between the baseline and follow-up serum creatinine and potassium levels. These findings, which are limited to descriptive studies, support the effectiveness of sacubitril/valsartan in improving heart function following CTRCD.

Introduction

The early diagnosis of cancer and the development of novel treatments have led to increased cancer-free survival; however, cancer therapy-related cardiac dysfunction (CTRCD) has increasingly become a concern (1). Chemotherapeutic agents that are associated with CTRCD include anthracyclines (e.g., doxorubicin), human epidermal growth factor 2 (HER2) inhibitors (e.g., trastuzumab), alkylating agents (e.g., cyclophosphamide) and taxanes (e.g., paclitaxel) (1,2). The incidence of CTRCD varies depending on the chemotherapeutic agent that is used (3-5). In a cohort of 2,625 patients who were receiving anthracycline-containing therapy, the overall incidence of cardiotoxicity was 9% (3). Rossi *et al* (4) reported severe cardiac adverse events in 32 (4.7%) of 681 trastuzumab-treated patients with metastatic breast cancer. In another study, the incidence of cyclophosphamide-induced cardiotoxicity with treatment at the therapeutic dose ranged from 7 to 28% (5).

Among the various definitions for CTRCD (1,2), the most accepted definition originates from the expert consensus of the American Society of Echocardiography and European Association of Cardiovascular Imaging, which defines CTRCD as a decrease in the left ventricular ejection fraction (LVEF) of >10%, or to a value <53%, confirmed by repeat imaging (6). Although the standard drug therapy used for heart failure (HF) may be helpful for diagnosing CTRCD, there are no current recommendations for this treatment owing to limited evidence (1,2,6).

Several studies have evaluated the effectiveness of the HF therapy regimens, such as beta-blocker or angiotensin-converting enzyme inhibitors/angiotensin-II receptor blockers (ACEIs/ARBs), in HF prevention due to CTRCD; the results indicated that these drugs moderately attenuate the frequency of clinically overt cardiotoxicity and prevent ventricular remodeling (7-9). Sacubitril/valsartan, a novel angiotensin receptor neprilysin inhibitor, has been recommended for patients with HF with reduced LVEF (HFrEF) to alleviate the mortality and hospitalization risk (10,11). However, it has remained elusive whether sacubitril/valsartan is effective in patients with CTRCD, as these patients are usually excluded from clinical trials (11). Therefore, the present review was conducted to systematically evaluate the usefulness of sacubitril/valsartan as a treatment for CTRCD.

Materials and methods

Search strategy. The search strategy, study selection, and data extraction and analysis methods were pre-designed according to the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (12), although this review was not registered.

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Key words: sacubitril/valsartan, cancer therapy-related cardiac dysfunction, systematic reviews

Data source and search strategy. A systematic search was conducted to identify studies published in online databases, including PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Embase (https://www. elsevier.com/solutions/embase-biomedical-research), the Cochrane Library (https://www.cochranelibrary.com/advanced-search) and ClinicalTrials.gov (https://www.clinicaltrial.gov/) from their inception to May 13, 2021. The keywords included 'LCZ696', 'sacubitril/valsartan', 'sacubitril valsartan', 'cancer' and 'tumor'. EndNote X6.0 (Thomson Reuters) was used to manage records and exclude duplicates. To ensure comprehensiveness of the present analysis, the reference lists of identified studies were manually checked to identify other potentially eligible studies.

Study selection. The inclusion criteria were as follows: Studies of i) patients with CTRCD; ii) including treatment with sacubitril/valsartan; iii) including comparison or no comparison; iv) including at least one heart remodeling parameter, such as the New York Heart Association (NYHA) functional class (13), LVEF or N-terminal pro-B-type natriuretic peptide (NT-proBNP), as the outcomes; and v) with an experimental or observational study design. There were no restrictions on the indication for treatment, dose or the clinical setting in which sacubitril/valsartan was administered.

Review articles, systematic reviews, meta-analyses, commentaries, editorials and meeting abstracts were excluded from the analysis.

Data extraction and quality assessment. Data extraction and evaluation of the quality of the studies were performed independently by two researchers (YH and LLM). Disagreements, if any, were resolved with a third investigator (YYZ, CBF, WFX or HZ). The following general study information was retrieved: Author, publication year, study design, country, cancer type, chemotherapy, numbers of cases, age, LVEF measurement and follow-up duration.

The 2011 Oxford Criteria were used for grading the level of evidence of the included studies (14). The criteria developed by Murad *et al* (15) in 2018 were used to assess the quality of the included studies, wherein scores of <3, 3-5 and 6-8 indicated low-quality, moderate-quality and good-quality evidence, respectively (16).

Statistical analysis. A meta-analysis was not performed, as all of the included studies were descriptive studies. A total of three outcome variables were assessed, namely NYHA functional class, LVEF and NT-proBNP. The assessments were performed at baseline and on completion of the sacubitril/valsartan intervention. All variables were qualitatively analyzed.

Results

Search results and study characteristics. Following the search strategy, a total of 109 articles were obtained from the online databases. After excluding all duplicates, 86 articles were retained. After checking the titles and abstracts and reviewing the full texts of these articles, 5 studies (two from Spain and one each from Canada, Argentina and Italy) (17-21) eventually met the inclusion criteria and were included in the review. Fig. 1 illustrates the literature search protocol.

The five studies, including one letter to the editor (which includes the original research data) and four case series, were all descriptive studies that enrolled patients with CTRCD who were treated with sacubitril/valsartan. Of the total of 109 patients, 52 had breast cancer, 34 had lymphoma and 23 had other cancers. Depending on the type of the tumor, most of the patients were treated with anthracyclines (e.g., doxorubicin and epirubicin), anti-HER2 agents (e.g., trastuzumab) and other chemotherapeutic agents. The follow-up period of the studies ranged from 2 to 24 months. Table I presents the detailed characteristics of the included studies.

Level of evidence and quality assessment. The level of evidence of the five studies was graded as 4, as per the 2011 Oxford Criteria (14). With regard to quality assessment, all studies were scored as 4-5, which is considered good-quality evidence. Although a score of 6-8 indicates good quality as per Murad *et al* (15), questions 4, 5 and 6 are mostly relevant to cases of adverse drug events; therefore, this scoring was not included in the present article. Table II presents the detailed results of the quality assessment of the included studies.

Treatment characteristics of sacubitril/valsartan. Data from the present review of the selected studies (17-21) revealed interindividual variations in the time from anticancer therapy to HFrEF (5-141 months) or from HFrEF to sacubitril/valsartan treatment (1-52 months). Prior to undergoing sacubitril/valsartan treatment, patients received triple HF therapy, including ACEI/ARB, beta-blockers, mineralocorticoid receptor antagonists and diuretics, as relevant. The dose of sacubitril/valsartan was titrated from a low dose [e.g., 50 mg twice a day (b.i.d.)] gradually to the maximum tolerated target dose (e.g., 100 or 200 mg b.i.d.).

Effect of sacubitril/valsartan on patients with CTRCD. In terms of the changes from the basal echocardiography, sacubitril/valsartan treatment improved the LVEF of patients with CTRCD (Table III). Furthermore, a reduction in NT-proBNP levels was evident (Table III). In addition, patients exhibited an improvement in exercise tolerance at follow-up, as indicated by the change in the NYHA functional class (at the end of follow-up, 48 and 47% of patients had NYHA class I and II, respectively; Table III and Fig. 2). Regardless of the dosage or treatment duration of sacubitril/valsartan, these clinical, echocardiographic and biochemical improvements were observed.

Furthermore, certain studies reported improvements in other cardiac remodeling parameters, such as left ventricular internal diameter in diastole, the ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e') and mitral regurgitation (18); left ventricle end-diastolic or systolic volume index, left ventricle mass index, global right ventricle ejection fraction, right ventricle end-diastolic or systolic volume index, and global circumferential or longitudinal strain feature tracking (20); and left ventricle end-diastolic or systolic volume, E/e' and global longitudinal strain (21).

Table I. Characteristics of the studies evaluating sacubitril/valsartan treatment for patients with cancer therapy-related cardiac dysfunction.

Author, year	Type of study	Country	Level of evidence	Sample size (male/female)	Patient age, years	History of cardiovascular disease	Cancer type	Chemotherapy	Measurement of LVEF	Follow-up duration (months)	Funding	(Refs.)
Sheppard and Anwar, 2019	Case series study	Canada	4	1 female	68	No risk factors for heart disease	Mantle cell lymphoma	R-CHOP/R-DHAP induction chemotherapy	Echocardiography, MRI	6	No	(17)
				1 female	76	/	ER/PR-positive, HER2-negative left-sided breast cancer	FEC and tamoxifen for 5 years followed by letrozole (discontinued due to intolerance)	Echocardiography	/		
Gregorietti, 2020	Case series study	Argentina	4	3/25	56.2±13.4	Hypertension, 50%; smoking, 43%; hypercholesterolemia, 36%; diabetes, 29%; ischemic cardiac disease, 7%	Left breast cancer 64.3%	Doxorubicin, 82.1%; Cyclophosphamide, 82.1%; Docetaxel, 10.7%; Trastuzumab, 28.6%; Pertuzumab, 14.3%	Echocardiography	24	No	(18)
Vecchis and Paccone, 2020	Case series study	Italy	4	1 female	55	/	Hodgkin lymphoma	ABVD	Echocardiography, MRI	4	Novartis Pharma	(19)
				1 female	65	/	Invasive ductal carcinoma in the right breast with esophageal metastasis	Anastrozole, TAC and cyclophosphamide	Echocardiography	2	S.p.A	

Table I. Continued.

Author, year	Type of study	Country	Level of evidence	Sample size (male/female)	Patient age, years	History of cardiovascular disease	Cancer type	Chemotherapy	Measurement of LVEF	Follow-up duration (months)	Funding	(Refs.)
Martín-García, 2020a	Letter to the editor	Spain	4	4/6	65-78		6 lymphoma, 2 breast cancer, 1 myeloma and 1 lung cancer	Anthracyclines, 80%; Alkylating agents,80%; Antimicrotubule agents, 60%; Rituximab, 60%; Anti metabolites, 20%; PD-1 inhi bitors, 20%; Trastuzumab, anti VGEF antibodies, lenalidomide or pomalidomide, 10%	MRI	>3	European Regional Development Fund (PIE14/00066), Spanish Cardiovascular Network (CIBERCV)	(20)
Martín-García, 2020b	Case series study	Spain	4	24/43	63±14	Hypertension, 43%; dyslipidaemia, 54%; diabetes, 28%	30 Breast cancer and 26 lymphoma	Anthracyclines, 70%; Alkylating agents, 60%; Antimicrotubule agents, 50%; Antimetabolites, 25%; Tyrosine kinase inhibitors,22%; Anti-HER2 humanized antibody, 12%; Topoisomerase inhibitors, 6%; PD-1 inhibitors, 3%	Echocardiography	Median, 4.6	European Regional Development Fund (PIE14/00066), Spanish Cardiovascular Network (CIBERCV)	(21)

Age is presented as the mean ± standard deviation or range. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; CHOP/R-DHAP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone/rituximab, dexamethasone, cytarabine and cisplatin; FEC, 5-fluorouracil, epirubicin and cyclophosphamide; ABVD, adriamycin (doxorubicin), bleomycin, vinblastine and dacarbazine; TAC, docetaxel, doxorubicin and cyclophosphamide; MRI, magnetic resonance imaging; PD-1, programmed death 1; LVEF, left ventricular ejection fraction.

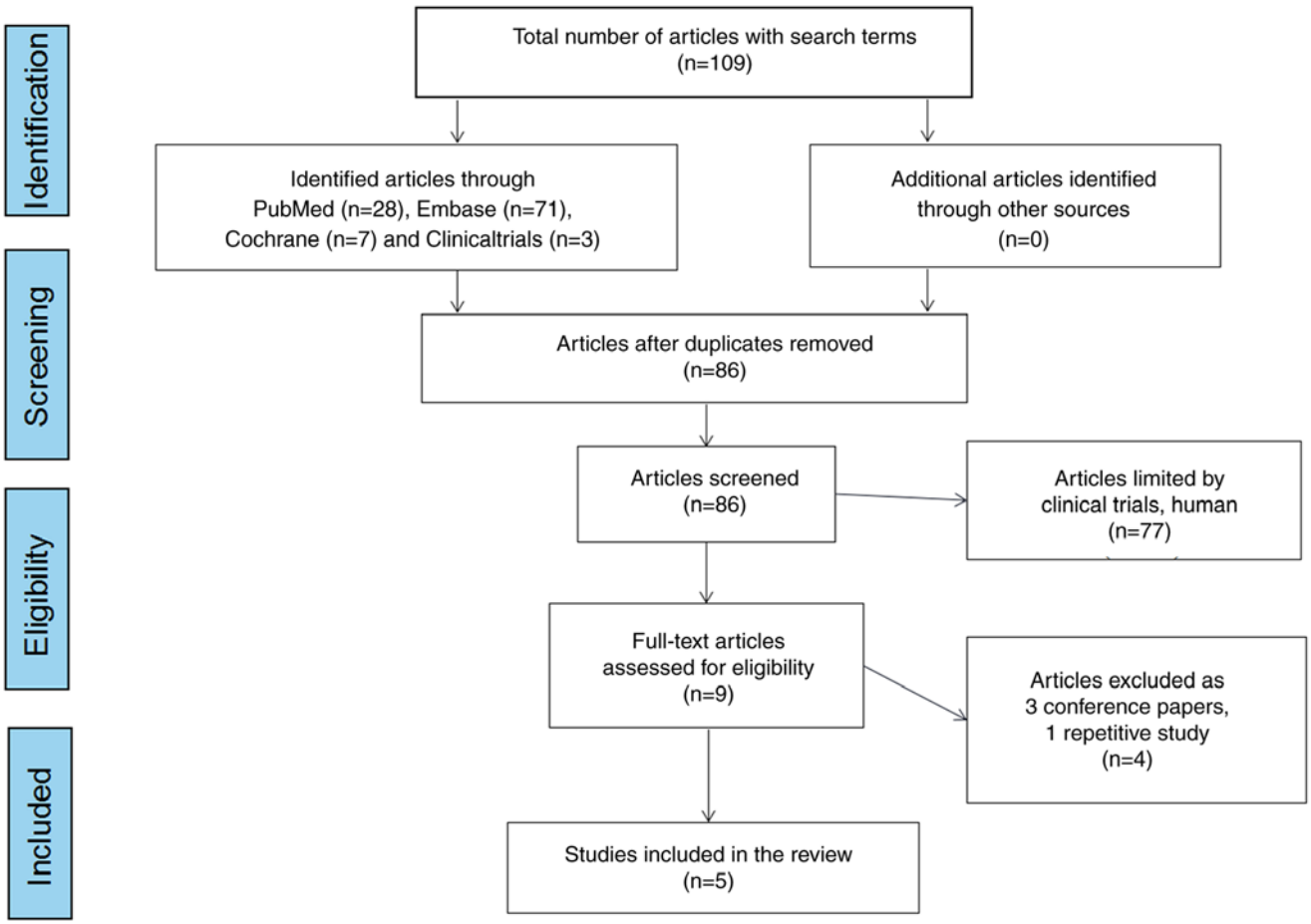

Figure 1. Flow chart illustrating the study selection process.

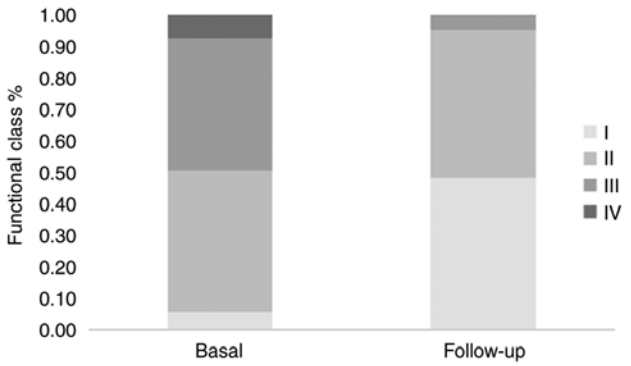

Figure 2. New York Heart Association functional class compared between baseline and follow-up.

Effect of sacubitril/valsartan on creatinine or potassium. In 2020, Gregorietti *et al* (18) and Martín-García *et al* (21) both reported a lack of a difference between the baseline and follow-up creatinine and potassium serum levels.

Discussion

A total of five studies, which comprised 109 patients, were included in the present review. The findings from this review supported the hypothesis that sacubitril/valsartan was effective and safe for patients with CTRCD, based on improved LVEF and exercise tolerance, as indicated by the change in the NYHA class and reduction in NT-proBNP levels; however, no change in the serum creatinine or potassium level was identified. The evidence was weak, as only descriptive studies were included.

Dexrazoxane remains the only clinically available option to prevent anthracycline-induced cardiomyopathy. In addition, current guidelines recommend pre-therapy, and once LVD occurs, post-therapy LVEF evaluation and discontinuation of chemotherapy, together with the initiation of standard HF therapy comprising beta-blockers and ACEI/ARB (22,23). Although the results of related clinical studies revealed the effectiveness of ACEI and beta-blockers against anticancer drug-induced cardiomyopathy, which was indicated by symptom relief, improved LVEF and decreased NYHA class, these agents have only been evaluated in a small number of small-sample studies in the clinical setting (1-3). Thus, additional prospective multicenter studies with a larger number of patients are warranted to obtain a more definitive conclusion.

Furthermore, sacubitril/valsartan is recommended for patients with HFrEF in the European Society of Cardiology guidelines (10), but there is also a lack of evidence of its efficacy and safety in CTRCD. Indeed, outside of the descriptive studies included in the present review, there are no exhaustive data on the subject. Based on current evidence, the following is also revealed: i) Patients with a

Table II. Quality assessment of the studies included in the review.

Domain	Questions	Sheppard, 2019 (17)	Gregorietti, 2020 (18)	Vecchis, 2020 (19)	Martín-García, 2020 (20)	Martín-García, 2020 (21)
Selection	1. Does the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?	0	1	0	0	1
Ascertainment	2. Was the exposure adequately ascertained?	1	1	1	1	1
	3. Was the outcome adequately ascertained?	1	1	1	1	1
Causality	4. Were other alternative causes that may explain the observation ruled out?	/	/	/	/	/
	5. Was there a challenge/rechallenge phenomenon?	/	/	/	/	/
	6. Was there a dose-response effect?	/	/	/	/	/
	7. Was the follow-up long enough for outcomes to occur?	1	1	1	1	1
Reporting	8. Is/are the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners\ make inferences related to their own practice?	1	1	1	1	1
Score		4	5	4	4	5

cardiovascular disease history should be highly alert to the occurrence of CTRCD (Table I); and ii) there are interindividual variations in the time from anticancer therapy to HF (5-141 months), and therefore, patients should pay attention to the occurrence of CTRCD during the entire treatment process (Table III).

Current studies reveal a multifactorial pathogenesis of CTRCD. A review indicated that anthracycline-induced cardiomyopathy is related to the stabilization of topoisomerase II, which causes DNA double-strand breaks, genomic instability and impaired mitochondrial biogenesis capacity; furthermore, this condition resulted in semiquinone cycling, which causes Complex I impairment, loss of membrane potential, and activation of mitophagy; non-canonical Wnt signaling, which upregulates autophagosome formation; autophagolysosome accumulation due to impaired lysosomal enzyme activity; and calcium mishandling, which causes impaired contractile function (24). Furthermore, it was reported that trastuzumab may block the myocardial HER-2 receptor pathway, which mediates cardioprotective function. Mitochondrial impairment is caused by HER-2 inhibition, which results in decreased antioxidant reserve and reactive oxygen species (ROS) accumulation, as well as the inhibition of the downstream signaling of the PI3K/Akt pathway that causes upregulation of the proapoptotic Bcl-2 family protein Bcl-xS and downregulation of the antiapoptotic protein Bcl-xL; the abovementioned sequence of events is considered the primary etiopathogenetic mechanism of HER2 inhibitor-induced cardiomyopathy (25).

Experimental studies of the molecular mechanisms mediating the potential benefits of sacubitril/valsartan in CTRCD are scarce. In a study using a rabbit model of doxorubicin-induced HF, sacubitril/valsartan treatment reduced inflammation and oxidative stress, which resulted in improved cardiac function (26). Another study demonstrated that doxorubicin increased angiotensin-II receptor type I expression through ERK1/2 activation by inducing mitochondrial ROS-triggered heat-shock factors 2-related nuclear translocation and activation; this indicates the potential mechanisms of action of ACEI and ARB (27). Thus, further investigations are required in this field.

There are certain limitations to this systematic review. First, only five descriptive studies on sacubitril/valsartan were included in this review, and it was thus not feasible to perform a quantitative analysis; therefore, all variables underwent qualitative analysis. Furthermore, only studies published in English were included. In addition, publication bias could not be assessed, as the level of evidence included grade 5 as per the 2011 Oxford Criteria. Finally, methodological quality was addressed through an appropriate method; thus, cautious interpretation of the results is advised in clinical practice.

In conclusion, the evidence from the present review limited to descriptive studies supports the effectiveness of sacubitril/valsartan in the improvement of heart function following CTRCD. Further studies are warranted to assess the long-term benefit and safety of sacubitril/valsartan in patients with CTRCD.

Table III. Heart remodeling parameters before and after sacubitril/valsartan treatment.

Author, year	Cardiovascular pharmacological treatment	Time from HFrEF to S/V initiation, months	Time from anticancer therapy to HFrEF, months	Dose of sacubitril/ valsartan	NYHA functional class		LVEF, %		NT-proBNP, pg/ml		(Refs.)
					Before	After	Before	After	Before	After	
Sheppard and Anwar, 2019	Bisoprolol, Candesartan, Spironolactone, Furosemide as required, Nitroglycerin	12	1.5	→200 mg b.i.d.	II	/	33	59	68,281	2,783	(17)
	Enalapril, Carvedilol, Eplerenone, Furosemide	72	3	50 mg bid →100 mg b.i.d	/	/	25	28	4676	/	
Gregorietti, 2020	Beta-blockers, 93%; ACEI, 43%; ARB, 46%; Digitalis, 32%; Mineralo-corticoid receptor antagonist, 64%; Diuretics 71%	6.1±3.2	1.6±0.4	100 mg in 12 patients; 200 mg in 16 patients	III, 78.6%; IV, 21.4%	I, 57.1%; II, 42.9%	26.7±5.4	32.3±5.5	997.5 (663.8-2380.8)	416.5 (192.0 -798.2)	(18)
Vecchis, 2020	Carvedilol, Enalapril, Canrenone, Furosemide as required	8	1	50 mg bid →100 mg b.i.d	/	/	22	55	1,5281	1,800	(19)
	Ramipril, Carvedilol, Canrenone, Furosemide as required	5	>6	50 mg bid →100 mg b.i.d	/	/	26	45	1,2467	/	

Table III. Continued.

Author, year	Cardiovascular pharmacological treatment	Time from HFrEF to S/V initiation, months	Time from anticancer therapy to HFrEF, months	Dose of sacubitril/ valsartan	NYHA functional class		LVEF, %		NT-proBNP, pg/ml		(Refs.)
					Before	After	Before	After	Before	After	
Martín-García, 2020	Triple HFrEF therapy	31 (9-113)	11 (2-24)	24/26 mg 70% →49/ 51 mg 50% →97/ 103 mg 10%	II, 60%; III, 30%; IV, 10%	I, 40%; II, 60%	35±8	47±9	1,063 (492-1,818)	458 (217-648)	(20)
Martín-García, 2020	ACEI/ARB, 80%; Beta-blocker, 85%; Mineralocorti-coid receptor antagonists, 76%; Diuretics, 52%	43 (10-141)	13 (2-52)	50 mg b.i.d. 78% →50 mg b.i.d. 60% →100 mg b.i.d. 32% →200 mg b.i.d. 8%	II, 61%; III, 28%; IV, 1%	I, 45%; II, 47%	33 (27-37)	42 (35-50)	1,552 (692-3, 624)	776 (339-1, 458)	(21)

Values are expressed as the mean ± standard deviation or mean (interquartile range). NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-II receptor blockers; S/V, sacubitril/valsartan; HFrEF, heart failure with reduced LVEF; b.i.d, twice a day.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Technology Plan of Zhejiang Medical and Health Science (grant no. 2019KY604), 2021 Zhejiang Pharmaceutical Association Hospital Pharmacy Special Scientific Research Funding Project (grant no. 2021ZYY41), the Traditional Chinese Medicine Scientific Research Fund Project of Zhejiang Province (grant no. 2021ZB263) and NINGBO Medical & Health Leading Academic Discipline Project (grant no. 2022-F06).

Availability of data and materials

Not applicable.

Authors' contributions

YH, YZ, WX, CF, HZ and LM contributed to the study conception and design. Material preparation and data collection and analysis were performed by YH, LM and YZ. The first draft of the manuscript was written by YH and it was revised by WX, CF and HZ. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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