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Treatment of Heart Failure with Sacubitril/Valsartan in Hondurans with Reduced Left Ventricular Ejection Fraction: A Three-Year Experience

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ABSTRACT

Background: Heart Failure with Reduced Ejection Fraction (HFrEF) is a paramount medical condition affecting more than 23 million individuals worldwide. It is one of the leading causes of morbidity and mortality, particularly in the western world, making it a vital topic of discussion in the current clinical trials.
Objective: This study aimed to describe the response to sacubitril/valsartan in a group of Hondurans with heart failure and reduced Left Ventricular Ejection Fraction (LVEF) between January 2018 and June 2020.
Methods: This observational, descriptive, retrospective cohort study was conducted on 105 adult patients with HFrEF who received treatment with angiotensin-receptor antagonist/neprilysin inhibitors (sacubitril/valsartan) in a single medical center in Honduras. The study participants included the patients with LVEF < 40% treated with sacubitril/valsartan for at least one year. The patients also received optimal medical therapy for HFrEF according to the American Heart Association guidelines. The data were analyzed using the SPSS 25.0 software.
Results: The results showed that the main etiology of HFrEF was ischemic heart disease (41%). The LVEF changed from a median of 30% to 45% after one year of treatment. Additionally, the overall Glomerular Filtration Rate (GFR) remained unchanged. However, the N-Terminal Pro B-type Natriuretic Peptide (NT-ProBNP) decreased from a median of 8800 pg/mL to 1900 pg/mL after 12 months.
Conclusions: The study population had sociodemographic and clinical similarities with the Latin American Cohort in the PARADIGM-HF trial with the significant improvement of the LVEF and functional class. However, the median level of NT-ProBNP was 8800 pg/mL at baseline in the current study, which was dramatically higher than 1760 pg/mL reported in the PARADIGM-HF trial, suggesting the need for further analyses in the Honduran population.

1. Introduction

Heart Failure (HF) is one of the fastest expanding cardiovascular conditions affecting more than 23 million individuals worldwide (1, 2). Despite advances in treatment and the increased life expectancy in recent years, it continues to be a significant cause of morbidity, mortality, and healthcare costs worldwide (3-5). The prevalence of HF has been found to be approximately 1 - 2% in the adult population, reaching up to 10% in adults older than 70 years. Additionally, at 55 years of age, the lifelong risk of HF has been estimated as 33% in males and 28% in females (6, 7). In the last 30 years, there has been an improvement in the survival of patients with HF and a decrease in the age-adjusted mortality rate due to advancements in diagnosis

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and novel medical therapies (8).

HF can be classified based on the Left Ventricular Ejection Fraction (LVEF). In HF with Reduced Ejection Fraction (HFrEF), the LVEF is less than 40%. In HF with preserved EF (HFpEF), however, the LVEF is greater than 50%. An EF between 40% and 49% is considered an intermediate zone called HF with borderline EF or HF with mid-range EF (HFmrEF) (9).

Current regimens for HFrEF focus on blocking the Renin-Angiotensin-Aldosterone System (RAAS) and the sympathetic nervous system using Angiotensin-Converting Enzyme (ACE) inhibitors, Angiotensin Receptor Blocker of angiotensin 2 (ARB), B-adrenergic Blockers (BB), or Mineralocorticoid Receptor Antagonists (MRA) (10). Despite the use of targeted therapies for nearly two decades, many HF patients continue to have worse cardiac function, increasing heart failure events, and higher morbidity and mortality (5, 11).

In 2015, the Food and Drug Administration approved the use of Sacubitril/Valsartan (SAC/VAL) after the PARADIGM-HF. A double-blind randomized clinical trial revealed a significant reduction in the number of heart failure hospitalizations, all-cause mortality, cardiovascular mortality, and risk of sudden death after its use. It also demonstrated a significant cardiovascular benefit and an improvement in patient survival (6, 10, 12-14). SAC/VAL has been approved for HFrEF in more than 90 countries around the world. It has also been endorsed by the guidelines of the American Heart Association and European Society of Cardiology. Additionally, a joint statement issued by the American College of Cardiology/American Heart Association/American Heart Failure Society recommended this drug even for patients with HFpEF when symptoms persisted despite medical therapy with ACEi, BB, ARB, MRA, and/or ivabradine (10, 14-16).

In Honduras, SAC/VAL was first approved in 2018. The present study is the first analysis of its clinical course in the Honduran population with HFrEF. The drug supported the principle of neurohormonal modulation in HF and the improvement of patients' LVEF. It also facilitated reverse left ventricular remodeling and was associated with lower mortality rates and heart failure events in patients with HFrEF (17).

2. Objectives

The present study aims to share the clinical experience of a single center using SAC/VAL in patients with HFrEF to analyze the improvement of HF and its effect on the LVEF between January 2018 and June 2020.

3. Methods

This observational, descriptive, retrospective cohort study was conducted on the records of 105 adult patients who received treatment with SAC/VAL in a single medical center for HFrEF in San Pedro Sula, Honduras between January 2018 and June 2020. The patients with LVEF < 40% treated with SAC/VAL for at least one year were included. These patients should have received optimal medical therapy for HFrEF according to the American Heart Association guidelines. They were also required to have at least three months of sustained use of the maximum tolerated dose of BB, ACEi or ARB, and MRAs supplemented with the regular use of a diuretic (furosemide or spironolactone). NT-ProBNP > 600 pg/mL was also required before starting the treatment. The titration with SAC/VAL was individualized according to the cardiologist's clinical criteria and each patient's drug tolerance. It should be noted that several patients had various degrees of hemodynamic instability and a worsening New York Heart Association (NYHA) functional class. BB therapy was maintained in the study population, except for those with major side effects. Besides, SAC/VAL titration was initiated with 50 mg (24 mg/26 mg) and was increased according to the medical criteria until reaching the maximum tolerated dose. The SAC/VAL titration reached at the end of the study was used for data analysis. In hypotensive patients, it was necessary to implement individualized strategies, warranting dose adjustments and different administration timings of BB and diuretics.

The retrospective clinical and echocardiographic data were collected at four different time points according to the patients' follow-up consultations: pre-baseline, at three months, at six months, and at one year of therapy with SAC/VAL. The patients who did not have complete laboratory and imaging tests at each of the evaluation points or had insufficient echocardiographic image quality for evaluation were excluded. The patients with stage IV-V renal failure (Glomerular Filtration Rate (GFR) < 30 ml/min/1.73 MDRDm2) according to the Modification of Diet in Renal Disease (MDRD) study equation as well as those who had never been treated with the sustained use of the RAAS inhibitors were excluded, as well. All the patients met the inclusion criteria and none was excluded. It is worth mentioning that the participants were selected via convenience sampling.

Sociodemographic variables (sex, age), clinical variables such as the NYHA functional class (taken at each follow-up visit), medical history, toxic habits, and final dose of SAC/VAL were taken into account for the retrospective analysis. The results of diagnostic images such as chest radiography for the Cardiothoracic Index (CTI) were also obtained before the beginning of therapy and at the six-month follow-up. Additionally, LVEF measurement by Transthoracic Echocardiogram (TTE) was done before starting the medical therapy and at the one-year follow-up. The LVEF was determined by the Teicholtz and Simpson method (in case of ischemic heart disease) using a General Electric Vivid E9 ultrasound machine and 4 MHz electronic transducers with biphasic tracking. Electrocardiograms were used as adjuvants to determine the etiology of the heart disease. Moreover, laboratory variables including GFR were assessed using the MDRD equation before starting the treatment and after three months. NT-pro-BNP levels were also recorded at baseline and after 12 months of treatment.

The corresponding permits were requested at the cardiologic institution to begin the retrospective analysis while the Catholic University of Honduras Institutional Review Board approved the required research protocol (approval No. EXE-2020-40). Afterwards, the necessary patient data were collected. In doing so, a file was used

to record the variables. Each file was transferred to a comparison table in Microsoft Excel. Subsequently, the database was exported to the SPSS 25.0 software. At first, Kolmogorov-Smirnov test was used to determine the normal distribution of the data. Then, frequency and percentage were reported for categorical variables, mean ± standard deviation for normally distributed continuous variables, and median and Interquartile Range (IQR) for non-normally distributed ones. To compare the characteristics at baseline and follow-up, paired t-test was used for continuous variables and a two-sample proportion test was used for categorical ones. $P \leq 0.05$ was considered statistically significant.

4. Results

This study was conducted on 105 patients with HFrEF treated with SAC/VAL. The median age of the patients was 66 years [IQR: 55.5-76.0]. Additionally, 52.4% of the patients were female and 48.6% were male. The sociodemographic and clinical variables have been presented in Table 1.

Treatment with SAC/VAL was done at three dosages (24/26 mg, 49/51 mg, and 97/103 mg) twice a day. For most of the patients, the treatment was started with 24/26 mg and the dose was progressively titrated to the maximum tolerated dose. At the six-month follow-up, 10.5% of the patients (n = 11) achieved tolerance with a dose of 24/26 mg, 29.5% (n = 31) reached a titrated dose of 49/51 mg, and 60% (n = 63) completed the follow-up at the optimal dose of 97/103 mg.

Considering the medical history, all the patients had at least one underlying comorbidity. The main comorbidity was hypertension (92.4%) followed by dyslipidemia (61.9%) (Table 1). Moreover, the initial electrocardiograms of the patients showed that 58.1% of the cases (n = 61) had the sinus rhythm, 8.6% (n = 9) had atrial fibrillation, 6.7% (n = 7) presented a complete left bundle branch block, 13.3% (n = 14) had ischemic heart disease, and 8.1% (n = 40) had left ventricular hypertrophy (Table 2).

Table 1. Sociodemographic and Clinical Characteristics and Medical History of the Patients Prior to the Use of Sacubitril/Valsartan

Sociodemographic Characteristics	N (%)
Age, median	66 [55.5-76.0]
Gender	
Female	55 (52.4)
Male	50 (47.6)
Pathological background	
High blood pressure	97 (92.4)
Dyslipidemia	65 (61.9)
Diabetes mellitus	23 (21.9)
Previous AMI	17 (16.2)
Obesity	11 (10.5)
Chronic renal failure	4 (3.8)
Valve disease	3 (2.9)
Hypothyroidism	3 (2.9)
Previous CVA	3 (2.9)
Cancer	1 (1.0)
Initial New York Heart	
Association functional class	
Class I	0 (0.0)
Class II	6 (5.7)
Class III	31 (29.5)
Class IV	68 (64.8)
Initial LVEF, median (%)	30.0 [25.0-36.0]
Initial GFR, median (ml/min/1.73m^2)	55.0 [45.0-67.0]
Initial NT Pro-BNP, median (pg/mL)	8,800 [7,000-10,000]

Abbreviations: IQR, interquartile range; AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate; NT Pro-BNP, N-terminal prohormone B-type natriuretic peptide; CVA, cerebrovascular accident.

Table 2. Electrocardiographic, Echocardiographic, and Radiological Characteristics and Performed Interventions

Images Results	N (%)
Electrocardiographic diagnosis	
Sinus rhythm	61 (58.1)
Infarction QS, V1-V6, 1AVL	14 (13.3)
Auricular fibrillation	9 (8.6)
LBBB	7 (6.7)
Sinus tachycardia	3 (2.9)
LBBB	3 (2.9)
RBBB	2 (1.9)
Trifascicular blockage	2 (1.9)
Sinus bradycardia	1 (1.0)
AV ventriculi 3rd grade	1 (1.0)
AF	1 (1.0)
Extrasystole (A/V)	1 (1.0)
Echocardiographic findings	
LV hypertrophia	40 (38.1)
Etiology of the IC	
Dilated	87 (82.9)
Ischemic origin	43 (41.0)
Hypertensive origin	31 (29.5)
Chagas etiology	6 (5.7)
Etiology Mix	6 (5.7)
Viral origin	1 (1.0)
Not dilated	2 (1.9)
Ischemic origin	1 (1.0)
Hypertensive origin	1 (1.0)
Idiopathic cardiopathy	16 (15.3)
Radiological findings	
Initial heart disease grade	
Normal	4 (3.8)
Grade I	0 (0.0)
Grade II	8 (7.6)
Grade III	29 (27.6)
Grade IV	64 (61.0)
Procedure/device	45 (42.9)
Unicameral pacemaker VVIR	13 (12.4)
Bicameral pacemaker DDDR	23 (21.9)
Tri cameral pacemaker TRC	9 (8.6)
CDI	11 (10.5)
Angioplasty	30 (28.6)
1 vessel	22 (21.0)
2 vessels	6 (5.7)
3 vessels	2 (1.9)
Open heart surgery	2 (1.9)
Valvuloplasty balloons	1 (1.0)
Only medical therapy	32 (30.5)

Abbreviations: LBBB, complete left bundle branch block; LBBB, incomplete left bundle branch block; RBBB, complete right bundle branch block; AF, ventricular fibrillation; LV, left ventricle; IC, heart failure; VVIR, ventricular pacing with inhibition and self-regulating heart rate; DDDR, dual chamber pacing and inhibition pacemaker with self-regulating heart rate; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator.

The main echocardiographic diagnosis was dilated cardiomyopathy of ischemic origin in 41% of the cases (n = 43) followed by hypertensive dilated cardiomyopathy in 29.5% (n = 31) and idiopathic origin in 9.5% of the patients (n = 10).

At the beginning of the study, 64.8% (n = 68), 29.5% (n = 31), and 5.7% (n = 60) of the patients were in NYHA functional classes IV, III, and II, respectively. Following six months of treatment with SAC/VAL, 58.1% of the patients (n = 61) were in the functional class II (P = 0.004), 28.6% (n = 30) were in class III (P < 0.001), 9.5% (n = 10) were in class IV (P = 0.003), and 3.8% (n = 4) were in class I. Based on the results, 82.9% of the patients (n = 87) presented improvement, 16.2% (n = 17) had unchanged functional classes, and 1% (n = 1) showed worse baseline conditions (Figure 1).

Based on the echocardiograms, the median LVEF was 30% before the start of the treatment [IQR: 25 - 36]. Additionally, 23.3% of the patients (n = 24) had LVEF less than 25%, ranging from 9% to 40%. At the one-year follow-up, the median LVEF was 45% [IQR: 38.0 - 49.0]. Besides, the median improvement was 14.6% compared to the baseline LVEF, and the difference was statistically significant (95% CI: 13.0 – 16.1; P < 0.001). The results revealed the improvement of LVEF in 94.3% of the cases (n=99) after treatment with SAC/VAL, while 3.8% (n = 4) presented no changes in this regard. On the other hand, LVEF was found to be worsened in 1.9% of the patients (n = 1) (Figure 2).

The degree of cardiomegaly was calculated using the CTI. All the patients had chest radiographs before the therapy and after six months. Based on the results, 61% of the patients (n = 64) showed grade IV cardiomegaly and 27.6% (n = 29) presented with grade III prior to the use of SAC/VAL. According to the follow-up radiograph, 53.3% of the patients (n = 56) had grade II cardiomegaly and 37.1% (n = 39) showed grade III. Overall, 76.2% of the patients (n = 80) showed a radiographic improvement of their cardiomegaly manifested through a decrease in the CTI in the control chest X-ray, 21% (n = 22) maintained the same degree of cardiomegaly, and 2.9% (n = 3) had a worsened CTI (Table 2).

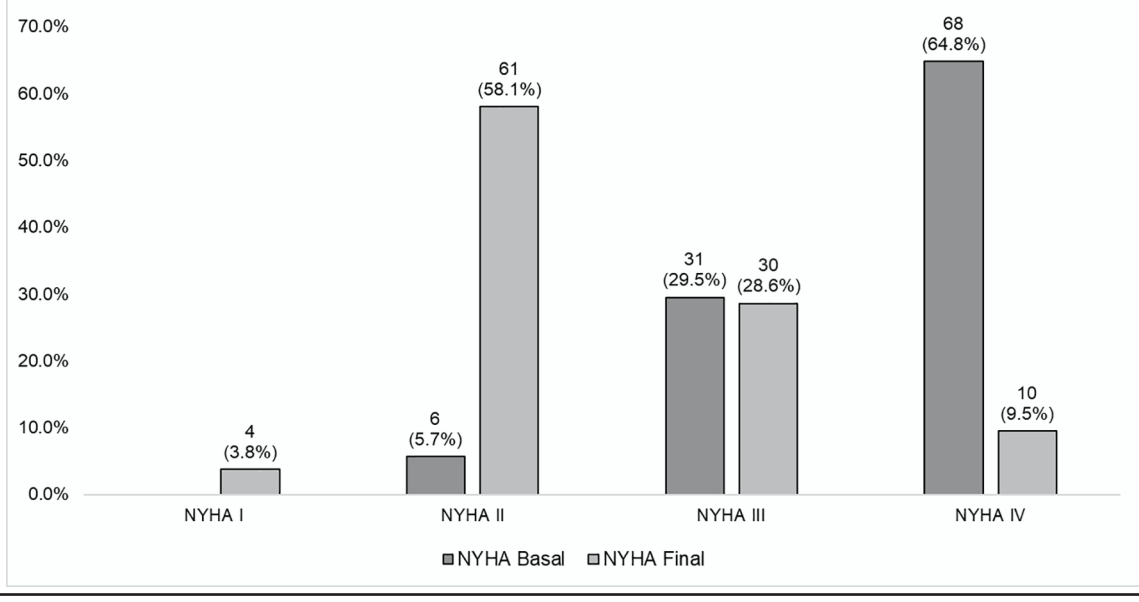
The median GFR was 55 ml/min/1.73 m2 [IQR: 45.0 – 67.0] prior to the initiation of SAC/VAL and 58 ml/min/1.73 m2 [IQR: 45.0–68.0] at three months. Additionally, the median N-Terminal Pro B-type Natriuretic Peptide (NT-ProBNP) was 8800 pg/mL [IQR: 7000 - 10000] before the treatment and 1900 pg/mL [IQR: 900 - 3000] at 12 months. Out of the 105 patients, 69.5% (n = 73) underwent surgical procedures and 42.9% (n = 45) required the placement of a pacemaker-type electrical stimulation device such as Cardiac Resynchronization Therapy (CRT) and/or Implantable Defibrillators (ICDs). Totally, 11 ICDs were placed, nine of which were placed with triple-chamber pacemakers and the other two with bicameral and unicameral chambers. Moreover, 30.5% of the patients (n = 32) only underwent medical therapy. The performed interventions have been listed in Table 2.

5. Discussion

SAC/VAL was included in the HF management guidelines of the European Society of Cardiology in 2016 and in the American Heart Association guidelines in 2017 (18). Since 2018, it has been approved for its use in Honduras. The present study was the first descriptive report regarding the use of SAC/VAL in patients with HFrEF in the Honduran population. The results showed that SAC/VAL was beneficial in reducing LVEF and improving the functional status of HFrEF.

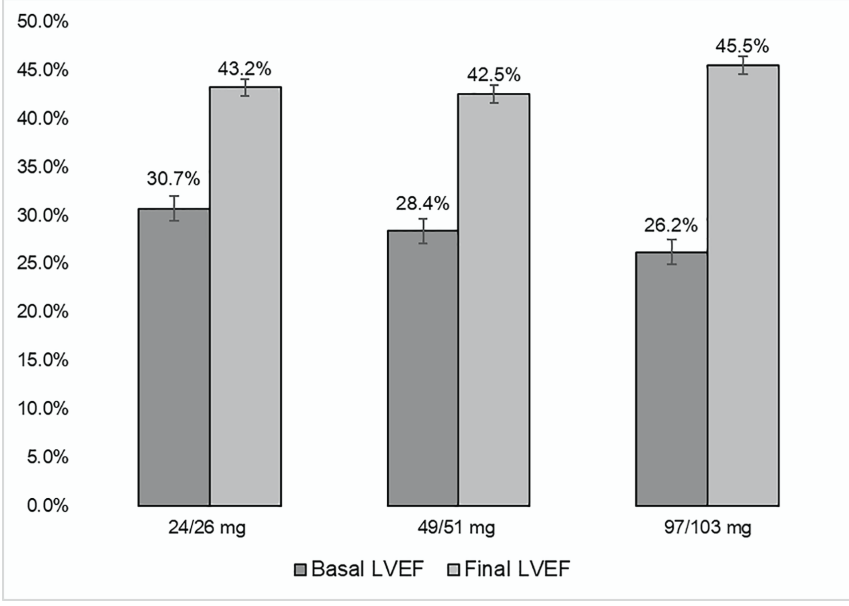
In this study, the predominant comorbidities were hypertension (92.4%), dyslipidemia (61.9%), and type 2 diabetes mellitus (21.9%), which was similar to the PARADIGM-HF study and its Latin American subgroup. Additionally, the leading cause of HF turned out to be ischemic heart disease whose rate was 43% in the PARADIGM-HF study and 41% in the present one (19).

Figure 1. Improvement of Functional Class (NYHA) with the Use of Sacubitril/Valsartan



[a] NYHA, functional classification of heart failure according to the New York Heart Association

Figure 2. Improvement of the Left Ventricular Ejection Fraction after Using Sacubitril/Valsartan



LVEF, left ventricular ejection fraction

In the current investigation, analysis of the NYHA functional class demonstrated that 82.9% of the patients improved after drug therapy. However, 94.3% of the patients had a baseline NYHA functional class III or IV. In the PARADIGM-HF Latin American subgroup, NYHA II predominated with an overall rate of 82%. In the present study, NYHA functional class was worsened in one patient, and degree of cardiomegaly was worsened in 2.9% of the population. Nonetheless, lack of adherence to pharmacological therapy and failure to stop toxic habits made it difficult to attribute this result to the use of SAC/VAL (19). Furthermore, adherence to therapies and the physician-patient relationship were essential to ensure medication compliance and a favorable prognosis.

In the current research, the median of LVEF increased from 30% to 45% after one year of treatment. Almufleh et al. also conducted a study in 2017 and reported similar results after three months of pharmacotherapy Ejection fraction improvement and reverse. American Journal of Cardiovascular Disease (20). This could be justified by the fact that patients with improved LVEF had a better prognosis in terms of long-term survival. As the dose of SAC/VAL was increased in the present study, the results showed that LVEF improved by 12.5% at 24/26 mg, 14.1% at 49/51 mg, and 19.3% at 97/103 mg. It should be noted that the clinical characteristics of each patient should be the fundamental pillar for determining the dose to be used. In the current study, more than half of the patients reached the optimal dose of 97/103 mg of SAC/VAL, which was in agreement with the findings of a Spanish study performed by Fraile et al. in 2018 (21).

Regarding the GFR after SAC/VAL use, the present study findings were in line with those of the retrospective research carried out by Fu-Chih Hsiao et al. in 2019, which revealed no significant change in the GFR (22). Moreover, the median level of NT-ProBNP was 8800 pg/mL at baseline in the current study, which was dramatically higher than 1760 pg/mL reported in the Latin American subgroup of the PARADIGM-HF trial. In addition to the improvement in LVEF and NYHA functional class, the decrease in NT-ProBNP from a median of 8800 pg/mL to 1900 pg/mL at 12 months was a paramount evidence of the decrease in the severity of HF.

The present study had several limitations. First and foremost, the descriptive and retrospective cohort study design did not reveal the causal relationship between different SAC/VAL titrations and the clinical improvement. Secondly, it was a single-center study and the results cannot be generalized to other Honduran populations due to the very diverse ethnic groups throughout the country. Thus, further analytical research is warranted in diverse populations to elucidate if the results are applicable and reproducible in different regions of the country.

This study will help solve the problem of shortage of reports in Honduras, giving physicians in the country and nearby regions access to more accurate information about individuals' behaviors in the face of exposure to SAC/VAL.

5.1. Conclusion

The study findings revealed a significant improvement in both LVEF and NT-ProBNP level after treatment with SAC/VAL. The NT-ProBNP level and NYHA functional class were also higher compared to the Latin American subgroup in the PARADIGM-HF trial. However, no significant changes were observed in the GFR. All in all, the patients who received SAC/VAL showed an overall improvement in their symptoms and quality of life.

5.2. Ethical Approval

EXE-2020-40.

5.3. Informed Consent

The ethics committee of the Universidad Católica de Honduras conducted an approval exempt from informed

consent due to the retrospective nature of the information. CardioCenter has written institutional permission for access and management of the information contained in its clinical records.

5.4. Data Reproducibility

The data presented in this study are openly available in one of the repositories or will be available on request from the corresponding author by this journal representative at any time during submission or after publication. Otherwise, all consequences of possible withdrawal or future retraction will be with the corresponding autor.

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Authors' Contribution

S FR and A RD, diagnosed, treatment, analyzed and interpreted the patients clinical information and conceived the idea, A C and M B wrote the paper, T J coordinated, worked on data collection, T I worked on data collection, S FJ and M R reviewed and edited the final draft. All authors critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript. All authors read and approved the final manuscript.

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The authors have no financial interests related to the material in the manuscript**.**

References

1. Filippatos G, Farmakis D, Alexanian I, Bistola V, Chrysohoou C, Fountoulaki K*, et al.* How to develop a national heart failure clinics network: a consensus document of the Hellenic Heart Failure Association. *ESC Heart Failure*. 2020;**7**(1):15-25.
2. Long B, Koyfman A, Gottlieb M. Diagnosis of Acute Heart Failure in the Emergency Department: An Evidence-Based Review. *Western Journal of Emergency Medicine*. 2019;**20**(6):875-84.
3. Cleland JG, Freemantle N, Daubert J-C, Toff W, Leisch F, Tavazzi L. Long-term effect of cardiac resynchronisation in patients reporting mild symptoms of heart failure: a report from the CARE-HF study. *Heart*. 2008;**94**(3):278-83.
4. Roger VL. Epidemiology of Heart Failure. *Circulation Research*. 2013;**113**(6):646-59.
5. Yandrapalli S, Andries G, Biswas M, Khera S. Profile of sacubitril/valsartan in the treatment of heart failure: patient selection and perspectives. *Vascular health and risk management*. 2017;**13**:369.
6. da Silva PM, Aguiar C. Sacubitril/valsartan: An important piece in the therapeutic puzzle of heart failure. *Revista Portuguesa de Cardiologia (English Edition)*. 2017;**36**(9):655-68.
7. Mills J, Vardeny O, Anker S, al. e. El papel de los inhibidores de neprilisina en la enfermedad cardiovascular. [In Spanish]. *Curr Heart Fail Rep*. 2015;**12**(1):389 - 94.
8. Braunwald E. Heart Failure. *JACC: Heart Failure*. 2013;**1**(1):1-20.
9. Redfield MM. Heart failure with preserved ejection fraction. *New England Journal of Medicine*. 2016;**375**(19):1868-77.
10. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS*, et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European Heart Journal*. 2016;**37**(27):2129-200.
11. Martens P, Beliën H, Dupont M, Vandervoort P, Mullens W. The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction. *Cardiovascular therapeutics*. 2018;**36**(4):e12435.
12. De Vecchis R, Ariano C, Di Biase G, Noutsias M. Sacubitril/valsartan for heart failure with reduced left ventricular ejection fraction. *Herz*. 2019;**44**(5):425-32.
13. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR*, et al.* Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;**371**:993-1004.
14. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Colvin MM*, et al.* 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Journal of the American College of Cardiology*. 2017;**70**(6):776-803.
15. Biglane JB, Becnel MF, Ventura HO, Krim SR. Pharmacologic therapy for heart failure with reduced ejection fraction: closing the gap between clinical guidelines and practice. *Progress in cardiovascular diseases*. 2017;**60**(2):187-97.
16. Khder Y, Shi V, McMurray JJ, Lefkowitz MP. Sacubitril/valsartan (LCZ696) in heart failure. *Heart Failure*. 2016:133-65.
17. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. *Journal of the American College of Cardiology*. 2010;**56**(5):392-406.
18. Morales-Parra MP, Salazar-Niño JF, Caycedo-González LA, González-Torres DV, Jaramillo-Jaramillo M, Buitrago-Sandoval AF*, et al.* Experiencia con sacubitril/valsartán en una clínica de falla cardiaca. *Revista Colombiana de Cardiología*. 2020;**27**(1):7-12.
19. Kristensen SL, Martinez F, Jhund PS, Arango JL, Bělohlávek J, Boytsov S*, et al.* Geographic variations in the PARADIGM-HF heart failure trial. *European heart journal*. 2016;**37**(41):3167-74.
20. Almufleh A, Marbach J, Chih S, Stadnick E, Davies R, Liu P*, et al.* Ejection fraction improvement and reverse remodeling achieved with Sacubitril/Valsartan in heart failure with reduced ejection fraction patients. *American journal of cardiovascular disease*. 2017;**7**(6):108.
21. Rodil Fraile R, Malafarina V, Tiberio López G. Sacubitril–valsartan in heart failure and multimorbidity patients. *ESC heart failure*. 2018;**5**(5):956-9.
22. Hsiao F-C, Wang C-L, Chang P-C, Lu Y-Y, Huang C-Y, Chu P-H. Angiotensin receptor neprilysin inhibitor for patients with heart failure and reduced ejection fraction: real-world experience from Taiwan. *Journal of cardiovascular pharmacology and therapeutics*. 2020;**25**(2):152-7.