Our Experience With Sacubitril/Valsartan in Chronic Heart Failure Management - HFrEF in the Ambulatory Setting

Nabil Naser¹,², Mehmed Kulic³, Zaim Jatic⁴

ABSTRACT

Background: The prevalence of chronic heart failure (CHF) is up to 1-2% of the adult population in developed countries, rising to >10% after the age of 70. Heart failure with reduced ejection fraction (HFrEF) remains a prevalent clinical syndrome associated with significant morbidity and mortality. Objective: The aim of this study was to evaluate the clinical efficacy of sacubitril/valsartan in a group of ambulatory patients with heart failure with reduced ejection fraction (HFrEF) and its effect on the hemodynamic, metabolic, renal, and cardiac remodeling parameters. Methods: From January 2018 to May 2021, 106 patients with chronic heart failure with reduced ejection fraction (HFrEF) were prospectively enrolled. Patients treated with sacubitril/valsartan (ARNI) were compared with an arm of the same size (n = 53) and matched by age and gender who were taking a standard optimal medical therapy for HFrEF. Results: The 106 patients completing the study were characterized by age: 69.5 ± 8.0, 64% are male gender. The mean duration of follow-up in the 2 treatment arms was 12 months. In the ARNI arm, we evaluate the hemodynamic, metabolic, renal, and cardiac remodeling parameters upon the initial evaluation and at the end of the follow-up after 12 months treatment with sacubitril/valsartan. The LVEF values increased significantly (p < 0.001) in the ARNI arm compared to the OMT arm, 42.1 % vs. 30.1%. The LVMI decreased from a baseline value of 153.1 g/m² to 147.8 g/m² with significant improvement only in the arm treated with ARNI. The eGFR values increased significantly (p < 0.001) in the ARNI arm compared to the OMT arm 70.1 vs. 64.9 mL/min/1.73 m². Initiation and titration of sacubitril-valsartan was associated with a reduction in NT-pro-BNP concentration, the values of NT-pro-BNP improved significantly only in the arm treated with ARNI 3107.1 vs. 5678.2. Mortality and re-hospitalization due to HF were lower in the arm treated with ARNI compared to the control (20.3 vs. 32.4 % and 25.3 vs. 46.6 %, respectively; p < 0.05). Conclusion: Sacubitril/valsartan is an important advancement in the treatment of HFrEF. Sacubitril/valsartan induce “hemodynamic recovery”. This study provides real-world data demonstrating incremental improvements in functional and echocardiographic outcomes in optimally treated patients with HFrEF switched to sacubitril/valsartan in ambulatory setting.

Keywords: Sacubitril/Valsartan, Chronic heart failure management, Heart failure with reduced ejection fraction (HFrEF), Ambulatory settings.

1. BACKGROUND

The new universal definition of heart failure indicates that heart failure is not a single pathological diagnosis, but a clinical syndrome consisting of cardiac symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral oedema). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise. The prevalence of chronic heart failure (CHF) is up to 1-2% of the adult population in developed countries, rising to >10% after the age of 70. Heart failure with reduced ejection fraction (HFrEF) remains a prevalent clinical syndrome associated with significant morbidity and mortality. Despite significant advances in heart failure with reduced ejection fraction pharmacotherapy, 5-year mortality remains 50%. The primary goals of treatment include improving functional capacity, quality of life, preventing hospital admissions, and reducing mortality. In 2015, a novel angiotensin receptor- nephriysin inhibitor (ARNI) sacubitril/valsartan was approved by European Medicines Agency (EMA).
and Food and Drug Administration (FDA) to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic HFrEF. Sacubitril/valsartan is recognized as a significant therapeutic advancement and endorsed by international guidelines. PARADIGM-HF is the landmark clinical trial comparing the long-term efficacy and safety of sacubitril/valsartan 97 to 103 mg twice daily to enalapril 10 mg twice daily in over 8,000 patient’s ambulatory outpatients with chronic HFrEF. Current guidelines recommend switching angiotensin converting enzyme inhibitors (ACE-i) or angiotensin receptor blockers (ARBs) to sacubitril/valsartan (ARNI) in stable outpatients affected by heart failure with reduced ejection fraction (HFrEF) who remain symptomatic (Class II-III of the New York Health Association (NYHA) classification) despite being on optimal medical therapy. Sacubitril/valsartan has been shown to improve mortality and reduce hospitalizations in patients with heart failure with reduced ejection fraction (HFrEF).

**2. OBJECTIVE**

The aim of this study was to evaluate the clinical efficacy of sacubitril/valsartan in a group of ambulatory patients with heart failure with reduced ejection fraction (HFrEF) and its effect on the hemodynamic, metabolic, renal, and cardiac remodeling parameters.

**3. PATIENTS AND METHODS**

From January 2018 to May 2021, 106 patients with chronic heart failure with reduced ejection fraction (HFrEF) were prospectively enrolled. PARADIGM HF criteria were applied for patient inclusion. The inclusion criteria for participating in the study were as follows: adult patients with class II–III of the New York Health Association (NYHA) classification despite standard optimal medical therapy (OMT), left ventricle ejection fraction (LVEF) of ≤40%, terminal pro-brain natriuretic peptide (NT-pro-BNP) ≥ 900 pg/mL, estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m², serum potassium <5.2 mmol/L, systolic and/or diastolic BP ≥ 110/70 mmHg. The exclusion

| Items                      | All (N = 106) | OMT (N = 53) | ARNI (N = 53) | P value |
|----------------------------|--------------|--------------|--------------|---------|
| Age (years)                | 69.5 ± 8.0   | 69.3 ± 7.9   | 69.7 ± 8.1   | 0.797   |
| Male gender (%)            | 64           | 65           | 64           | 0.840   |
| Body Mass Index (g/m²)     | 27.1 ± 3.9   | 26.8 ± 3.5   | 27.3 ± 4.4   | 0.519   |
| Systolic blood pressure (mmHg) | 130.9 ± 9.7 | 132.1 ± 9.1 | 129.7 ± 10.4 | 0.209   |
| Diastolic blood pressure (mmHg) | 74.8 ± 9.6 | 75.4 ± 9.5   | 74.3 ± 9.6   | 0.555   |
| Heart rate (bpm)           | 67.9 ± 8.6   | 68.5 ± 8.4   | 67.4 ± 8.8   | 0.512   |
| Creatinine (μmol/L)        | 110 ± 35     | 111 ± 34     | 109 ± 37     | 0.773   |
| eGFR (mL/min/1.73 m²)      | 64.6 ± 23.3  | 64.5 ± 22.6  | 64.8 ± 23.9  | 0.947   |
| Blood glucose (mmol/L)     | 6.3 ± 1.6    | 6.2 ± 1.5    | 6.4 ± 1.3    | 0.522   |
| HbA1c (%)                  | 6.3 ± 1.5    | 6.3 ± 1.7    | 6.4 ± 1.4    | 0.742   |
| Potassium (mmol/L)         | 4.1 ± 0.7    | 4.1 ± 0.5    | 4.0 ± 0.8    | 0.442   |
| NT-pro-BNP (pg/mL)         | 5439.1 ± 3487.9 | 5368.7 ± 3565.5 | 5509.4 ± 3410.4 | 0.836   |
| NYHA Class (%)             |              |              |              |         |
| II                         | 55           | 45.3         | 54.7         | 0.776   |
| III                        | 45           | 46.2         | 53.8         |         |
| Dyslipideamia (%)          | 65.4         | 65.2         | 65.6         | 0.985   |

Table 1. Demographic and general characteristics of patients upon initial assessment, by treatment arms. eGFR: estimated glomerular filtration ratio, HbA1C: glycoside hemoglobin, ACEIs: angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA: mineralocorticoid antagonist; CRT: cardiac resynchronization therapy, ICD: Intracardiac defibrillator.
Tricuspid annular plane systolic excursion.

Table 2. Echocardiographic parameters in all patients and in both OMT and ARNI arms. LVMI: Left ventricle mass index, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; TAPSE: Tricuspid annular plane systolic excursion.

criteria were a history of hypersensitivity or intolerance to ACEI or ARB, history of angioedema, symptomatic hypotension and/or systolic BP < 100 mmHg, serum potassium ≥5.3 mmol/L, eGFR <30 mL/min/1.73 m2, correctable valvulopathy, acute coronary syndrome within < 3 months, recent coronary revascularization within the last 3 months, dementia or inability to cooperate.

Patients treated with Sacubitril/Valsartan (ARNI) were compared with an arm of the same size (n = 53) and matched by age and gender who remained symptomatic despite optimal medical treatment (OMT) at 3 months with ACEI, or ARB (in case of intolerance to ACEI), beta-blocker and MRA. We conducted a complete medical history, physical examination, electrocardiogram, transthoracic echocardiogram, blood analysis including potassium, renal function and NT-pro-BNP for each participant at baseline and during follow-up period. The mean duration of follow-up in the 2 treatment arms was 12 months. Sacubitril/Valsartan (ARNI) therapy was administered in addition to OMT twice a day at different dosages of 50mg, 100mg or 200mg, respectively, after the suspension of the treatment with ACEI or ARB. In detail, for patients taking ACEI therapy, ARNI treatment was administered at least 72h after stopping the ACEI, while in patients taking ARBs, ARNI treatment was administered 36h after stopping the ARB.

The choice of the initial dose of sacubitril/valsartan was based on baseline systolic BP, eGFR, and potassium values. To evaluate the effectiveness and the titration of the ARNI and OMT treatment, the NYHA class and the values of systolic BP, serum potassium and creatinine were analyzed upon the initial visit, at month 1 and 6, and at the end of the follow-up, while NT-pro-BNP and left ventricle EF and cardiac remodeling parameters were assessed upon the initial visit after 6 months and at the end of follow-up in both arms.

Echocardiography represents the key investigation for the assessment of cardiac function. As well as the determination of the LVEF and other important parameters. Transthoracic echocardiography was systematically performed 24-72 h prior to sacubitril/valsartan introduction using a commercially available system (Philips Epic 7, Vivid E9, GE Healthcare) and repeated at the end of follow up period of 12 months after optimal sacubitril/valsartan treatment. Echocardiographic examinations were performed by an experienced sonographer who acquired a complete 2-dimensional (2D) TTE including 4 and 2-chamber apical LV views. We measured LV dimensions (LVEDD, LVESD, IVS, and LVPW) using two-dimensional guided M-mode with the parasternal long axis view at the papillary muscle level, and thereafter the biplane (modified Simpson’s) method to measure LVEDV and LVESV. Left ventricle ejection fraction (LVEF) was estimated by Simpson’s method using the apical four (A4C) and apical two (A2C) chamber views using LV end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) estimates as follows: LVEF = (LVEDV - LVESV)/LVEDV according to guidelines. LV diastolic dysfunction was graded in each patient according to the latest guidelines. Mitral regurgitation was evaluated according to the criteria of the European Association for Cardiovascular Imaging (EACVI). Based on previous studies, an (absolute) improvement in LVEF ≥ 5% was considered to be a significant response to sacubitril/valsartan. All statistical analyses were performed using SAS StatView 5.0” software.

4. RESULTS

Demographic and general characteristics of 106 enrolled patients upon initial assessment, by treatment arms are summarized in Table 1. The 106 patients completing the study were characterized by age: 69.5 ± 8.0, 64% are male gender, 74% of all patients with ischemic heart disease, 61% with arterial hypertension, 56% with chronic kidney disease, ≈40% with chronic obstructive pulmonary disease and ≈37% with diabetes mellitus. eGFR (mL/min/1.73 m2) 64.6 ± 23.3, NT-pro-BNP (pg/mL) 5439.1 ± 3487.9. NYHA Classes: II in 55% and III in 45% of patients. The proportion of patients taking ACEIs or ARBs, diuretics, beta-blockers, mineralocorticoid antagonist, CRT and ICD is shown in Table 1. The Echocardiographic parameters in all patients and in both OMT and ARNI arms are shown in Table 2. The left ventricle mass index (LVMI kg/m2) in all patients was 152.8 ± 11.4, left ventricle ejection fraction (LVEF %) for all patients was 29.0 ± 5.2, mitral regurgitation ≥ II Grade was found in 54%.

In the OMT arm, the patients received the maximum tolerated dose of ACEI or ARBs, MRA and beta blockers. In the patient with chronic HFrEF, the generally
recommended starting dose of sacubitril/valsartan is one 24 mg/26 mg tablet twice daily unless the patient is frankly hypertensive and/or is taking a large dose of ACEi/ARB prior to ARNI initiation. The dose of sacubitril/valsartan should be doubled every 2–4 weeks until the optimal dose of one 97 mg/103 mg tablet twice daily is reached, based on patient tolerability. In the ARNI group the maximal dosage (200 mg) with sacubitril/valsartan was obtained in 41/53 pts (77.4%) and in the resting population studied 12/53 pts (22.6%) the mean dosage was 100 mg a day.

In the ARNI arm, the hemodynamic, metabolic, renal, and cardiac remodeling parameters upon the initial evaluation and at the end of the follow-up after 12 months treatment with sacubitril/valsartan are summarized in Table 3. The LVEF values increased significantly (p < 0.001) in the ARNI arm compared to the OMT arm, 42.1% vs. 30.1%. (Figure 1A). The LVMI decreased from a baseline value of 153.1 g/m2 to 147.8 g/m2 with significant improvement only in the arm treated with ARNI (Figure 1B). The eGFR values increased significantly (p < 0.001) in the ARNI arm compared to the OMT arm 70.1 vs. 64.9 mL/min/1.73 m2. (Figure 1C). Initiation and titration of sacubitril-valsartan was associated with a reduction in NT-pro-BNP concentration, the values of NT-pro-BNP improved significantly only in the arm treated with ARNI 3107.1 vs. 5678.2 (Figure 1D).

The values of systolic and diastolic BP, HbA1c and creatinine decreased in both arms, but more significantly in the arm treated with ARNI compared to the control (117.0 vs. 120.2 and 67.4 vs. 74.5 mmHg, 5.7 vs. 5.9 % and 108 vs. 111.8 μmol/L respectively; p < 0.05).

Mortality and re-hospitalization due to HF were lower in the arm treated with ARNI compared to the control (20.3 vs. 32.4% and 25.3 vs. 46.6%, respectively; p < 0.05). No patient left the study voluntarily or because of the onset of adverse events (Figure 2).

At the final follow-up, 51% of patients in the ARNI treatment arm were taking the 97/103 mg dose of sacubitril/valsartan, 33% the 49/51 mg dose and 17% the 24/26 mg dose.

5. DISCUSSION

Currently, the incidence of HF in Europe is about 3/1000 person-years (all age-groups) or about 5/1000 person-years in adults. The prevalence of HF appears to
be 1-2% of adults. The prognosis of patients with HF has improved considerably since the publication of the first treatment trials a few decades ago. However, it remains poor, and quality of life is also markedly reduced. The improvement in prognosis has been confined to those with HFrEF. Mortality rates are higher in observational studies than in clinical trials. The 1-year and 5-year mortality rates after diagnosis, for all types of HF patients, were 20% and 53%, respectively. According to the recently published universal definition of heart failure, recent ESC and ACC/AHA Guidelines for the diagnosis and treatment of acute and chronic heart failure, patients with HF are classified based on their LVEF in 4 categories: a) HFrEF = heart failure with reduced ejection fraction (LVEF ≤40%); b) HFrEmEF = heart failure with mildly reduced ejection fraction (LVEF 41- 49%); c) HFrpEF = heart failure with preserved ejection fraction (LVEF ≥ 50%), and d) HFimpEF = heart failure with improved EF: HF with a baseline LVEF of ≤40%, and follow-up measurement of LVEF >40% (1-4).

Despite optimal medical therapy with Angiotensin Converting Enzyme Inhibitors (ACE-I) or Angiotensin Receptor Blockers (ARB), Beta-blockers and Mineralocorticoid Receptor Antagonists (MRA), many heart failure patients with reduced ejection fraction (HFrEF) exhibit a residually depressed cardiac function, paralleled by an increased risk for heart failure hospitalization and cardiovascular mortality. In the PARADIGM-HF trial, sacubitril/valsartan, an ARNI, was shown to be superior to enalapril in reducing hospitalizations for worsening HF, CV mortality, and all-cause mortality in patients with ambulatory HFrEF with LVEF ≤40% (changed to ≤35% during the study) (2, 3). Additional benefits of sacubitril/valsartan included an improvement in symptoms and quality of life, a reduction in the incidence of diabetes requiring insulin treatment, and a reduction in the decline in eGFR, as well as a reduced rate of hyperkalaemia. Additionally, the use of sacubitril/valsartan may allow a reduction in loop diuretic requirement (5-10).

Remodeling of the myocardium is central to the progression of HF with reduced ejection fraction (HFrEF), and occurs in response to injury, hemodynamic changes, or neurohormonal activation. Remodeling consists of changes in cardiac geometry, function, or both, reflected by reduced left ventricular ejection fraction (LVEF) and increased LV volumes. Cardiac remodeling is associated with risk for cardiovascular events, including death and hospitalization for HF, and represents an important target for HF therapy (10, 11). Reduction in NT-proBNP during guideline directed medical therapy (GDMT) for HFrEF is associated with reverse LV remodeling (1, 2, 10).

The PROVE-HF study adds information regarding associations between ARNI therapy, change in NT-proBNP, and cardiac remodeling. Reduction in NT-proBNP following treatment with sacubitril-valsartan was associated with an increase in LVEF, and reductions in indexed LV and LA volumes as well as E/e′ ratio (9, 10). In line with these findings, the results of this study suggest that patients with NT-proBNP reduction following ARNI initiation are likely to experience reverse cardiac remodeling. Our study reports on the reverse remodeling response to therapy with sacubitril/valsartan. Importantly, an incremental improvement of ≥ 5% in LVEF was noticed after switching therapy from 1 Class I therapy (ACE-I or ARB) to another Class I therapy (sacubitril/valsartan). Analyses of changes in cardiac remodeling indices demonstrated a significant increase in LVEF and corresponding reduction in LV volumes as early as 6 months; such changes continued to 12 months. Reverse myocardial remodeling manifested by reduced LV size and improved function is central to the benefits of most HF treatments and is associated with an improved prognosis (7-10).

In the published metaanalysis of twenty studies enrolling 10,175 patients by Wang Y et al., ARNI improved functional capacity in patients with HFrEF, including increasing NYHA class and 6 minute walking distance. Moreover, ARNI outperformed angiotensin-converting enzyme inhibitors/angiotensin receptor blockers in terms of cardiac reverse remodeling with striking changes in left ventricular EF, diameter, and volume. Improving in filling pressure, mitral regurgitation degree, pulmonary systolic pressure and LVEF, that is “hemodynamic recovery”, effectively improved NYHA class and quality of life (12, 22).

Pharmacotherapy is the cornerstone of treatment for HFrEF and should be implemented before considering device therapy, and alongside non-pharmacological interventions. There are three major goals of treatment for patients with HFrEF: (i) reduction in mortality, (ii) prevention of recurrent hospitalizations due to worsening HF, and (iii) improvement in clinical status, functional capacity, and quality of life (8-11).

Modulation of the renin-angiotensin-aldosterone (RAAS) and sympathetic nervous systems with angiotensin-converting enzyme inhibitors (ACE-I) or an angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers, and mineralocorticoid receptor antagonists (MRA) has been shown to improve survival, reduce the risk of HF hospitalizations, and reduce symptoms in patients with HFrEF. These drugs serve as the foundations.
of pharmacotherapy for patients with HFrEF. Therefore, it is recommended that an ACE-I or ARB is replaced by sacubitril/valsartan in ambulatory patients with HFrEF, who remain symptomatic despite optimal medical treatment (1-6).

According to the recent 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure, Guide directed medical therapy (GDMT) has expanded to include four classes: a) renin-angiotensin system inhibition (RASi) with angiotensin receptor-neprilysin inhibitors (ARNI), angiotensin-converting enzyme inhibitors (ACEI), or angiotensin (II) receptor blockers (ARB) alone; b) beta blockers; c) mineralocorticoid receptor antagonists (MRA); and d) sodium-glucose cotransporter-2 inhibitors (SGLT2). ARNI is now recommended as first-line RASI to reduce morbidity and mortality in HFrEF (Class of Recommendation 1a). In symptomatic patients with HFrEF who tolerate ACEi or ARB, replacement with ARNI is recommended for further reduction in morbidity and mortality (2). The 2021 ESC published guidelines recommends the use of ARNI as a replacement for ACE-I in suitable patients who remain symptomatic on ACE-I, beta-blocker, and MRA therapies; however, an ARNI may be considered as a first-line therapy instead of an ACE-I - (Class of Recommendation 1B) in reducing the risks of cardiovascular death and hospitalization (1). In addition, a meta-analysis provided evidence that sacubitril/valsartan had fewer drug risks compared with ACEIs/ARBs, such as angioedema, hyperkalemia, cough, dizziness, renal dysfunction and arterial hypotension (6, 7, 10-13).

In order to reduce hospitalizations and mortality, the use of multidisciplinary HF management programmes (HF-MPs), which enable patients to have the correct investigations, an accurate diagnosis, appropriate evidence-based therapy, education, and suitable follow-up (16, 17). Adequate patient self-care is essential in the effective management of HF and allows patients to understand what is beneficial, and to agree to self-monitoring and management plans. HF patients who report more effective self-care have a better quality of life, lower admission rates, and reduced mortality (17, 18, 21). Patients with HF, even if symptoms are well controlled and stable, require follow-up to ensure continued optimization of therapy, to detect asymptomatic progression of HF or its comorbidities and to discuss any new advancements in care. The new guidelines recommend follow-up at intervals no longer than 6 months to check symptoms, heart rate and rhythm, BP, full blood count, iron, electrolytes, and renal function (1-8).

6. CONCLUSION

This study provides real-world clinical practice data demonstrating incremental improvements in functional and echocardiographic outcomes in optimally treated patients with HFrEF switched to sacubitril/valsartan. Sacubitril/valsartan is an important advancement in the treatment of HFrEF. Sacubitril/valsartan induce “hemodynamic recovery”. The efficacy of sacubitril/valsartan in the treatment of HF can be summarized in the following 7 key perspectives: reduction in the risks of mortality and hospitalization, reversal of cardiac remodeling, regulation of biomarkers of HF, improvements in NYHA class, improvement of quality of life, improvement of renal function and regulation of metabolism in HF patients.

• Patient Consent Form: All participants were informed about subject of the study.
• Author’s contribution: A.D.B. gave substantial contributions to the conception and design of the work. A.D.B., V.K., I.S., S.B and A.B gave substantial contribution to acquisition of data. A.D.B., T.D., Z.V.A. and A.B gave substantial contribution to analysis and data interpretation. A.D.B., V.K., I.S. and S.B. had a part for drafting the article. A.D.B., T.D., Z.V.A gave substantial contribution in critically revising and approval final version to be published.
• Conflicts of interest: There are no conflicts of interest.
• Financial support and sponsorship: None.

REFERENCES

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A. et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21; 42(36): 3599-3726. doi: 10.1093/ eurheartj/ehab368.

2. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Dzau VR, Dzau VR, Evers L et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. null2022,0(0). doi.org/10.1016/j.jacc.2021.12.011.

3. Bozkurt B, Coats AJ, Tsuttsui H, Abdelhamid M, Adamopoulos S, Albert Net al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail. 2021 Mar 1; 27(3): 205-210. doi: 10.1016/j.cardfail.2021.01.022.

4. Bozkurt B, Hersberger RE, Butler J, Grady KL, Heidenreich PA, Issler ML et al. ACC/AHA Key Data Elements and Definitions for Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Heart Failure). J Am Coll Cardiol. 2021 Apr 27; 77(16): 2053-2150. doi: 10.1016/j.jacc.2020.11.012.

5. Li B, Zhao Y, Yin B, Helian M, Wang X, Chen F, Zhang H, Sun H, Meng B, An F. Safety of the neprilysin/renin-angiotensin system inhibitor LCZ696. Oncotarget. 2017 May 31; 8(47): 83323-83333. doi: 10.18632/ oncotarget.18312.

6. Huang Y, Zhang Y, Ma L, Zhou H, Fang C, Chen C. Adverse Events of Sacubitril/Valsartan: A Meta-analysis of Randomized Controlled Trials. J Cardiovasc Pharmacol. 2021 Aug 1; 78(2): 202-210. doi: 10.1097/ FJC.0000000000001049.

7. McMurray JJ, Packer M, Desai AS, Gong J et al. Baseline characteristics and treatment of patients in prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). Eur J Heart Fail. 2014 Jul 16(7): 817-825. doi: 10.1002/ejhf.115.

8. Solomon S, Clandgett B, Packer M, et al. Efficacy of Sacubitril/Valsartan Relative to a Prior Decompensation:The PARADIGM-HF Trial. J Am Coll Cardiol. 2016 Oct 4(10): 816-822. doi: 10.1016/j.jchf.2016.05.002.

9. Murphy S, Prescott M, Camacho A, et al. Atrial Natriuretic Peptide and
Treatment With Sacubitril/Valsartan in Heart Failure With Reduced Ejection Fraction. J Am Coll Cardiol HF. 2021 Feb; 9(2): 127-136. doi: org/10.1016/j.jchf.2020.09.013.

10. Januzzi JL, Prescott MF, Butler J, et al. 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(11): 1085-1095. doi: 10.1001/jama.2019.12821.

11. Daubert MA, Adams K, Yow E, et al. NT-proBNP goal achievement is associated with significant reverse remodeling and improved clinical outcomes in HFREF. JACC Heart Fail. 2019; 7(2): 158-168. doi: 10.1016/j.jchf.2018.10.004.

12. Wang Y, Zhou R, Lu C, Chen Q, Xu T, Li D. Effects of the Angiotensin-Nephrin-Nephrin Inhibitor on Cardiac Reverse Remodeling: Meta-Analysis. J Am Heart Assoc. 2019 Jul 2; 8(13): e012272. doi: 10.1161/ JAHA.119.012277.

13. Damk W, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz M, Prescott MF, Shi VC, Rouleau JL, Swedberg K, Zile MR, Packer M, Desai AS, Solomon SD, McMurray Jv. Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. JACC Heart Fail. 2018; 6: 489-498.

14. Desai AS, Vardeny O, Claggett B, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Zile MR, Lefkowitz M, Shi V, Solomon SD. Reduced risk of hyperkalemia during treatment of heart failure with mineralocorticoid receptor antagonists by use of sacubitril/valsartan compared with enalapril: a secondary analysis of the PARADIGM-HF Trial. JAMA Cardiol. 2017; 2: 79-85.

15. Gheorghiade M, Shah AN, Vadugananathan M, Butler J, Bonow RO, Rosano GM, et al. Recognizing hospitalized heart failure as an entity and developing new therapies to improve outcomes: academics', clinicians', industry's, regulators', and payers' perspectives. Heart Fail Clin. 2013 Jul; 9(3): 285-290, v-vi. doi: 10.1016/j.hfc.2013.05.002.

16. Anker SD, Schroeder S, Atar D, Bax JJ, Cecconi C, Cowie MR, Crisp A, Dominjon F et al. Traditional and new composite endpoints in heart failure clinical trials: facilitating comprehensive efficacy assessments and improving trial efficiency. Eur J Heart Fail. 2016; 18: 482-489.

17. Gayat E, Arrigo M, Littnerova S, Sato N, Parenica J, Ishihara S, Spinaj J, Muller C, et al. Heart failure oral therapies at discharge are associated with better outcome in acute heart failure: a propensity-score matched study. Eur J Heart Fail. 2018; 20: 345-354.

18. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, et al. Heart Failure Association (HFA) of the European Society of Cardiology (ESC). European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. Eur J Heart Fail. 2016 Jun; 18(6): 613-625. doi: 10.1002/ejhf.566.

19. Martens P, Belièn H, Dupont M, Vandervepoort M, Mullens W. The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction. Cardiovase Ther. 2018 Aug;36(4):e12435. doi: 10.1111/1755-5922.12435.

20. Wachtler R, Senni M, Belohlavek J, Strabuzynska-Migaj E, Witte KK et al. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. Eur J Heart Fail. 2019 Aug;21(8):998-1007. doi: 10.1002/ejhf.1498.

21. Naser N. Clinical Implications of Functional Mitral Regurgitation Severity in Patients With Heart Failure With Reduced Ejection Fraction (HF-REF). Med Arch. 2022; 76(1): 17–22. doi: 10.5455/medarch.2022.76.17-22.

22. Romano G, Vitale G, Ajello L, Agnese V, Bellavia D, Caccamo G, Corrado E et al. The Effects of Sacubitril/Valsartan on Clinical, Biochemical and Echocardiographic Parameters in Patients with Heart Failure With Reduced Ejection Fraction: The "Hemodynamic Recovery". J Clin Med. 2019 Dec; 8(12):2165. doi: 10.3390/jcm8122165.

23. Seforovic JP, Claggett B, Seidellmann SB, Seely EW, Packer M, Zile MR, Rouleau JL, Swedberg K, Lefkowitz M, Shi VC, Desai AS, McMurray Jv, Solomon SD. Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial. Lancet Diabetes Endocrinol 2017;5:333-340.

24. Naser N, Kulic M, Dolic M, Dzubur A, Durak A, Pepic E, Smajic E, Krusic Z. The Cumulative Incidence of Stroke, Myocardial infarction, Heart Failure and Sudden Cardiac Death in Patients with Atrial Fibrillation. MEDARCH. 2017 OCT; 1(5): 316-319. doi: 10.5455/medarch.2017.1.316-319.

25. Yandrapalli S, Khan MH, Rochlani Y, Aronov WS. Sacubitril/valsartan in cardiovascular disease: evidence to date and place in therapy. Ther Adv Cardiovasc Dis. 2018 Aug;12(8):217-231. doi: 10.1177/1759944718784536.

26. Naser N, Dzubur A, Kulic Z, Kovacevic K, Kulic M, Sokolovic S, Terzic I, Haxhibeqiri-Karabdic I, Hondo Z, Brdzanovic S, Miseljic S. Echo-cardiographic Assessment of Ischemic Mitral Regurgitation, Mechanism, Severity, Impact on Treatment Strategy and Long Term Outcome. Acta Inform Med. 2016 JUN; 24(3): 172-177. doi: 10.5455/aim.2016.24.172-177.

27. Masic I, Naser N, Zildzic M. Public Health Aspects of COVID-19 Infection With Focus on Cardiovascular Diseases. Mater Sociomed. 2020 Mar; 32 (1): 71-76. DOI: 10.5455/msm.2020.32.71-76.

28. Masic I, Hadziahmetovic M, Donev D, Polhhozani A, Ramadani N, Skoplak A, Pasagic A, Roshi E, Zunic L, Zildzic M. Public health aspects of the family medicine concepts in South eastern europe. Mater Sociomed. 2020 Mar; 32 (1): 71-76. DOI: 10.5455/msm.2020.32.71-76.

29. McDonagh TA, Blue L, Clark AL, Dahlstrom U, Ekmann I, Lainscak M et al. European Society of Cardiology Heart Failure Association Standards for delivering heart failure care. Eur J Heart Fail. 2011 Mar;13(3):235-241. doi: 10.1093/eurjhf/hfq221.

30. Jonkman NH, Westland H, Groenwold RH, Ageren A, Anguita M, Blue L et al. What Are Effective Program Characteristics of Self-Management Interventions in Patients With Heart Failure?: An Individual Patient Data Meta-analysis. J Card Fail. 2016 Nov;22(11):861-871. doi: 10.1016/j.cardfail.2016.06.422.

31. Riegel B, Bennett JA, Davis A, Carlton B, Montague J, Robin H, Glaser D. Cognitive impairment in heart failure: issues of measurement and etiology. Am J Crit Care 2002;11:520-528.

32. Felker GM, Anstrom KJ, Adams KE, Ezekowitz JA, Fiuza M, Houton-Miller N, Januzzi JL Jr, Mark DB, Pita IL, Passmore G, Whellan DJ, Yang H, Cooper LS, Leifer ES, Desvigne-Nickens P, O’Connor CM. Effect of Natriuretic Peptide-Guided Therapy on Hospitalization or Cardiovascular Mortality in High-Risk Patients With Heart Failure and Reduced Ejection: A Randomized Clinical Trial. JAMA. 2017 Aug 22;318(8):713-720. doi: 10.1001/jama.2017.10565.

33. Seforovic JP, Claggett B, Seidellmann SB, Seely EW, Packer M, Zile MR et al. Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post hoc analysis from the PARADIGM-HF trial. Lancet Diabetes Endocrinol 2017;5:333–340

34. Solomon SD, Vadugananathan M, Claggett B, Packer M, Zile M et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. Circulation 2019;141(5):352–361

35. Ganesanathan S, Shah N, Shah P, Elsayed H, Phillips J, Parkes A, Morgan A, Yousef Z. Real-world treatment switching to sacubitril/valsartan in patients with heart failure with reduced ejection fraction: A cohort study. Open Heart. 2020 Oct;7(2):e001305. doi: 10.1136/openhrt-2020-001305.