Thi-Qar Medical Journal (TQMJ): Vol. (27), No. (1), 2024
Web Site: https://jmed.utq.edu Email: utjmed@utq.edu.iq
ISSN (Print):1992-9218 ISSN (Online): 3006-4791

Evaluation of Sacubitril-Valsartan for Heart Failure in Thi-Qar Patients/ Iraq

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Abstract

Background:

Heart failure is known as defect in blood ejection from heart attained from structural or functional cardiac disorders which lead in impairment in the ability of the ventricle to fill with or eject blood, ended with complex clinical syndrome with significant symptoms and clinical signs[1,2]. HF influences 23-26 million patients globally.[4,5] Ischemic heart disease, myocardial infarction, hypertension, and valvular heart disease considered as the major reasons of heart failure .The combination of an angiotensin II receptor antagonist and a neprilysin inhibitor is a novel choice in heart failure management.[17]

Patients and Methods:

This is an interventional study which has been performed in the Teaching Cardiac Center in Thi-Qar Governorate in Nasiriyah city in Iraq. All participants are patients who either recently diagnosed as heart failure (6 months to 1 year) or diagnosed since (1 to 3 years). Key criteria for the study has been involved socio-demographic characteristics as age (years) (40-60 or more than 60), Body Mass Index(BMI), educational level of patients, occupation, history of tobacco smoking or alcohol intake, the history of co-morbidities as Atrial fibrillation (AF), Diabetes Mellitus (DM) (types I and II), Dyslipidemia, Chronic kidney disease(CKD) and Chronic obstructive pulmonary disease(COPD).

Results:

The number of both genders is equal in my study. After 6 weeks follow up period from starting to take ARNI, (27.02%) of them improved regarding EF. About (72.98%) from them had initial increment in ejection fraction by about (4 -8%). Good prognosis regarding vital signs and symptoms of heart failure were remarkable.

Conclusion:

- Chronic symptomatic patients with HFrEF (NYHA class II or III) who tolerate an ACEI or ARB can be changed safely to sacubitril/valsartan (ARNI), to obtain additional decreases in morbidity and mortality.

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- The main barrier that prevents cardiologists in Thi Qar to prescribe ARNI is the cost of the drug because most of the Iraqi patients are unable to buy this expensive medication.

Recommendations:

1-All patients with HFrEF (NYHA class II - III) should receive ARNI.

2-This medication should be provided in all Iraqi hospitals and Cardiac centers because this drug is very expensive and patients may not be able to buy it.

3-Explaining the concept of the medication related burden and further studies are recommended to include adherence assessment of patients toward treatment.

Key words: Heart failure; Angiotensin Receptor-Neprilysin Inhibitor (ARNI); Sacubitril/Valsartan(ARNI); ejection fraction.

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Introduction:

1. Definition of Heart Failure

Heart failure (HF) is defined as any impairment in the cardiac blood ejection arises from disorders in the structure or functions of heart that results in impair the ability of the different to fill with or eject blood, leads to a complicated clinical syndrome with typical symptoms and clinical signs. It's the final stage of multi cardiovascular diseases e.g., coronary artery disease (CAD), arterial hypertension, previous myocardial infarction(MI) and dilated cardiac myopathy (DCM) and still one of the main causes of hospitalization. [1,2,3]

2. Epidemiology of Heart Failure

HF influences 23-26 million patients globally. Its prevalence is estimated to increase by 25% during the next decade and the 5 years' survival likelihood is only 50 percent and is one of the leading causes of hospital admission and death in elderly people. [4,5,11]. In the previous ten years HF recorded as a global pandemic condition with a growing impact on public health, affecting approximately 1–2% of the adult population in developed countries that causes global burden for health-care systems as its coasty condition[6,7,8]. Many patients worldwide are affected by HF, that is associated with high 5-years mortality rates (45%–60%) and recurrent and prolonged hospitalizations.[9,10]

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3. Etiology and Risk Factors of Heart Failure

As noted that the most clinical reasons of HF involve ischemic heart disease (IHD) , (MI), hypertension, and valvular heart disease (VHD). Another possible causes as familial or genetic cardiomyopathies; amyloidosis; cardiotoxicity with cancer or other treatments or substance abuse such as alcohol, cocaine, or methamphetamine; tachycardia, right ventricular pacing or stress-induced cardiomyopathies; peripartum cardiomyopathy; myocarditis; autoimmune causes, sarcoidosis; iron overload, including hemochromatosis; and endocrine metabolic defects as thyroid disease and other nutritional causes may be involved.[12]

4. Pathophysiology of Heart Failure

The complexity in pathophysiology of this syndrome is logical issue due to it incorporates the activation of both the sympathetic nervous system (SNS) and renin angiotensin-aldosterone system (RAAS) to preserve both cardiac output and organ perfusion[13,14.] When SNS is activated, this causes both positive inotropic and chronotropic effects to ensure blood supply to the vital organs and this considered as fastest accommodative responding in HF. The overactivation of SNS results in negative effects, as epinephrine cardiomyocytes direct toxicity, ended with cardiomyocytes hypertrophy and apoptosis. At the same time (RAAS) is also activated to maintain hemodynamic stability leads to sodium and water retention, vasoconstriction and hypertension, elevated aldosterone levels and sympathetic tone, fibrosis and eventually cardiac remodeling and hypertrophy. On the other side, the natriuretic peptide (NP) system in HF patients is also stimulated as endogenous compensatory mechanism to counteract RAAS. The net result is further aggravation of sodium retention, vasoconstriction, and volume overload which can seriously affect long-term prognosis. The end effects are further changes in the left ventricular chamber geometry and left ventricular remodeling. The heart cannot pump enough blood to meet the body's requirements, and thus, there is a disruption in metabolic and functional processes[3]. Since NPs are degraded by the enzyme neprilysin, is an endopeptidase that breakdown endogenous vasoactive peptides, including NP, bradykinin, and adrenomedullin. This concept of neprilysin inhibition could be an important therapeutic target in HF. [15,16].

5. Interesting role of Angiotensin Receptor-Neprilysin Inhibitor (ARNI) in Heart Failure Treatment

The combination of an angiotensin II receptor antagonist and a neprilysin inhibitor is a new influent in HF management.[17] Sacubitril/Valsartan, a first-in-class angiotensin receptor-neprilysin inhibitor (ARNI). Sacubitril, the first neprilysin inhibitor; converted to

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Sacubitrilat by esterase and regulates the NP system by inhibits the degradation of brain natriuretic peptides(BNP) leading to increases the level of BNP. The final results are vasodilation, sodium excretion and improvement of cardiac remodeling as shown in Figure 1[19]. Combination of Sacubitril with ARB Valsartan has high proved efficacy and tolerability among HF patients.[18] Treatment with Sacubitril/Valsartan was related with more reductions in loop diuretic dose and fewer increases in dose compared with Enalapril, proposing that the treatment with Sacubitril/Valsartan may reduce the requirement for loop diuretics relative to Enalapril in patients with heart failure with reduced ejection fraction(HFrEF).[20]

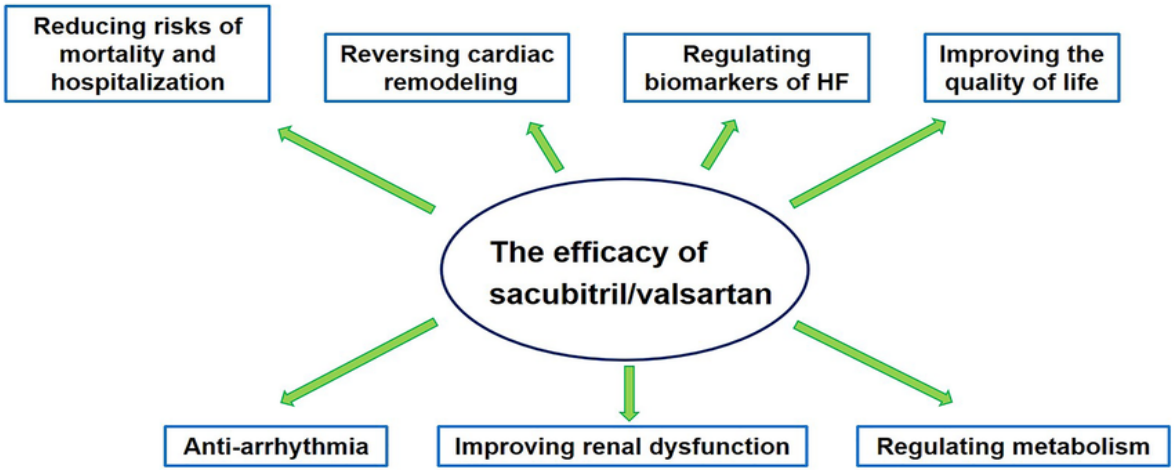

Figure 1. The efficacy of Sacubitril/Valsartan in the treatment for HF patients.[19]

6. Method

Study Design

This is interventional study has been performed in Teaching Cardiac Center in Thi-Qar governorate-Nasiriyah city in Iraq. 50 patients has been enrolled in the study. All participants are patients who either recently diagnosed as HF (6 months to 1 year) or diagnosed since (1 to 3 years). PARADIGM-HF trial explained the impact of the Sacubitril/ Valsartan on CV mortality and HF hospitalizations in patients with left ventricular ejection fraction (LVEF) 40% and NYHA functional classes II to IV HF with that of Enalapril [21]. Key criteria for the study has been involved socio-demographic characteristics as age (years) (40-60 or more than 60), (BMI), educational level of patients, occupation, history of tobacco smoking or alcohol intake, the history of co-morbidities as (AF), (DM) (types I and II), Dyslipidemia, (CKD) and (COPD). Etiologies of HF have been checked as CAD (eg, MI or ischemia), cardiomyopathy, Hypertension or multifactorial .Symptoms as

exertional dyspnea, , orthopnea , shortness of breath (SOB) , paroxysmal nocturnal dyspnea , exercise intolerance and weakness have been noted .Assessment of medications history, vital parameters as systolic blood pressure(SBP), diastolic blood pressure(DBP), pulse rate ,respiratory rate , and hemoglobin(HB),red blood cells (RBCs) ,white blood cells (WBCs) ,platelets count have been recorded. Parameters related to administration of Sacubitril/Valsartan as assess blood pressure (BP), blood urea nitrogen (BUN), creatinine, estimated glomerular function (eGFR), electrolytes as serum potassium and sodium in addition to N-terminal ProBrain Natriuretic Peptide (NT-Pro BNP) and C-reactive protein (CRP) also have been checked. All data have been estimated at baseline and after initiation by about 6 weeks. The exclusion criteria for this study have been pregnant patients, those with ages less than 18 and more than 80 years old, patients with hyperkalemia or reduced $_e$GFR and patients who are intolerable to ARNI due to prominent hypotension.

7.Results and Discussion

The study recruited 50 patients with HF attained to the Teaching Cardiac Center in Thi-Qar governorate-Nasiriyah city in Iraq. About half of the patients (59.45%) were males and the others (40.55%) were females. The patients were adults with average age of (55 ±20) years. The majority either illiterate (40.54%) or had primary school (86.48%) degrees. Most of patients are living in urban areas (80%). The (79%)of patients had previous history of smoking and (8%) of them are still active smokers. No one was alcohol drinkers. (27.02%) have history of hypertension since about 4-9 years. (43%) have previous history of percutaneous coronary intervention (PCI) and correspondingly (8%) had been exposed to coronary artery bypass grafting (CABG). (40.54 %) of patients with history of diabetes mellitus type 2. (62.16%) of total patients with ischemic heart disease(IHD) and (27.02 %) diagnosed by cardiologists with dilated cardiac myopathy (DCM). (24.32%) have been found with atrial fibrillation(AF). From the all patients (10.81 %) have history of thyroid gland disorders. Only (2.7 %) have a history of malignancy and the same percent to describe those with pulmonary hypertension (PHT) or asthma. (67.56%), (32.44%) represent NYHA classII and classIII at base line respectively. (86.48%), (13.52%) of total percent of patients had Heart Failure with reduced Ejection Fraction(HFrEF) and Heart Failure with mildly reduced Ejection Fraction(HFmrEF) respectively. After 6 weeks follow up period from starting to take ARNI,(27.02%) of them had been Heart Failure with improved Ejection Fraction (HFimpEF). About (72.98%) of them have initial increase in ejection fraction(EF) by about (4 -8%).Good prognosis regarding to HF signs and symptoms as remarkable disappearance of dyspnea, particularly on exertion, orthopnea, shortness of breath (SOB), Paroxysmal nocturnal dyspnea, exercise intolerance and weakness. Also decreasing in some biomarkers as NT-Pro BNP and CRP to some extents. Also it has been found that decrease in rate of hospitalization by about 50%.

8-Recommendations and Conclusion

According to the results obtained from the patients, we can conclude that chronic symptomatic patients with HFrEF (NYHA class II or III) who tolerate an ACEI or ARB can be switched to Sacubitril/Valsartan(ARNI), to further reduce in morbidity and mortality. The new HF guidelines[22] now recommend ARNI in patients with HFpEF and HFmrEF. The main barrier that prevents cardiologists in Thi Qar, Iraq from prescribe ARNI is the cost of the drug so that most of the Iraqi patients unable to buy it. Another issue is the tolerability to the side effects of ARNI represented by hypotension especially in those with ages more than 65 years old. Encourage all HF patients to continue to take ARNI , involvement cost-effectiveness study for ARNI and adopt suitable interventional strategies to ensure providing drug to all patients who deserve . Explaining the concept of the medication related burden and further studies are recommended to include adherence assessment of patient toward treatment.[23]

9- References

1-Wilson S Colucci, MD (https://www.uptodate.com/contents/heart-failure-clinical-manifestations-and-diagnosis-in-adults/contributors .Heart failure: Clinical manifestations and diagnosis in adults .

2-Amir Hossein Behnoush , Amirmohammad Khalaji , Nasim Naderi and others.ACC/AHA/HFSA 2022 and ESC 2021 guidelines on heart failure comparison

3-Navya Sakhamuri , Sreekartthik Athiyaman , Bhawna Randhi and other. Sacubitril/Valsartan in Heart Failure Hospitalization: Two Pills a Day to Keep Hospitalizations Away? .

4-H K Chopra, G S Wander, Tiny Nair and others .Angiotensin Receptor-Neprilysin Inhibitor Therapy and Cardiac Remodeling in Heart Failure: Consensus Statement from India.

5-Joana Cabral, Henrique Vasconcelos, Paulo Maia-Araújo and others. Sacubitril/valsartan in everyday clinical practice: an observational study based on the experience of a heart failure clinic

6-Michel Komajda, Stefan D. Anker, Martin R. Cowie and others. Physicians' adherence to guidelinerecommended medications in heart failure with reduced ejection fraction: data from the QUALIFY global survey.

7-Helena Norberg,Ellinor Bergdahl and Krister Lindmark.Eligibility of sacubitril–valsartan in a real-world heart failure population: a community-based single-centre study.

8-Paul A. Heidenreich, Biykem Bozkurt, Vice ChairDavid Aguilar, Larry A. Allen and others. 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.

9-Sashiananthan Ganesananthan , Nisar Shah, Parin Shah and others. Real- world treatment switching to sacubitril/valsartan in patients with heart failure with reduced ejection fraction: A cohort study .

10-Lindsey R. Sangaralingham,Jeson Sangaralingham,Nilay D. Shah, PhDXiaoxi Yao and others. Adoption of Sacubitril/Valsartan for the Management of Patients With Heart Failure.

11-Speranza Rubattu & Filippos Triposkiadis. Resetting the neurohormonal balance in heart failure (HF):the relevance of the natriuretic peptide (NP) system to the clinicalmanagement of patients with HF.

12-Mingsong Zhang , Yifei Zou , Yangxue Li and others. The history and mystery of sacubitril/valsartan: From clinical trial to the real world.

13- Domingo Pascual, Antoni Bayé, Paola Beltrán and others . Sacubitril-Valsartan, Clinical Benefits and Related Mechanisms of Action in Heart Failure With Reduced Ejection Fraction.

14-Daisuke Usuda, Toshihiro Higashikawa, Yuta Hotchi and others. Angiotensin receptor blocker neprilysin inhibitors .

15-Chan Soon Park, Jin Joo Park, Alexandre Mebazaa and others .Characteristics, Outcomes, and Treatment of Heart Failure With Improved Ejection Fraction.

16-Nicolò Ghionzoli, Francesco Gentile , Anna Maria Del Franco and others. Current and emerging drug targets in heart failure treatment.

17-Massimo F. Piepoli, Rizwan I. Hussain, Josep Comin-Colet and others .OUTSTEP-HF: randomised controlled trial comparing short-term effects of

18-Scott D. Solomon, Brian Claggett, Milton Packer Efficacy of Sacubitril/Valsartan Relative to a Prior Decompensation The PARADIGM-HF Trialand others .

19- Mehmet Kış, Oktay Şenöz2, Tuncay Güze and others . The Relationship Between N-Terminal Pro-Brain Natriuretic Peptide Level and LeftVentricular Metabolic Index inPatients with Heart Failure with Mildly Reduced Ejection Fraction .

20-Andrea Di Lenarda , Gabriele Di Gesaro , Filippo Maria Sarullo and others . Sacubitril/Valsartan in Heart Failure with Reduced Ejection Fraction: Real World Experience from Italy (the REAL.IT Study) .

22-Abdelfatah A. Elasfar , Waleed Alhabeeb , Salma Elasfar and others .Heart Failure in the Middle East Arab Countries: Current and Future Perspectives .

23-Pia M. Schumacher , Nicolas Becker, Ross T. Tsuyuki and others. The evidence for pharmacist care in outpatients with heart failure: a systematic review and meta-analysis .