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

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Abstract

Background:

Heart failure (HF) is defined as any structural and/or functional impairment of cardiac blood ejection raised from a structural or functional cardiac disorders that impair the ability of the ventricle to fill with or eject blood, leads to a complex clinical syndrome with typical symptoms and clinical signs[1,2]. HF influences 23-26 million patients globally.[4,5] The major causes of HF include ischemic heart disease (IHD) ,myocardial infarction (MI), hypertension, and valvular heart disease (VHD). The association of an angiotensin II receptor antagonist and a neprilysin inhibitor is a new actor in HF management.[18]

Patients and Methods:

This is an observational analytical Cohort 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%) of them had initial increament in ejection fraction by about (4 -8%). Good prognosis regarding 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 switched safely to sacubitril/valsartan (ARNI), to further reduce morbidity and mortality.
- 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 structural and/or functional impairment of cardiac blood ejection raised from a structural or functional cardiac disorders that impair the ability of the ventricle to fill with or eject blood, leads to a complex clinical syndrome with typical symptoms and clinical signs[1,2]. It is the end stage of various cardiovascular diseases (e.g., coronary artery disease, hypertension, previous myocardial infarction and dilated cardiac myopathy) and still one of the main causes of hospitalization. [1,3]

2. Epidemiology of Heart Failure

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

3. Etiology and Risk Factors of Heart Failure

The major causes of HF include ischemic heart disease (IHD) ,myocardial infarction (MI), hypertension, and valvular heart disease (VHD). Other causes can include familial or genetic cardiomyopathies; amyloidosis; cardiotoxicity with cancer or other treatments or substance abuse such as alcohol, cocaine, or methamphetamine; tachycardia, right ventricular (RV) pacing or stress-induced cardiomyopathies; peripartum cardiomyopathy; myocarditis; autoimmune causes, sarcoidosis; iron overload, including hemochromatosis; and thyroid disease and other endocrine metabolic and nutritional causes.[12]

4. Pathophysiology of Heart Failure

(HF) is complex pathophysiological and clinical syndrome[13], involving activation of the sympathetic nervous system (SNS) and the renin angiotensin-aldosterone system (RAAS) to maintain cardiac output and organ perfusion[14] .Activation of the sympathetic nervous system is the fastest adaptive response mechanism in HF leading to positive inotropic and chronotropic effects that maintain perfusion of vital organs through blood redistribution. The renin-angiotensin aldosterone (RAAS) system is also activated to maintain hemodynamic stability. However, over-activated sympathetic nerves can have negative effects, such as direct toxicity of epinephrine to cardiomyocytes, and inducing cardiomyocyte hypertrophy and apoptosis. Activation of the RAAS system leads to sodium and water retention, vasoconstriction and hypertension, elevated aldosterone levels and sympathetic tone, fibrosis and eventually cardiac remodeling and hypertrophy . In addition, the reduced effectiveness of the natriuretic peptide (NP) system in HF patients can further aggravate sodium retention, vasoconstriction, and volume overload which can seriously affect long-term prognosis. [15,16] An endogenous compensatory mechanism, the natriuretic peptide (NP) system is also activated, although insufficiently to counteract the RAAS effects. Since NPs are degraded by the enzyme neprilysin, is an endopeptidase that breakdown endogenous vasoactive

peptides, including NP, bradykinin, and adrenomedullin. It was assumed that its inhibition could be an important therapeutic target in HF.[16] The final result of this imbalance is an over activation of the sympathetic nervous system (SNS), initially aimed at restoring the circulatory homeostasis. Chronic stimulation of SNS causes a systemic spill-over of catecholamines, attributed to their increased release and reduced reuptake, and to an excessive intra-myocardial production.[17] Regarding the mechanism of HF, vasoconstriction and fluid retention are caused by the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS), and the natriuretic peptides (NPs) secreted by the myocardium, which is itself both volume- and pressure-overloaded, promote vasodilation and diuresis [18] .There is a significant loss of balance between sympathetic and parasympathetic afferent systems. Blunting of baroreflex occurs in association with hyperactive chemo and ergo reflexes. The final result of this imbalance is an overactivation of the sympathetic nervous system (SNS)[19]. This process has adverse effects in the long term. Myocyte biology alters with the induction of cardiomyocyte apoptosis and necrosis, finally leading to myocardial fibrosis. The end effects are further changes in the left ventricular chamber geometry and left ventricular remodeling. Providing optimal blood flow to the organs is pivotal function of the heart. In these patients, the heart cannot pump enough blood to meet the body's requirements, and thus, there is a disruption in metabolic and functional processes. [3]

Table (1) Criteria for Heart failure classification [2]

Type Of HF	ACC/AHA/HFSA Criteria	ESC Criteria
Hfref	**LVEF ≤ 40%**	**LVEF ≤ 40%**
Hfimpef	**Previous LVEF ≤ 40% And Follow-Up LVEF > 40%**	**N/A**
Hfmref	**LVEF 41%–49% And Evidence Of Spontaneous Or Provokable Increased LV Filling Pressures**	**LVEF 41%–49%**
Hfpef	**LVEF ≥ 50% And Evidence Of Spontaneous Or Aggravating Increased LV Filling Pressures**	**LVEF ≥ 50% And Objective Evidence Of Cardiac Structural And/Or Functional Abnormalities Consistent With The Presence Of LV Diastolic Dysfunction/Raised LV Filling Pressures, Including Raised Natriuretic Peptides**

HF, heart failure; HFimpEF, heart failure with improved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; N/A, not available.

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

The association of an angiotensin II receptor antagonist and a neprilysin inhibitor is a new actor in HF management.[18] Sacubitril/valsartan, a first-in-class angiotensin receptor-neprilysin inhibitor (ARNI).[20] Sacubitril, the first neprilysin inhibitor; converted to sacubitrilat by esterase and regulates the natriuretic peptide 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. [21] Sacubitril combined with ARB valsartan, its high efficacy and tolerability among

HF patients has proved.[20] Treatment with sacubitril/valsartan was associated with more loop diuretic dose reductions and fewer dose increases compared with enalapril, suggesting that treatment with sacubitril/valsartan may reduce the requirement for loop diuretics relative to enalapril in patients with heart failure with reduced ejection fraction.[22]

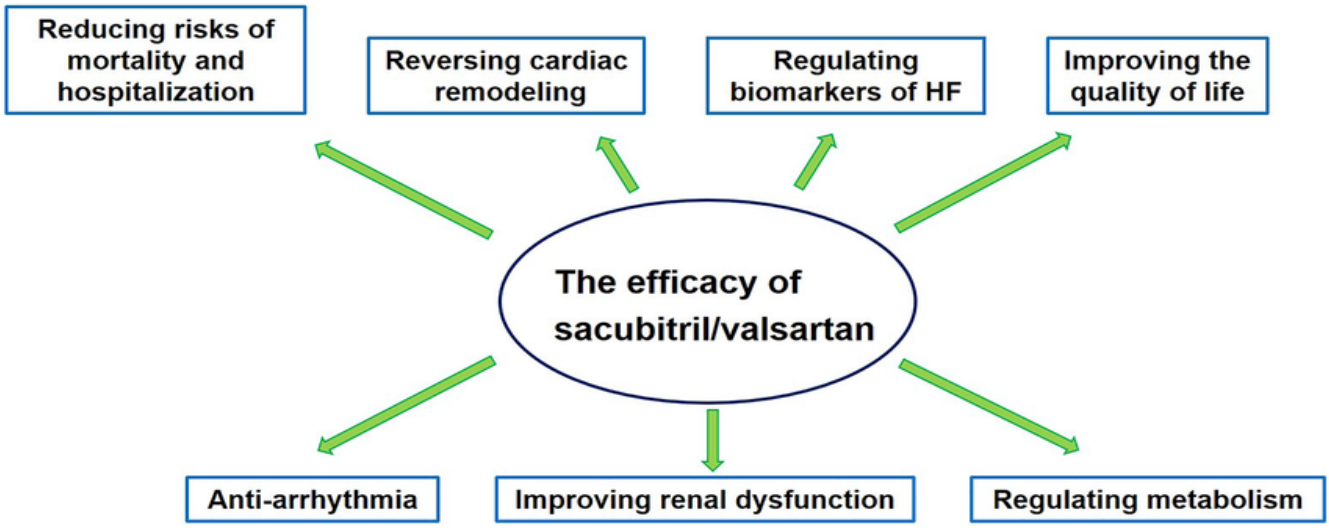

Figure (1). The efficacy of sacubitril/valsartan in the treatment for HF patients.[21]

6. Methods

Study Design : This is observational analytical Cohort study has been performed in Teaching Cardiac Center in Thi-Qar governorate-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). Taking in consideration what PARADIGM-HF trial proved about the impact of the angiotensin receptor neprilysin inhibitor sacubitril/ valsartan with that of enalapril on CV mortality and HF hospitalizations in patients with left ventricular ejection fraction (LVEF) 40% and NYHA functional classes II to IV HF[23], 37 patients has been enrolled in the study. 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). Etiologies of HF have been checked as coronary artery diseases (eg, myocardial infarction or ischemia), cardiomyopathy (any type;eg,drug-induced),Hypertension or multifactorial. Heart failure patients are classified according to Echocardiogram as Heart failure with reduced ejection fraction(HFrEF) or Heart Failure with preserved ejection fraction (HFpEF).NYHA class of HF Symptoms .Symptoms as dyspnea, particularly on exertion , orthopnea , shortness of breath (SOB) , Paroxysmal nocturnal dyspnea , exercise intolerance and weakness .Assessment of medications history, vital parameters as systolic blood pressure(SBP), diastoli 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 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 also have been checked. All data have been estimated at baseline and after initiation by about 4-6 weeks. The exclusion criteria for this study have been pregnant patients, those with ages less than 15 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 heart failure from the Teaching Cardiac Center in ThiQar governorate-Nasiriyah city in Iraq. About half of the patients (59.45%) were males and the others (40.54%) 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%),(32.43%) represent NYHA classII and classIII at base line respectively. (86.48%), (13.51%) of total percent of patients had HFrEF and HFmrEF respectively. After 6 weeks follow up period from starting to take ARNI,(27.02%) of them has been HFimpEF. About (72.98%) of them have initial increase in ejection fraction 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 N-terminal ProBrain Natriuretic Peptide (NT-Pro BNP) and C-reactive protein to some extent.Also it has been found that decrease in rate of hospitalization by about 50% .

8- Conclusion and Recommendations

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 morbidity and mortality. The new HF guidelines[24] 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 heart failure 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 a further studies are recommended to include adherence assessment of patient toward treatment.[25]

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