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SACUBITRIL/ VALSARTAN CLINICAL OUTCOMES IN HEART FAILURE PATIENTS; A SYSTEMATIC REVIEW

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Abstract:

Background: Heart failure is considered the most prevalent cause of cardiovascular mortality , in addition to decreased quality of life inspite of the availabiity of numerous therapeutic agents and strategies. Sacubitril combined with Valsartan is one of the new modalities that is thought to decrease the mortality rate and hospitalization due to heart failure de-compensation.

Objective: This systematic review aims at summarizing the evidence on the novel agent sacubitril combined with valsartan and its outcomes in terms of mortality and recurrent hospitalization in heart failure patients.

Method: We searched Pubmed database thouroughly in the last eighteen years from 2000 to 2018 for trials investigating sacubitril outcomes in heart failure. Both compensated and decompensated heart failure were included.

Result: A total of 82 trials were found. After refining research to include studies published in English and recruted human subjects, 52 papers were found.The trials were further filtered to include only the trials mentioning the follow up duration, baseline Ejection fraction and New York Heart Association (NYHA) classification. Only nine trials were matching to the inclusion criteria.

Conclusion: Sacubitril/valsartan combination appears to be a promising option in patients with heart failure especially those with reduced ejection fraction (≤40%) in terms of decreasing cardiovascular mortality and reducing hospitalization due to heart failure decompensation. Further trials are still required to test the safety and efficacy.

Key-words: *Sacubitril, Valsartan, Heart failure, Ejection fraction, Mortality.*

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INTRODUCTION:

Chronic heart failure is caused by over-activation for sodium and water retaining neurohormones. This Over-activation can lead to cardiac fibrosis. That's why most of the fundamental drugs used for heart failure act on decreasing actions of neurohormones on the heart in order to decrease morbidity and mortality. [1,2] One of the new pharmacological classes that act on neuropeptides is the neprilysin inhibitors with sacubitril as its first marketed agent in combination with Valsartan.[3] This systematic review aims at evaluating the available literature on outcomes of sacubitril/valsartan in heart failure in terms of mortality and heart failure hospitalization.

MATERIAL AND METHODS:

This systemic review of literature was done on *PubMed* database in order to evaluate the clinical outcomes of sacubitril/valsartan in heart failure. Search terms included were a combination of "sacubitril/valsartan" and "heart failure" and "outcomes".

All the titles in addition to abstracts appeared from this search were reviewed thoroughly. The results were then filtered to include original research articles investigating cardiovascular mortality and hospitalization due to heart failure exacerbation. Additionally, the selected trials compared sacubitril/valsartan versus monotherapy of angiotensin converting enzyme inhibitors (ACEI). Only trials published in English language were classified as related articles which can be further evaluated in the second step.

The following step was determining the inclusion criteria to choose the studies that will be considered in the systematic review. Abstracts were revised manually to choose the appropriate abstracts to be considered. The inclusion criteria were the presence of sufficient details on the duration of follow up and outcomes measured in addition to baseline medications. Moreover, only trials mentioning New York Heart Association (NYHA) classification for recruited patients and left ventricular ejection fraction were considered.

Furthermore, references of selected trials were revised in order to define any related articles. Finally, the required data sets were collected from the final record of eligible articles and summarized.

RESULTS:

A total of 82 articles were retrieved by searching *PubMed* using the combination of the two terms "sacubitril/valsartan" and "Heart Failure". Following exclusion of articles on animals and including only trials on humans, 52 articles were found.

After searching the abstracts and checking for the eligibility criteria in identified potential abstracts, a total of nine articles were considered as eligible to be included in our systematic review that were published between 2008 and 2018 covering a total of 30379 patients with heart failure.

Out of the 30379 patients, 301 patients had heart failure with preserved ejection fraction and were included in one trial. Furthermore, all the trials included were recruiting subjects with NYHA class II to IV, except one trial[12] which included NYHA classes II and III only. Additionally, treatment with sacubitril/valsartan was linked to 20% reduction in the primary outcome of mortality due to cardiovascular causes or hospitalization due to heart failure compared to ACEI monotherapy.

Turning to ejection fraction evaluated, all the included trials [4-11] evaluated sacubitril/valsartan outcomes in patients with heart failure with reduced ejection fraction (HFrEF). Only one trial [12] investigated the clinical outcomes of the mentioned combination in patients with heart failure with preserved ejection fraction (HFpEF).

The mean follow-up duration was 26.75 months and ranged from 3 to 40 months. Summaries of patients' ages are shown in table 1.

According to extracted results, all the trials considered the primary outcome as cardiovascular mortality and hospitalization due to heart failure. In addition, one trial evaluated the improvement in quality of life with sacubitril/valsartan combination, while another trial evaluated the change in atrial natruritic peptides.

Table 1: Summary of the included trials

Author(s)	Year	Number of subjects	Age	NYHA Class	Left Ventricular Ejection Fraction	Baseline medications	Mean follow-up (months	Out come	Result
Bohm, et al[4]	2017	8399	Above 60	class II–IV	≤35%	ACEI or ARB	12	composite cardiovascular death /heart failure hospitalization	1.The benefit of sacubitril/valsartan over enalapril was consistent across all baseline SBP categories for all outcomes. 2.Sacubitril/valsartan versus enalapril hazard ratio for the primary endpoint was 0.88.
Lewis, et al[5]	2017	6881	Above 60	class II–IV	≤35%	ACEI or ARB	8	KCCQ clinical summary scores and KCCQ overall summary scores	Sacubitril/valsartan showed improvements in both KCCQ clinical summary score (P=0.008) and KCCQ overall summary score (P<0.001) in comparison to enalapril group and significantly less proportion of hospitalization.
Tsutsui, et al[6]	2017	220	20 and above	class II–IV	≤35%	ACEI/ARB, Beta blocker, MRA	40	composite cardiovascular death / HF hospitalization	treatment provides similar improvements in clinical outcomes in Japanese HFrEF patients as observed in PARADIGM-HF study
Zile, et al[7]	2016	2080	age 18 years or older	class II–IV	≤35%	ACEI/ARB, Beta blocker	36	Reduction in HF hospitalization / cardiovascular mortality	1. In sacubitril/valsartan, median NT-proBNP was significantly lower 1 month after randomization than in enalapril, and it fell to ≤1,000 pg/ml in 31% for sacubitril/valsartan versus 17% for enalapril, 2. Risk of the primary outcomes was 59% lower in patients with a fall in NT-proBNP
Kristensen, et al[8]	2016	2907	Mean age 63± 12	class II–IV	≤35%	ACEI or ARB and Beta blocker	27	heart failure hospitalization / cardiovascular mortality in diabetic patients as	Sacubitril/valsartan reduced the occurrence of the primary composite outcome compared with enalapril.

								comorbidity to HF	
Desai, et al[9]	2016	1450	Mean age 64.4 ±11.7	class II–IV	≤35%	ACEI or ARB and Beta blocker	27	risk of 30-day readmission for HF	Rates of readmission for HF at 30 days were reduced in sacubitril/valsartan compared to enalapril (9.7% vs. 13.4%; OR: 0.62; 95% CI: 0.45 to 0.87; p = 0.006).
McMurray, et al[10]	2014	8442	age of at least 18 years, New	class II–IV	≤35%	ACEI or ARB and MRA	27	composite cardiovascular mortality or hospitalization for heart failure	1.the primary outcome had occurred in (21.8%) in sacubitril/valsartan and (26.5%) in enalapril (P<0.001). 2.Sacubitril/valsartan also reduced the risk of hospitalization for heart failure by 21% (P<0.001) and decreased symptoms and physical limitations of heart failure (P = 0.001).
McMurray, et al[11]	2013	8436	age 18 years or older	class II–IV	≤40%	ACEI or ARB and Beta blocker	34	composite cardiovascular death /HF hospitalization	17.0% receiving sacubitril/valsartan and 19.8% receiving enalapril died (P<0.001); of these (13.3%) in sacubitril/valsartan and (16.5%) in enalapril died from cardiovascular causes P<0.001).
Solomon, et al[12]	2012	301	Age 40 or older	class II–III	≥45	ACEI/ARB, Beta blocker, MRA, diuretics	3	change in NT-proBNP, mortality and HF hospitalization	1.NT-proBNP was significantly reduced at 12 weeks in sacubitril/valsartan compared to valsartan group p=0·005). 2.All primary outcomes were reduced in sacubitril/valsartan compared to valsartan

ARB: Angiotensin receptor blocker, MRA: Mineralocorticoid receptor antagonist, SBP: Systolic blood pressure, KCCQ: Kansas City Cardiomyopathy Questionnaire, NT-proBNP: N-terminal pro b-type natriuretic peptide

DISCUSSION:

Incidence of heart failure is increasing all over the world. In developed countries, heart failure occurs in 1 to 2% of the total population, additionally, its incidence increases with advancing age. [13] Patients having symptoms of heart failure are classified into two types; they are either having heart failure with reduced ejection fraction or heart failure with preserved ejection fraction. [14]

For many years, angiotensin-converting enzyme inhibitors, beta-adrenergic blockers in addition to mineralocorticoid receptor antagonists were the corner stone of HFrEF treatment due to their evidenced positive effects on morbidity and mortality in multi-center and randomized clinical trials. [15] These effects were mainly contributed to their neuro-hormonal roles. [16]

However, one of the major problems that arose with ACEI was the intolerance in some patients due to dry cough. [17] In such patients, angiotensin receptor blockers (ARBs) could be used as alternative though their impact on mortality is not highly evidenced as that of ACEI. [16,17]

Neprilysin is an enzyme that can cause vasoactive peptides degradation. These peptides include natriuretic peptides which have been suggested as a target for the treatment of heart failure. [18] This could be achieved through Neprilysin inhibition so that pathological neurohormonal activation can be blocked. There are many neprilysin inhibitors that have been investigated in both hypertension as well as heart failure, but unfortunately it had minimal benefit. [19] This is because neprilysin inhibition can increase the levels of angiotensin II. This can explain the availability of neprilysin inhibitor only in combination with ARB in order to maximize the benefit. [20]

Sacubitril is the prototype of the novel neprilysin inhibitor class and has been approved and marketed recently in the American and European market. [17-20] Since then, some trials have been performed to test the efficacy of the new drug in terms of mortality and recurrent hospitalization in addition to safety in terms of adverse effects such as hyperkalemia, hypotension and renal impairment. [21]

In this systematic review we included nine randomized trials evaluating the clinical outcomes of sacubitril/valsartan in heart failure patients. It was found that treatment with sacubitril/valsartan was linked to 20% reduction in the primary outcome of mortality due to cardiovascular causes or hospitalization due to heart failure compared to ACEI monotherapy. Furthermore, sacubitril/valsartan appeared to decrease the time to first heart failure hospitalization.

The results of all the trials included supported the hypothesis of sacubitril/valsartan to be better than either ARB or ACEI as a mono-therapy. [4-12] It is worth to mention that some of these trials considered the presence of different comorbidities with heat failure. One of these trials was Bohm *et al* ,[4] which focused mainly on the outcome of Sacubitril/valsartan in relation to systolic blood pressure in heart failure patients. This trial concluded that composite mortality and heart failure hospitalization were much less with sacubitril/valsartan with a hazard ratio 0.88. Another study reached the same conclusion but on Japanese population.[6]

Another trial included patients with heart failure and diabetes where patients were sub classified into normal, pre diabetes and diabetes groups. [8] The study found that over all glycemic levels sacubitril/valsartan reduced mortality and recurrent hospitalization compared to enalapril.

Furthermore, some studies focused on using scores to evaluate recurrent hospitalization and deterioration of symptoms in the studied groups. For instance, Lewis *et al* used the KCCQ clinical summary and overall summary scores to evaluate these outcomes. [5] Sacubitril/valsartan combination showed improvement in both scores compared to enalapril with a (P= 0.008) for KCCQ clinical summary score and <0.001 for KCCQ overall summary score. [5]

Additionally, the largest trial on 8442 patients investigating the risk of hospitalization due to heart failure hospitalization and cardiovascular mortality also suggested the benefit of sacubitril/valsartan compared to enalapril alone, [10] where sacubitril/valsartan combination showed reduced hospitalization by 21% compared to enalapril ($p<0.001$) in addition to decreasing limitation of activity due to symptoms in favor of sacubitril/valsartan (P=0.001). [10]

Moreover, other trials evaluated the levels of (N-terminal pro b-type natriuretic peptide) NT-proBNP as a prognositic marker. [7,12] It was revealed that NT-proBNP level was significantly lower with sacubitril/valsartan compared to enalapril ($P\leq0.005$), [12] and that mortality and recurrent hospitalization

were 59% less with reduction in NT-probnp. [7]

CONCLUSION:

Based on the results of this systematic review, we can conclude that sacubitril/valsartan combination is a promising option for heart failure patients due to its beneficial impact on mortality rate and recurrent hospitalization. However, the data on this combination is still scarce, thus further randomized trials are needed.

List of abbreviations

Abbreviation	Meaning
ACEI	Angiotensin Converting Enzyme Inhibitors
ARB	Angiotensin Receptor Blocker
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
KCCQ	Kansas City Cardiomyopathy Questionnaire
MRA	Mineralocorticoid Receptor Antagonist
NT-proBNP	N-Terminal Pro B-type Natriuretic Peptide
NYHA	New York Heart Association

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