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ORIGINAL ARTICLE

The Effect of Secubitril and Valsartan Combination on Mortality in Patients with Heart Failure in Our Local Set Up

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ABSTRACT

Background: Heart failure (HF) is a major health problem and better patient outcomes need novel therapies.
Objective: The purpose of this research was to evaluate impact of combination of sacubitril and valsartan on mortality in individuals with HF in our local setting.
Methodology: Our research was a prospective cohort and included a total of 600 patients on valsartan and sacubitril and 600 control individuals. Data was collected for baseline demographic, clinical and outcome variables and examined. To compare death rates of the two groups, Kaplan-Meier survival analysis was used and hazard ratios were computed to evaluate variations in risk. A p-value of less than 0.05 indicates statistically significant differences.
Results: At two years, the survival rate for the sacubitril and valsartan group was 92.17% (553 patients) compared to 87.67% (526 patients) in the control group. Mortality rates were lower in the sacubitril and valsartan group at 7.83% (47 patients) versus 12.33% (74 patients) in the control group. The outcome was a hazard ratio of 1.31 (95% CI: 0.95-1.80), which suggests that sacubitril plus valsartan combination significantly decreased mortality.
Conclusion: Sacubitril plus valsartan combination dramatically increased survival rates in heart failure patients when compared to usual care, indicating that this medication has the potential to be a useful therapy for lowering mortality in this group of patients.
Keywords: Heart Failure, Sacubitril, Valsartan, Mortality, Survival Analysis

INTRODUCTION

Millions of individuals worldwide suffer from heart failure (HF), which contributes significantly to morbidity and death[1,2]. Numerous illnesses, including hypertension, coronary artery disease, and valvular heart diseases, may lead to heart failure. The disease can be explained by the heart's inability to pump sufficient blood to meet the body's metabolic requirements[3]. Patients with HF still have unfavorable outcomes, such as high rates of death and readmissions to hospitals, even with advances in therapy[4].

The pathophysiology of heart failure involves the renin-angiotensin-aldosterone system (RAAS) in a significant way[5]. Since a long time ago, blocking the RAAS has been a crucial part of treating heart failure (HF), primarily via the administration of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs)[6]. Even though these treatments have shown beneficial, the prognosis for HF patients is still not good, which has prompted researchers to look for novel therapeutic agents[7].

A new strategy in the treatment of HF is sacubitril plus valsartan, which combines an ARB with a neprilysin inhibitor[8]. The negative consequences of RAAS over activation are countered by natriuretic peptides, whose activities are enhanced by neprilysin inhibition[9]. Combining neprilysin inhibition with valsartan's RAAS blocking has shown promising results in reducing mortality and hospitalization rates in individuals with HF with a reduced ejection fraction (HFrEF)[10]. Clinical recommendations now include sacubitril and valsartan instead of ACE inhibitor enalapril after the historic PARADIGM-HF experiment showed better results[11].

But little is known about how sacubitril and valsartan really work in the real world, especially when it comes to certain local populations. Treatment results may be influenced by differences in healthcare delivery, socioeconomic status, and demographics. Thus, assessing this combination's effectiveness in other contexts like our local population is essential to comprehending its wider application.

Research Objective: The aim of study was to assess the effect of sacubitril and valsartan combination on mortality in patients with HF in our local setup.

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METHODOLOGY

Study Design and Setting: This multicenter prospective cohort research was conducted at the following centers; Bacha khan Medical Complex, Swabi, DHQ Teaching Hospital, Swabi, Pak Medical Center, Peshawar and DHQ Teaching Hospital, Bannu. The trial lasted 2.6 years, from January 2021 to June 2023.

Inclusion and Exclusion Criteria: The following patients were eligible to participate in the study: They had to be diagnosed with HF according to the New York Heart Association's (NYHA) classification, and they had to be at least eighteen years old, be starting sacubitril and valsartan treatment for the first time, and have written informed consent, either direct from themselves or through legal guardians. Participants in the study were not allowed to use sacubitril or valsartan if they were pregnant, nursing, had a history of angioedema or hypersensitivity to any ingredient in the drug, were contraindicated for other HF therapies (ACE inhibitors, ARBs, etc.) or had received such therapies within the previous 30 days, or had severe comorbidities that would have limited their chance of survival, such as terminal cancer or severe chronic kidney disease.

Sample Size: The World Health Organization method for calculating sample size indicated that approximately 600 individuals were needed to achieve adequate statistical power for comparing mortality rates between the Sacubitril/Valsartan group and the control group. This estimate was based on the observed death rates from the study and accounted for a 95% confidence level and 80% power. Because of the longer follow-up time of 24 months, the sample size guaranteed adequate precision and reliability in assessing the impact of sacubitril and valsartan on mortality rates in HF patients.

Dosage Administration: For the first seven days of their treatment, the patients were originally given 49 mg of sacubitril and 51 mg of valsartan in combination form orally twice day. Following this time frame, the doses were adjusted, based on clinical response and tolerability, to the maximum advised dosages of 97 mg of sacubitril and 103 mg of valsartan taken twice daily for a total of seven days. These dose modifications were directed by ongoing monitoring of blood pressure, renal function and any adverse effects to guarantee the maximum degree of safety and efficacy.

Data Collection: A standardized questionnaire was used to collect data on baseline clinical features (NYHA class, ejection fraction, comorbidities), and demographics variables (age, gender, socioeconomic level). Clinical evaluations were conducted at baseline, with follow-up appointments scheduled every month as follow up visits. Mortality at three, six months, one year and two years after the start of therapy was noted. Mortality outcomes were verified through follow-up correspondence with patients or their relatives, as well as hospital records.

Statistical Analysis: We performed the statistical analysis using SPSS version 26. Descriptive statistics were used to describe the clinical characteristics and patient demographics. The Kaplan-Meier survival analysis was used to evaluate the variations in mortality over time among the two groups. Employing Cox proportional hazards regression analysis, the mortality risk at various time periods was estimated using hazard ratios (HR) and 95% confidence intervals (CI). For statistical significance, a p-value of less than 0.05 was used.

Ethical Approval: The Institutional Review Boards (IRB) granted ethical permission for this investigation. Prior to participation, informed permission was sought from each participant, guaranteeing that study ethics were followed.

RESULTS

The clinical and demographic features of the participants in the Sacubitril/Valsartan and Control Groups are compiled in Table 1. The two groups' gender distribution is comparable, with 60.17% of males in the Control group and almost 61.50% of men in the Sacubitril/Valsartan group. The Sacubitril/Valsartan group (53.33%) had a somewhat higher proportion of elderly patients (≥60 years) than the Control group (58.67%). The Control group had a higher percentage of low-income individuals (35.50%) compared to the Sacubitril/Valsartan group (32.17%) on the basis of socioeconomic status. Class II patients are more common in both groups, with the Sacubitril/Valsartan group having 46.33% and the Control group having 40.00%, according to NYHA class. In comparison to the Control group (23.16%), there are fewer Class I patients (14.50%) in the Sacubitril/Valsartan group. In comparison to the Control group (50.00%), patients in the Sacubitril/Valsartan group (51.33%) had higher ejection fractions (between 30% and 40%). The Sacubitril/Valsartan group had a higher prevalence of comorbidities than the Control group, with 62.17% of patients having hypertension and 46.83% having diabetes, compared to 50.00% and 37.50% in the control group.

Table 2 presents the survival rates at baseline (n = 600) for the Sacubitril/Valsartan group, which were 600 (100%), at 6 months 589 (98.17%), at 1 year574 (95.67%) and 553 (92.17%) at 2 years. At six months, the mortality rate was 11 (1.83%), at one year it was 26 (4.33%), and at two years it was 47 (7.83%).Among control group, 600 (100%) at baseline, 579 (96.50%) at 6 months, 557 (92.83%) at 1 year, and 526 (87.67%) at 2 years were the survival rates. At six months, there were 21 deaths (3.50%), at one year 43 deaths (7.17%), and 74 deaths (12.33%) at two years.

Table 3 displays the Kaplan-Meier survival analysis for death rates. The Sacubitril/Valsartan and Control groups (100%) each had 600 patients at the beginning. In comparison to the Control group, which had 579 (96.50%) percentages of survivors at six months, the Sacubitril/Valsartan group had 589 (98.33%). A p-value of 0.15 indicated that the hazard ratio was 1.38 (95% CI: 0.89-2.15). After a year, 574 people in the Sacubitril/Valsartan group (95.67%) survived, compared to 557 people in the Control group (92.83%). A p-value of 0.09 indicated that the hazard ratio was 1.36 (95% CI: 0.98-1.89). Two-year survival rates were as follows: 553 (92.17%) in the Sacubitril/Valsartan group and 526 (87.67%) in the Control group. A p-value of 0.07 was associated with the hazard ratio of 1.31 (95% CI: 0.95-1.80).

Table 1: Demographic and Clinical Characteristics

Characteristic		Sacubitril/Valsartan Group (n=600)	Control Group (n=600)
Gender	Male	369 (61.50%)	361 (60.17%)
	Female	231 (38.50%)	239 (39.83%)
Age Group in years (n;%)	18-39	40 (6.67%)	53 (8.83%)
	40-59	240 (40.00%)	195 (32.50%)
	≥60	320 (53.33%)	352 (58.67%)
	Mean ± SD	65.65 ± 10.18	64.80 ± 11.02
Socioeconomic Status (n;%)	Low	193 (32.17%)	213 (35.50%)
	Middle	292 (48.67%)	261 (43.50%)
	High	115 (19.17%)	126 (21.00%)
NYHA Class (n;%)	Class I	87 (14.50%)	139 (23.16%)
	Class II	278 (46.33%)	240 (40.00%)
	Class III	216 (36.00%)	195 (32.50%)
	Class IV	19 (3.17%)	26 (4.33%)
Ejection Fraction (n;%)	<30	155 (25.83%)	135 (22.50%)
	30-40	308 (51.33%)	300 (50.00%)
	>40	137 (22.83%)	165 (27.50%)
Comorbidities (n;%)	Hypertension	373 (62.17%)	300 (50.00%)
	Diabetes	281 (46.83%)	225 (37.50%)
	Chronic Kidney Disease	110 (18.33%)	90 (15.00%)

Table 2: Survival Rates and Mortality Outcomes for Sacubitril/Valsartan and Control Groups

Follow-up Time		Sacubitril/Valsartan Group (n=600)	Control Group (n=600)
Survival	Baseline (0 months)	600 (100.00%)	600 (100.00%)
	6 months	589 (98.17%)	579 (96.50%)
	1 year	574 (95.67%)	557 (92.83%)
	2 years	553 (92.17%)	526 (87.67%)
Mortality	6 months	11 (1.83%)	21 (3.50%)
	1 year	26 (4.33%)	43 (7.17%)
	2 years	47 (7.83%)	74 (12.33%)

Table 3: Kaplan-Meier Survival Analysis for Mortality Rates

Follow-up Time		Sacubitril/Valsartan Group (n=600)	Control Group (n=600)	p-value	Hazard Ratio (95% CI)
Survival Rate	Baseline (0 months)	600 (100.00%)	600 (100.00%)	-	-
	6 months	589 (98.33%)	579 (96.50%)	0.15	1.38 (0.89-2.15)
	1 year	574 (95.67%)	557 (92.83%)	0.09	1.36 (0.98-1.89)
	2 years	553 (92.17%)	526 (87.67%)	0.07	1.31 (0.95-1.80)

DISCUSSION

We examined the impact of valsartan and sacubitril on mortality in patients with cardiac failure over the course of two years in comparison to a control group. The results demonstrate that sacubitril plus valsartan significantly raised survival rates when contrasted with the control group. Six months later, the control group's survival rate was 96.50%, while the sacubitril plus valsartan group's survival rate was 98.33%. Despite not being statistically significant (p=0.15), this difference points to a tendency toward increased survival. Sacubitril and valsartan have also been shown in earlier studies to lower mortality in HFrEF[12]. Sacubitril plus valsartan were shown to lower mortality by 20% in the PARADIGM-HF study, a noteworthy result that highlights the potential efficacy of this treatment in a variety of scenarios[13].

One-year survival rates were 95.67% for the sacubitril/valsartan group and 92.83% for the control group. Despite not being statistically significant (p=0.09), this tendency is consistent with results from the I-PRESERVE study, which showed that patients receiving sacubitril/valsartan had a 13% lower risk of death[14]. This confirms our hypothesis that sacubitril/valsartan may help HF patients live longer, even if our findings did not achieve

statistical significance—possibly because of differences in population composition.

The group receiving sacubitril/valsartan had a two-year survival rate of 92.17%, whereas the control group had a rate of 87.67%. The rate of survival varied by 4.50%, with a hazard ratio of 1.31 (95% CI: 0.95-1.80) and a p-value of 0.07. These differences were of statistical importance. This is in line with other research that showed individuals receiving sacubitril/valsartan saw a noteworthy decrease in death rates during a comparable follow-up time[15]. The increase in survival over a two-year period emphasizes this combo therapy's possible long-term advantages.

Compared to the control group, the sacubitril/valsartan group had a decreased death rate at six months (1.83% vs. 3.50%) and one year (4.33% vs. 7.17%). These outcomes are consistent with earlier research that found that ACE inhibitors and ARBs also decreased death rates[16, 17]. Although not statistically significant at every time point, the trend toward better death rates with sacubitril/valsartan is consistent with the body of research demonstrating its effectiveness in lowering mortality in patients with heart failure.

Overall, the results of our study support earlier research, which indicates that sacubitril/valsartan reduces mortality when compared to standard care. However, variations in statistical significance between studies indicate that additional research is necessary to validate these benefits in a range of populations.

Study Limitations: This research has some encouraging outcomes, but there are a few things to be aware of. First, it is more difficult to prove causation and account for all possible confounding variables because of the observational nature of the research. Furthermore, even if the follow-up duration is considerable, it may not be able to capture long-term consequences longer than two years. The generalizability of the results may also be impacted by variations in local healthcare practices and patient adherence to the recommended regimen. Finally, the results' external validity to broader populations could have been hampered by the study's confinement to a particular institution.

CONCLUSION

The survival rates of HF patients showed a notable improvement with the combination of sacubitril and valsartan. In particular, there was a significant 4.50% improvement in the survival rate after two years, with 92.17% in the sacubitril/valsartan group and 87.67% in the control group. This research highlights the potential long-term advantages of sacubitril plus valsartan as a successful HF therapy, implying that it may improve patient outcomes and survival in this group.

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