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**Original Research Article**

# A randomized controlled trial to compare ramipril and sacubitril/valsartan in post-acute coronary syndrome patients with left ventricular systolic dysfunction in terms of improvement in ejection fraction

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## ABSTRACT

**Background:** Ramipril and sacubitril/valsartan are used in the management of ACS patients with left ventricle systolic dysfunction. The objective of the study was to compare ramipril and sacubitril/valsartan in improving LVEF in post ACS patients with LVEF <40%.
**Methods:** A randomized, prospective, open label, comparative study was carried out in department of pharmacology and cardiology at Dr. R. P. G. M. C. Kangra at Tanda, Himachal Pradesh. The study was carried for a period of one and a half year. Out of 80 patients, 38 patients were in ramipril group and 42 were in sacubitril/valsartan group. Data was presented as mean±SD, frequency and percentage. Student's t test and chi square test were used and p value<0.05 was considered significant.
**Results:** In both the groups, a statistically significant improvement was observed in terms of improvement in LVEF at 6th month when compared to baseline, however, at 6th month both the groups were comparable in terms of LVEF improvement with p value of 0.275.
**Conclusions:** The study concluded that both the drugs have same efficacy in improving LVEF in post ACS patients at 6th month.

**Keywords:** Sacubitril, Valsartan, Ramipril, ACS, LVEF

## INTRODUCTION

Cardiovascular diseases are one of the most common causes of death worldwide and is the leading cause of death among men and women. In 2021, ischemic heart disease accounted for 9.44 million deaths worldwide and 185 million DALYs. The age standardized incidence varies among and within countries.[1]

Ischemic heart disease (IHD) in form of acute coronary syndrome (ACS) is the main component of CVD.

The term ACS refers to any group of clinical symptoms compatible with acute myocardial ischemia and covers the spectrum of clinical conditions ranging from unstable angina (UA) to non- ST-segment elevation myocardial infarction (NSTEMI) to ST-segment elevation myocardial infarction (STEMI).[2]

Patients in India who have acute coronary syndromes have a higher rate of STEMI than do patients in developed countries.[3]

The presence of left ventricular systolic dysfunction after myocardial infarction is associated with a higher risk of the subsequent development of heart failure with reduced ejection fraction (HFrEF).[4,5] Following MI, a series of hemodynamic and structural changes occur in response to a reduction in stroke volume secondary to impaired systolic function in the area of myocardium subtended by the infarct-related artery. This process is referred to as "left ventricular remodeling".[6-8] Initially protective, these changes, which are driven by activation of the body's neurohumoral systems, become maladaptive over time and promote progressive dilatation of the left ventricle, further reductions in the left ventricular ejection fraction (LVEF) and, ultimately, the development of the signs and symptoms of the syndrome of HFrEF.[9,10]

Ramipril is a prodrug belonging to the ACE inhibitor class of medications. It produces blood pressure lowing effects by antagonizing the effect of the RAAS.[11] Ramipril may be used in the treatment of hypertension, congestive heart failure, nephropathy, and to reduce the rate of death, myocardial infarction and stroke in individuals at high risk of cardiovascular events.[12]

Ramipril also causes an increase in plasma renin activity likely due to a loss of feedback inhibition mediated by ATII on the release of renin and/or stimulation of reflex mechanisms via baroreceptors.[13]

A recently developed class of drugs called angiotensin receptor neprilysin inhibitors (ARNIs) increase concentrations of natriuretic peptides by inhibiting neprilysin (NEP). NEP inhibition increases angiotensin II (AT II), a potent endogenous vasoconstrictor. It also causes myocardial necrosis and fibrosis. ARNIs, such as sacubitril/valsartan (LCZ696), therefore, combine NEP inhibition with blockade of AT II receptor. Use of this drug has shown improvement of cardiac function, reversal of cardiac remodeling, improvement of exercise capacity, and, most importantly, reduction of cardiovascular mortality and hospitalizations in HF patients. The ARNI sacubitril/valsartan induces greater reductions in blood pressure than do ACEIs and ARBs, which may lead to concerns among physicians regarding its routine use in patients with low SBP.[14]

As there is no cited literature to compare the efficacy of the above-mentioned drugs in our setup, so this study was planned to compare sacubitril/valsartan with ramipril in post-ACS patients at 6 months in terms of change in ejection fraction.

## METHODS

This was a prospective open labelled randomized controlled trial conducted in the department of pharmacology and department of cardiology, Dr. R. P. G. M. C. Kangra at Tanda. The study was conducted after approval from institutional ethical committee for a period of one and a half year (one year of enrollment and six months follow-up). Patients were randomized using computer generated random number table. All patients of age more than 18 years and having LVEF≤40% during the prespecified-period and gave written consent were included in the study. Patient were treated with aspirin, clopidogrel, statins and beta blocker as per guidelines. Patients with history of angioedema, symptomatic hypotension or a SBP<100 mmHg, with eGFR<30 ml/min/1.73m$^2$, pregnant females or lactating mothers, any contraindications to study drugs, or patients of cardiomyopathy, stroke, severe pulmonary disease, TIA, acute decompensated heart failure or with aortic or mitral valve disease except mitral regurgitation were excluded from the study.

The study population included all the patients of post ACS fulfilling inclusion criteria in department of Cardiology. After admission, detailed history was recorded regarding presenting complaints, their duration severity, sequence of onset of symptoms, mode of onset, progression, change in the pattern at the time of presentation and atypical symptoms. A careful and detailed cardiology examination of each patient was made including ECG, complete hemogram, RFT, electrolytes and echo cardiography was done to look for heart failure. Patients of ACS with LVEF<40% were randomly assigned Sacubitril/Valsartan or ramipril in addition to standard therapy before hospital discharge. Treatment was started on day before discharge. Patients who were already on ARBs or ACE inhibitors were started newer medication after wash off period i.e. 36 hours.

SAC/VAL was started at a dose of 12/13 mg BID in patients with SBP between 100-140 mmHg and dose was escalated to 24/26 mg BID after 2 weeks and then was doubled after 2-4 weeks to target dose of 97/103 (if tolerated) for 6 months, and in patients with SBP >140 mmHg, dose was started at 24/26 mg BID and was escalated in similar way. Ramipril was started at a dose of 2.5 mg OD in patients and was escalated to 2.5 mg BID after 2 weeks and then was doubled after 2-4 weeks to target dose of 10 mg (if tolerated) for 6 months.

NYHA Functional Class was evaluated at baseline and at 6$^{th}$ month. Echocardiography was done at baseline and then at 6$^{th}$ month follows up and ejection fraction was calculated by Modified Simpson method. Patients were enquired about any symptomatic status, postural symptoms or any condition that preclude continuation of drug. Patients were monitored for drug compliance at every visit.

### *Statistical analysis*

The data was recorded on a predesigned proforma and was analyzed using Epi-Info software. Quantitative variables were presented as mean±SD and qualitative variables were presented as frequency and percentage. Chi-square test was used as test of significance for categorical variables

and t-test was used as test of significance for quantitative variables. P value<0.05 was considered as significant.

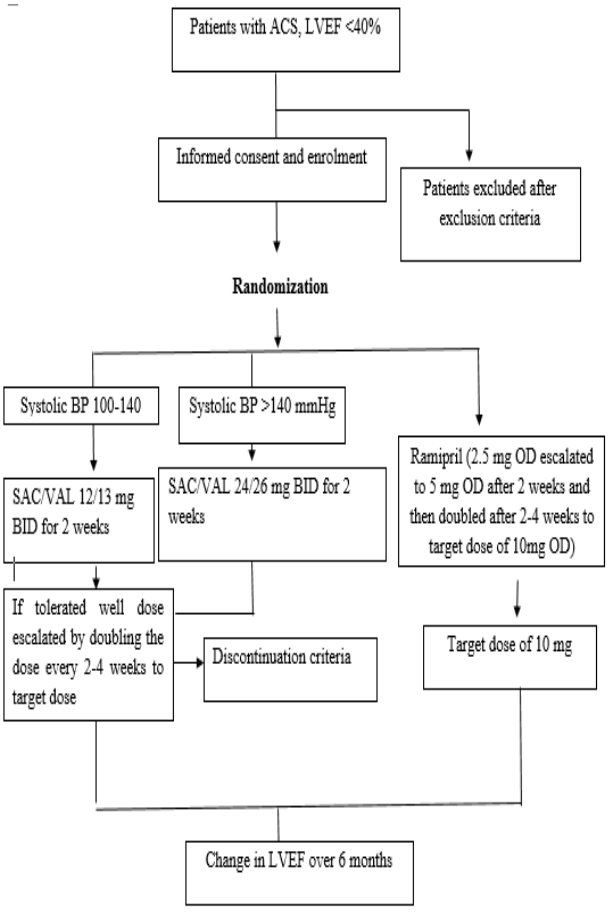


**Figure 1: Study methodology flow chart.**

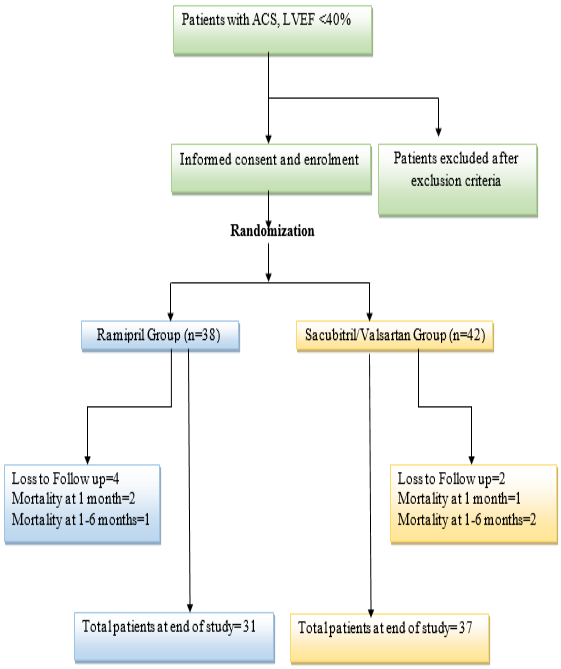


**Figure 2: Consort flow chart.**

## RESULTS

A total of 80 patients were included in the study with 38 patients in ramipril group and 42 patients in sacubitril/valsartan group.

In ramipril group, there were 4/38 (10.5%) patients who were lost to follow up and 3/38 (7.9%) died. In sacubitril/valsartan group, there were 2/42 (4.76%) patients who were lost to follow up and 3/42 (7.14%) patients died. There was no statistically significant difference between the groups in terms of lost to follow up and mortality and those patients were included as per intention to treat analysis. In ramipril group, mean age was 64.21±10.26 years while in sacubitril/valsartan group, mean age was 62.19±12.58 years. Both the groups were comparable in terms of mean age (p=0.437) and sex distribution (p=0.081). Demographic profile of enrolled patients is shown in Table 1.

### *Distribution as per type of ACS*

In ramipril group, most of the patients had NSTEMI with a count of 17 (44.7%) followed by AW MI which was seen in 10 (26.31%) patients. LW MI was seen in 1 (2.6%) patient each. In sacubitril/valsartan group, most common type of ACS was AW MI which was seen in 20 (47.6%) patients followed by NSTEMI in 14 (33.3%) patients. The groups were comparable in terms of type of ACS (p value 0.168).

### *Ejection fraction at baseline*

In ramipril group, there were maximum patients had EF of 35-40% with a count of 10 (26.3%). In sacubitril/valsartan group, maximum patients had EF of 25-30% (13; 30.9%) followed by 11 (26.2%) with EF of 15-20%. The groups were comparable in terms of EF at baseline (p value 0.456).

### *Ejection fraction at 6 months*

In ramipril group, EF of 15-20% and 35-40% was observed in 6 (15.8%) patients each and EF of 30-35% and 40-45% was observed in 5 (13.2%) patients each. In sacubitril/valsartan group, EF of 35-40% was observed in 11 (26.2%) patients. EF of 15-20%, 20-25% and 25-30% was observed in 2 (4.8%), 6 (14.3%) and 4 (9.5%) patients respectively. There was no statistically significant difference between the groups in terms of EF at 6 months (p value 0.275).

### *Ejection fraction at baseline and at 6 months in ramipril group*

It was observed that in ramipril group, minimum EF at baseline was 10-15% which was seen in 1 patient while at 6 months, minimum EF observed was 15-20% which was seen in 6 patients. The maximum EF at baseline was 35-40% present in 9 patients which increased to maximum of

55-60% at 6 months in 2 patients. A statistically significant difference was observed in EF of patients at baseline and at 6 months with p value of 0.004 suggesting that there was improvement in EF of patients in ramipril group after 6 months of drug administration.

***Ejection fraction at baseline and at 6 months in sacubitril/valsartan group***

It was observed that in sacubitril/valsartan group, minimum EF at baseline was 10-15% which was seen in 1 patient while at 6 months, minimum EF observed was 15-20% which was seen in 2 patients. The maximum EF at baseline was 35-40% present in 7 patients which increased to maximum of 55-60% at 6 months in 1 patient. EF of 35-40% was observed in 7 patients at baseline which increased to 11 patients at 6 months. A statistically significant difference was observed in EF of patients at baseline and at 6 months with p value of 0.015 suggesting that there was improvement in EF of patients in sacubitril/valsartan group after 6 months of drug administration.

**Table 1: Demographic profile of enrolled subjects.**

| Variables | | Ramipril N (%) | Sacubitril/valsartan N (%) | P value |
|---|---|---|---|---|
| **Sex** | Female | 16 (42.1) | 10 (23.8) | 0.081 |
| | Male | 22 (57.89) | 32 (76.2) | |
| **Smoker** | Yes | 20 (52.6) | 30 (71.4) | 0.082 |
| | No | 18 (47.3) | 12 (28.57) | |
| **Alcoholic** | Yes | 13 (34.2) | 10 (23.8) | 0.304 |
| | No | 25 (65.78) | 32 (76.2) | |
| **DM** | Yes | 12 (31.5) | 13 (30.9) | 0.951 |
| | No | 26 (68.4) | 29 (69.1) | |
| **HTN** | Yes | 18 (47.36) | 12 (47.6) | 0.082 |
| | No | 20 (52.6) | 30 (71.4) | |
| **AF** | Yes | 1 (2.6) | 2 (4.76) | 0.616 |
| | No | 37 (97.3) | 40 (95.23) | |

**Table 2: Distribution of patients as per ejection fraction at baseline.**

| EF baseline | Ramipril N (%) | Sacubitril/valsartan N (%) | P value |
|---|---|---|---|
| **10-15** | 1 (2.6) | 1 (2.38) | 0.456 |
| **15-20** | 6 (15.78) | 11 (26.2) | |
| **20-25** | 8 (21) | 7 (16.6) | |
| **25-30** | 7 (18.4) | 13 (30.9) | |
| **30-35** | 6 (15.78) | 3 (7.14) | |
| **35-40** | 10 (26.3) | 7 (16.6) | |
| **Total** | 38 (100) | 42 (100) | |

**Table 3: Distribution of patients as per ejection fraction at 6 months**

| EF 6 month | Ramipril | Sacubitril/valsartan | P value |
|---|---|---|---|
| **15-20** | 6 (15.8) | 2 (4.8) | 0.275 |
| **20-25** | 2 (5.3) | 6 (14.3) | |
| **25-30** | 4 (10.5) | 4 (9.5) | |
| **30-35** | 5 (13.2) | 7 (16.7) | |
| **35-40** | 6 (15.8) | 11 (26.2) | |
| **40-45** | 5 (13.2) | 3 (7.1) | |
| **45-50** | 1 (2.6) | 3 (7.1) | |
| **50-55** | 0 | 1 (2.4) | |
| **55-60** | 2 (5.3) | 0 | |
| **Total** | 31 (100) | 37 (100) | |

**Table 4: Distribution of patients as per ejection fraction at baseline and at 6 months in ramipril group.**

| Ramipril | EF at baseline | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **EF at 6 months** | **10-15** | **15-20** | **20-25** | **25-30** | **30-35** | **35-40** | **Total** | **P value#** |
| **Lost to follow up/died** | 0 | 2 | 0 | 3 | 1 | 1 | 7 | |
| **15-20** | 1 | 4 | 0 | 1 | 0 | 0 | 6 | 0.004** |

Continued.

| Ramipril | EF at baseline | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **20-25** | 0 | 0 | 2 | 0 | 0 | 0 | 2 | |
| **25-30** | 0 | 0 | 3 | 1 | 0 | 0 | 4 | |
| **30-35** | 0 | 0 | 1 | 2 | 2 | 0 | 5 | |
| **35-40** | 0 | 0 | 2 | 0 | 2 | 2 | 6 | |
| **40-45** | 0 | 0 | 0 | 0 | 0 | 5 | 5 | |
| **45-50** | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| **55-60** | 0 | 0 | 0 | 0 | 1 | 1 | 2 | |
| **Total** | 1 | 6 | 8 | 7 | 6 | 10 | 38 | |

Note: **- Very highly significant, #- Very highly significant.

**Table 5: Distribution of patients as per ejection fraction in sacubitril/valsartan group at baseline and at 6 months**

| Sacubitril/valsartan | EF at baseline | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **EF at 6 months** | **10-15** | **15-20** | **20-25** | **25-30** | **30-35** | **35-40** | **Total** | **P value#** |
| **Lost to follow up/died** | 1 | 2 | 0 | 0 | 0 | 2 | 5 | |
| **15-20** | 0 | 2 | 0 | 0 | 0 | 0 | 2 | 0.015* |
| **20-25** | 0 | 3 | 2 | 0 | 1 | 0 | 6 | |
| **25-30** | 0 | 2 | 1 | 1 | 0 | 0 | 4 | |
| **30-35** | 0 | 0 | 1 | 6 | 0 | 0 | 7 | |
| **35-40** | 0 | 2 | 2 | 4 | 2 | 1 | 11 | |
| **40-45** | 0 | 0 | 0 | 2 | 0 | 1 | 3 | |
| **45-50** | 0 | 0 | 0 | 0 | 0 | 3 | 3 | |
| **55-60** | 0 | 0 | 1 | 0 | 0 | 0 | 1 | |
| **Total** | 1 | 11 | 7 | 13 | 3 | 7 | 42 | |

Note: *- Highly significant, #- Very highly significant.

## DISCUSSION

This study was designed to compare the efficacy in terms of improvement of ejection fraction in post-acute coronary syndrome patients with LVEF <40%. In the two treatment groups ramipril is compared with sacubitril/valsartan. This was a randomized prospective study done to evaluate the improvement in EF of ramipril and sacubitril/valsartan in post-acute coronary syndrome patients.

In our study, the mean age of patients with ACS in Ramipril group was 64.21±10.26 years while in sacubitril/valsartan group the mean age was 62.19±12.58 years. SPACE registry observed that the mean age of patients was 58 years while ACC National Cardiovascular Data Registry (NCDR) Acute Coronary Treatment and Intervention Outcomes Network (ACTION) registry reported mean age of 64 years, GRACE registry observed age of 66 years and Kerala ACS registry (60.4 ± 12.1 years).[13-16]

### *Sex distribution*

In our study there were 26 (32.5%) females and 54 (67.5%) males. Similarly, in SPACE registry, researchers observed that 77% of all patients of ACS were males and studies by Sidhu et al and Singh et al also reported that 75.5% and 76.58% of patients were males respectively.[13,17,18] In our study, 50 (62.5%) patients were smoker and both groups were comparable in terms of smokers. Himbert et al also observed that smokers were more frequently diagnosed with ST-segment elevation myocardial infarction (46.0%) than former smokers (27.4%) and non-smokers (30.2%) (p<0.001).[19] Similarly, Yagi et al also observed that after adjusted multivariate analysis, only current smoking was an independent predictor of ACS (Odds ratio, 2.20; 95% CI, 1.28-3.78; p=0.004).[20] Cigarette smoke exposure (CSE) seems to alter the balance of antithrombotic/prothrombotic factors and profibrinolytic/antifibrinolytic factors by affecting the functions of ECs, platelets, fibrinogen, and coagulation factors and hence leads to ACS.[21]

### *History of alcohol intake*

In our study, 28.7% patients were having history of alcohol intake and the groups were comparable in terms of alcohol intake history. However, findings from interheart, a 52-country case-control study of individuals with first myocardial infarction (MI), supported the fact that-alcohol use‖ was associated with a reduction in the odds ratio for first-time MI.[22]

### *History of diabetes*

In our study, 31.2% of patients were diabetic and both the groups were comparable in terms of history of diabetes however, other studies have reported that the relative risk of myocardial infarction (MI) is 50% higher in diabetic men and 150% higher in diabetic women and the prevalence of acute MI is 3-5 times higher in patients with DM in US population studies.[23-25]

Patients with type 2 DM have similar risk for cardiac events as subjects with a prior MI.[26] The risk of recurrence of MI in diabetic patients is more than 40%.[27]

### *History of HTN*

In our study, 37.5% patients were hypertensive, and both the groups were comparable in terms of history of HTN. As arterial hypertension is one of the main factors leading to atherogenesis and the development of vulnerable plaques whose instability or rupture (which in turn results in thrombosis and vessel occlusions) are responsible for the development of ACS but we didn‘t had significant number of patients with hypertension.[28]

### *Type of ACS*

In India, STEMI has been reported as 60.6% and 69.9% and NSTEMI as 39.4% and 30.1%, however in Himachal Pradesh, NSTEMI (54.5%) has been reported more than STEMI (45.5%).[3,29,30] Similarly, we observed that there were 58.75% patients who had STEMI while 38.75% had NSTEMI and unstable angina was observed among 2.5% patients which is similar to Indian data but is contradictory to prevalence reported regarding Himachal Pradesh. Most common type of STEMI observed in our study was AW MI 37.5%. Similar to our observation, Gupta et al also reported that amongst the STEMI, majority of the cases (55.3%) had anterior wall MI (AWMI) followed by inferior wall MI (IWMI) (31.55%).[31] Badui et al also observed that AW MI was the most common STEMI which was seen in 59.8% cases.[32]

### *Change in EF at 6 months*

In our study, we observed that there was no statistically significant difference between the groups in terms of EF at 6 months (p value=0.275). In ramipril group there was statistically significant improvement in EF after 6 months as compared to baseline value (p value 0.004). Similar to ramipril group, in Sacubitril/valsartan group there was statistically significant improvement in EF after 6 months as compared to baseline value (p value 0.015).

Both the drugs were having similar results in terms of improving EF after 6 months administration. In Paradise-MI trial both the drugs were comparable in terms of EF at 8 months (p value=0.79).[33] However, Save-shock trial reported significant difference between the drugs in terms of EF at 6 months (p value 0.002).[34]

### *Safety*

Our study results showed no adverse events in terms of hypotension, renal dysfunction, hyperkalemia and angioedema. This observation suggests that both drugs are safe in the given population.

### *Limitations*

This study being post graduate thesis was time bound and was conducted during COVID-19 times and hence the sample size was not calculated considering that all the patients fulfilling the inclusion criteria will be included in the study.

Further, being the post graduate thesis, the follow-up could not be extended beyond 6 months.

Follow-up for longer duration and with larger sample size would have added more evidence about safety and efficacy of our drugs.

## CONCLUSION

In patients who experience ACS with left ventricular systolic dysfunction when treated with sacubitril/valsartan or with ramipril there was similar improvement in ejection fraction at 6$^{th}$ month when compared to baseline.

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