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Original Article

Efficacy and safety of sacubitril/valsartan compared with enalapril in patients with chronic heart failure and reduced ejection fraction: Results from PARADIGM-HF India sub-study

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ABSTRACT

Objectives: To determine efficacy and safety of sacubitril/valsartan compared with enalapril in Indian patients of PARADIGM-HF trial.
Methods: A randomized, double-blind, active-controlled, phase III sub-study (NCT01035255) was conducted between April 2010 and May 2014. Patients with chronic heart failure (HF), aged >18 years with left ventricular ejection fraction ≤40% were randomized (1:1) to receive either sacubitril/valsartan 200 mg twice-daily or enalapril 10 mg twice-daily. The primary endpoint was to compare efficacy of sacubitril/valsartan to enalapril in delaying time-to-first occurrence of the composite endpoint (cardiovascular [CV] death or HF hospitalization).
Results: The trial was stopped after a median follow-up of 27 months, because the boundary for benefit with sacubitril/valsartan had crossed. Among 637 Indian patients in PARADIGM-HF (sacubitril/valsartan, n = 322 and enalapril, n = 315), the primary outcome, CV death, and the first hospitalization for HF occurred in 21.81% and 24.76% (HR 0.89; 95% CI, 0.646−1.231), 17.45% and 20.63% (HR 0.87; 95% CI, 0.605−1.236), and 7.48% and 9.52% (HR 0.78; 95% CI, 0.461−1.350) patients in the sacubitril/valsartan and enalapril group, respectively. The all-cause mortality (19.0% vs. 21.9%) and adverse events (78.4% vs. 82.2%) were comparatively lower in the sacubitril/valsartan than enalapril group. No significant difference was seen between the benefits of treatment in Indian and the total PARADIGM-HF cohort (p value for interaction >0.05).
Conclusion: Results support the use of sacubitril/valsartan in Indian patients with chronic HF with reduced ejection fraction with treatment benefits similar to global PARADIGM-HF cohort.

1. Introduction

A substantial and sustained rise in the estimated prevalence and incidence rates of heart failure (HF) in India is a grave concern for public health and the key risk factors include high prevalence of cardiovascular (CV) and metabolic diseases.[1,2] Trivandrum Heart Failure Registry in India demonstrated a higher 3-year all-cause mortality (44.8%) in patients hospitalized for HF with higher incidence for patients with HF with reduced ejection fraction (HFrEF) (46.2%) compared to HF with preserved EF (40.8%).[3]

Sacubitril/valsartan, an angiotensin receptor neprilysin inhibitor (ARNI), has been shown to improve mortality and morbidity in patients with HFrEF without increasing the risk of angioedema.[4,5] In the Prospective comparison of ARNI with angiotensin converting enzyme inhibitor (ACEi) to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF), sacubitril/valsartan reduced the risk of CV death and HF hospitalization compared with enalapril in patients with chronic HFrEF.[6] This article reports results of a PARADIGM-HF sub-analysis that evaluated the efficacy and safety of sacubitril/valsartan in patients

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with chronic HFrEF among Indian population and the heterogeneity in treatment effects between Indian and global PARADIGM-HF cohorts.

2. Methods

This was a sub-analysis of PARADIGM-HF (NCT01035255), a multicenter, randomized, double-blind, active-controlled phase III trial, that included data from 44 Indian study sites (April 2010–May 2014) (Supplementary Table 1). The study was conducted according to the ethical principles of the Declaration of Helsinki. The study protocol was approved by Ethics Committee/Institutional Review Board affiliated to each study site. All patients provided written informed consent.

At screening visit, all eligible patients entered a single-blind, active run-in period (5–10 weeks) and received enalapril 10 mg twice-daily (BID), followed by sacubitril/valsartan at 100 mg BID, and then at 200 mg BID. Patients who tolerated all the target doses were then randomized (1:1) to receive either sacubitril/valsartan 200 mg BID or enalapril 10 mg BID during a double-blind period and followed up to 44 months (Supplementary Fig. 1).

The detailed inclusion and exclusion criteria are described elsewhere.[7] The key inclusion criteria were patients with chronic HF (New York Heart Association [NYHA] class II–IV), aged ≥18 years; HFrEF defined by a LVEF ≤40% (changed to ≤35% by protocol amendment 1; December 2010).

2.1. Endpoints

The primary endpoint was to compare efficacy of sacubitril/valsartan to enalapril in delaying time to first occurrence of the composite endpoint (CV death or HF hospitalization). Secondary endpoints were evaluation of time to all-cause mortality, assessment of improvement in the clinical summary score for HF symptoms and physical limitations by the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 8-months, evaluation of time to new onset atrial fibrillation and time to first occurrence of decline in renal function (details elsewhere published).[7] Adverse events (AEs) and serious AEs (SAEs) were evaluated. Heterogeneity in treatment effects between Indian and global PARADIGM-HF cohort was assessed.

2.2. Statistical methods

Data were analyzed using SAS (version 9.3). Primary and secondary variables were evaluated using full analysis set (FAS).[7] Hazard ratios (HR) were estimated using Cox proportional analysis and forest plot analysis was used for heterogeneity assessment of treatment effects. A $p < 0.05$ was considered statistically significant.

3. Results

A total of 637 patients were randomized (sacubitril/valsartan, n = 322 and enalapril, n = 315) in the double-blind period (Fig. 1). The trial was stopped early since the margin for overwhelming benefit of sacubitril/valsartan was crossed. Demographics and baseline clinical characteristics were comparable between the two groups (Table 1). The mean age was 57.03 years and the majority were men (78.18%). The incidences of comorbidities were similar between the two groups (Supplementary Table 2).

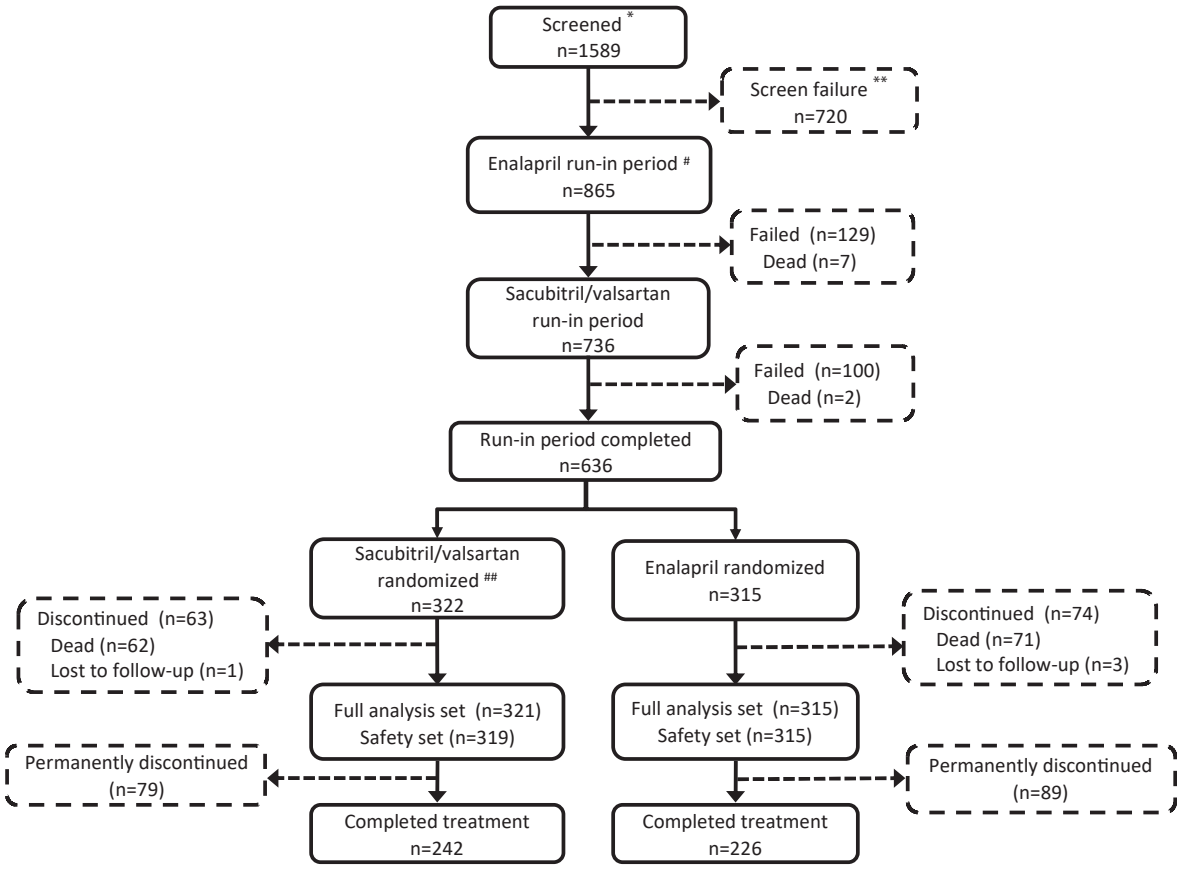

Fig. 1. CONSORT diagram.

Table 1
Comparison of Demographic characteristics of PARADIGM HF and India sub-analysis.

Baseline characteristics	Sacubitril/valsartan		Enalapril	
	India (n = 322)	Global (n = 4187)	India (n = 315)	Global (n = 4212)
Age (years), mean (SD)	56.31 (12.13)	63.8 (11.5)	57.77 (11.38)	63.8 (11.3)
Sex				
Men	247 (76.71)	3308 (79.0)	251 (79.68)	3259 (77.4)
Women	75 (23.29)	879 (21.0)	64 (20.32)	953 (22.6)
Baseline LVEF, mean (SD)	27.46 (5.86)	29.6 (6.1)	27.48 (5.69)	29.4 (6.3)
NYHA class				
I	16 (4.97)	180 (4.3)	21 (6.67)	209 (5.0)
II	266 (82.61)	2998 (71.6)	251 (79.68)	2921 (69.3)
III	38 (11.80)	969 (23.1)	42 (13.33)	1049 (24.9)
IV	2 (0.62)	33 (0.8)	1 (0.32)	27 (0.6)
BMI (kg/m^2), mean (SD)	23.54 (3.93)	28.1 (5.5)	23.45 (3.95)	28.2 (5.5)
SBP (mmHg), mean (SD)	117.25 (13.05)	122 (15)	116.96 (12.95)	121 (15)
Hypertension	137 (42.55)	2969 (70.9)	124 (39.37)	2971 (70.5)
Diabetes	113 (35.09)	1451 (34.7)	122 (38.73)	1456 (34.6)
NT-proBNP (pmol/L), median (range)	179.48 (97.35, 354.12)	192.46 (104.43, 372.17)	177.71 (98.18, 379.61)	188.09 (104.55, 389.99)
BNP (pmol/L), median (range)	74.98 (42.48, 145.45)	73.70 (44.80, 136.99)	74.48 (43.23, 146.70)	72.54 (44.22, 134.39)

Data shown as n (%), unless otherwise specified.
BMI, body mass index; eGFR, estimated glomeruli filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

3.1. Primary efficacy outcomes

The primary outcome occurred in 21.81% and 24.76% of patients in the sacubitril/valsartan and enalapril groups, respectively (HR 0.89; 95% confidence interval [CI], 0.646–1.231). Death due to CV events occurred in 17.45% and 20.63% of patients in the sacubitril/valsartan and enalapril group, respectively (HR 0.87; 95% CI, 0.605–1.236). The first hospitalization for HF was reported in 7.48% and 9.52% of patients receiving sacubitril/valsartan and enalapril (HR 0.78; 95% CI, 0.461–1.350) (Table 2).

3.2. Secondary efficacy outcomes

Patients in the sacubitril/valsartan group had comparatively reduced all-cause mortality compared to the enalapril group (19.0% vs. 21.9%). Incidence of renal dysfunction was similar in both the groups (sacubitril/valsartan, 4.05% and enalapril, 3.17%). New onset atrial fibrillation occurred in three patients each in both the groups (Table 2).

The mean change in the KCCQ clinical summary score from baseline to 8-month was −4.65 and −3.64 in the sacubitril/valsartan and enalapril groups, respectively (treatment difference −1.01 points; 95% CI, −5.45-3.42). Changes from baseline in the subdomains of KCCQ were not consistent, with lower reduction in scores for sacubitril/valsartan over enalapril in symptom stability and self-efficacy but higher reduction in scores for sacubitril/valsartan over enalapril in the remaining subdomains (Supplementary Table 3)

3.3. Safety analysis

Adverse events were comparatively lower in sacubitril/valsartan group (78.37%) than enalapril group (82.22%). The most common (>10%) AEs were cough, hyperkalemia, hypotension, and dyspnea (Table 3). The respective incidence of cough (23.49% vs. 13.48%), hyperkalemia (15.56% vs. 9.72%), and dyspnea (12.06% vs. 6.27%), except hypotension (8.75% vs. 11.91%) was more common in enalapril group as compared to sacubitril/valsartan group. Because of its greater vasodilator effects, treatment with sacubitril/valsartan was associated with a higher rate of symptomatic hypotension, but there was no increase in the rate of discontinuation because of possible hypotension-related adverse effects. The incidence of SAEs was lower in the sacubitril/valsartan group (31.97%) compared to the enalapril group (40.32%). Treatment-related SAEs were

Table 2
Primary and Secondary efficacy parameters.

Parameters	Sacubitril/valsartan (n = 321)[a]	Enalapril (n = 315)[b]	Sacubitril/valsartan vs Enalapril HR (95% CI)
Primary endpoint			
Primary composite	70 (21.81)	78 (24.76)	0.89 (0.646, 1.231)
CV death	56 (17.45)	65 (20.63)	0.87 (0.605, 1.236)
First HF hospitalization	24 (7.48)	30 (9.52)	0.78 (0.461, 1.350)
Secondary endpoint			
All-cause death	61 (19.00)	69 (21.90)	0.88 (0.629, 1.252)
Renal dysfunction[c]	13 (4.05)	10 (3.17)	1.35 (0.589, 3.072)
Time to first new onset of atrial fibrillation[d]	3 (0.99)	3 (1.00)	0.98 (0.198, 4.872)

Data shown as n (%).
HF, heart failure; HR, hazard ratio; CI, confidence interval; n, total number of events; N, total number of patients.
[a] For time to first new onset of atrial fibrillation n = 304.
[b] For time to first new onset of atrial fibrillation n = 300.
[c] Time to renal dysfunctions: Three types of renal dysfunctions: (i) 50% decline in eGFR.(ii) >30 mL/min/1.73 m^2 decline in eGFR to a value below 60 mL/min/1.73 m^2; (iii) reaching ESRD.
[d] Analysis was performed on a subset of FAS, for patients without atrial fibrillation history before randomization. Events occurred in double-blind period up to 31 March 2014 were included.

Table 3
Summary of adverse events (≥5% in any group).

Parameters	Sacubitril/valsartan (n = 319)[a]	Enalapril (n = 315)	Total (N = 634)
Overall adverse events	250 (78.37)	259 (82.22)	509 (80.28)
Cough	43 (13.48)	74 (23.49)	117 (18.45)
Hyperkalemia	31 (9.72)	49 (15.56)	80 (12.62)
Hypotension	38 (11.91)	27 (8.57)	65 (10.25)
Renal impairment	31 (9.72)	27 (8.57)	58 (9.15)
Dyspnea	20 (6.27)	38 (12.06)	58 (9.15)
Cardiac failure	25 (7.84)	28 (8.89)	53 (8.36)
Upper respiratory tract infection	26 (8.15)	25 (7.94)	51 (8.04)
Asthenia	24 (7.52)	25 (7.94)	49 (7.73)
Dizziness	22 (6.90)	24 (7.62)	46 (7.26)
Pyrexia	20 (6.27)	22 (6.98)	42 (6.62)
Constipation	15 (4.70)	21 (6.67)	36 (5.68)
Peripheral edema	15 (4.70)	18 (5.71)	33 (5.21)
Diabetes mellitus	18 (5.64)	14 (4.44)	32 (5.05)
Productive cough	15 (4.70)	17 (5.70)	32 (5.05)
Anemia	12 (3.76)	18 (5.71)	30 (4.73)
Arthralgia	18 (5.64)	11 (3.49)	29 (4.57)
SAEs	102 (31.97)	127 (40.32)	229 (36.11)
Patients who permanently discontinued the study drug due to an AE	18 (5.64)	19 (6.03)	37 (5.83)

Data shown as n (%).
[a] Total 634 patients from double-blind study medication (319 patients exposed to sacubitril/valsartan and 315 patients exposed to enalapril) formed the Safety Set.

observed in nine and 14 patients of the sacubitril/valsartan and enalapril groups, respectively. Cardiac disorders were the leading cause of study drug discontinuation in the both treatment groups (sacubitril/valsartan group, 5 [1.57%] and enalapril group, 9 [2.86%]) and were as follows- Cardiac failure chronic- 2 (sacubitril/valsartan arm), Cardiac failure congestive- 2 (sacubitril/valsartan arm) and 2(enalapril arm), Cardiac arrest- 1 (sacubitril/valsartan) and 3 (enalapril arm), Acute myocardial infarction- 1 (enalapril arm), Cardiopulmonary failure- 1 (enalapril arm), Myocardial infarction- 1 (enelapril arm), and Ventricular arrhythmia- 1 (enalapril arm). There was one confirmed angioedema case (0.3%) in each treatment group.

3.4. Heterogeneity analysis of treatment effect of sacubitril/valsartan

Treatment benefits of sacubitril/valsartan between Indian and PARADIGM-HF cohorts for all outcomes were similar (p value of interaction: primary composite outcome, 0.54; CV death, 0.71; HF hospitalization, 1.00; and all-cause mortality, 0.80) (Fig. 2).

4. Discussion

PARADIGM-HF is the largest clinical trial conducted globally that demonstrated effectiveness of sacubitril/valsartan over enalapril and provided evidence to support the replacement of ACEis or angiotensin II receptor blockers with sacubitril/valsartan in the management of chronic HF.[6]

The overall results of the present sub-analysis of PARADIGM-HF trial revealed that compared to enalapril, sacubitril/valsartan had better efficacy in reducing the risks of CV death, HF hospitalization, and all-cause mortality in Indian population. These findings are consistent with global study (PARADIGM-HF).[6] Patients randomized to sacubitril/valsartan had reduced primary composite outcome with fewer adverse events compared to enalapril.

For sacubitril/valsartan group, mean BMI (kg/m^2) and proportion of hypertensive patients in global population (28.1 and 70.9%) were higher compared to Indian population (23.54 and 42.55%). The lower incidence of hypertensive patients and lower average BMI observed in Indian population than global populations might be due to the lower sample size and population heterogeneity or vast lifestyle and dietary differences between Indian and global populations. Majority of patients belonged to NYHA class II in both the study populations (India, 82.61% and global, 71.6%). Prevalence of diabetes (34.7% vs. 35.09%), mean baseline LVEF (29.6 vs. 27.46), and median NT-pro BNP levels (pmol/L) (192.46 vs.179.46) were similar between global and Indian patients, respectively. The mean eGFR (mL/min/1.73 m^2) in global and Indian populations was similar (70 vs.75.92). Incidence of prior HF hospitalization (46.58% vs. 62.3%), stroke (2.80% vs. 8.5%), atrial fibrillation (4.97% vs. 36.2%) and permanent pacemaker implantation were lower in Indian population compared to global population.[6,8]

Primary endpoint analysis of global PARADIGM-HF trial revealed that treatment with sacubitril/valsartan was more effective in reducing the risk of death from CV causes or hospitalization for HF than with enalapril (HR in the sacubitril/valsartan group, 0.80; 95% CI, 0.73–0.87; P < 0.001).[6] Similarly, in Indian population, the sacubitril/valsartan treatment was more effective in reducing the incidence of primary composite outcome of death from CV causes or hospitalization for HF (HR, 0.89; 95% CI, 0.646–1.231) and in reducing the incidence of the CV death alone and hospitalization for HF alone, when compared with the enalapril. These results concord with the primary outcomes of the global PARADIGM-HF trial.[6]

Secondary endpoint analysis of this study revealed that the overall efficacy outcomes were consistent between the two treatment groups, suggesting equivalent effect of both treatments in achieving secondary endpoints. The KCCQ data showed only small inconsistent changes across the domains probably due to the small sample size. The overall profile of safety events revealed no significant difference between the two treatment groups. However, the overall incidence of AEs was lower in the sacubitril/valsartan group in comparison to the enalapril group and these results are in line with the AE related observations for the global patient population.[6] The patients in the enalapril group experienced a higher incidence of AEs related to cardiac disorders (29.21%) compared to the sacubitril/valsartan group (25.71%), largely due to the AEs of cardiac failure. Deaths due to CV causes were experienced in majority of patients from both treatment groups. However, it is noteworthy that incidence of death as well as SAEs was comparatively higher in enalapril group than sacubitril/valsartan group suggesting superiority of sacubitril/valsartan over enalapril. The comparatively higher incidence of hypotension in sacubitril/valsartan group is attributable to the greater blood pressure lowering

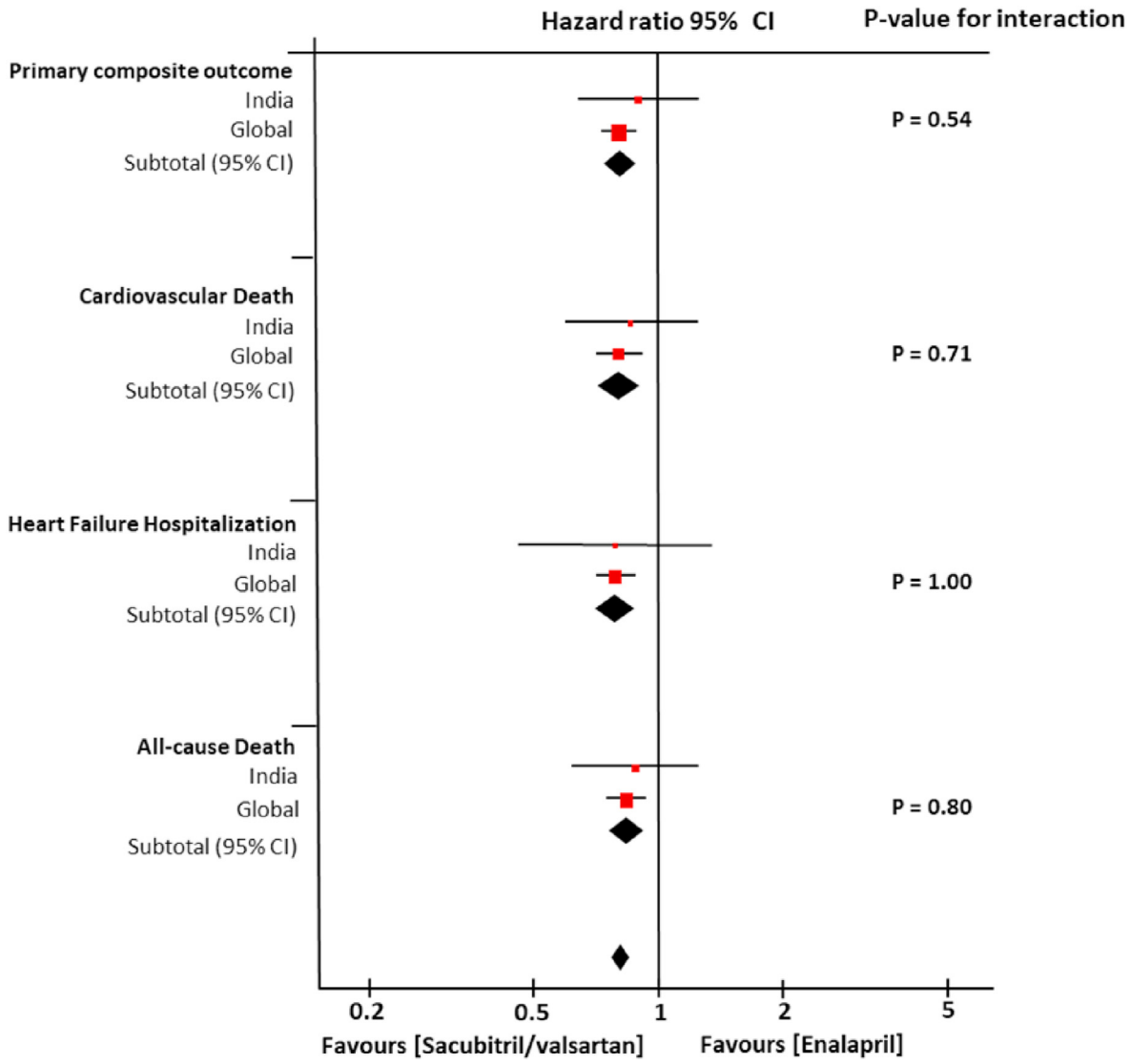

Fig. 2. Heterogeneity analysis of treatment effect of sacubitril/valsartan between Indian and PARADIGM-HF cohorts for all outcomes.

effect of sacubitril/valsartan treatment.[5] Hypotension neither resulted in more SAEs nor lead to more permanent discontinuations with sacubitril/valsartan relative to enalapril. In the present study, there was no imbalance between two treatment groups in terms of incidence of renal dysfunction, adverse liver events and angioedema. These observations indicate that the treatment of sacubitril/valsartan was well-tolerated in the Indian patients and concord with observations seen in the global population.[6]

A post-hoc analysis based on total PARADIGM-HF cohort has demonstrated that though there are several regional differences in the study population (including in age, clinical profile, comorbidities, background treatment), they did not modify the benefit of sacubitril/valsartan.[9] However, when all patients from Asian region were evaluated, the event rates were comparatively lower in patients who received sacubitril/valsartan than enalapril. The rate of HF hospitalization was lower and the rate of mortality was higher in South Asian population than other Asian groups; however, the overall any cause mortality was higher among Asians than total PARADIGM-HF cohort.[2] Overall, sacubitril/valsartan was well tolerated. Cough was the most commonly reported adverse event, however, the incidence was comparatively lower in sacubitril/valsartan group than enalapril group, consistent with Asian population[2] and total PARADIGM-HF cohort.[6]

A recently published data of pooled analysis of the PARADIGM-HF trial and the Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE (ATMOSPHERE) trial compared the patient characteristics and clinical outcomes within Asia and between Asia, Europe and the Americas. They revealed that along with differences observed in patient characteristics and outcomes between Asia and other global regions, the variations were also observed among Asian countries.[10] A study reviewing the development of sacubitril/valsartan and the evidence for its efficacy and safety in Asian patients with HFrEF observed no difference between the benefits of treatment in Asians and the total PARADIGM-HF cohort or between the different regions of Asia.[2] These findings are in accordance with the present study suggesting no difference in the treatment benefits between Indian and global PARADIGM-HF cohorts and provide evidence for acceptance of sacubitril/valsartan as a treatment option for Indian population.

Several recent observations from various trials support the efficacy and safety of sacubitril/valsartan in patients with HFrEF. In 2018, TRANSITION study showed that sacubitril/valsartan can be

safely initiated shortly after an acute heart failure episode, both in the hospital and in an out-patient setting and in a wide range of stabilized patients.[11] A recently published results of Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure (PROVE-HF) trial revealed that the patients with HFrEF treated with sacubitril/valsartan achieved rapid reduction in NT-proBNP, an established biomarker for heart failure severity and prognosis and was weakly yet significantly correlated with improvements in markers of cardiac volume and function at 12 months indicating reverse cardiac remodeling at one year.[12] Similarly, PIONEER-HF open label 4-week extension trial also demonstrated efficacy of sacubitril/valsartan in delivering reductions in NT-proBNP and supports the initiation of sacubitril/valsartan in hospital and as a first-choice systolic heart failure therapy in stabilized patients.[13] Another Phase IV EVALUATE-HF trial that assessed sacubitril/valsartan's effect on remodeling of the blood vessels of the heart and ventricular-vascular coupling compared with enalapril revealed that both drugs did not improve the primary endpoint of change in aortic impedance (a measure of vascular stiffness); however, sacubitril/valsartan improved the structure and function of the left ventricle compared to enalapril that corroborate PROVE-HF trial observations.[12,14] Authors also reported comparable safety profile as observed in PARADIGM-HF.[6]

In conclusion, sacubitril/valsartan effectively reduced the risks of CV death, HF hospitalization and all-cause mortality in patients with chronic HF compared to enalapril with acceptable safety profile and treatment benefits were similar between Indian and global PARADIGM-HF cohorts.

5. Key message

In this sub-analysis of Indian patients of PARADIGM HF, treatment with sacubitril/valsartan was superior to enalapril and safe in reducing the risk of CV death, HF hospitalization and all-cause mortality and the findings are in concordance with the results of the global trial.

Author contributions

Anil Ranjeetmal Jain: Concepts, Design, Definition of intellectual content, Clinical studies, Experimental studies, Formal analysis, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review, Guarantor. Rakesh Kumar Aggarwal: Concepts, Design, Definition of intellectual content, Clinical studies, Experimental studies, Formal analysis, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review, Guarantor. Srinivas Rao Nanyam: Design, Definition of intellectual content, Clinical studies, Experimental studies, Formal analysis, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review, Guarantor. Gauri Billa: Formal analysis, Manuscript review, Guarantor. Shankar Kumar: Design, Literature search, Formal analysis, Manuscript preparation, Manuscript editing, Manuscript review, Guarantor.

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Conflicts of interest

Anil Ranjeetmal Jain, Rakesh Kumar Aggarwal, and Srinivas Rao Nanyam have no conflict of interest to declare. Gauri Billa and Shankar Kumar are full time employees of Novartis Healthcare Private Limited.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2020.09.016.

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