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Angiotensin Receptor Neprilysin Inhibitor Effect on End Diastolic Volumes on 2D Echocardiography

Ashish Kumar D.M.

Assistant Professor, Department of Cardiology, National Institute of Medical Sciences and Research, NIMS University Rajasthan, Jaipur

Abstract: ***Heart failure remains a major public health challenge, with a growing burden driven by population aging and increasing survival of patients with cardiovascular disease. Sacubitril/ Valsartan, an angiotensin receptor neprilysin inhibitor, has shown clinical benefits in patients with heart failure with reduced ejection fraction, yet evidence regarding sex related differences in cardiac remodeling remains limited. This prospective, randomized, open label study with blinded end point assessment enrolled 310 patients with chronic heart failure in an equal male to female ratio and evaluated changes in left ventricular mass, Tei index, clinical outcomes, and safety over 6 months of therapy. Echocardiographic assessment demonstrated demonstrated a marked reduction in left ventricular mass and significant improvement in Tei index in both groups. After adjustment for baseline for baseline left ventricular mass and treatment, regression of left ventricular mass was greater in males than in females, while improvements in Tei index were comparable between sexes. Rates of mortality, heart failure hospitalization, hypotension, renaldysfunction, and angioedemadid not differ significantly between groups. These findings support the value of serial echocardiographic evaluationof left ventricular mass and Tei INDEX as practical measures of treatment response in patients receiving Sacubitril/Valsartan andhighlight the presence of sex related response in patients receiving Sacubitril/Valsartan and highlight the presence of sex related differences in cardiac structural remodeling during therapy.***

Keywords: Heart Failure, Sacubitril Valsartan, Left Ventricular Mass, Tei Index, Sex Differences

1. Introduction

The prevalence of HF continues to rise over time with the aging of the population. The number of people diagnosed with heart failure is increasing and projected to rise by 46 % by 2030, resulting in more than 8 million people with heart failure. An estimated 6.5 million American adults ≥20 years of age had HF between 2011 and 2014 compared with an estimated 5.7 million between 2009 and 2012.[1,2] Heart failure affects 5 million Americans, and nearly 50% of these are women.[3]

Sacubitril/Valsartan is an angiotensin receptor neprilysin inhibitor (ARNI) approved for treatment of heart failure (HF). Sacubitril promotes effects of natriuretic peptides by inhibiting Neprilysin which is an endopeptidase, degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin.[4-6] Neprilysin inhibition increases the levels of these substances, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive Left Ventricular remodelling.[7,8] Valsartan blocks angiotensin II type 1 receptors. It has been shown to reduce morbidity and CV related mortality in patients of HFrEF.[9]

Sex has profound impact on apoptosis in cardiac myocytes.[10] Observational clinical studies and post-mortem and experimental studies suggest presence of important differences in cardiac remodelling between males and females when exposed to pressure overload, volume overload, myocardial ischemia and diastolic heart failure.[11] Females have been previously shown to have greater reduction in LV mass than men in hypertensives with losartan based treatment.[12] Females have been grossly underrepresented in various heart failure trials even though they represent 50% of the disease burden.[3] Here we aim to remove this bias and perform a trial with head to head female to male comparison.

Left Ventricular mass has been shown to been prognostically linked to heart failure and has been shown to reduce following Aortic Valve Replacement in aortic stenosis/regurgitation with heart failure.[13-15] Similar LV mass reduction was also seen in heart failure patients post cardiac resynchronization therapy.[16] Tei index is independent of ventricular geometry, blood pressure, heart rate ,age and sex, has prognostic value in patients with symptomatic heart failure.[17-19] Here we aim to use these parameters to study gender differences in effects of Sacubitril/Valsartan therapy .

2. Methods

Study Design

ARTIM HF is a prospective, randomized, open-label trial with blinded end-point adjudication. The trial was conducted at single centre (Department of Cardiology, National Institute of Medical Sciences and Research, NIMS University Rajasthan, Jaipur). The trial protocol was approved by the ethics committee at our institution.

Patients and Randomization

Trial enrolment was from January 2, 2017 until April 2, 2018. Patients were eligible for inclusion if they were over the age of 18 years and, New York Heart Association (NYHA) class II, III, or IV symptoms, and an ejection fraction <40%.

Exclusion criteria included symptomatic hypotension, a systolic blood pressure of less than 100 mm Hg, an estimated glomerular filtration rate (eGFR) below 30 ml per minute per 1.73 m2 of body-surface area, a serum potassium level of more than 5.2 mmol per litre, or a history of angioedema or unacceptable side effects during receipt of

ACE inhibitors or ARBs. Baseline characteristics are were similar in female and male groups apart from LV mass (Table 1).

Study Procedures

Patients were started on Sacubitril/Valsartan in doses of 50 mg twice a day, to minimize the risk of angioedema caused by overlapping ACE and neprilysin inhibition, ACE inhibitors/ARB's were withheld 48 hours before starting Sacubitril/Valsartan therapy. Patients were evaluated clinically and for adverse effects every 2 weeks and dose adjusted up to maximally tolerated dose or 200 mg twice a day dose, whichever was achieved earlier. The dose of the study drug could be reduced in patients who had unacceptable side effects. Patients were evaluated clinically every 2 weeks during the first 3 months of therapy and every month thereafter. This was in addition to optimum guideline directed medical therapy.[20]

2D Echocardiography Studies were performed according to American Society of Echocardiography guidelines[21] using Philips iE 33 system (Philips Medical Systems, Bothell, WA, USA) quipped with 3.0–3.5 MHz and 2.0–2.5 MHz transducers with M-mode, 2-D and pulsed, continuous and colour-flow Doppler capabilities, was done for LVEF, LV mass, Tei index evaluation at baseline and followed up at 3 and 6 months while being on the drug. LV mass measurement done by linear 2D echocardiographic M-mode provides prognostic information beyond traditional cardiovascular risk factors.[22-25] Same method of LV mass assessment in parasternal long axis view using Devereux and Reichek "cube" formula was used in our study.[26]

$LV\ mass = 0.8 \times 1.04 \times [(IVS_d + LVID_d + PWT_d)^3 - LVID_d^3] + 0.6$

IVS_d : ventricular septal thickness at end diastole, $LVID_d$: LV internal diameter at end diastole, PWT_d: inferolateral(posterior) LV wall thickness at end diastole.

Tei index=IVCT+IVRT/LVET, calculated by 2D echo by Pulsed Wave Doppler method in apical 4 chamber view.[17,18] IVCT: isovolumic contraction time, IVRT :isovolumic relaxation time, LVET :left ventricular ejection time.

2D echocardiography evaluation was done by two independent investigators who were routinely doing echocardiography at our centre and were did not know which patients were enrolled in the trial and the mean of the two values was taken as our final value. In case of discrepancy between results of both investigators (LV mass difference > 10 gm), cardiac MRI was done and echocardiographic LV mass closest to the cardiac MRI evaluated LV mass was taken as the final value.

Study Outcomes:

The primary outcome was a composite of death from cardiovascular causes or a first hospitalization for heart failure. The secondary outcomes were the time to death from any cause, the change from baseline to 6 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ)[27] (on a scale from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure),the time to a new onset of atrial fibrillation, and thetime to the first occurrence of a decline in renal function (which was defined as end-stage renal disease or as a decrease in the eGFR of at least 50% or a decrease of more than 30 ml per minute per 1.73 m2 from randomization to less than 60 ml per minute per 1.73 m2). Adjudication of these outcomes was carried out in a blinded fashion by a clinical-end-points committee according to prespecified criteria.

Statistical Analysis: Assuming a between person standard deviation in LV mass of 15.61 gm and a correlation between an individual's baseline and follow up LV mass of 0.8, sample size was calculated to be 153 in each group that would provide ≥80% power (at p=0.05) to detect 5 gm difference in LV mass at final follow up, even if 15% of participants discontinued allocated study treatment.

Data management and analysis were performed using XLSTAT 2018 (Microsoft Corporation, WA, USA) software. Data are presented as mean ± SD for continuous variables and as proportions for categorical variables. Time-to-event data were evaluated with the use of Kaplan–Meier estimates and Cox proportional hazards models, with treatment and region as fixed-effect factors; hazard ratios, 95% confidence intervals, and two-sided P values were calculated with the use of the Cox models. We assessed the consistency of the treatment effect among subgroups and used a repeated-measures covariance model to evaluate the KCCQ score, with baseline values as covariates; a score of zero was used for patients who had died. Differences in clinical and echocardiographic variables at baseline and after 6 months of Sacubitril/Valsartan treatment within sex were assessed by the paired t-test for repeated measurements. Between sex differences in clinical and echocardiographic variables were assessed by analysis of covariance. A general factorial model was used for analysis of covariance, and multiple simple contrasts were obtained after adjustment of the confidence intervals with Sidak's method to compare LV hypertrophy regression between sexes after adjustment for baseline LV mass and after Sacubitril/Valsartan therapy. Two-tailed P<0.05 indicated statistical significance.

3. Results

Study Patients:

310 patients at our centre we recruited with males and females in 1:1 ratio. The groups were balanced with respect to baseline characteristics. Most patients were receiving recommended pharmacologic therapy for chronic heart failure.

Study-Drug Administration and Follow-Up:

Except for discontinuations owing to death, the study drug was discontinued in 51 patients (16.4%) receiving Sacubitril/Valsartan, of which 27 were females and 24 were males. = 0.02). At the last assessment, among patients taking the study medication, the mean (±SD) dose of Sacubitril/Valsartan was 375±71 mg, 346±74 in females and 404±69 in males. Two patients in the male group and 1 patient in the female group were lost to follow-up, and their data were censored at the last contact. The mean duration of follow-up was 185±15 days, with no significant between group difference.

Study Outcomes:
At 6 months, there were no significant changes from baseline in hypotension and serum creatinine (Table 4) level between the two groups. Angioedema was confirmed by blinded adjudication in 1 patient in the female group and in 1 patient in the male group (P > 0.05). No patient had airway compromise or required mechanical airway protection.

There were no significant mortality/ morbidity differences between groups (Table 3). There were 16 (10.4%) deaths in female group and 17(10.9%) deaths in female group (P value >0.05), (Figure 4) and 26(18.1%) heart failure hospitalizations in female group and 17 (10.9%) in male group (P value >0.05) (Figure 1).

As compared to baseline, on Echocardiography follow up at 6 months (Table 2), LV EF increased from 27.98±5.19% to28.10±5.16% (p value >0.05) in females and from 29.04±4.74% to 29.11±4.69% (p value>0.05) in males. LV Tei index reduced from 0.704±0.12 to 0.629±0.12 (p value<0.001) in females and from 0.721±0.11 to 0.645±0.009 (p value <0.001) in males (Figure 3). LV mass was reduced from 187.63±28.88gm to 164.96±24.01gm in females (p value<0.001), from 226.07±10.66gm to 183.59±24.50 gm in males (p value<0.001). However, on correction for baseline LV mass and therapy, LV mass was 180.30±11.52gm in females and 168.45±11.64gm in males (p value <0.001). Reduction in LV mass was more in males as compared to females (Figure 2). LV mass regression was greater in men, by 11.85 g, after adjusting for baseline LV mass and Sacubitril/Valsartan therapy.

4. Discussion

In our study involving patients with chronic heart failure and a reduced ejection fraction, the inhibition of both the angiotensin II receptor and neprilysin with Sacubitril/Valsartan effect on mortality and repeat heart failure hospitalization was the same in both female and male groups and the difference in between groups was nonsignificant (p value >0.05). Also, we observed significant reduction in Left Ventricular mass in patients enrolled in the trial and this effect was more in males as compared to females (p value < 0.05). We also found significant improvement in Tei index at 6 months as compared to baseline values in both female and male groups but when comparing Tei index of females and males at 6 moths of therapy, the difference was not significant (p>0.05).

Earlier studies compared Sacubitril/Valsartan with enalapril but our study had most of the patients on ARB therapy before switching over to Sacubitril/Valsartan, which provided cross-over model for comparison with same group of drugs (ARB).

The benefit of Sacubitril/Valsartan was established in earlier trials but here we try to establish the underlying physiological causes that lead to those clinical benefits. We identified Left Ventricular mass and Tei index as reliable and reproducible indicators of functional improvement in myocardial function which translates into clinical and mortality benefit, was seen in patients who were already receiving all other drugs known to improve survival among patients with heart failure (i.e., beta-blockers and mineralocorticoid-receptor antagonists).

We also tried to asses these indices for comparison between females and males and found statistically significant difference in Left Ventricular mass (p <0.05).

5. Study Limitations

Firstly, the short study duration restricts our ability to assess long term effects of Sacubitril/Valsartan on survival and its correlation with LV mass. Yet even with this short follow up duration, we were able to achieve statistically significant regression in LV mass and Tei index Secondly, the infeasibility or imprecision of the determination of the Tei index in patients with atrial fibrillation. But, patients with atrial fibrillation were very few in number in our study. Thirdly, LV mass estimation depends on many circumstances including context, regression to the mean, echocardiography laboratory experience and patient's general condition, a test- retest variability of 10 % should always be considered when comparing two LV mass values.[28] We overcame that limitation by having two independent Operators perform the evaluation and resolving discrepancies by use of cardiac MRI which is the gold standard for LV mass estimation.

6. Conclusion

Our results suggest that serial measurements of LV mass and Tei index using echocardiography are useful for assessing the therapeutic efficacy of Sacubitril/Valsartan. LV mass regression is more in males than females on Sacubitril/Valsartan therapy.

Clinical Perspectives
LV mass and Tei index can be used as more efficient and objective tools for follow up of patients with HFrEF as compared to simple clinical evaluation (NYHA classification which only gives importance to between class transitions ignoring minute within class finer improvements) and exhaustive questionnaires (which are subjective). These are also more cost effective compared to costly and invasive investigations (BNP, NT proBNP).

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Table 1: Patient characteristics at baseline

Characteristics*	Females (n=154)	Males (n=156)	P Value
Age—yr	60±12	61±13	>0.05
Systolic blood pressure—mmHg	136±16	139±17	>0.05
Heart rate—beats/min	90±17	88±14	>0.05
Body-mass index§	23±4.6	24±9.9	>0.05
Serum creatinine—mg/dl	1.06±0.21	1.11±0.28	>0.05
Rural setting – no.(%)	94(61.0)	110(70.5)	>0.05
Urban setting – no.(%)	60(39)	46(29.5)	>0.05
Clinical features of heart failure	107(69.4)	112(71.8)	>0.05
Ischemic cardiomyopathy—no.(%)	47(30.5)	44(28.2)	>0.05
Non ischemic cardiomyopathy—no.(%)			
NYHA functional class—no.(%)†			
II	105(68.1)	104(66.7)	>0.05
III	39(25.3)	43(27.5)	>0.05
IV	10(6.5)	9(5.8)	>0.05
Medical history – no. (%)			
Hypertension	100(64.9)	106(67.9)	>0.05
Diabetes	49(31.8)	55(35.2)	>0.05
Atrial fibrillation	9(5.8)	11(7.1)	>0.05
Hospitalization for heart failure	91(59.1)	90(57.6)	>0.05
Myocardial infarction	82(53.2)	89(57.1)	>0.05
Treatments at randomization—no.(%)			
Pretrial use of ACE inhibitor	136(88.3)	135(86.5)	>0.05
Pretrial use of ARB	18(11.6)	21(13.4)	>0.05
Diuretic	131(85.1)	139(89.1)	>0.05
Digitalis	28(18.2)	36(23.1)	>0.05
Beta-blocker	119(77.3)	103(66.0)	<0.05
Mineralocorticoid antagonist	94(61)	89(57.1)	>0.05
Implantable cardioverter–defibrillator	1(.006)	1(0.006)	>0.05
2D Echo Parameters			
Left Ventricular ejection fraction—%	27.98±5.19	29.04±4.74	>0.05
Left Ventricular Mass	187.63±28.88	226.07±10.66	<0.001
Tei Index	0.704±0.12	0.721±0.11	>0.05

* Plus–minus values are means ±SD. There were no significant differences between the two groups except for the use of Beta-blocker (P<0.05) and LV mass (P<0.001), with values not adjusted for multiple testing. Percentages may not total 100 because of rounding.
†The data for New York Heart Association (NYHA) class reflect the status of patients at the time of enrollment. Patients were required to have at least NYHA class II symptoms at study enrollment.

Table 2: Echocardiographic follow- up

	Female			Male			Female vs male
Parameters	baseline	6 month	P value	baseline	6 month	P value	P value (6 mth.)
LV mass(gm)	187.63±28.88	164.96±24.01	<0.001	226.07±10.66	183.59±24.50	<0.001	<0.001
LV Tei index	0.704±0.12	0.629±0.12	<0.001	0.721±0.11	0.645±0.09	<0.001	>0.05
LV EF(%)	27.98±5.19	28.10±5.16	>0.05	29.04±4.74	29.11±4.69	>0.05	>0.05

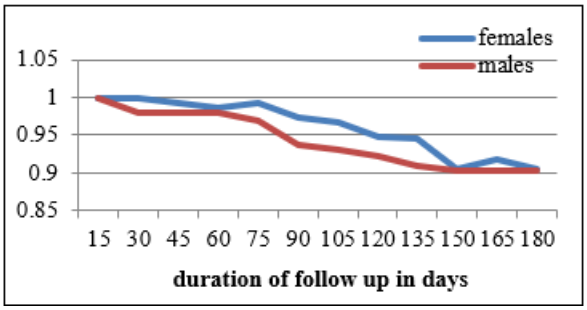

Figure 1: First heart failure hospitalization

Figure 1: Kaplan- Meier Curves for Outcomes in each group, Shown are estimates of the probability first hospitalization for Heart failure (P value >0.05).

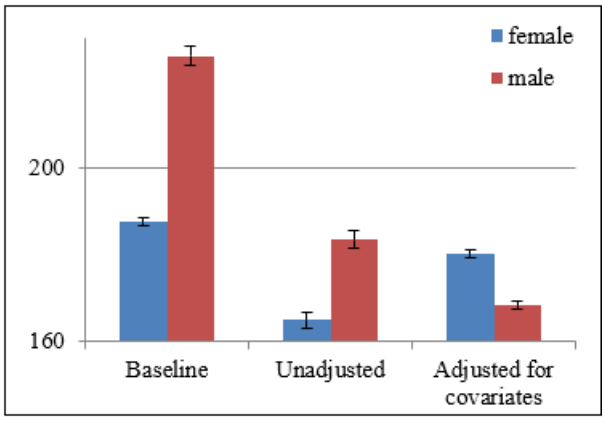

Figure 2: LV mass

Figure 2: Baseline (left panel), Unadjusted (middle panel) and adjusted (right panel) LV mass in grams (Y-axis) in males and females at 6 months of Sacubitril/Valsartan treatment. Data are expressed as means and error bars represent standard errors