The impact of sacrubitril/valsartan on clinical treatment and hs-cTnT and NT-ProBNP serum levels and the left ventricular function in patients with chronic heart failure

BACKGROUND

- Chronic heart failure is a debilitating and potentially life-threatening condition that is persistent and progressive. Common signs and symptoms associated with heart failure include shortness of breath, swelling of the lower extremities, chest pain, and fatigue.
- Beta-blockers and ACE inhibitors or ARBs are the backbone of heart failure with reduced ejection fraction (HFrEF) management. Sacubitril-valsartan (Entresto) is an angiotensin receptor-neprilysin inhibitor (ARNI) that is indicated for the treatment of patients with symptomatic HFrEF.

OBJECTIVE

- To determine the impact of sacubitril-valsartan (Entresto) on clinical response and high-intensity cardiac troponin T (hs-cTnT), N-terminal pro-brain natriuretic peptide (NT-ProBNP) serum levels, the improvement of the left atrial diameter (LAD), and left ventricular end diastolic dimensions (LVEDD), and the left ventricular ejection fraction (LVEF) in patients with chronic heart failure (CHF).

METHODS

- **Design**: Single site, randomized, parallel, controlled trial
- **Inclusion criteria**: Age > 60 years; definite diagnosis of CHF (New York Heart Association [NYHA] Class II-IV, with LVEF less than or equal to 40%); withdrawal of the use of ACE inhibitors for at least 36 hours; no tumors or autoimmune diseases
- **Exclusion criteria**: Acute heart failure; serious disease of the liver, kidney, or other important organs; heart failure secondary to underlying disease; systolic blood pressure < 90 mmHg; heart rate <55 bpm; hyperkalemia; mental illness; poor compliance; allergies to the medications used in this study.
- **N = 120 total** (60 in each treatment group)
    - Sacubitril-valsartan (Entresto) 49/51 mg BID **+** standard of care for 8 weeks
    - Valsartan 80 mg QD **+** standard of care for 8 weeks
- **Primary outcome measure**: Changes in hs-cTnT and NT-ProBNP serum levels and improvement in LAD, LVEDD, and LVEF
- **Secondary outcome measures**: Clinical improvement, adverse reactions, rehospitalizations
- **Data handling**: Intent-to-treat

RESULTS

- All patients completed the study (60 in each group)
- **Primary outcome measure**:
    - Statistically significant changes seen between sacubitril-valsatan and valsartan alone
    - Tables taken from reference

Table III. The Levels of hs-cTnT and NT-ProBNP in Serum before and after the Treatments (pg/mL), $x \pm s$

Groups	n	hs-cTnT		P value	NT-ProBNP		P value
		Before the treatments	After the treatments		Before the treatments	After the treatments	
Sacrubitil/valsartan group	60	24.47 ± 7.54	17.92 ± 4.74*#	0.001	10356.94 ± 5447.68	3881.59 ± 2087.79*#	< 0.001
Valsartan group	60	29.75 ± 10.03	25.81 ± 7.36*		9518.17 ± 5905.17	6278.35 ± 2643.11*	
P		0.092	0.001		0.670	0.006	

Compared with the valsartan group after the treatments, levels of hs-cTnT and NT-ProBNP in serum in the sacrubitil/valsartan group were lower, $^{\#}P < 0.05$. While compared with the sacrubitil/valsartan group before the treatments, the clinical treatments could improve the levels of serum hs-cTnT and NT-ProBNP in the sacrubitil/valsartan group, $^{*}P < 0.05$ and the same in the valsartan group.

Table IV. The Measurements of LAD, LVEDD, and LVEF before and after the Treatments, $x \pm s$

Group	n	LAD (mm)		P value	LVEDD (mm)		P value	LVEF (%)		P value
		Before the treatments	After the treatments		Before the treatments	After the treatments		Before the treatments	After the treatments	
Sacrubitil/ valsartan group	60	49.41 ± 5.22	42.18 ± 4.87	< 0.001	68.06 ± 6.20	60.35 ± 7.12*#	< 0.001	31.12 ± 6.65	45.35 ± 4.49	< 0.001
Valsartan group	60	49.65 ± 4.91	46.53 ± 4.80		67.06 ± 3.97	64.51 ± 4.34*		30.41 ± 6.11	36.47 ± 5.21	
P value		0.893	0.013		0.579	0.048		0.749	0.000	

After the treatments, compared with the valsartan group, the measurements of LAD and LVEDD in sacrubitil/valsartan group decreased obviously, and the LVEF improved greatly, $^{\#}P < 0.05$. Compared with the sacrubitil/valsartan/valsartan group before the treatments, the clinical treatments could improve the measurements of LAD, LVEDD, and LVEF in the sacrubitil/valsartan/valsartan group, $^{*}P < 0.05$.

- **Secondary outcome measures**: (Taken from reference)

Table II. The Effect of the Treatments of the Two Groups

Results	sacrubitil/valsartan group ($n = 60$)	valsartan group ($n = 60$)	P value
Therapeutic effect, n (%)	53 (88.33) *	42 (70.00)	0.013
Remarkable effect	18 (30.00)	4 (6.67)	
Effect	35 (58.33)	38 (63.33)	
No effect	7 (11.66)	18 (30.00)	
Adverse reaction, n (%)	8 (13.33) *	17 (28.33)	0.043
Angioedema	0 (0.00)	0 (0.00)	
Hypotension	7 (11.67)	7 (11.67)	
Hyperkalemia	0 (0.00)	3 (5.00)	
Severe renal insufficiency	1 (1.67)	7 (11.67)	
Clinical events needing rehospitalization, n (%)	8 (13.33) *	17 (28.33)	0.043
Cardiac function worsen	6 (10.00)	15 (25.00)	
Acute myocardium infarction	2 (3.33)	1 (1.67)	
Severe renal insufficiency	1 (1.67)	7 (11.67)	
Stroke	0 (0.00)	0 (0.00)	

Compared with the valsartan group after the treatments, the positively effective rate of clinical treatments of the sacrubitil/valsartan group was higher, and the adverse reaction was lower.$^{*}P < 0.05$.

- **Author's conclusion:** Sacubitril-valsartan treatment of patients with CHF improves their symptoms and is deserving of clinical application. This is also evident from significantly improved levels of serum hs-cTnT, NT-ProBNP, and the left ventricular function.

STRENGTHS

- Randomized, controlled trial
- No dropouts
- Measured concentrations of substances not commonly measured in practice

LIMITATIONS

- No blinding, short study duration, and small sample size
- Target doses with appropriate dosage titrations for heart failure were not used in either treatment group
- Definitions used for clinical assessments were subjective and not well-defined (e.g., 'remarkable' effect)
- No adherence data provided
- Only participants > 60 years were studied

CONCLUSION

- Sacubitril-valsartan showed promising results in lowering hs-cTnT and NT-ProBNP serum levels as well as improvements of LAD, LVEDD, and LVEF when comparing data before and after treatments ($p < 0.001$).
- More patients experienced positive clinical effects in the sacubitril-valsartan group compared to the valsartan group (88% vs 70%); ($p < 0.013$).
- Sacubitril-valsartan resulted in a reduction in the biomarkers associated with heart failure and improved clinical outcomes over an 8-week period.
- However, this may not be an option for patients severely hypotensive or with severe renal insufficiency.
- Well-designed double-blind studies with appropriate dosage titrations are needed to further define differences in efficacy and in heart failure biomarker concentrations between sacubitril-valsartan and other heart failure therapies.

Reference:

1. Gao Y, Xing C, Hao W, Zhao H, Wang L, Luan B, and Hou A. The impact of sacrubitril/valsartan on clinical treatment and hs-cTnT and NT-ProBNP serum levels and the left ventricular function in patients with chronic heart failure. *Int Heart J.* 2020; 61(1):1-6.

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