ORIGINAL ARTICLE
DOI 10.4070/kcj.2011.41.2.61

Print ISSN 1738-5520 / On-line ISSN 1738-5555

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Effect of Valsartan on N-Terminal Pro-Brain Natriuretic Peptide in Patient With Stable Chronic Heart Failure: Comparison With Enalapril

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ABSTRACT

Background and Objectives: The plasma concentration of N-terminal pro-brain natriuretic peptide (NT-pro-BNP) is a strong prognostic indicator for patients with heart failure (HF) across all stages of the condition. Several clinical trials have demonstrated convincingly that neurohormonal modulation on the renin angiotensin system (RAS) decreases plasma NT-pro-BNP level and results in favorable outcomes. But there are still limited comparative data on the neuro-hormonal modulatory effects of two RAS inhibitors: angiotensin converting enzyme inhibitor and angiotensin receptor blocker. **Subjects and Methods:** This study was a prospective, multi-center, randomized, open-label, controlled, and non-inferiority study involving 445 patients with left ventricular ejection fraction (LVEF) less than 45%. Patients were assigned to receive either valsartan (target dose of 160 mg bid) or enalapril (target dose of 10 mg bid) for 12 months. We compared plasma NT-pro-BNP, high sensitive C-reactive protein (hs-CRP) level and echocardiographic parameters before and after treatment with valsartan or enalapril. **Results:** The NT-pro-BNP and hs-CRP levels were significantly decreased after 12 months of treatment with valsartan and enalapril. The percentage change was similar between both groups. LVEF improved and left ventricular internal dimensions were decreased in both groups, and there were no significant differences between two groups. **Conclusion:** Valsartan is as effective on improving plasma NT-pro-BNP level as enalapril in patients with stable chronic HF. **(Korean Circ J 2011;41:61-67)**

KEY WORDS: Brain natriuretic peptide; Angiotensin-converting enzyme inhibitors; Angiotensin receptor blocker; Congestive heart failure.

Introduction

Activation of the renin-angiotensin-aldosterone system (RAS) promotes structural remodeling of the heart and the progression of heart failure (HF).[1)2)] Angiotensin converting enzyme inhibitors (ACE inhibitor) act principally by blocking the formation of angiotensin II.[3)] In the CONSENSUS and SOLVD studies, enalapril significantly reduced mortality and hospitalizations for HF in patients with chronic congestive HF and reduced ejection fractions.[4)5)] On the other hand, angiotensin receptor blocker (ARB) selectively inhibits angiotensin II type 1 receptors. In the Val-HeFT study, valsartan improved symptoms of HF, left ventricular (LV) function, LV dilation and reduced the risk of hospitalization for HF.[6)]

Neurohormone activation is characteristic of HF, and elevation of circulating N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels, and other neurohormones is directly

Received: May 9, 2010
Revision Received: June 22, 2010
Accepted: July 6, 2010
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• The authors have no financial conflicts of interest.

related to mortality and morbidity.[7][8] In addition, plasma NT-pro-BNP, secreted mainly from the ventricle, has been known as a useful prognostic indicator in patients with HF.[9][10]

In the present study, we evaluated the effects of valsartan on plasma NT-pro-BNP levels, and cardiac remodeling in HF patients with HF, compared to patients treated with enalapril.

Subjects and Methods

Patient population

This was a multi-center, prospective, randomized, and open labeled design study. Patients with stable, symptomatic HF {New York Heart Association (NYHA) functional class II or III} who were on prescribed HF therapy with LV ejection fraction (LVEF) <45% were enrolled from March 2004 to February 2006 at 10 clinical centers in the Youngnam province of South Korea. Patients were excluded from the study if they had congenital heart disease, unstable angina, recent acute myocardial infarction, primary hepatic failure, renal failure (serum creatinine >2.5 mg/dL), life-threatening ventricular arrhythmia or active cancer.

Patients with stenotic valvular heart disease were also excluded. In addition, patients receiving any ARB or ACE inhibitor within 1 month of study enrollment were excluded. This study was approved by the ethics review board at each institution. All patients provided written informed consent before enrollment in this study.

Study protocol

Six hundred and two (n=602) stable HF outpatients were randomly assigned to two groups {Valsartan group (n=306) and enalapril group (n=296)}. The starting dose is 40 mg and 5 mg for valsartan and enalapril respectively, and then increased to a maximum dose of 320 mg or 20 mg, according to systolic blood pressure (>90 mmHg), absence of any sign or symptom of hypotension, and absence of serum creatitine >50% from baseline. If the patient satisfied one of above three criteria, the dosage of drugs was reduced to the previous level. All concomitant drugs to control HF were allowed, except ARB or ACE inhibitors.

We performed echocardiography, NT-pro-BNP and high sensitive C-reactive protein (hs-CRP) levels before and after 12 months of treatment. Also, we evaluated drug tolerance, such as blood pressure, symptom or sign, serum creatinine and potassium levels at 1, 3, 6, 9, and 12 months (Fig. 1).

Echocardiography

Following the recommendations of the American Society of Echocardiography,[11] LVEF was assessed using the Simpson's biplane equation for calculating volumes. The LV dimension and left atrial diameter for assessing cardiac remodeling were measured in the parasternal long axis view with an M-mode at each center.

Measurement of plasma N-terminal pro brain natriuretic peptide level

Blood samples were drawn after participants had been in the sitting position for 10 minutes. Specimens were placed in 5 mL ethylenediaminetetraacetic acid tubes, immediately centrifuged and frozen at -80°C. Plasma NT-pro-BNP levels were measured by an automated system (Elecsys 2010, Roche Diagnostics, Indianapolis, Ind), with identical methodology at each center.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) 12.0 (SPSS inc., Chicago, IL, USA) statistical software package was used for all calculations. Data are presented as mean±standard deviation for continuous variables, and as percentages for the categorical data. Changes in NYHA functional class were assessed using Wilcoxon matched pairs signed rank test. Differences between each group were analyzed by the unpaired Student t-test and by paired Students t-test between before (baseline) and after (12 months) treatment. Linear correlation

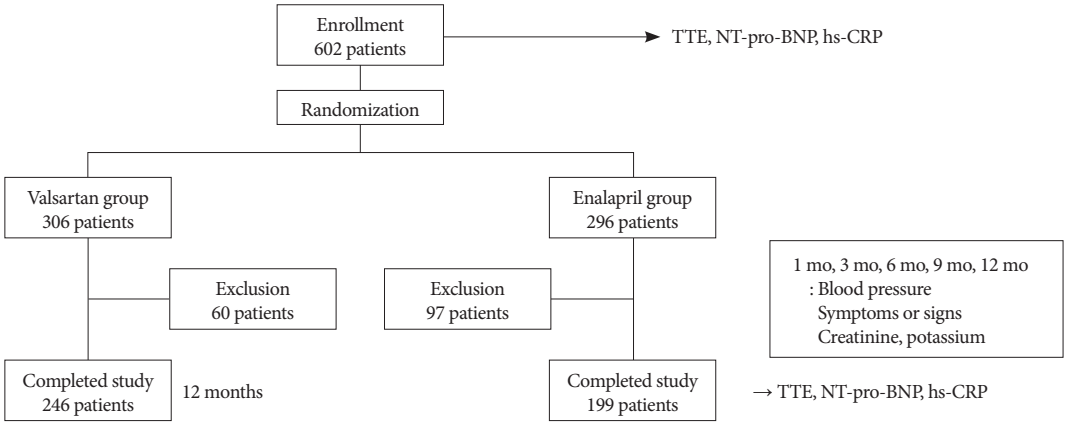

Fig. 1. Study design. TTE: transthoracic echocardiography, NT-pro-BNP: N-terminal pro-brain natriuretic peptide, hs-CRP: high sensitive C-reactive protein.

analysis (Pearson) was used to test correlations between changes in NT-pro-BNP level and change in LV end diastolic dimension (LVEDD) and LVEF. Categorical data were analyzed using the Chi-square test. A $p<0.05$ was regarded as statistically significant.

Results

Demographic characteristics

Among the enrolled patients, 60 patients in the valsartan group and 97 patients in the enalapril group withdrew from the study because of coughing, angioedema, dizziness, hyperkalemia, renal insufficiency and hypotension. Specifically, 9 patients in the valsartan group (2.9%) and 29 patients in the enalapril group (9.8%) were intolerant to study drugs because of severe coughing. Two hundreds forty six patients were included in the analysis (mean dose 99.4 mg) in the valsartan group and 199 patients (mean dose 10.7 mg) in the enalapril group.

Table 1 presents the demographic characteristics of the study population. The proportion of male in the enalapril group

Table 1. Demographic characteristics of subjects

	Valsartan group	Enalapril group	p
No. of patients	246	199	
Age (years)	63.6±11.4	61.5±12.9	NS
Male (%)	144 (58.5)	139 (69.8)	0.014
Systolic blood pressure (mmHg)	122.0±16.3	123.6±18.7	NS
Diastolic blood pressure (mmHg)	75.8±11.1	76.0±12.5	NS
Heart rate (bpm)	79.2±14.4	79.3±16.1	NS
Hypertension (%)	70 (28.5)	45 (22.6)	NS
Ischemic heart disease (%)	90 (36.6)	67 (33.7)	NS
Prior myocardial infarction (%)	40 (16.3)	39 (19.6)	NS
Prior cerebrovascular attack (%)	8 (3.3)	5 (2.5)	NS
Diabetes (%)	64 (26.0)	30 (15.1)	0.005
Hyperlipidemia (%)	10 (4.1)	17 (8.5)	0.049
Atrial fibrillation (%)	50 (20.3)	31 (15.6)	NS
New York Heart Association class (%)			NS
II	143 (58.1)	108 (54.3)	
III	103 (41.9)	91 (45.7)	
Concomitant medication (%)			
Digoxin	77 (33.3)	58 (32.8)	NS
Beta blocker	113 (48.9)	98 (55.4)	NS
Calcium channel blocker	37 (16.1)	28 (15.8)	NS
Diuretics	150 (64.9)	122 (68.9)	NS
Statin	69 (29.9)	42 (23.7)	NS

Table 2. Biochemical and echocardiographic parameters

	Valsartan group	Enalapril group	p
Hemoglobin (g/dL)	12.8±2.1	13.4±2.0	0.001
White blood cell (10^3/mm^3)	7.73±2.52	8.36±2.97	0.017
Blood urea nitrogen (mg/dL)	18.5±7.2	17.7±6.6	0.014
Creatinine (mg/dL)	1.05±0.30	1.09±0.29	NS
Sodium (mg/dL)	140.1±4.3	140.6±3.7	NS
Potassium (mg/dL)	4.15±0.63	4.20±0.62	NS
pro-BNP (pg/mL)	3,769.7±5,748.2	3,211.3±6,047.5	NS
hs-CRP (mg/dL)	2.29±6.33	1.89±3.10	NS
LVEF (%)	35.1±8.2	34.5±8.7	NS
LVESD (mm)	49.2±10.2	47.9±9.1	NS
LVEDD (mm)	59.4±9.9	57.8±8.4	NS
LA diameter (mm)	44.8±7.7	42.8±7.4	0.011

BNP: brain natriuretic peptide, hs-CRP: high sensitive C-reactive protein, LVEF: left ventricle ejection fraction, LVES/DD: left ventricular end systolic/diastolic dimension, LA: left atrium

was higher. The incidence of diabetes was higher in the valsartan group. The systolic and diastolic blood pressure of patients in both groups was significantly decreased after receiving study medication (valsartan: 122.0/75.8 mmHg vs. 117.3/72.8 mmHg, enalapril: 123.6/76.0 mmHg vs. 120.3/74.3 mmHg, respectively, p<0.05). However, the percentage change in systolic and diastolic blood pressure was not different between both groups.

Table 2 summarizes the baseline biochemical and echocardiographic parameters. The level of serum creatinine and potassium were not different between both groups. The level of serum uric acid in the enalapril group was significantly increased, compared to the valsartan group. The LA diameter was significantly higher in the valsartan group.

Comparison of New York Heat Association functional class

Fig. 2 summaries the change in the NYHA functional class of the patients. Patients in both groups improved after 12 months of treatment, compared to the baseline values (p<0.001).

Comparison of echocardiographic findings

The LVEF and LVEDD in both groups were significantly improved 12 months after treatment initiation. However, the percentage changes before and after treatment was not different in both groups (Table 3)(Fig. 3). Changes in LVEF and LVEDD were significantly correlated with change in NT-pro-BNP level (Fig. 4).

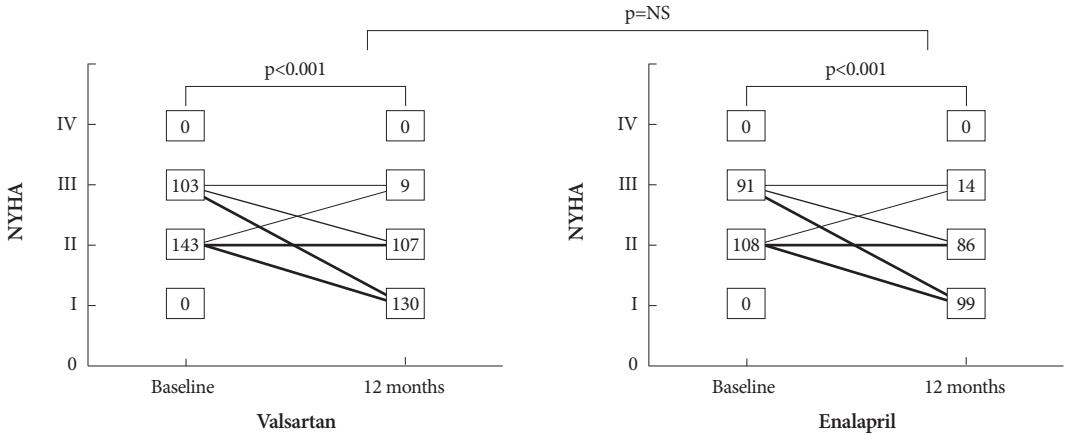

Fig. 2. Changes in NYHA functional class during treatment in the two groups. NYHA: New York Heart Association.

Table 3. Change of echocardiographic parameters, pro-BNP level, and hs-CRP level

	Valsartan group	Enalapril group	p
LV ejection fraction (%)			
Baseline	35.1±8.2	34.5±8.7	NS
After 12 months	42.7±10.5*	41.9±11.1*	NS
% change	26.4±40.5	32.4±49.4	NS
LV systolic dimension (mm)			
Baseline	49.2±10.2	47.9±9.1	NS
After 12 months	45.6±10.0*	44.7±10.2*	NS
% change	-6.6± 17.0	-6.8±19.4	NS
LV diastolic dimension (mm)			
Baseline	59.4±9.9	57.8±8.4	NS
After 12 months	56.4±8.8*	55.5±8.2*	NS
% change	-4.5±11.3	-3.1±15.1	NS
Log pro-BNP (pg/mL)			
Baseline	3.16±0.67	3.05±0.66	NS
After 12 months	2.61±0.62*	2.60±0.65*	NS
% change	-15.3±21.0	-13.6±20.1	NS
Log hs-CRP (mg/dL)			
Baseline	-0.24±0.69	-0.26±0.76	NS
After 12 months	-0.56±0.54*	0.49±0.74*	NS
% change	-105.7±589.6	-73.3±294.9	NS

*p<0.05 compared to baseline. BNP: brain natriuretic peptide, hs-CRP: high sensitive C-reactive protein, LV: left ventricle

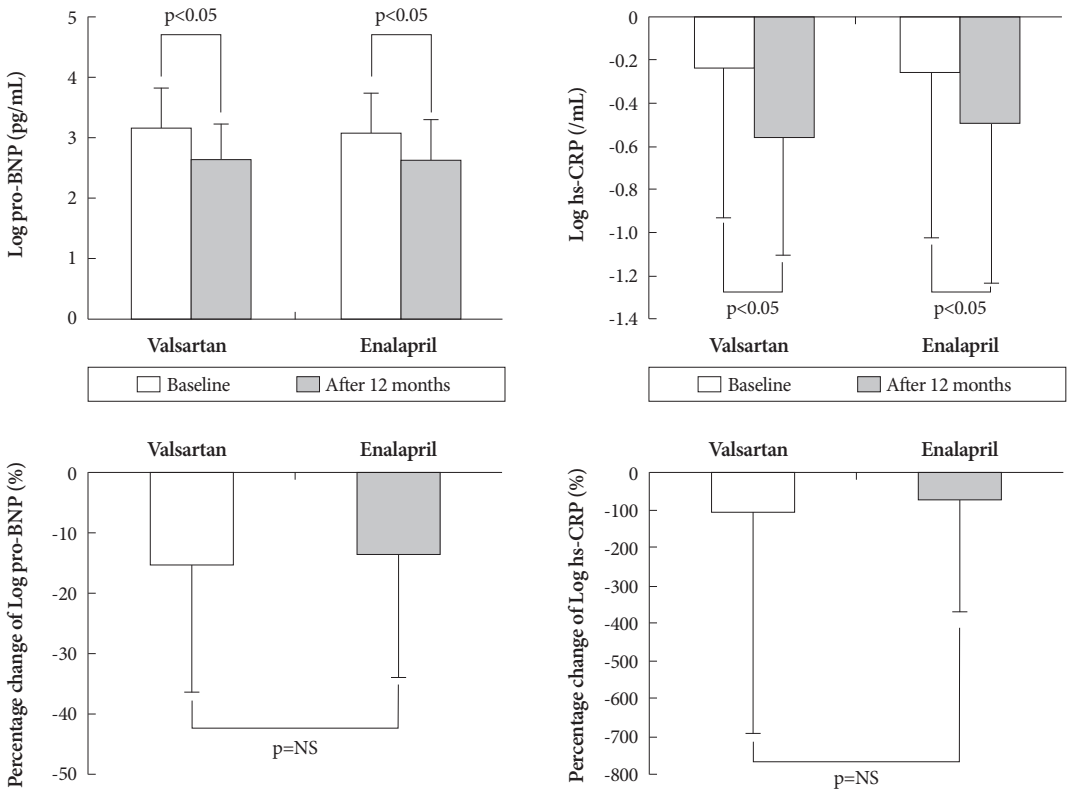

Fig. 3. Change of NT-pro-BNP and high sensitive C-reactive protein before and after treatment. NT-pro-BNP: N-terminal pro-brain natriuretic peptide, hs-CRP: high sensitive C-reactive protein.

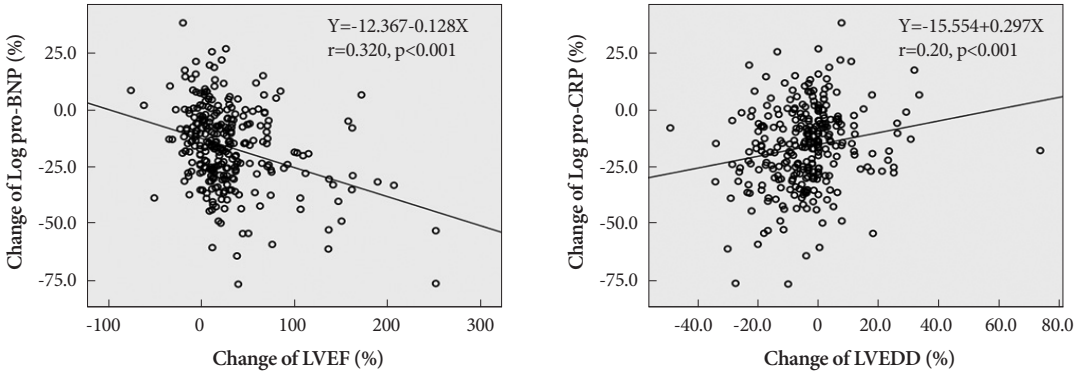

Fig. 4. Change of NT-pro-BNP according to change of left ventricular ejection faction (LVEF) and LV end diastolic dimension (LVEDD). NT-pro-BNP: N-terminal pro-brain natriuretic peptide, hs-CRP: high sensitive C-reactive protein.

Comparison of plasma N-terminal pro-brain natriuretic peptide and high sensitive C-reactive protein levels

Plasma NT-pro-BNP and hs-CRP levels in both groups were significantly reduced after 12 months of treatment. The percentage change demonstrated no difference between both groups (Table 3)(Fig. 3).

Discussion

The main finding of this study was that treatment of valsartan significantly improved plasma NT-pro-BNP level and echocardiographic parameters in patients with HF, compared to treatment with enalapril.

The plasma level of NT-pro-BNP, which is secreted mainly from the ventricle, is a well-established powerful risk marker in HF. Several authors have reported that plasma NT-pro-BNP is a prognostic predictor of morbidity and mortality in patients with HF.[12-14] In addition, Maeda et al.[15] mentioned that sustained high plasma level of NT-pro-BNP after standard treatment was an independent risk factor for mortality in patients with HF. Moreover, treatment of HF guided by plasma NT-pro-BNP concentration has been reported to reduce cardiovascular events.[16]

ACE inhibitors and ARB reduce the mortality of patients with HF partly by preventing LV remodeling, and plasma

NT-pro-BNP may be a useful marker of LV remodeling.[17] Tsutamoto et al.[13] demonstrated that perindopril significantly reduced plasma NT-pro-BNP and increased LVEF in patients with chronic HF. In Val-HeFT, valsartan significantly reduced plasma NT-pro-BNP after 24 months of therapy.[18] In our study, there are consistent results on plasma NT-pro-BNP levels and LV remodeling at 12 months after enalapril and valsartan treatment.

Kasama et al.[19] stated that plasma NT-pro-BNP and LV volume were significantly decreased 6 months after valsartan treatment in patients with HF, but not after enalapril treatment. In contrast, the percentage change of plasma NT-pro-BNP is not different between both drugs in the present study. We hypothesize that this difference may be due to study drug dosage. We tried to escalate to the target dosage of the study drugs (average dose per day 99.4 mg in valsartan vs. 10.7 mg in enalapril), which is higher that that used in previously reported studies. Plasma NT-pro-BNP concentration is reported to correlate with LVEF abnormalities and LV end diastolic pressure, as well as with LV mass.[20] In the present study, change of plasma NT-pro-BNP is significantly correlated to change in LVEF and LVEDD after 12 months. Because NT-pro-BNP has been suggested to be a marker for ventricular remodeling,[21] these findings suggest that valsartan and enalapril might have reversed ventricular remodeling.

The prevalence of ACE inhibitor induced cough has been known to be different between races.[22] Woo et al.[23] found that ACE inhibitor-related cough in the Hong Kong population was significantly higher than the primarily white Auckland population (53% vs. 18%, respectively). Nishizawa et al.[24] reported a 45% incidence of ACE inhibitor-induced cough among Asian women associated with 15% treatment cessation, and about a 30% incidence among Asian men with 5% treatment cessation. In our study, ACE inhibitor was discontinued in about 10% of patients due to severe cough. However, the prevalence of cough varied with method of data collection, analysis and symptom reporting.[25]

There is a major limitation to this study. We did not run a core laboratory for assessment of NT-pro-BNP level and echocardiographic parameter despite this being a multi-center and prospective study. However, we measured the NT-pro-BNP level by same ELISA method and echocardiographic parameters by recommendation.

In conclusion, the results suggest that RAS inhibitor can significantly improve plasma NT-pro-BNP levels, echocardiographic parameters and clinical findings in patients with HF. Valsartan, the most commonly used angiotenisn receptor blocker, is as effective as enalapril in the treatment of patients with stable chronic HF.

Acknowledgments

This study was sponsored by Norvatis Korea.

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