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Bisoprolol Reduce Left Ventricular Hypertrophy in Arg389Arg Hypertensive Patients Receiving Angiotensin-II Receptor Blocker

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Abstract

Left ventricular hypertrophy (LVH) is commonly present in patients with hypertension (HT). Angiotensin-II and chronic stimulation of β1-adrenergic receptors (β1-AR) contribute to LVH progression in hypertensive patients. Angiotensin-II Receptor Blocker (ARB) has been shown effectively regression left ventricular mass index. The aim of this study was to identify the efficacy of Bisoprolol reducing left ventricular hypertrophy (LVH) in Arg389Arg hypertensive patients receiving ARB. This prospective pre-post test cohort study included 39 male hypertensive patients who met the inclusion criteria. Patients underwent 24-hour Ambulatory Blood Pressure Monitoring (ABPM) procedures, echocardiographic examination to assess LVH pre-post 6 months of ARB treatment. Regimen was optimized based on office blood pressure. Arg389Gly β1-AR polymorphism was examined using the Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) method and confirmed by sequenzing method.

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As the results, frequency of Arg389Arg and Arg389Gly/Gly389Gly were 46.15% and 53.85%, respectively. In hypertensive patients with LVH, frequency of Arg389Arg and Arg389Gly/Gly389Gly were 23.08% and 17.95%, respectively. The reduction of LVMI, LVmass, or RWT (Relative Wall Thickness) after 6-months of ARB treatment (Valsartan or Telmisartan) in Arg389Arg or Arg389Gly/Gly389Gly hypertensive patients were not significant. However, Bisoprolol reduce LVMI from 137.50±22.62 to 63.67±28.08 g/m^2 (p=0.028), LVmass 240.17±40.14 to 130.67±22.39 gram (p=0.028), and RWT 0.49±0.08 to 0.36±0.11 in Arg389Arg hypertensive patients receiving ARB. Our study conclude that ARB treatment for 6-months did not reduce significantly LVMI, LVmass, and RWT in both Arg389Arg and Arg389Gly/Gly389Gly hypertensive patients. β1-AR blocker (Bisoprolol) reduce LVH in Arg389Arg hypertensive patients receiving ARB significantly.

Keywords: left ventricular hypertrophy; Arg389Arg; angiotensin-II receptor blocker.

1. Introduction

Left ventricular hypertrophy (LVH) is commonly present in hypertensive (HT) patients. It could strongly predict cardiovascular mortality and morbidity [1-3], and was associated with increased incidence of atrial fibrillation, left ventricular dysfunction, and heart failure [4-6].

Experimental and clinical evidence suggests that angiotensin-II contributes as a significant pathway to the progress of hypertrophy and left ventricular remodeling in hypertension through apoptosis of cardiomyocyte, myocardial fibrosis, and changes in wall composition and intramiocard artery geometry in the hypertrophied left ventricle [7]. There were several meta-analyses concerning the effect of 5 different classes of antihypertensive drugs on LVH [8-10]. Although their conclusions had some differences, all of them agreed on a point that regression was worse with beta-blockers and better with angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARBs). On the basis of these previous clinical researches and meta-analyses, the expert consensus document on hypertension from American suggested that ACEI or ARBs should generally be used in hypertensive patients with LVH [11].

The human β1 adrenergic receptor (ADRB1) is a member of the family of seven-transmembrane G-protein-coupled receptors, and expressed in cardiac myocytes [12]. Chronic stimulation of ADRB1 results in cardiac hypertrophy and heart failure [13]. The expression of ADRB1 RNA has been reported to be significantly higher in spontaneously hypertensive rat [14]. It also has been shown that chronic stimulation of cardiac ADRB1 has detrimental effects on the heart in the transgenic models with cardiac over-expression of ADRB1 [15,16]. The ADRB1 gene has been cloned in 1987 and localized to chromosome 10 [17]. Two common polymorphisms, Arg389-Gly and Gly49Ser, were identified in 1999 [18]. Arg389Gly is located in the intracellular cytoplasmic tail near the seventh transmembrane region of the receptor, which is a putative protein binding domain. The Arg389 variant mediates a higher isoproterenol-stimulated adenylate cyclase activity than does Gly389 variant in vitro [19]. The Ser49Gly polymorphism is located in the extra-cellular amino-terminal region of the receptor, but no studies have been published on the potential functional consequences of this polymorphism [20]. The Arg389Gly polymorphism has been shown to be associated with heart failure, acute myocardial infarction, hypertensive status and the variability of left ventricular remodeling and blood pressure in response to beta-

blockade [21-26]. Patients carrying the Arg389Arg genotype had an increase significantly in the left ventricular septal thickness; left ventricular posterior wall thickness; left ventricular mass index; and relative wall thickness as compared with those carrying genotypes Arg389Gly and Gly389Gly [27]. We hypothesized that Bisoprolol reduce left ventricular hypertrophy (LVH) in Arg389Arg hypertensive patients receiving ARB.

The aim of this study was to identify the efficacy of Bisoprolol reducing left ventricular hypertrophy (LVH) in Arg389Arg hypertensive patients receiving ARB.

2. Materials and Methods

The observational cohort of prospective pre-post test studies from January 1st, 2014 to June 9th, 2017 included 39 patients with inclusion criteria: men; age 40-75 years old; hypertension (JNC-7) criteria [28] as diastolic blood pressure equal to or over 90 mmHg and/or systolic blood pressure equal to or over 140 mmHg (average of 2 measurements)) that has not/ not been in antihypertensive treatment or dropped out of antihypertensive treatment for at least 2 weeks or untolerable to Angiotensin Converting Enzyme (ACE) Inhibitor; have health insurance; have high adherence (score 8 in answering the Morisky Medication Adherence Scale (MMAS) questionnaire in therapy; and willing to sign research informed consent. The exclusion criterias included severe disease that may limit longterm survival such as diabetes, hypertrophic cardiomyopathy, valvular heart diseases, pulmonary hypertension, coronary heart diseases, left heart failure stage C or D, impaired renal function, impaired liver function, active bleeding, or patients undergoing corticosteroid treatment based on medical history, physical examination, electrcardiography, echocardiography and biochemical measurements. All investigators were trained at the Cardiovascular Institute, Malang Saiful Anwar Hospital. Patients underwent 24-hour Ambulatory Blood Pressure Monitoring (ABPM) procedure, echocardiogram with M-mode using parasternal long axis (PLAX) view to measure LVMI, LVmass, RWT as LVH parameters before and after 6 months of ARB-based therapy and regimens during follow-up was optimized according office blood-pressure. The examination of the β1-adrenergic receptor polymorphism of Arg389Gly begins with DNA isolation; followed by Polymerase Chain Reaction (PCR) using ddH2O 6µl, PCR mix 10 µl, 1µl DMSO, 1µl forward, 1µl reverse, 1µl DNA through pre-denaturation stage 95ºC for 3 min, denaturation 95ºC for 30 seconds, annealing 60ºC for 30 seconds , extension 72ºC for 30 seconds, post-extension 72ºC for 10 minutes with 530bp target amplikon. Finally, Restriction Fragment Length Polymorphism (RFLP) using BcgI 2 unit enzyme; 1µl buffer; SAM 0,5µl; ddH2O 4,5µl; 3µl DNA was done and RFLP results confirmed by sequenzing method. Processing and data analysis statistical tests were performed using IBM SPSS statistic version 18.0. The Hardy-Weinberg balance was tested on all polymorphisms by comparing genotypes in the study subjects and genotype predictions using $\chi 2$ tests. Numerical variables are shown in the standard deviation ± form. The log transformation was performed on echocardiography results to improve the normality of the data. Different tests were evaluated with student t-test for normal distributed data, while the Mann-Whitney different test was performed for abnormally distributed data. Two tailed $P < 0.1$ is considered statistically significant.

3. Results

3.1 Characteristics of Research Subjects

From January 2014 - June 2017, 39 male hypertensive patients who met the inclusion criteria were found with an average age of 56.4 years old. There were 18 patients with homozygous Arg389 (46.15%), and Gly389 carriers were 21 patients (53.85%) in which 3 patients were homozygous Gly389 (7.69%) (Table 1). Patient population was classified by genotype Arg389Arg (AA) and Arg389Gly/Gly389Gly (AG/GG).

Table 1: Baseline Characteristics of Research Subjects

Variable	AA (n=18)	AG / GG (n=21)	P value
Age (years)	58.6 ± 8.46	54.5 ±11.33	0.247
Durations of Hipertensi (years)	8.6 ± 6.84	8.6 ± 7.43	0.745
BMI (kg/m^2)	25.1 ± 4.83	26.4 ± 3.75	0.096
SBP (mmHg)	139.8 ± 15.25	141.5 ± 16.79	0.751
DBP (mmHg)	88.4 ± 12.28	89.1 ± 12.21	0.864
LV ST (mm)	1.2 ± 0.35	1.2 ± 0.32	0.374
LV PWT (mm)	1.3 ± 0.26	1.2 ± 0.28	0.376
LVMi (g/m^2)	119.9 ± 47.25	118.0 ± 51.18	0.673
LVMass	204.4 ± 82.01	212.5 ± 90.12	1.000
RWT (%)	0.6 ± 0.16	0.5 ± 0.16	0.100

BMI, body mass index; SBP, systolic blood pressure;DBP, diastolic blood pressure; LV ST, left ventricular septal thickness; LV PWT, left ventricular posterior wall thickness; LVMi, left ventricular mass index; LV mass, left ventricular mass; RWT, relative wall thickness.

3.2 Analysis Variable Research

3.2.1 Reduction Variables before and After ARB-Based Treatment in LVH-Hypertensive Patients Group with Genotype of Adrenergic Receptors β1(Arg389Arg and Arg389Gly/Gly389Gly)

Sixteen of the 39 samples that completed this study met the LVH echocardiography criterias (LVMi value >115g/m^2 and/ or LVmass >224 grams).

The follow-up of 6 months of ARB-based treatment in hypertensive patients with LVH showed a reduce in BMI, SBP, DBP, LVMi, LVmass, and RWT levels (Table 2).

In the LVH group with Arg389Arg genotype, there was significant difference of LVMi (p=0,038) and LVmass (p=0,027) values before and after 6 months follow-up of ARB-based treatment (Figure 1). In the LVH group with the Arg389Gly/Gly389Gly genotype, there was significant difference of LVmass (p=0,010) on before and after 6 months follow-up of ARB-based treatment (Figure 2).

Table 2: Parameters of Reduction Variables before and After ARB-Based Treatment in LVH-Hypertensive Patients Group with Genotype of Adrenergic Receptors β1

Variable	LVH-Hypertensive Patients Group			
	Genotype Arg389Arg (n=9)		Genotype Arg389Gly/ Gly389Gly (n=7)	
	Before Treatment	6-months follow up (AfterTreatment)	Before Treatment	6-months follow up (After-Treatment)
BMI (kg/m^2)	23.9 ± 2.40	23.0 ± 2.10	27.2 ± 4.77	27.7 ± 4.30
SBP (mmHg)	142.9 ± 12.37	137.5 ± 14.14	156.0 ± 16.20	144.8 ± 15.34
DBP (mmHg)	90.7 ± 10.40	86.5 ± 13.02	94.4 ± 16.94	85.4 ± 9.54
LVMi (g/m^2)	156.3 ± 36.20	102.0 ± 56.79*	178.6 ± 42.48	142.3 ± 73.17
LVMass	267.9 ± 58.79	186.4 ± 81.06*	317.3 ± 79.00	179.8 ± 44.20*
RWT (%)	0.6 ± 0.12	0.5 ± 0.20	0.5 ± 0.13	0.5 ± 0.16

*p < 0,05

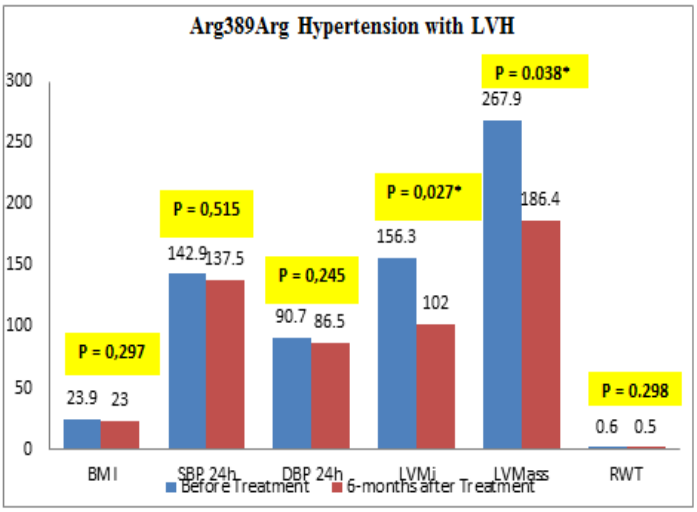

Figure 1: Parameter graph of reduction variables before and after ARB-based treatment in Arg389Arg hypertensive patients with LVH

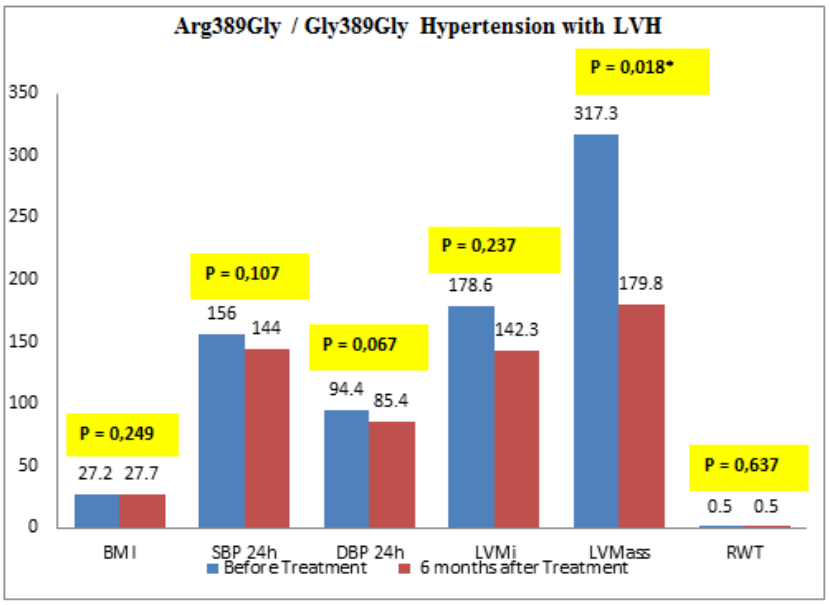

Figure 2: Parameter graph of reduction variables before and after ARB-based treatment in Argota9Gly/Gly389Gly hypertensive patients with LVH

3.2.2 Reduction Variables before and After ARB-Based Treatment in Non LVH-Hypertensive Patients Group with Genotype of Adrenergic Receptors β1

Twenty-three of the 39 samples that completed this study did not meet the LVH echocardiography criteria (LVMi values ≤115 g / m2 and or LVmass ≤ 224 grams).

Results of a 6-month follow-up of ARB-based treatment in the hypertensive patient without LVH group showed an increase in SBP, DBP, LVMi, and LVmass values in the Arg389Arg genotype group. While in the genotype group Arg389Gly / Gly389Gly showed average changes before and after therapy tended to be constant (Table 3).

Table 3: Parameters of Reduction Variables before and after ARB-Based Treatment in Non-LVH Hypertensive Patients Group with Genotype of Adrenergic Receptors β1

Variable	**Non-LVH Group (n=23)**			
	Arg389Arg (n=9)		**Arg389Gly/Gly389Gly (n=14)**	
	Before Treatment	**6 months Follow up (After Treatment)**	**Before Treatment**	**6 months Follow up (After Treatment)**
BMI (kg/m^2)	25.5 ± 4.40	25.33 ± 3.94	24.9 ± 2.91	25.5 ± 2.45
SBP (mmHg)	136.7 ± 17.88	141.4 ± 19.00	134.2 ± 11.90	134.9 ± 11.56
DBP (mmHg)	86.1 ± 14.16	89.2 ± 12.14	86.4 ± 8.61	83.7 ± 8.99
LVMi (g/m^2)	83.4 ± 21.10	103.1 ± 23.96	87.8 ± 15.17	89.5 ± 23.76
LVMass	141.0 ± 42.17	179.2 ± 51.47	160.1 ± 27.24	153.1 ± 60.9
RWT (%)	0.6 ± 0.19	0.5 ± 0.26	0.5 ± 0.17	0.5 ± 0.17

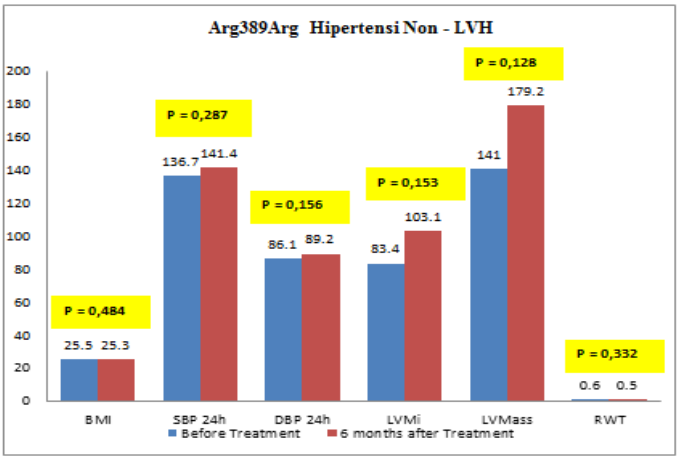

Figure 3: Parameter graph of reduction variables before and after ARB-based treatment in Arg389Arg hypertensive patients without LVH

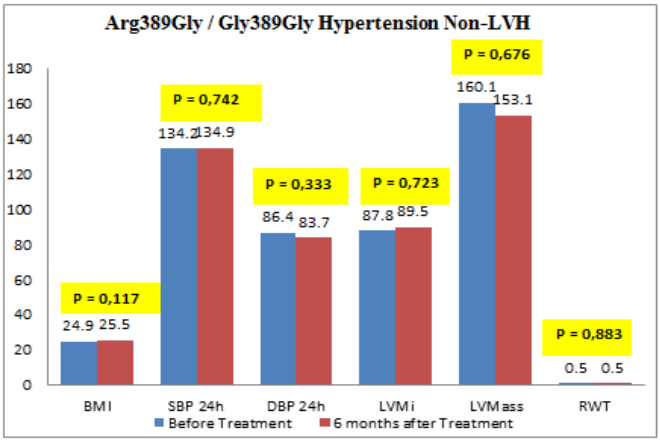

Figure 4: Parameter graph of reduction variables before and after ARB-based treatment in Arg389Gly/Gly389Gly hypertensive patients without LVH

3.2.3 Role of Treatment Based on Angiotensin-II Receptor Blocker (ARB) and Combination with Beta-Blocker in Reduce Left Ventricular Hypertrophy

Analysis of ARB impact on LVMi reduction variable parameter; LVmass; and RWT were divided into three categorical groups, ie the variable group of ARB telmisartan, valsartan, and combination ARB and beta-blocker groups to LVH reduction divided into Arg389Arg (AA) and Arg389Gly/Gly389Gly (AG/GG) groups. Valsartan or telmisartan administration in the group of patients with positive left ventricular reduction in genotype AA or AG/GG did not show significant relationship (Table 4). Administration of ARB with beta-blocker in the group of patients who had left ventricular mass reduction showed significant association with LVMi, LVmass, and RWT reduction in the genotype AA group with p-value LVMi 0.028; p-value LVmass 0,028; and p-value RWT 0.027. While giving ARB with beta-blocker in genotype group AG/GG did not show significant relationship.

Table 4: LVH Reduction Based on Antihypertensive Treatment

Reduction LVH in Hypertensive Patients						
	Arg389Arg (n=12)			**Arg389Gly/Gly389Gly (n=10)**		
Variable	**Before Treatment**	**6-Months After Treatment**	**p**	**Before Treatment**	**6-Months After Treatment**	**p**
ARB Telmisartan (n = 6)	**Arg389Arg (n=4)**			**Arg389Gly/Gly389Gly (n=2)**		
SBP	138,68 ± 7,18	140,25 ± 22,61	0,715	144,75 ± 24,40	138,05 ± 22,56	0,180
DBP	87,60 ± 11,98	90,03 ± 19,64	0,715	89,30 ± 6,36	80,20 ± 10,47	0,180
LVMI	131,00 ± 16,83	59,5 ± 29,72	0,068	155,50 ± 65,76	69,50 ± 23,33	0,180
LVMass	237,25 ± 35,22	136,25 ± 18,52	0,068	282,50 ± 144,96	122,00 ± 29,70	0,180
RWT	0,52 ± 0,05	0,39 ± 0,08	0,068	0,42 ± 0,11	0,41 ± 0,06	0,655
ARB Valsartan (n = 5)	**Arg389Arg (n=2)**			**Arg389Gly/Gly389Gly (n=3)**		
SBP	152,05 ± 18,46	133,95 ± 5,73	0,180	158,97 ± 21,05	148,97 ± 22,10	0,593
DBP	95,40 ± 9,62	84,6 ± 8,91	0,655	101,17 ± 17,43	85,70 ± 13,37	0,285
LVMI	150,50 ± 34,65	72 ± 16,97	0,180	115,33 ± 39,43	99,33 ± 14,84	0,285
LVMass	246,00 ± 65,05	119,5 ± 33,23	0,180	202,67 ± 67,57	176,00 ± 35,04	0,285
RWT	0,43 ± 0,14	0,3 ± 0,17	0,180	0,73 ± 0,15	0,59 ± 0,27	0,593
ARB + Beta-blocker (n = 11)	**Arg389Arg (n=6)**			**Arg389Gly/Gly389Gly (n=5)**		
SBP	143,13 ± 12,11	138,15 ± 17,99	0,753	153,28 ± 20,76	144,60 ± 20,18	0,345
DBP	90,20 ± 10,99	88,22 ± 15,98	0,917	96,42 ± 14,29	83,50 ± 11,21	0,080
LVMI	137,50 ± 22,62	63,67 ± 25,08	0,028	131,40 ± 48,40	87,40 ± 22,66	0,080
LVMass	240,17 ± 40,14	130,67 ± 22,39	0,028	234,60 ± 97,20	154,40 ± 41,34	0,080
RWT	0,49 ± 0,08	0,36 ± 0,11	0,027	0,60 ± 0,21	0,51 ± 0,21	0,500

4. Discussion

This study identifies the efficacy of Bisoprolol reducing left ventricular hypertrophy (LVH) in Arg389Arg hypertensive patients receiving ARB. The patients involved in the study were grouped into Arg389Arg or AA (18 patients) and Arg389Gly/Gly389Gly or AG/GG (21 patients, where 3 of them in Gly389Gly allele).

4.1 Role of Arg389Gly Adrenergic Receptor β1 Polymorphism to LVH reduction in Hypertensive Patients

ADRB1 is the predominant beta-adrenergic receptor expressed on the cardiomyocyte responsive to circulating epinephrine and local norepinephrine derived from cardiac sympathetic nerves [29,30]. Previous studies have shown that sympathetic nervous activity via ADRB1 regulates numerous physiological events and a wide range

of physiological responses, including cardiac chronotropy and inotropy, vascular and smooth muscle tone, and carbohydrate and lipid metabolism [31]. Sympathetic nervous activity plays an important role in the development of hypertension and its complications [32]. Among the many mechanisms that control cardiac function, the stimulation of the frequency and force of contraction by epinephrine and norepinephrine via specific beta-adrenergic receptors is the most prominent and, functionally, the most relevant pathway [33]. It is well known that nearly 70% of cardiac beta-adrenergic receptors are of the β1-subtype, and the minority are of the β2-subtype [34]. In rodents, sustained activation of ADRB1 from infusions of beta-agonists results in cardiac hypertrophy [35] and over-expression of ADRB1 in transgenic animals causes progressive cardiomyopathy and heart failure [16,35].

In vitro studies have shown that Arg389 variant of the ADRB1 enhances the β-adrenergic receptor response to agonist stimulation compared with Gly389 variant, suggesting that Arg389Gly polymorphism is of functional importance. An in vitro study has been shown that the cells transfected with Arg389Gly β1-adrenergic receptor show an increase of approximately 200% of β-adrenergic activity in response to agonist stimulation as compared with the cell carrying β1 Gly389 receptor [19]. This study showed significantly reduction of LVMI and LVmass in homozygous Arg389 hypertensive patients with LVH receiving ARB.

The study also showed Gly389 carrier genotype was significantly associated with LV mass reduction response to ARB-based treatment in hypertensive patients group with LVH. This was due to the dominant influence of alell Arg389 in this study group. This reasoning is supported by data on the number of samples of patients who have genotype Gly389Gly in this study only 3 patients from 39 samples (7.69%) with 2 patients in the hypertension group with LVH and 1 patient in the non-LVH hypertension group. While the samples were Arg389Gly genotype 18 people from 39 samples (46.15%) with 5 patients in the hypertension group with LVH (12.82%) and 16 patients in the non-LVH hypertension group (41.02%).

At the end of the study, 19 patients (48.72%) of 39 samples failed to achieve a blood pressure target of ≤140/90 mmHg, in which 8 patients with Arg389Arg (AA) genotype were obtained; 10 patients with genotype Arg389Gly (AG); and 1 patient with genotype Gly389Gly (GG). Patients who fail to achieve blood pressure targets have high adherence levels in taking the drug (evidenced by an MMAS score of 8 at the second follow-up to the sixth month). So the number of patients who reached the target of blood pressure at the end of the study were 20 patients (51.28%). This condition may explain why in the non-LVH hypertension group there was an increase in LV mass at the sixth months follow-up period.

4.2 Relation between Arg389Gly Adrenergic Receptor β1 Polymorphism with Left Ventricular Hypertrophy Reduction by Type and Combination of ARB-Based Treatment

Combination of ARB-based and beta-blocker (Bisoprolol) treatment in Arg389Arg group (wildtype) showed significant reduction of LVMI before combination ARB-Bisoprolol 137,50 ± 22.62 g/m^2 and after administration for 6 months to 63.67 ± 25.08 g/m^2 ($p = 0.028$), as well as the LV mass reduction from 240.17 ± 40.14 g/m^2 to 130.67 ± 22.39 g/m^2 ($p = 0.01$). This significant reduction in LVMi and LVmass indicates that the combination between ARB and Bisoprolol has an effect of improvement by reducing LVH. It effect caused

by the role of Bisoprolol in enhancing the inhibitory effects of both hemodynamic and neurohormonal factors. Angiotensin-II receptor blocker (ARB) in systemic will inhibit the effects of worsening of the heart through AT1 receptor inhibition pathway and maintain the effect of cardioprotective bond of Angiotensin-II with AT2 receptor, with the combination of beta-blocker then the bond between β-AR receptors will strengthen barriers both at systemic and cardiomyocyte level.

In a randomized, double-blind trial conducted by Thu¨rmann and his colleagues of 69 patients with untreated hypertension and from echocardiography had proven LVH, with left ventricular mass index (LVMi) >134g/m^2 in men and >110g/m^2 in women and / or end-diastolic septal thickness >12mm, obtained both angiotensin-II receptor blockers (valsartan) and atenolol for 8 months. Echocardiographic data of 58 patients were taken. After 8 months of getting valsartan (n = 29), the LVMi decrease from 127 ± 23 to 106 ± 25 g /m2 (ratio [R] = 0.83; 95% CI, 0.79-0.87; P, 0.0001 versus baseline). While with atenolol (n = 29), LVMi decreased slightly, from 127 ± 25 to 117 ± 27 g / m2 (R = 0.92; 95% CI, 0.86 -0.98; P50.0082 versus baseline). The average LVMI reduction was about 21 g/m^2 with valsartan and only 10 g/m with atenolol (R = 0.91; 90% CI, 0.85 -0.97 versus atenolol) [36].

This study showes unsignificant reducing LVH in Arg389Arg and Arg389Gly/Gly389Gly hypertensive patient receiving ARB (Valsartan or Telmisartan). However, bisoprolol reduce LVH significantly in Arg389Arg (wildtype) hypertensive patient receiving ARB but unsignificant LVH reduction in Arg389Gly/Gly389Gly (mutation group) hypertensive patients. It was caused by over-expression of Arg389Arg β1-AR, so β1-AR blocker (Bisoprolol) reduce LVH effectively in Arg389Arg compare Arg389Gly/Gly389Gly (mutation group).

5. Conclusion

Our study shows that ARB treatment for 6-months did not reduce significantly LVMI, LVmass, and RWT in both Arg389Arg and Arg389Gly/Gly389Gly hypertensive patients. β1-AR blocker (Bisoprolol) reduce LVH in Arg389Arg hypertensive patients receiving ARB significantly.

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