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Comparison of effects of nebivolol, carvedilol and irbesartan on left ventricular hypertrophy associated with hypertension

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Abstract. – OBJECTIVES: The aim of this study was to investigate if the new generation beta-blockers are as effective as irbesartan, which is an angiotensin receptor blocker (ARB), on left ventricular hypertrophy (LVH).

PATIENTS AND METHODS: The study included 85 patients (average age: 56.6±9.6 year) with stage 1 and 2 hypertension, who previously didn't receive an antihypertensive treatment, but diagnosed with LVH echocardiographically. The patients were divided into three different treatment groups: irbesartan (n=28), nebivolol (n=25) and carvedilol (n=32). The patients were reassessed clinically and echocardiographically at 3, 6 and 12 months after the treatments.

RESULTS: There was no statistically significant difference in baseline left ventricular mass index (LVMI) and other parameters among the three treatment groups ($p > 0.05$). Although there was no significant decrease in LVMI in irbesartan and carvedilol groups at 3 months after the treatment ($p > 0.05$), the values measured at 6 and 12 months ($p < 0.0001$) were significant. The decrease in LVMI in the nebivolol group was significant at 3, 6 and 12 months ($p < 0.0001$). There was a significant difference in measurements at 12 months ($p < 0.05$).

CONCLUSIONS: Both of the new generation beta-blockers were more effective than irbesartan in the regression of LVH. A significant regression in LVH was observed 3 months after nebivolol treatment and 6 months after irbesartan and carvedilol treatments.

Key Words:
New generation beta-blockers, Irbesartan, Left ventricular hypertrophy.

Introduction

High incidence of essential hypertension constitutes a major health problem because of higher mortality and morbidity rates[1]. It is known that left ventricular hypertrophy (LVH) associated with hypertension (HT) is an important factor, which increases cardiac mortality and morbidity, and many neurohumoral mechanisms, mainly hemodynamic factors, are involved in the development of LVH[2-4]. LVH can be determined only in 5 to 10% of hypertensive patients by electrocardiography while it can be detected by echocardiography up to 90% of randomly selected hypertensive adults[5]. It was shown that in general, treatment with antihypertensive agents results in the regression of LVH. There is no difference between agent groups in reaching target blood pressure levels[6]. However, it has been reported that there is a significant difference among classes of antihypertensive agents in the regression of LVH. Regarding the regression of LVH, a study comparing irbesartan of angiotensin receptor blocker (ARB) class with atenolol[7] showed that irbesartan was more effective than atenolol. On the other hand, although lowering effect of new generation beta blockers (carvedilol and nebivolol) on blood pressure has been demonstrated, limited number of studies are available on the regression of LVH as a monotherapy[8,9]. Among antihypertensive treatments, ARBs have the most favorable effect on the regression of LVH, whereas traditional beta blockers showed the weakest effect.

Several studies showed favorable effects of new generation beta blockers such as nebivolol and carvedilol on LVH. Nevertheless, reports which compared the effects of new generation beta blockers on LVH with ARBs are restricted. The primary objective of this study was to investigate whether or not new generation beta blockers are as effective as irbesartan, an ARB, on LVH. Secondary objective was to investigate if there was a difference between carvedilol and nebivolol groups in this respect. Finally, to assess the onset of significant effects of these three individual treatment groups on LVH.

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Patients and Methods

Patients Population

The study included 90 patients aged between 34 and 78 years with Stage I or 2 hypertension according to the European Society of Cardiology (ESC) criteria, who previously didn't receive an antihypertensive treatment, but diagnosed with LVH echocardiographically. Patients with Stage 3 hypertension who previously received or were currently on an antihypertensive treatment and/or patients with a secondary cause of hypertension and diseases underlying LVH.

Study Design

This was a clinical prospective cohort study. Patients were divided into three groups to receive irbesartan, carvedilol and nebivolol as a monotherapy. Patients were initiated on irbesartan 150 mg 1×1 or carvedilol 25 mg 1×1 or nebivolol 5 mg 1×1 during their first presentation. During the polyclinic examination after one month, the dose was titrated in patients who did'n't achieve target blood pressure (300 mg 1×1 for irbesartan, and 10 mg 1×1 for nebivolol, but remained 25 mg 1×1 for carvedilol). Echocardiographic assessments and evaluations were carried out by a blinded expert with experience in echocardiography. Clinical and echocardiographic follow up of patients was performed at 3, 6 and 12 months.

Assessments and Definitions

Assesment of Arterial Blood Pressure

Blood pressure was measured using a sphygmomanometer in accordance with the principles of standard blood pressure measurement while patients were seated at least after a 10 minute-rest. Patients with a mean blood pressure ≥ 140/90 mmHg in three subsequent blood pressure measurements during the first clinical examination were eligible. Their blood pressure was reassessed in the polyclinic at 3, 6 and 12 months after initiation of the treatment. HT was defined as a systolic blood pressure (SBP) of 140 mmHg or greater and/or a diastolic blood pressure (DBP) of 90 mmHg or greater in a patient with no antihypertensive medication or as receiving an antihypertensive agent[10]. Stage 1 hypertension was defined as SBP between 140 and 159 mmHg and DBP between 90 and 99 mmHg while Stage 2 hypertension was defined as SBP between 160 and 179 mmHg and DBP between 100 and 109 mmHg.

Echocardiographic Assessment

Echocardiographic examinations were performed using a Vivid 7 (GE, Oslo, Norway) system with a 2.5 Mhz transducer. It was performed with all participants in the left lateral decubitus position, and echocardiograms were obtained from standard parasternal and apical imaging. Left ventricular mass (LVM) was automatically calculated using the Devereoux formula in the echocardiography system. LVM index (LVMI) was obtained by dividing the left ventricular mass by the body surface area. LVMI ≥ 125 g/m^2 in men, and ≥ 110 g/m^2 in women was considered as LVH[11]. In M-mode measurements, interventricular septal thickness (IVST) or posterior wall thickness (PWT) greater than 1.1 cm was considered as LVH[12].

Statistical Analysis

Statistical analysis was performed using SPSS, version 17 software program (SPSS Inc., Chicago, IL, USA). Arithmetic means±standard deviations were calculated for quantitative variables while qualitative variables were given as frequency and percentage (%). For data analysis, Repeated Measured ANOVA test, and oneway ANOVA and Post Hoc Bonferroni tests, if appropriate, were used. A two-sided chi-square test was used to compare qualitative variables. A p value < 0.05 was considered statistically significant.

Results

Demographic, Clinical and Echocardiographic Characteristics

A total of 85 patients (25%) out of 188 patients (59%) who were recently diagnosed with LVH associated with hypertension and eligible for inclusion completed the study. The mean age was 56.6±9.6 years. Of these patients, 41 (48%) were male, and 44 (52%) were female. The baseline demographic, clinical and echocardiographic characteristics of patients are shown in Table I. No statistically significant difference was found in demographic, clinical and echocardiographic characteristics among the three treatment groups (irbesartan, nebivolol and carvedilol groups) (Table I).

Table I. Baseline clinical and echocardiographic parameters for treatment groups.

	Irbesartan (n = 28)	Nebivolol (n = 25)	Carvedilol (n = 32)	p
Age (years)	56.7 ± 10.7	57.7 ± 9.7	55.6 ± 8.7	0.70
Sex (%)				
Male	15 (53.6)	10 (40)	16 (50.0)	0.60
Female	13 (46.4)	15 (60)	16 (50.0)	
BSA (m^2)	1.86 ± 0.1	1.85 ± 0.1	1.92 ± 0.1	0.15
SBP (mmHg)	151.4 ± 8.5	153.4 ± 7.5	155.6 ± 6.7	0.10
DBP (mmHg)	92.0 ± 7.0	90.8 ± 5.3	93.6 ± 7.2	0.28
Pulse (atım/dk)	77.8 ± 7.1	78.3 ± 7.1	81.7 ± 5.9	0.06
IVST (mm)	12.8 ± 0.7	12.7 ± 0.7	12.6 ± 0.7	0.69
PWT (mm)	11.9 ± 1.0	11.8 ± 0.4	11.5 ± 0.6	0.042
LVM (g)	267.7 ± 26.1	258.6 ± 27.0	262.3 ± 21.6	0.40
LVMI (g/m^2)	144.2 ± 15.1	139.5 ± 12.4	137.3 ± 12.3	0.14

BSA: Body surface area; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; IVST: Interventricular septum thickness; PWT: Posterior wall thickness; LVM: Left ventricular mass; LVMI: Left ventricular mass index.

d Echocardiographic Changes From Baseline Among Treatment Groups

The changes in mean LVMI from baseline over time for all treatment groups is shown in Figure 1. While this reduction reached to a significant level within the first 3 months in the nebivolol group, it became statistically significant only at 6 months in the irbesartan and carvedilol groups despite reductions. The reduction in LVMI remained significant at 12 months after the treatment among the three groups. However, significant reduction in LVMI was maintained after 6 months in nebivolol and carvedilol groups, statististically insignificant change was observed in the irbesartan group (Figure 1). According to this figure, decrease in LVMI was not significant at 3 months in the irbesartan and carvedilol groups ($p > 0.05$), but significant at 6 and 12 months compared to baseline ($p < 0.0001$, respectively). The decrease in LVMI in the nebivolol group was significant at 3, 6 and 12 months ($p < 0.0001$, respectively). The mean reduction in LVMI was 2.6 g/m^2 in the irbesartan group, 5.3 g/m^2 in the nebivolol group, and 1.8

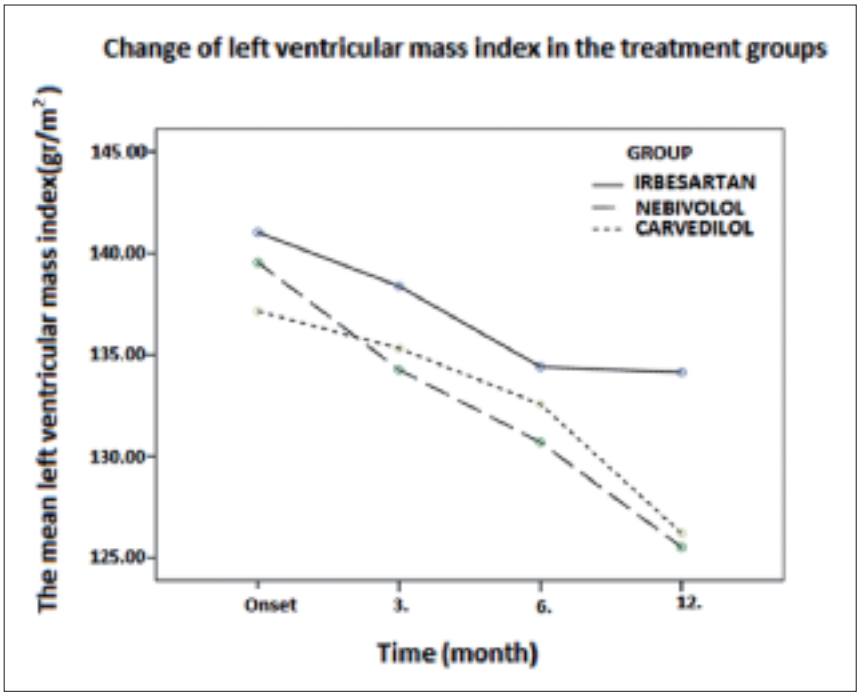

Figure 1. Change from baseline in treatment groups for left ventricular mass index.

Table II. Changes from baseline in some clinical and echocardiographic parameters in treatment groups.

	Irbesartan (n = 28)	Nebivolol (n = 32)	Carvedilol (n = 25)
LVMI, g/m^2			
Initial	141 ± 11.3	139.5 ± 12.4	137.1 ± 12.0
3 months later	-2.6 ± 7.8	-5.3 ± 4.4***	1.8 ± 5.1
6 months later	-6.6 ± 7.3***	-8.9 ± 6.2***	-4.6 ± 5.5***
12 months later	-6.9 ± 8.6***	-14.0 ± 11.5***	-10.9 ± 7.5***
SBP, mmHg			
Initial	151.4 ± 8.5	151.6 ± 7.5	155.6 ± 6.7
3 months later	-23.4 ± 11.8***	-19.6 ± 11.7***	-26.7 ± 11.3***
6 months later	-27.7 ± 10.9***	-29.0 ± 10.3***	-32.2 ± 10.0***
12 months later	-31.8 ± 12.9***	-32.0 ± 11.1***	-36.3 ± 9.2***
DBP, mmHg			
Initial	92.0 ± 7.0	90.8 ± 5.3	93.6 ± 7.2
3 months later	-12.9 ± 6.9***	-11.2 ± 5.6***	-13.9 ± 9.5***
6 months later	-17.5 ± 9.6***	-18.6 ± 6.7***	-18.4 ± 11.2***
12 months later	-14.5 ± 8.3***	-14.2 ± 7.9***	-18.4 ± 8.9***
Pulse, beats/min			
Initial	77.8 ± 7.1	78.3 ± 7.1	81.7 ± 5.9
3 months later	-0.4 ± 6.7	-12.0 ± 4.9***	-9.8 ± 8.0***
6 months later	-1.6 ± 8.6	-12.9 ± 6.5***	-14.8 ± 8.0***
12 months later	+3.0 ± 9.8	-14.2 ± 8.1***	-18.1 ± 6.6***

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. Against the initial values.

g/m^2 in the carvedilol group during 3 month follow-up, with significant increases in reductions at 6 months and 12 months (Table II). The reduction in SBP and DBP was significant at 3, 6 and 12 months compared to baseline for all treatment groups. While decrease in pulse rate was not significant at 3, 6 and 12 months compared to baseline in the irbesartan group, it was significant at 3, 6 and 12 months in the nebivolol and carvedilol groups compared to baseline (Table II). The reduction in SBP and DBP was significant at 3, 6 and 12 months compared to baseline for all treatment groups (Figures 2, 3). While decrease in pulse rate was not significant at 3, 6 and 12 months compared to baseline in the irbesartan group, it was significant at 3, 6 and 12 months in the nebivolol and carvedilol groups compared to baseline (Figure 4).

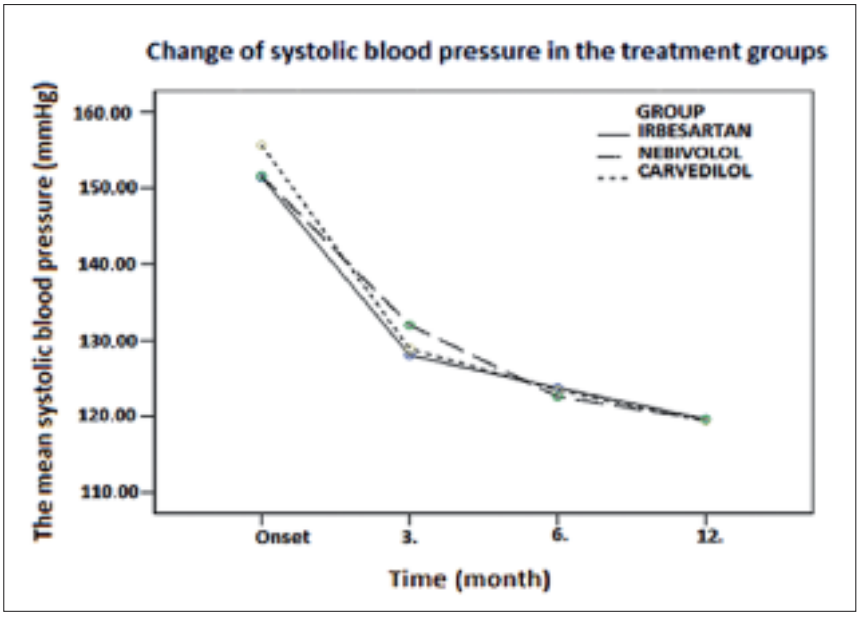

Figure 2. Change from baseline in treatment groups for systolic blood pressure.

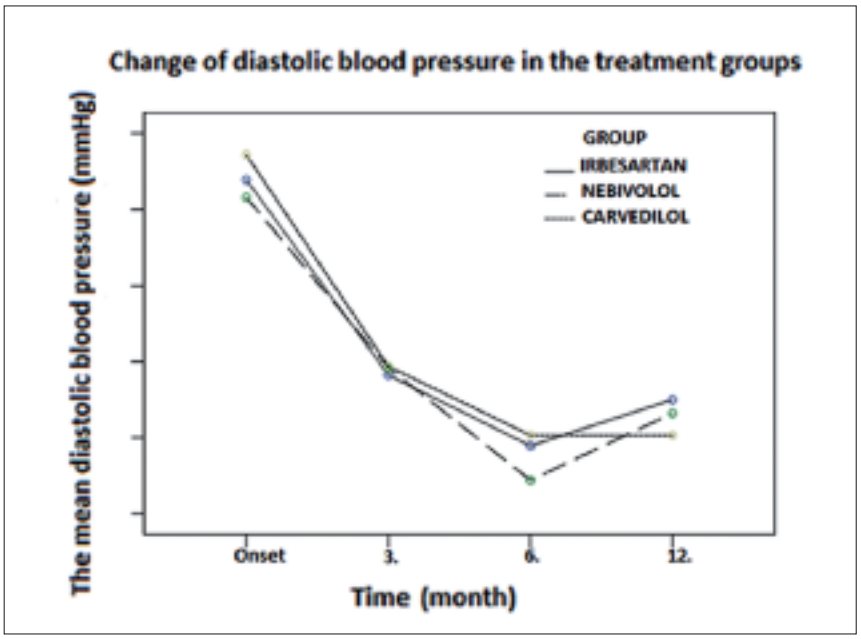

Figure 3. Change from baseline in treatment groups for diastolic blood pressure.

Discussion

This was a clinical, prospective cohort study which examined both the effects of irbesartan, an ARB and new generation beta blockers (nebivolol and carvedilol) on LVH associated with essential hypertension over time and whether or not there was a significant difference among treatment groups in this respect.

Effects on Left Ventricular Mass

We observed marked decreases in LVMI over time in all treatment groups. While this reduction reached to a significant level within the first 3 months in the nebivolol group, it became statistically significant only at 6 months in the irbesartan and carvedilol groups despite reductions. The reduction in LVMI remained significant at

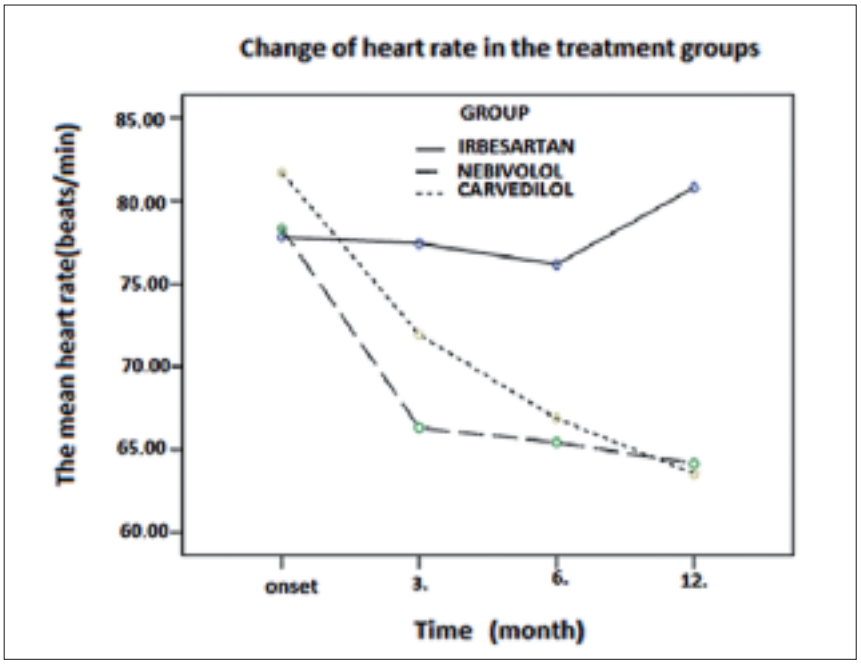

Figure 4. Change from baseline in treatment groups for heart rate.

12 months after the treatment among the three groups. However, significant reduction in LVMI was maintained after 6 months in nebivolol and carvedilol groups, a statististically insignificant change was observed in the irbesartan group (Figure 1). On the other hand, while there was no significant difference in baseline values for IVST and PWT among the groups (Table I), a significant reduction was observed in indiviual groups 12 months after the treatment compared to the baseline (Table II). At the same time, it was noted in the figure that baseline LVMI value was higher in the irbesartan group than in other two groups. While there was no significant difference in the mean LVMI at baseline, 3 and 6 months among the three treatment groups, interestingly statistically significant superiorities were observed both in nebivolol and carvedilol groups in reducing the mean LVMI at months 12 after treatment compared to the irbesartan group. No significant difference was observed in this respect between nebivolol and carvedilol groups (Figure 1). In the literature, a study comparing irbesartan with atenolol[13] evaluated 115 patients for reduction in LVMI, and found that the LVMI index was decreased by 5.76 g/m^2 in the irbesartan group, and by 0.45 g/m^2 in the atenolol group after a 3-month follow-up. However, an old generation beta blockers was used this study. In the present work, the mean reduction in LVMI was 2.6 g/m^2 in the irbesartan group, 5.3 g/m^2 in the nebivolol group, and 1.8 g/m^2 in the carvedilol group during 3-month follow-up, with significant increases in reductions at 6 months and 12 months (Table II). A subgroup analysis of a study comparing irbesartan and atenolol for cardiovascular effects at 6 months and 18 months reported that LVMI was decreased in the group receiving irbesartan at 18 months while there was no reduction of LVMI in the group receiving atenolol[14]. The LIFE study[7] made a comparison between losartan and atenolol in hypertensive patients with evidence of LHV in their ECG, and found that losartan had more significant improvement in LVH and left ventricular diastolic functions compared to atenolol. Another study comparing irbesartan with atenolol[15], and a study comparing valsartan again with atenolol[16] showed superiority of ARBs over treatment with atenolol in reducing LVH. In another study which also included new generation beta blockers[17] a decrease over 5 g/m^2 in LVMI compared to baseline was considered significant in treatment groups of carvedilol/lisinopril, atenolol/lisinopril, and lisinopril alone, and found that these three treatment protocols had similar effects on LVH. Galzerano et al[18] reported superiority of telmisartan over carvedilol in LVH regression. In a randomized prospective study with nebivolol, a new generation beta blocker, Latea et al[19] initiated valsartan (n=55) and nebivolol (n=53) in mild-to-moderate hypertensive patients, and followed their LVH and blood pressure for 6 months. Consequently, they reported that both treatments had similar effects in reducing LVH. A research which included 14 hypertensive patients with diastolic dysfunction[20] showed a reduction of 26 g/m^2 in LVMI compared to baseline with carvedilol up to 50 mg/daily after 4 months, while another study which included 22 hypertensive patients reported a 20 g/m^2 reduction in LVMI with carvedilol 25 mg after a 6-month treatment[21]. In the present study, the mean reduction in LVMI was 6.9 g/m^2 in the irbesartan group, 14.0 g/m^2 in the nebivolol group, and 10.9 g/m^2 in the carvedilol group one year after the treatment. These results were statistically significant. One of the most important findings in this study was to show that these new generation beta blockers were at least as effective as irbesartan, or even superior to it in reducing LVH. Although it is generally accepted that regression of LVH usually occurs only after 6 months, there are some investigators who determine regression within one month[22]. In a study with beta blockers, calcium channel blockers (CCB) and angiotensin converting enzyme (ACE) inhibitors and a follow-up period over 5 years, Franz et al[23] showed that regression was more than 10% within the first 8 weeks, reaching up to 25% in the first year, and 40% in the third year. In the present study, first nebivolol showed a significant reduction in LVMI in the first 3 months; and for other treatments, a statistically significant reduction was observed 6 months after the treatment.

Effect of Blood Pressure and Heart Rate on Left Ventricular Hypertrophy

In this report, all treatment groups were effective both in the regression of LVH and reducing systolic and diastolic blood pressures. A literature review showed that a study including old and new generation beta blockers[17] found that carvedilol/lisinopril, atenolol/lisinopril and lisinopril alone had similar effects on LVMI. It was concluded that achieving target blood pres-

sure levels were important rather than treatment regimen in reducing LVM. On the other hand, researches on LVH regression with traditional beta blockers report that beta-blockers had the least effect on LVM. This may be attributed to the fact that traditional beta blockers are less effective on central aortic pressure and, thus, they decrease the wall tension less than other groups of agents. A randomized study regarding this topic[24] compared nebivolol and metoprolol groups, and found that reductions in brachial blood pressure, heart rate, and mean blood pressure are similar in groups, while nebivolol was markedly superior in reducing central systolic and diastolic aortic pressure, central pulse rate and left ventricular wall thickness. It was an important study which showed superiority of nebivolol, a new generation beta blocker over traditional beta blockers. Another randomized double blind[25] compared nebivolol with placebo with respect to SBP, DBP, and heart rate. They found that the reductions in the nebivolol group were 12.4 mmHg in SBP, 11.1 mmHg in DBP, and 9.2 pulse/min in heart rate after 3 months. In the present study, there was a proportional reduction in SBP, DBP and pulse rate with nebivolol and carvediolol, the new generation beta blockers at the end of 1 year. Regarding this parameter, LIFE study[7] reported that LVMI was correlated to SBP and heart rate. These studies in literature and our results are important as it is likely that LVM can be decreased in parallel to the reduction in heart rate by new generation of beta blockers.

Conclusions

All treatment groups were effective in reducing LVH associated with hypertension and reducing blood pressure. The significant regression in LVH started 3 months after the nebivolol treatment, and 6 months after the irbesartan and carvedilol treatments. The regression was also maintained at 12 months for three treatment groups. Both of new generation beta blockers were more effective in the regression of LVH than irbesartan at 12 months after the treatment, but there was no significant difference between nebivolol and carvedilol treatments. In conclusion, both nebivolol and carvedilol were as effective as irbesartan in the regression of LVH associated with hypertension. However, it should be supported by further randomized prospective and multi-center studies.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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