The effect of combination therapy on regression of left ventricular hypertrophy in cases with hypertension

Bahar Boydak, *MD,* ***Sanem Nalbantgil,*** *MD,* ***Hasan Yilmaz,*** *MD,* ***Mehdi Zoghi,*** *MD,*
Filiz Ozerkan, *MD,* ***Istemi Nalbantgil,*** *MD,* ***Remzi Onder,*** *MD.*

ABSTRACT

Objective: Up to this date, it is well shown that several antihypertensive drugs have different regressive effect on left ventricular hypertrophy (LVH). However, there are different studies regarding the effect of antihypertensive combination therapies on regression of LVH. In this study, 2 different combinations ACE-I plus calcium channel blocker and ACE-I plus diuretic were compared in cases with hypertension whose BPs were not controlled by ACE-I alone.

Methods: Forty patients with mild to moderate hypertension were included in this study. The treatment was continued for 6 months in the Faculty of Medicine at Ege University, Turkey, between January and December 2003. Adequate response with lisinopril 20mg/daily failed to be achieved in all patients. Patients divided into 2 groups. There were no differences between the groups in patients' age, blood pressure (BP) and other clinical and laboratory range. First group patients received lisinopril 20mg + nifedipine GITS 30mg and second group patients received lisinopril 20mg + hydrochlorothiazide 25mg. The treatment was continued for 6 months. Blood pressure were measured every 2 weeks, echocardiographic findings, and blood and urinary analysis were performed before and at the end of treatment.

Results: Systolic and diastolic BP decreased significantly in both groups and no significant difference regarding BP was found between the 2 groups. Left ventricular mass index also decreased significantly in both groups. However, in the first group left ventricular mass index decreased more compared to the second group.

Conclusion: The effect of combination therapies with angiotensin converting enzyme inhibitor (ACE-I) plus diuretic and ACE-I plus calcium channel blocker on systolic and diastolic BP are similar. However, when LVH is present, regressive effect of the combination of ACE-I plus calcium channel blocker is superior to the combination of ACE-I plus diuretic.

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Many studies showed that left ventricular hypertrophy (LVH) is a potential independent predictor of cardiovascular complication of hypertension.[1,2] It is generally felt that antihypertensive treatment should not only lower blood pressure (BP) but also cause regression of LVH. All major classes of antihypertensive agents [angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers, diuretics, calcium channel blockers and beta-receptor blockers] can cause LVH regression but not all the same degree.[3,4] An analysis of covariance showed that the reversibility of LVH was significantly related to length of time of treatment and degree of BP reduction as well as some class of antihypertensive agents.[5,6]

From the Department of Emergency Cardiology (Boydak), Department of Cardiology (Nalbantgil S, Zoghi, Ozerkan, Nalbantgil I, Onder), Faculty of Medicine, Ege University, and Department of Cardiology (Yilmaz), Sifa Hospital, Izmir, *Turkey*.

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Address correspondence and reprint request to: Dr. Bahar Boydak, 1780/2 sokak, No. 9 D. 1, 35530 Karsiyaka, Izmir, *Turkey*. Tel. +90 (232) 3233712. Fax. +90 (232) 3883805. E-mail: boydak@med.ege.edu.tr

Several combinations of 2 or more drugs are recommended for the treatment of hypertension by JNC-VII[7] and WHO-ISH[8] guidelines. Many authors believe that combination therapy is more effective than treatment with monotherapy.[9-11]

There are many comparative studies regarding the regressive effect of different antihypertensive drugs,[3,4,12] but there are no more comparative studies regarding the effects of different combinations on the regression of LVH.

In this study, 2 different combinations ACE-I plus calcium channel blocker and ACE-I plus diuretic were compared in cases with hypertension whose BPs were not controlled by ACE-I alone.

Methods. Forty mild to moderate hypertensive (systolic BP > 140 < 180mm Hg and diastolic BP > 90 < 110mm Hg) male patients in whom adequate response with lisinopril 20mg/daily failed to be achieved, were investigated for the effects of combination therapies on regression of LVH. Patients were divided into 2 groups. There were no significant differences in patient's age, systolic and diastolic BP, duration of hypertension or risk factors in both groups (**Table 1**). Patients in the first group received Lisinopril 20mg plus nifedipine GITS 30mg and patients in the second group received lisinopril 20mg plus hydrochlorothiazide 25mg daily. The dose of drugs was not changed and the treatment was continued for 6 months.

Blood pressure was measured using arm cuffs and mercury-in-glass sphygmomanometers with patients in a sitting position and after having rested for 5 minutes. Measurements were repeated after 2 minutes and the mean values were taken for both measurements. After the physical examination, echocardiogram and echocardiographic measurements were carried out. Laboratory blood analysis and urinary analysis were performed.

For echocardiography, a Toshiba SSH 60 A echocardiograph fitted with Toshiba PSB-37 T transducer, 3.75MHZ was used. To avoid inter-observer variability, all echocardiograms in this analysis were taken and calculated by the same observer (Yilmaz H) who was unaware of the patient's identity or their BP. After a 20 minute rest in the supine position, M mode and 2 dimensional echocardiograms were obtained in a standard manner with the patient in the left lateral position. Left ventricular mass was calculated using the correlation of the cube formula by Devereux et al[13] for leading edge to edge measurement presented a left ventricular mass index (LVMI), which is left ventricle mass divided by body surface area measured in square meters (gr/m^2).

The treatment was continued for 6 months in the Faculty of Medicine at Ege University, Turkey, between January and December 2003. Blood pressure was measured every 2 weeks. Echocardiographic examination and laboratory tests were repeated at the end of the study. As a routine procedure, an informed written consent was obtained from all patients before study. The study was also approved by the local Ethics Committee.

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS), version 9, and all values were expressed as mean ± standard deviation. Echocardiographic measurements (before and after treatment), systolic and diastolic BP changes, laboratory findings in each group were compared using student's paired t-test.

Table 1 - Baseline demographic data.

Characteristics	**Group 1 N=20**	**Group 2 N=20**	***p***
Age	51.2 ± 5.6	52 ± 5.3	ns
Smokers	7	6	ns
Duration of hypertension (months)	48.3 ± 4	47.9 ± 4.4	ns
Systolic BP (mm Hg)	163.0 ± 8.7	163.9 ± 8.1	ns
Diastolic BP (mm Hg)	98.3 ± 2.9	98.2 ± 3	ns
Heart rate (beats/min)	76.7 ± 5.9	74.9 ± 6.3	ns
LVMI (gr/m^2)	174.3 ± 25.2	173.2 ± 19.6	ns
Fasting blood sugar (mg %)	98 ± 5.1	99.1 ± 4.9	ns
Serum creatinine (mg %)	1.04 ± 0.22	1.08 ± 0.26	ns
BUN (mg %)	22.6 ± 4	23.3 ± 3.6	ns
Total cholesterol (mg %)	212.8 ± 18.3	209.8 ± 20.1	ns
LDL cholesterol (mg %)	141.6 ± 12.5	139.7 ± 14.1	ns
HDL cholesterol (mg %)	40.6 ± 3.9	39.9 ± 3.4	ns

BP - blood pressure, LVMI - left ventricular mass index, BUN - blood urea nitrogen, LDL - low density lipoprotein, HDL - high density lipoprotein, ns - non significant

Results. At the end of the fourth week, systolic decreased below 140mm Hg and diastolic BP below 90mm Hg and continued for all the treatment duration. At the end of the sixth month, systolic and diastolic BP and LVMI decreased significantly ($p<0.01$) in both groups (**Table 2**). In the first group, systolic BP decreased from 163 ± 8.7 to 137.3 ± 4.9mm Hg ($p<0.001$) and diastolic BP decreased from 98.3 ± 2.9 to 87.7 ± 1.7 mm Hg ($p<0.001$). In the second group systolic BP decreased from 163.9 ± 8.1 to 136.2 ± 4.5mm Hg ($p<0.001$), and diastolic BP decreased from 98.2 ± 3 to 86.8 ± 2.5mm Hg ($p<0.001$). Decreases on systolic and diastolic BP were not different in both groups (**Figure 1**). In the first group LVMI decreased from 174.3 ± 5.2 to 121.6 ± 24.9gr/m^2 ($p<0.01$) and in the second group LVMI decreased from 173.2 ± 19.6 to 132.2 ± 16.2gr/m^2 ($p<0.02$). In the first group, LVMI

Table 2 - Blood pressures and echocardiographic measurements before and after treatment.

Characteristics	Group 1 Before	Group 1 After	Group 2 Before	Group 2 After
Systolic BP (mm Hg)	163.0±8.7	137.3±4.9‡	163.9±8.1	136.2±4.5‡
Diastolic BP (mm Hg)	98.3±2.9	87.7±1.7‡	98.2±3.0	86.8±2.5‡
PWT (mm)	12.7±1.0	10.7±1.0*	12.1±0.8	10.4±0.8*
ST (mm)	12.3±0.8	10.1±0.8*	12.4±0.7	10.7±0.7*
LVMI (gr/m²)	174.3±25.2	121.6±24.9*	173.2±19.6	132.2±16.2†

* $p<0.01$, † $p<0.02$, ‡ $p<0.001$,
BP - blood pressure, PWT - posterior wall thickness,
ST - septum thickness, LVMI - left ventricular mass index,

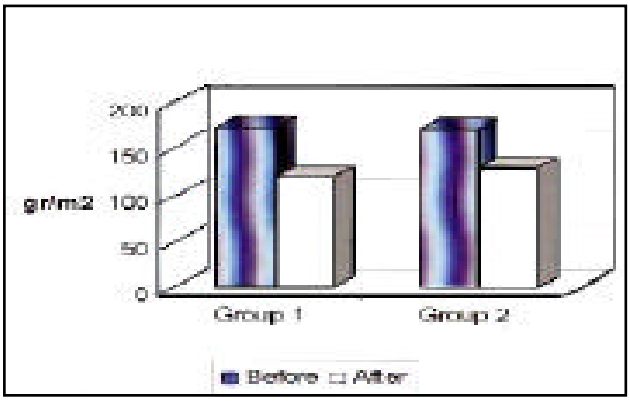

Figure 1 - The effect of treatment on left ventricular mass index. In group 1 (patients received lisinopril 20mg plus nifedipine GITS 30mg/daily); left ventricular mass index decreased significantly ($p<0.01$). In group 2 (patients received lisinopril 20mg plus hydrochlorothiazide 25mg/daily); left ventricular mass index decreased significantly ($p<0.02$).

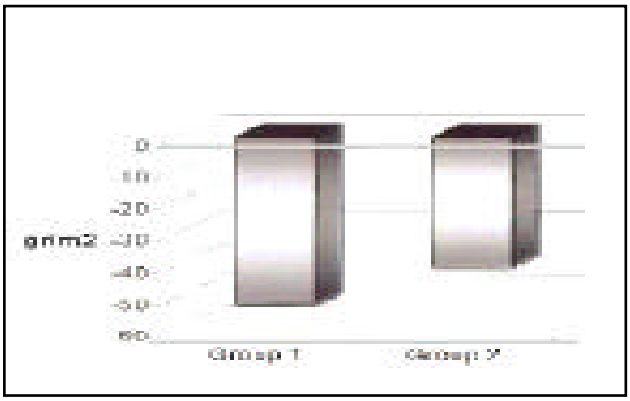

Figure 2 - In the first group left ventricular mass index decreased significantly more ($p=0.017$) compared to the second group.

decreased significantly more compared to the second group ($p=0.017$) (**Figure 2**).

There were no significant changes in laboratory findings. Side effects were similar in both groups and they spontaneously disappeared in a few days without the need for tapering off or discontinuing the drug.

Discussion. In this study, 2 drug combination, lisinopril 20mg plus nifedipine GITS 30mg and lisinopril 20mg plus hydrochlorothiazide 25mg were compared in cases with hypertension whose BP were not controlled by monotherapy with lisinopril 20mg. At the end of the fourth week, BP in each group decreased significantly and maintained a systolic BP below 140 mm Hg and diastolic BP below 90 mm Hg. Drug doses were not changed and treatment continued for 6 month. At the end of sixth month, decreases on systolic and diastolic BP in both groups were not different.

At the end of treatment, LVMI also decreased significantly in both groups, however, in the first group, LVMI decreased more significantly compared to the second group ($p=0.017$).

It is well demonstrated with clinical and experimental studies that LVH due to hypertension is regressed by antihypertensive agents.[5,6,14,15]

In the last decade, many authors believed that combination therapy is more effective than monotherapy in cases with hypertension. Combination with diuretic and ACE-I or angiotensin receptor blockers were widely used in the treatment of hypertension.[16] On the other hand, ACE-I and calcium channel blockers are also widely used in patients with cardiovascular disease and have beneficial effect beyond BP control alone. The renin angiotensin aldosterone system is implicated in LVH development and myocardial fibrosis in hypertension. Early studies in the 80s and 90s show that ACE-I could induce greater LVH regression than other antihypertensive drug at similar BP reduction.[17] Calcium channel blockers are a chemically heterogeneous group of substances that effectively reduce high BP in all age groups, show organ protective properties and have similar efficacy as ACE-I in LVH regression. Combination therapy with those 2 classes of drugs appears particularly useful in patients with hypertension, not only to lower BP, but also to achieve improved cardiovascular protection, both exhibit an additive effect.[11,18-23] However, until now, the regressive effect of this combination on the LVH was not compared with the other combination of antihypertensive drugs. In this study, we compared 2 combination therapies and found that the effect of the combination therapy with ACE-I plus diuretic and ACE-I plus calcium channel blocker on systolic

or diastolic BP were similar. When LVH is present, regressive effect of the combination of ACE-I plus calcium channel blocker is superior to combination of ACE-I plus diuretic.

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