Effects of Nebivolol on Artery Hypertension-Multicentre Study Bosnia And Herzegovina

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Abstract

Hypertension is a major risk factor for cardiovascular diseases; drugs that reduce blood pressure and simultaneously improve or reverse endothelian dysfunction, as nebivolol, may be advantageous in terms of cardiovascular protection. The objective of this study is to show the anti-hypertensive efficacy and safety of nebivolol (5 mg once a day) given to patients with arterial hypertension for 3 months. It should also provide information about drug's influence on laboratory tests - fasting blood glucose and serum cholesterol, triglyceride and creatinine concentrations. Six centers - Tuzla, Sarajevo, Mostar, Bihać, Zenica and Banja Luka participated in this prospective study with follow-up period of 3 months that included 3 visits. The study group consisted of 328 hypertensic patients. Results showed a significant decrease in both systolic and diastolic blood pressure and heart rate at the end of the study. Fasting blood glucose level and serum cholesterol, triglyceride and creatinine changed significantly during the study, with lower levels of all the tests. Nebivolol seems to be free from some of the problems that generally accompany not only the classical beta- blockers but sometimes also newer classes of antihypertensive drugs. With its high anti-hypertensive efficiency and safety, and presence of statically significant difference in laboratory tests and beneficial effects, absence of adverse interaction with glucose and lipid metabolism, patients treated with Nebivolol may show an optimal adherence to therapy.

KEY WORDS: arterial hypertension, endothelial dysfunction, nebivolol

Introduction

Arterial hypertension is a major modifiable risk factor for cardiovascular diseases that can, if untreated, result in serious morbidity and mortality from cardiac, cerebrovascular, vascular and renal diseases (1). The treatment of hypertension has evolved over the last years as we accumulated knowledge of the natural history, pathophysiology, and risk factors for hypertension as well as the effects of therapy and interactions of this factors. The goal of treating high blood pressure is to reduce blood pressure and prevent or reverse end- organe damage. Beta-adrenoreceptor blockers have long been established for the treatment of hypertension and much of the evidence that they reduce the risk of developing serious cardiovascular complications is based on clinical trials that used this class of drugs (2,3). They were recommended as one of the initial medications for the treatment of hypertension by the fifth and sixth National Committees on Detection, Evaluation and Treatment of High Blood Pressure and the World Health Organization-International Society of Hypertension (4 -7). Effective antihypertensive therapy should reduce vascular resistance without impairment of cardiac output, a measure of both systolic and diastolic function. Nebivolol, a highly selective ß1-adrenoreceptors blocker, actually decreases arterial blood pressure by reducing systemic vascular resistance without depressing left ventricular function (8,9), inducing an endothelium- dependent vasodilatation, which arises from the release of nitric oxide (NO). In hypertensic patients the basal and stimulated production of nitric oxide is reduced and the normal balance between vasodilating and vasoconstricting factors is modified with a decrease in vasodilation and an increase in vasoconstriction, so endothelial dysfunction may be considered as a target for the treatment of hypertension. The most common cause of death in patients with high blood pressure are complications from atherosclerosis. Nitric oxide plays a protective role as it prevents monocyte adhesion, platelet aggregation, vascular smooth-cell proliferation and migration, events known to be associated with arteriosclerosis and thrombosis development. Beta adrenergic blockers have been shown to reduce hypertension- related cardiovascular and cerebrovascular morbidity and mortality in long-term clinical trials (10,11). Antihypertensive therapy should be directed toward controlling all the patient' s cardiovascular risk factors. Fasting blood glucose, serum cholesterol and triglycerides and serum creatinine provide information on potential cardiovascular risk factors and also establish a baseline for the effects of drug therapy.

Materials and Methods

The study was designed as a prospective study with follow- up period of 3 months including 3 visits for each patient. The study population consisted of 328 patients, 177 female and 151 male, mean age 56,78±9,47, mean weight 80,59±14,29 and mean body mass index (BMI) 27,38±4,26. We included patients with blood pressure > 120/80 who were recruited from centers in Tuzla, Sarajevo, Mostar, Bihać, Zenica and Banja Luka. Patients were classified according to JNC classification in three groups: (Table 1-3; Figure 1,2)

1. Group with pre-hypertension (blood pressure level- 120-139/80-89 mm Hg) ,
2. Group with the first-degree hypertension (blood pressure level- 140-159/90-99 mm Hg) and
3. Group with the second-degree hypertension (blood pressure level 160-230/100-140 mm Hg).

At every follow-up visit a thorough clinical was performed (including measurements of systolic blood pressure, diastolic blood pressure and heart rate, which were

CATEGORY	SBP (MM HG)	DBP (MM HG)
NORMAL	<120	<80
PREHYPERTENSION	120-129	80-84
	130-139	85-89
STAGE I	140-159	90-99
STAGE II	160-179	100-109
	≥ 180	≥110

When a patient's systolic (sbp) and diastolic (dbp) blood pressures fall into different categories, the higher category should apply.

TABLE 1. Blood Pressure Classification by JNC 7.

AGE	ALL (N=328)	FEMALE (N=177)	MALE (N=151)
AV	56,78	56,89	56,66
SD	9,47	9,13	9,88
MAX	80,00	80,00	78,00
MIN	30,00	35,00	30,00
MED	56,00	56,00	56,00
COUNT	328,00	177,00	151,00

Note: AV – average value, SD – standard deviation, MAX – largest value, MIN – smallest value, COUNT – counts of numbers.

TABLE 2. Age of patients, all patients and distribution by sex

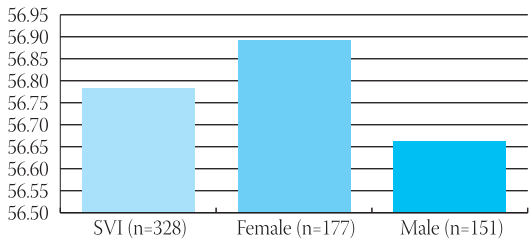

FIGURE 1. Mean age of all patients (n=328) and distribution by sex (F=177, M=151)

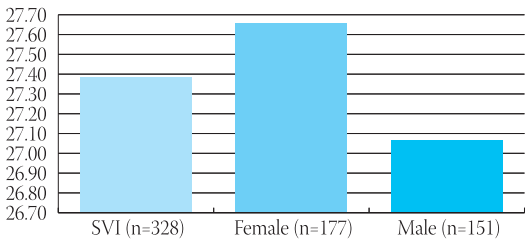

FIGURE 2. Mean body mass index (BMI): all patients and distribution by sex (F=177, M=151)

BMI	All (n=328)	FEMALE (n=177)	MALE (n=151)
AV	27,38	27,65	27,06
SD	4,26	4,72	3,65
MAX	49,59	41,82	49,59
MIN	17,86	17,86	19,33
MED	27,16	27,47	26,86
COUNT	328,00	177,00	151,00

Note: AV – average value, SD – standard deviation, MAX – largest value, MIN – smallest value, COUNT – counts of numbers.

TABLE 3. Body mass index (BMI), all patients and distribution by sex

evaluated prior to the drug intake using mercury sphyngomanometer) and blood samples drawn for blood chemistry (fasting blood glucose and serum cholesterol, triglyceride and creatinine). After initial evaluation patients were prescribed nebivolol in daily dose of 5 mg, and monitored during period of 3 months. We calculated basic descriptive statistical parameters (mean value-x, standard deviation- SD, largest value, smallest value, median) and used Student t-test, Wilcoxon Signed Rank Test and Kruskal-Wallis One Way Analysis of Variance on Ranks to determine statistical differences.

RESULTS

The study was completed by 328 patients (95,5%), while 18 patients (4,5%) withdrew.

Table 4. and Table 5. show results of descriptive statistic-mean and standard deviation for systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate at the start and at the end of study.

BLOOD PRESSURE CLASSIFICATION		SYSTOLIC BLOOD PRESSURE (SYS) MM HG		DIASTOLIC BLOOD PRESSURE (DIA) MM HG		MEAN ARTERIAL PRESSURE (MAP)	
	n	1. measurement ±SD	2. measurement ±SD	1. measurement ±SD	2. measurement ±SD	1. measurement ±SD	2. measurement ±SD
Prehypertension	13	130±0	122,3±4,29	89,23±2,77	80,77±4,94	102,82±1,85	94,62±4,42
		W= -55,000 T+ = 0,000 T-= -55,000 P(est.)= 0,002 P(exact)= 0,002		W= 81,000 T+ = 86,000 T-= -5,000 P(est.)= 0,004 P(exact)= 0,002		W= -66,000 T+ = 0,000 T-= -66,000 P(est.)= 0,003 P(exact)= <0,001	
Stage I	57	147,86±5,07	131,3±7,96	97,28±6,93	82,67±6,68	114,14±4,84	98,88±5,94
		W= -1431,000 T+ = 0,000 T-= -1431,000 (P = <0,001)		W= -1485,000 T+ = 0,000 T-= -1485,000 (P = <0,001)		W= -1596,000 T+ = 0,000 T-= -1596,000 (P = <0,001)	
Stage II	258	175,58±14,18	142,12±13,37	101,46±9,16	84,99±7,42	126,17±8,87	104,03±8,37
		W= -32880,000 T+ = 8,000 T-= -32888,000 (P = <0,001)		W= -32725,000 T+ = 85,500 T-= -32810,500 (P = <0,001)		W= -32896,000 T+ = 0,000 T-= -32896,000 (P = <0,001)	
All	328	168,8±18,47	139,4±13,44	100,19±9,1	84,4±7,28	123,06±10,3	102,74±8,26
		W= -51309,000 T+ = 25,500 T-= -51334,500 (P = <0,001)		W= -51146,000 T+ = 107,000 T-= -51253,000 (P = <0,001)		W= -52648,000 T+ = 1,000 T-= -52649,000 (P = <0,001)	

TABLE 4. Mean and standard deviation for systolic blood pressure, diastolic blood pressure and mean arterial pressure for all groups of patients, at the start and the end of study.

BLOOD PRESSURE CLASSIFICATION	1. MEASUREMENT ±SD	2. MEASUREMENT ±SD
PREHYPERTENSION	72,83±4,04	71,33±2,43
	t = 2,691 with 11 degrees of freedom. (P = 0,021)	
STAGE I	79,2±10,87	69,54±6,12
	W= -879,000 T+ = 33,500 T-= -912,500 (P = <0,001)	
STAGE II	85,23±15,17	72,63±8,23
	W= -24763,000 T+ = 1839,000 T-= -26602,000 (P = <0,001)	
ALL	83,74±14,54	72,1±7,87
	W= -37046,000 T+ = 2574,500 T-= -39620,500 (P = <0,001)	

TABLE 5. Mean and standard deviation for heart rate (HR) at the start and the end of study.

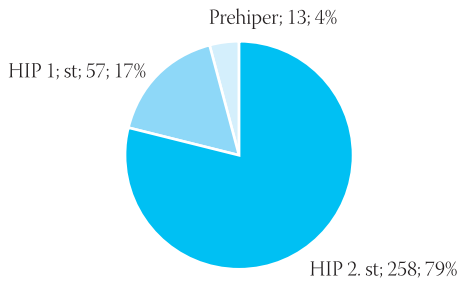

FIGURE 3. Distribution of patients by Blood Pressure Classification at the start of study

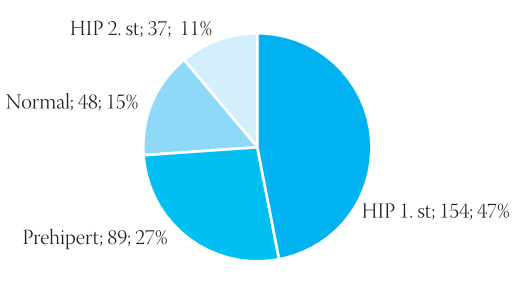

FIGURE 4. Distribution of patients by Blood Pressure Classification at the end of study

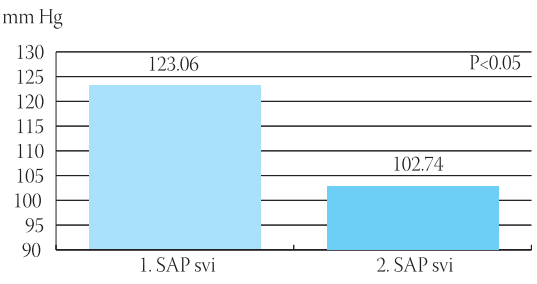

FIGURE 5. Differences in the mean values among mean arterial pressure (MAP) at the start and the end of study for all patients (ALL) (n=328)

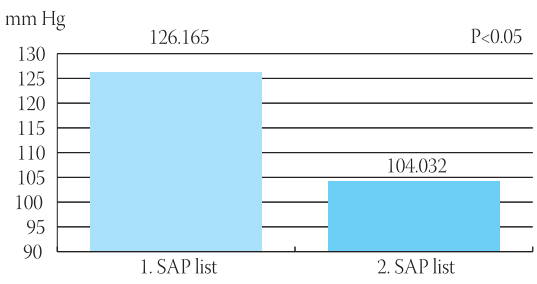

FIGURE 6. Differences in the mean values among mean arterial pressure (MAP) at the start and the end of study for patients in Group Grade 2 (HYP II) (n=258).

KRUSKAL-WALLIS ONE WAY ANALYSIS OF VARIANCE ON RANKS

We used ANOVA test – Kruskal Wallis to analyze one group of results, there we repeat measurement in some patients- four measurements of blood pressure and heart rate and table 6 shows descriptive statistic for subgroup of patients called GroupHYP 2, n=146. Table 12. show results of t-test and significance level for fasting blood glucose, serum creatinine, cholesterol and triglyceride at the start and the end of the study. There was a significant difference (p< 0,001) in fasting blood glucose, serum creatinine and triglyceride at the end of the study, with significant decrease, and statistical significant difference (p< 0,045) in serum cholesterol level at the end of the study, which is shown in Table 11. and 12.

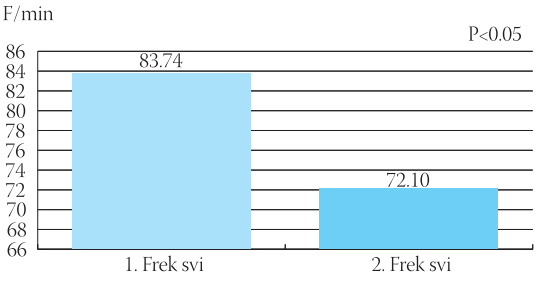

FIGURE 7. Differences in the mean values among mean heart rates at the start and the end of study for all patients (n=328).

COLUMN	SIZE	MEAN	STD DEV	STD. ERROR	C.I. OF MEAN
1.Sys II st	146	178,19	13,82	1,14	2,26
2.Sys II st	146	159,77	14,75	1,22	2,41
3.Sys II st	146	150,53	14,75	1,22	2,41
4.Sys II st	146	144,16	14,42	1,19	2,36
1.Dia II st	146	103,60	9,25	0,77	1,51
2.Dia II st	146	94,78	9,34	0,77	1,53
3.Dia II st	146	89,90	9,11	0,75	1,49
4.Dia II st	146	85,87	8,12	0,67	1,33
1.Map II st	146	128,46	8,56	0,71	1,40
2.Map II st	146	116,44	9,78	0,81	1,60
3.Map II st	146	110,11	9,85	0,82	1,61
4.Map II st	146	105,30	9,11	0,75	1,49
1.HR II st	146	84,63	14,12	1,17	2,31
2.HR II st	146	77,51	10,59	0,88	1,73
3.HR II st	146	74,64	9,17	0,76	1,50
4.HR II st	146	72,30	9,29	0,77	1,52

Note: Mean – average value, Std. Dev – standard deviation, Std. Error – standard error, CI – confidence of interval, Size – counts of numbers

TABLE 6. Descriptive statistic for Group HYP 2, n=146.

GROUP	N	MEDIAN	25%	75%
1.Map II st	146	126,667	122,667	132
2.Map II st	146	116,667	110	123,333
3.Map II st	146	110	103,333	116,333
4.Map II st	146	103,333	98,333	110

H = 287,306 with 3 degrees of freedom. (P = <0,001)

TABLE 7. Kruskal-Wallis One Way Analysis of Variance on Ranks

COMPARISON	DIFF OF RANKS	Q	P<0,05
4.Map II st vs 1.Map II st	314,77	15,94	Yes
3.Map II st vs 1.Map II st	249,72	12,65	Yes
2.Map II st vs 1.Map II st	157,39	7,97	Yes

The differences in the median values among the treatment groups are greater than would be expected by chance; there is a statistically significant difference (P = <0,001)

TABLE 8. Multiple Comparisons versus Control Group (Dunn's Method)

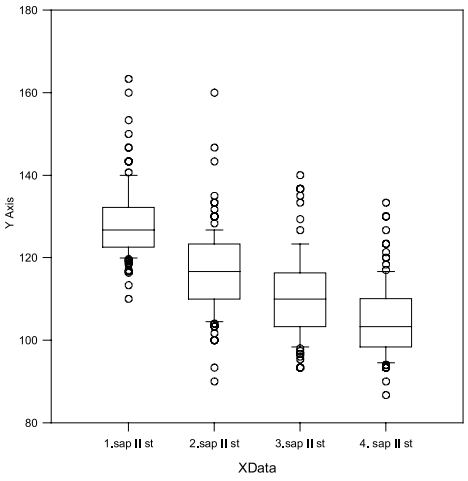

FIGURE 8. ANOVA (Kruskal Wallisov) for repeat measurement of blood pressure.

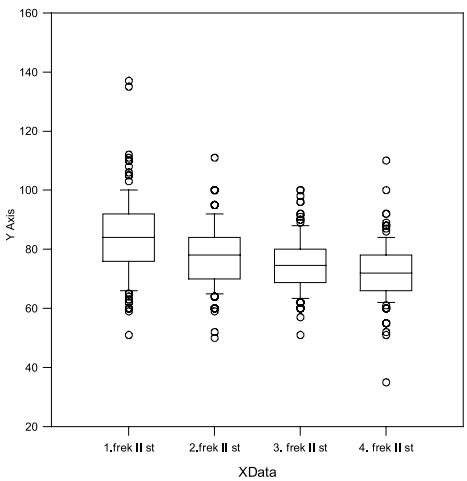

FIGURE 9. ANOVA (Kruskal Wallisov) test for repeat mesurement of heart rate

Heart Rate (F/min) ANOVA test for Group HYP 2, n=146.

KRUSKAL-WALLIS ONE WAY ANALYSIS OF VARIANCE ON RANKS

GROUP	N	MISSING	MEDIAN	25%	75%
1.HR II st	146	0	84	76	92
2.HR II st	146	0	78	70	84
3.HR II st	146	0	74,5	69	80
4.HR II st	146	0	72	66	78

H = 80,120 with 3 degrees of freedom. (P = <0,001)

MULTIPLE COMPARISONS VERSUS CONTROL GROUP (DUNN'S METHOD) :

COMPARISON	DIFF OF RANKS	Q	P<0,05
4.HR II st vs 1.HR II st	166,404	8,426	Yes
3.HR II st vs 1.HR II st	131,065	6,637	Yes
2.HR II st vs 1.HR II st	83,051	4,205	Yes

COLUMN	SIZE	MEAN	STD DEV	STD. ERROR	C.I. OF MEAN
1. Sys I st	42	152,93	6,75	1,04	2,10
2. Sys I st	42	141,55	10,90	1,68	3,40
3. Sys I st	42	135,95	8,21	1,27	2,56
4. Sys I st	42	134,52	8,25	1,27	2,57
1. Dia I st	42	95,41	6,48	1,00	2,02
2. Dia I st	42	87,00	8,09	1,25	2,52
3. Dia I st	42	84,12	7,99	1,23	2,49
4. Dia I st	42	81,67	7,62	1,18	2,38
1. Map I st	42	114,58	4,08	0,63	1,27
2. Map I st	42	105,18	7,87	1,21	2,45
3. Map I st	42	101,40	6,78	1,05	2,11
4. Map I st	42	99,29	6,72	1,04	2,09
1. HR I st	42	83,62	11,45	1,77	3,57
2. HR I st	42	74,19	9,50	1,47	2,96
3. HR I st	42	70,60	7,63	1,18	2,38
4. HR I st	42	67,67	5,86	0,91	1,83

Note: Mean – average value, Std. Dev – standard deviation, Std. Error – standard error, CI – confidence of interval, Size – counts of numbers

TABLE 9.: Descriptive statistic for Group HYP 1, n=42

ANOVA test for MAP Group HYP 1.

KRUSKAL-WALLIS ONE WAY ANALYSIS OF VARIANCE ON RANKS

GROUP	N	MEDIAN	25%	75%
1. Map I st	42	113,333	111,333	116,667
2. Map I st	42	105	100	110
3. Map I st	42	100	96,667	106,667
4. Map I st	42	99,167	93,333	103,333

H = 78,795 with 3 degrees of freedom. (P = <0,001)

MULTIPLE COMPARISONS VERSUS CONTROL GROUP (DUNN'S METHOD) :

COMPARISON	DIFF OF RANKS	Q	P<0,05
4. Map I st vs 1. Map I st	86,429	8,143	Yes
3. Map I st vs 1. Map I st	75,024	7,068	Yes
2. Map I st vs 1. Map I st	52,595	4,955	Yes

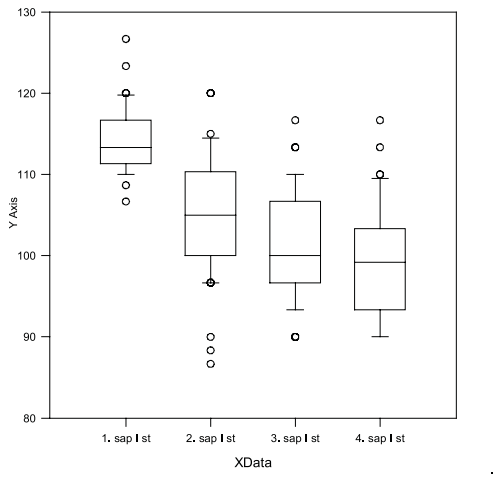

FIGURE 10. ANOVA (Kruskal Wallisov) test for repeat measurement of blood pressure in sub-group HYP 1 (n=42)

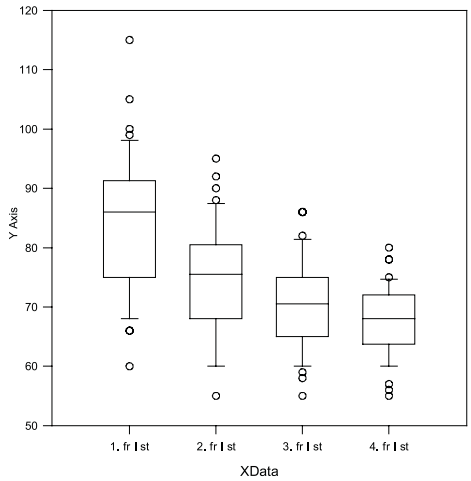

FIGURE 10. : ANOVA (Kruskal Wallisov) test for repeat measurement of heart rate in HYP 1 (n=42)

Heart Rate (F/min) ANOVA test for Group HYP 1, n=42

KRUSKAL-WALLIS ONE WAY ANALYSIS OF VARIANCE ON RANKS

GROUP	N	MEDIAN	25%	75%
1. HR I st	42	86	75	91
2. HR I st	42	75,5	68	80
3. HR I st	42	70,5	65	75
4. HR I st	42	68	64	72

H = 48,531 with 3 degrees of freedom. (P = <0,001)

MULTIPLE COMPARISONS VERSUS CONTROL GROUP (DUNN'S METHOD) :

COMPARISON	DIFF OF RANKS	Q	P<0,05
4. HR I st vs 1. HR I st	70,119	6,606	Yes
3. HR I st vs 1. HR I st	54,083	5,095	Yes
2. HR I st vs 1. HR I st	35,655	3,359	Yes

	N	MINIMUM	MAXIMUM	MEAN	STD. DEVIATION
FASTING BLOOD GLUCOSE	328	2,80	14,00	6,05	1,70
CREATININE	328	56,20	226,00	85,00	20,67
CHOLESTEROL	328	3,20	18,00	6,13	3,93
TRIGLYCERIDE	328	0,84	12,80	2,18	1,11

TABLE 10. Mean and standard deviation of fasting blood glucose, serum creatinine, cholesterol and triglycerides at the start of the study

	N	MINIMUM	MAXIMUM	MEAN	STD. DEVIATION
FASTING BLOOD GLUCOSE	328	2,30	12,00	5,37	1,16
CREATININE	328	40,00	230,00	78,71	19,65
CHOLESTEROL	328	2,60	15,00	5,68	3,64
TRIGLYCERIDE	328	0,70	11,00	1,90	1,02

TABLE 11. Mean and standard deviation of fasting blood glucose, serum creatinine, cholesterol and triglycerides at the end of the study

	t-test	p
FASTING BLOOD GLUCOSE	7,45	0,001
CREATININE	5,56	0,001
CHOLESTEROL	2,01	0,045
TRIGLYCERIDES	5,11	0,001

TABLE 12. Results of t-test with significance level for fasting blood glucose, serum creatinine, cholesterol and triglyceride

Discussion

Results of our study shows that the study was completed by 328 patients (95,5%), while 18 patients (4,5%) were withdrawn (Figure 3,4) Blood pressure improvement was registered in 314 (95,73%) patients while in 14 (4,27%) patients blood pressure did not change significantly for 10/5 mm Hg (sys/dia), and in 48 (14,63%) patients blood pressure is fully normalized with level <120/80 mm Hg. (Table 4, 5; Figure 5-7) We used (Kruskal Wallis One Way ANOVA on Ranks) for 2 sub- groups of patients, where we used repeated measurement. The results showed statistically significant difference in blood pressure level on the first control ($P<0,05$) in 188 patients (57,32%). (Table 6,9; Figure 8-10) Results of our study show improvement of serum parameters- fasting blood glucose, creatinine, cholesterol and trygliceride, with statistical significant difference ($p<0,05$) at the end of study. (Table 10-12) Considering these results, in this study nebivolol is demonstrated to be suitable for therapy in arterial hypertension. The results provide evidence of good tolerability profile and lower incidence of adverse effects on glucose and lipids metabolism. Different studies compared the efficacy of Nebivolol with other antihypertensive drugs. The percentage of patients with fully normalized blood pressure was significantly higher with nebivolol than with nifedipine (54% vs 42%) (12). In the studies comparing nebivolol with nifedipine or amlodipine heart rate was decreased by nebivolol and slightly increased with the two dihydropiridines: the lower heart rate is a potential advantage of nebivolol, due to the epidemiological relation between heart rate and cardiovascular morbidity (13,14). Nebivolol was also compared with other beta-blockers, such as atenolol (15,16) and metoprolol (17). Therefore, the antihypertensive efficacy of nebivolol was superior or similar to that of other beta-blocking drugs. Antihypertensive drug must have not only blood pressure – lowering properties, but also influence other critical cardiovascular, metabolic, and renal end points. The impairment of nitric oxide (NO) bioactivity, the main feature of endothelial dysfunction, is a key factor in the pathogenesis of many common cardiovascular diseases. High levels of blood glucose can impair not only vascular tone but also blood flow, both depending on NO controlled endothelial function (18). High blood glucose level or dislipidaemia can affect by several mechanisms- such as oxidative stress- endothelial function thus leading to vascular damage, so opportunities of treatment can arise from nebivolol, some effects of which were shown to be just mediated by NO. In most of the studies nebivolol did not significantly alter blood glucose or plasma lipid levels (19). Nebivolol seems to be free from some of the problems that generally affect not only the classical beta- blockers but sometimes also the newer classes of antihypertensive drugs. With its high anti-hypertensive efficiency and safety, and finding of statically significant difference in laboratory tests and beneficial effects, without adverse interaction with glucose and lipids metabolism, patients treated with Nebivolol may show an optimal adherence to therapy.

Conclusions

Nebivolol administered in a single daily dose of 5 mg lowers both systolic and diastolic blood pressure in patients with arterial hypertension. It is simple one daily dosage, that can be given to patients of all groups. The major objective of our study is to provide an adequate cardiovascular protection by appropriate reduction of blood pressure values. Results data of our study provide evidence of antihypertensive effects, good tolerability profile and lower incidence of adverse effects on glucose and lipids metabolism of Nebivolol, which is in relationship with that obtained by other authors.

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