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Beta-blockers and their impact on blood pressure and heart rate

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Abstract

The aim of the study is to determine the impact of beta-blockers on blood pressure and heart rate in patients that use these drugs during treatment of arterial hypertension. The sample included 120 patients from the "Dom Zdravlja'' Živinice. Patients were monitored for 3 years. No statistically significant difference in the values of systolic and diastolic blood pressure as well as heart rate in patients using beta-blockers and other groups of antihypertensives was determined during monitoring period after 12, 24 and 36 months of treatment. Also, there was no statistically significant impact of the applied therapy on these values in the observed time intervals. In order to determine statistically significant difference between treatments, we compared their values sorted by time. No statistically significant difference was found in systolic blood pressure and heart rate between groups, but a statistically significant difference in diastolic blood pressure was found between groups after 12 and 36 months of therapy. No statistically significant difference was found in the values of systolic and diastolic blood pressure, as well as heart rate after 12, 24 and 36 months of treatment by comparing the same values within the group of beta-blockers (patients using bisoprolol and carvedilol and patients using other beta-blockers). Also, there was no statistically significant impact of the applied therapy on the change of these values during observed period. In order to determine statistically significant difference between the treatments, we compared their values sorted by time. There was no statistically significant difference in the values of systolic and diastolic blood pressure and heart rate between the groups. Also, the condition of patients who used beta-blockers in the treatment of hypertension did not require increasing the dose in order to achieve the required parameters. Therefore, in our research, haven't been proven the worse effect of beta-blockers on blood pressure and heart rate when compared to other antihypertensive drugs. Also, all drugs showed equal effectiveness within the group of beta-blockers.

Keywords: Arterial hypertension; Beta-blockers; Bisoprolol; Carvedilol

1. Introduction

Beta-blockers were used in the treatment of hypertension in the early 1960s. (1) They bind to beta-adrenergic receptors, resulting in competitive and reversible antagonism of the effect of beta-adrenergic stimulation in various organs. (2) Indications that are accepted for beta-blockers are: coronary heart disease, arterial hypertension, arrhythmias, heart failure, hypertrophic obstructive cardiomyopathy, glaucoma, central, endocrine, gastrointestinal and other cardiovascular indications. In this regard, the use of beta-blockers in the treatment of arterial hypertension, especially as monotherapy in uncomplicated essential hypertension, causes a lot of questions.

There is evidence that beta-blockers may be inferior to some classes of drugs when it comes to certain outcomes such as risk of myocardial infarction, ICV, and overall mortality. (3)

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Due to it, beta-blockers are not used as much as they should be according to evidence-based medicine, primarily due to poorer tolerability compared to other groups of drugs. (4)

That is the reason why authors of the English guidelines NICE (National Institute for Health and Clinical Excellence) from 2006 (5) no longer include beta-blockers in the routine algorithm during treatment of arterial hypertension due to, in their opinion, less effectiveness when compared to other antihypertensives.

Contrary to these opinions, there are numerous authors who believe that only lowering of blood pressure is important for the effect of antihypertensive drugs, so these differences are only theoretically and statistically, but not clinically significant. Thus, in a recently published meta-analysis of the effect of antihypertensives in the prevention of cardiovascular diseases, it was determined that the most important effect is lowering blood pressure. Beta-blockers showed better effect than other drugs during treatment of arterial hypertension in post-infarction patients in the first two years after the infarction.

Therefore, it seems that the authors of the European guidelines for the treatment of arterial hypertension have a justified view that all basic groups of antihypertensives are equal and the difference between them is not important in practice. (6).

Our aim was to obtain relevant data that will confirm or disprove previous research related to the use of beta-blockers during the treatment of hypertension. The social preventive aim is to take appropriate measures in order to improve the health status of the population.

2. Methods

The sample included 120 patients in the family medicine clinic from the "Dom zdravlja'' Živinice. The research is coordinated with the legal and ethical norms of research, as well as the protocol of the ethics committee of the "Dom zdravlja" Živinice.

The patients in the study were divided into two groups. The tested experimental group included 60 patients who used beta-blockers during treatment of hypertension. The control group included 60 patients who used some other antihypertensive drugs during treatment of hypertension. Patients were classified by gender (male and female) and age (41-50, 51-60, 61-70, >70 years old). This was a retrospective-prospective study, where patients were followed over a period of three years and measurements were made: after 12 months, after 24 months and after 36 months.

As a statistical method of data processing was used in two way ANOVA. Two-way ANOVA gives us the following information:

- Does measured data, observing the data of both groups combined, depend statistically significantly on the duration of the treatment (12, 24, 36 months);
- Do the values of the repeated measurements depend statistically significantly on the applied therapy; and
- Is there a statistically significant difference in the values of the measured quantities in patients who apply different therapies?
- If a statistically significant difference was found, then we additionally carried out a comparison in a post hoc analysis using the Bonferroni correction.

3. Results

Two-way ANOVA did not reveal a statistically significant difference in systolic blood pressure values after 12, 24 and 36 months of treatment ($F(2,117)=0.161$, $P=852$).

Also, there was no statistically significant impact of the applied therapy on systolic blood pressure values during observed period ($F(2,117)=0.140$, $P=0.870$).

In order to determine the existence of a statistically significant difference between the treatments, we compared their values over time. There was no statistically significant difference in systolic blood pressure values between the groups ($t=0.92$, $P=0.356$).

Table 1 Descriptive statistics. Systolic blood pressure (mmHg) by tested groups and length of treatment

Lenght of treatment	Group	Mean	SD	N
12 months	Control group	134,0	13,6	60
	Beta-blockers	131,2	17,8	60
	In total	132,6	15,8	120
24 months	Control group	133,4	11,5	60
	Beta-blockers	132,0	14,2	60
	In total	132,7	12,8	120
36 months	Control group	132,7	16,1	60
	Beta-blockers	131,0	18,1	60
	In total	131,9	17,1	120

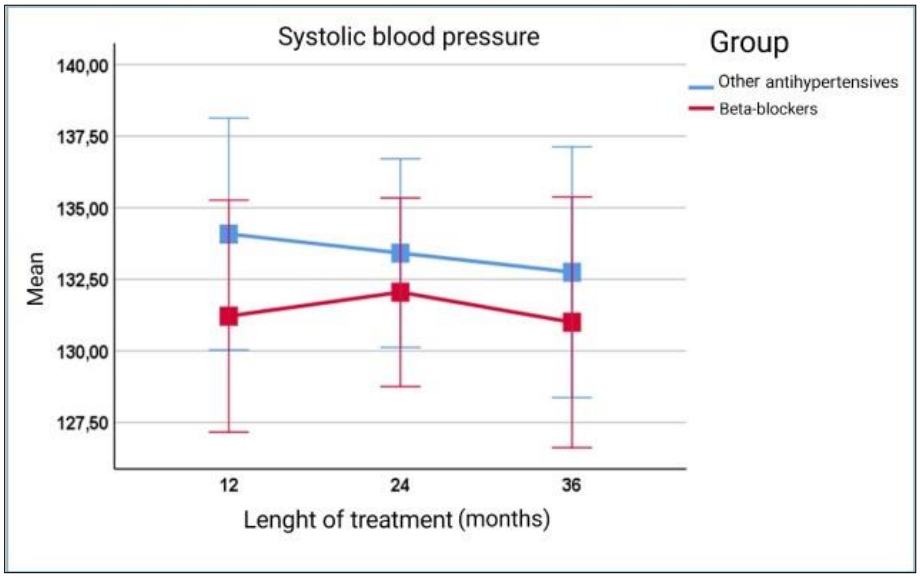

Figure 1 Mean values of systolic blood pressure (mmHg). Vertical lines represent the 95% confidence interval (95% CI) of the mean

Table 2 Descriptive statistics. Diastolic blood pressure (mmHg) by examined groups and length of treatment

Length of treatment	Group	Mean	SD	N
12 months	Control group	83,2	8,1	60
	Beta-blockers	79,9	9,8	60
	In total	81,5	9,1	120
24 months	Control group	81,7	6,5	60
	Beta-blockers	80,4	8,6	60
	In total	81,1	7,6	120
36 months	Control group	83,4	7,9	60
	Beta-blockers	79,9	9,1	60
	In total	81,7	8,7	120

There was no statistically significant difference in diastolic blood pressure after 12, 24 and 36 months of treatment (F(2,117)=0.320, P=727).

Also, there was no statistically significant impact of the applied therapy in the change of diastolic blood pressure during the observed period (F(2,117)=1.202, P=0.304).

In order to determine the existence of a statistically significant difference between the treatments, we compared their values over time. A statistically significant difference was determined in diastolic blood pressure values between the groups (t=2.69, P=0.022).

The results of the post hoc analysis (subsequent testing) carried out for the purpose of comparing diastolic blood pressure values in the control group (CG) and BB after 12, 24 and 36 months, are presented in Table 3. Due to multiple comparisons in the post hoc analysis, we used Bonferroni correction.

Table 3 Post hoc testing results of the statistical significance of the difference in mean values of diastolic blood pressure between treatments 12, 24 and 36 months after the start of the treatment

Length of treatment	(I) Group	(J) Group	Difference (I-J)	t	P
12 months	Control group	Beta-blockers	3.250*	1.98	0.050
24 months	Control group	Beta-blockers	1.333	0.96	0.340
36 months	Control group	Beta-blockers	3.500*	2.25	0.027

*Statistically significant

Looking at the length of treatment, a statistically significant difference between treatments was found after 12 months (t=1.98, P=0.05) and after 36 months (t=3.5, P=0.027), while no statistically significant difference in diastolic blood pressure between groups was found after 24 months of treatment (t=1.33, P=0.340). The Difference column (I-J) shows that the diastolic blood pressure in the control group is statistically significantly higher after 12 and after 36 months.

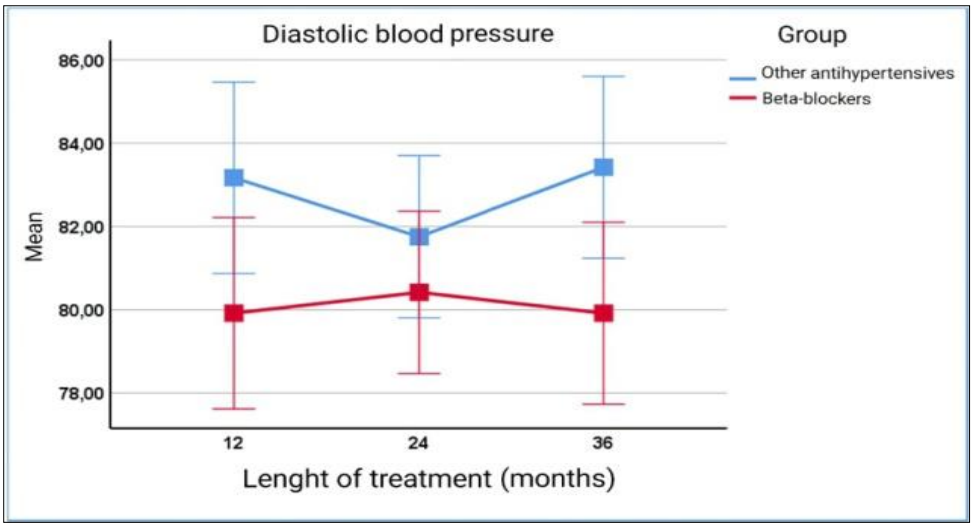

Figure 2 Mean values of diastolic blood pressure (mmHg). Vertical lines represent the 95% confidence interval (95% CI) of the mean

Table 4 Descriptive statistics. Heart rate by examined groups and length of treatment

Length of treatment	Group	Mean	SD	N
12 months	Control group	72,0	11,1	30
	Beta-blockers	74,4	16,7	48
	In total	73,5	14,8	78

24 months	Control group	71,7	10,3	30
	Beta-blockers	75,2	16,2	48
	In total	73,8	14,2	78
36 months	Control group	74,1	12,1	30
	Beta-blockers	75,6	15,3	48
	In total	75,0	14,1	78

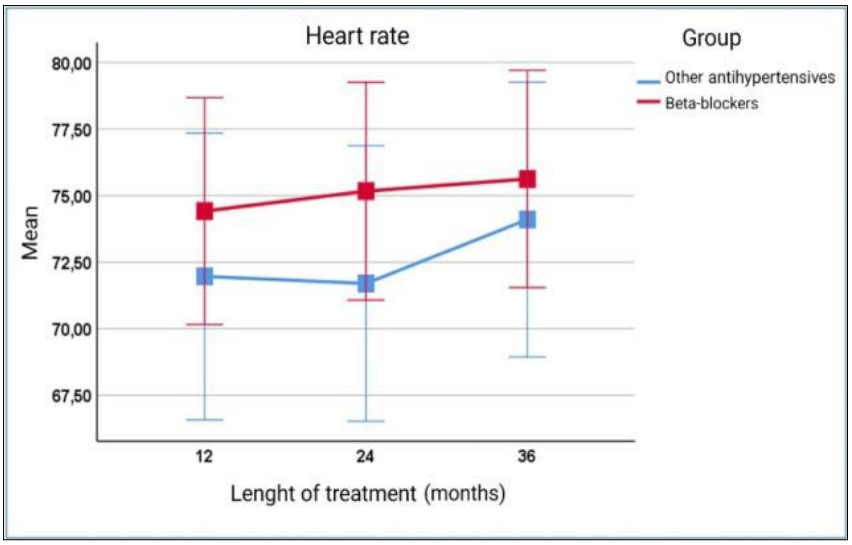

Figure 3 Mean values of heart rate (bpm). Vertical lines represent the 95% confidence interval (95% CI) of the mean

Two-way ANOVA did not reveal a statistically significant difference in heart rate values after 12, 24 and 36 months of treatment ($F(2,75)=0.612$, $P=0.545$). Also, no statistically significant influence of the applied therapy on the change in heart rate value in the observed time intervals was found ($F(2,75)=0.384$, $P=0.682$). In order to determine the existence of a statistically significant difference between the treatments, we compared their values over time. There was no statistically significant difference in heart rate values between the groups ($t=0.89$, $P=0.374$).

Table 5 Systolic blood pressure values by treatment duration and groups

Length of treatment	**Group**	**Mean**	**SD**	**N**
12 months	Bisoprolol and Carvedilol	134,8	18,4	40
	Other BB	124,2	14,5	20
	In total	131,2	17,8	60
24 months	Bisoprolol and Carvedilol	132,8	14,1	40
	Other BB	130,5	14,4	20
	In total	132,1	14,2	60
36 months	Bisoprolol and Carvedilol	132,0	19,5	40
	Other BB	129,0	15,3	20
	In total	131,0	18,1	60

Two-way ANOVA did not reveal a statistically significant difference in systolic blood pressure values after 12, 24 and 36 months of treatment ($F(2,57)=0.409$, $P=666$). Also, there was no determined statistically significant influence of the applied therapy on the value of systolic blood pressure in the observed period ($F(2,57)=1.961$, $P=0.150$).

In order to determine the existence of a statistically significant difference between the treatments, we compared their values over time. There was no statistically significant difference in systolic blood pressure values between the groups (t=1.495, P=0.140).

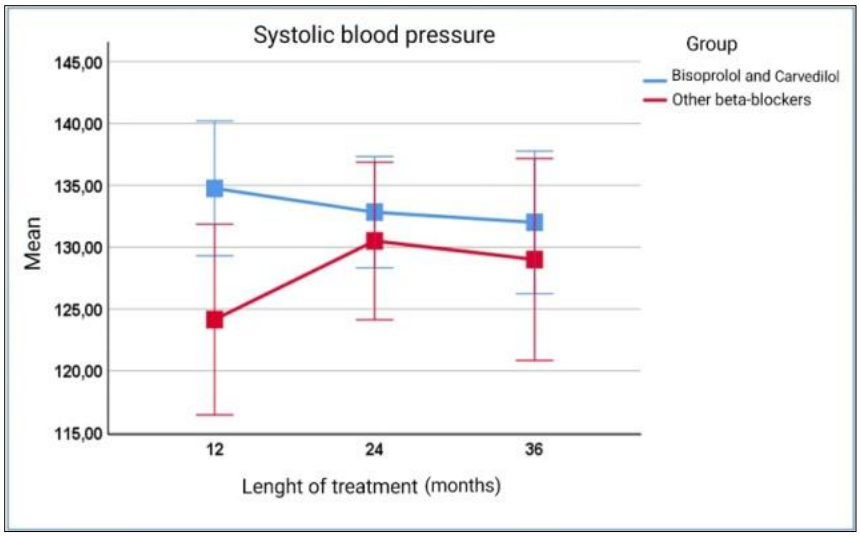

Figure 4 Mean values of systolic blood pressure (mmHg). Vertical lines represent the 95% confidence interval (95% CI) of the mean

Table 6 Values of diastolic blood pressure by treatment duration and groups

Length of treatment	Group	Mean	SD	N
12 months	Bisoprolol and Carvedilol	79,5	10,5	40
	Other BB	80,8	8,5	20
	In total	79,9	9,8	60
24 months	Bisoprolol and Carvedilol	80,9	9,1	40
	Other BB	79,5	7,6	20
	In total	80,4	8,6	60
36 months	Bisoprolol and Carvedilol	80,0	10,0	40
	Other BB	79,8	7,3	20
	In total	79,9	9,1	60

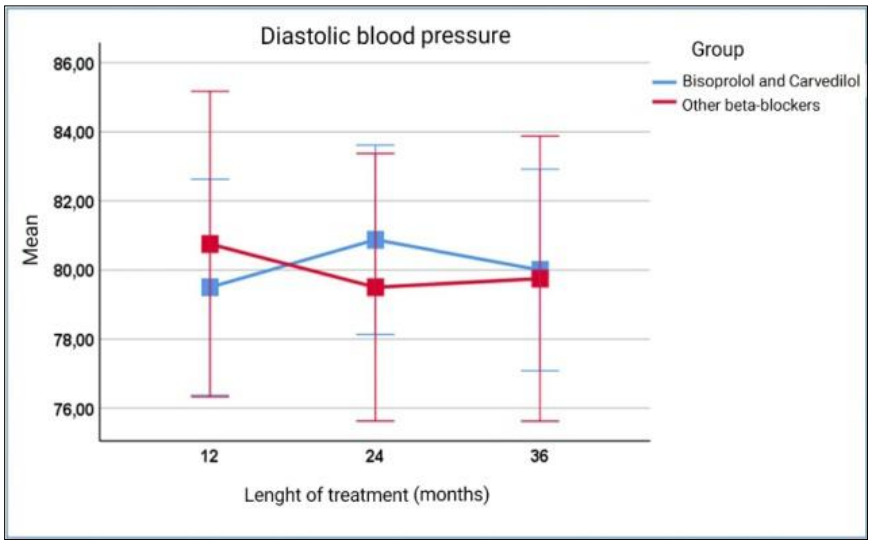

Figure 5 Mean values of diastolic blood pressure (mmHg). Vertical lines represent the 95% confidence interval (95% CI) of the mean

There was no statistically significant difference in diastolic blood pressure after 12, 24 and 36 months of treatment (F(2,57)=0.027, P=0.973).

Also, there was no statistically significant impact of the applied therapy on the change in the value of diastolic blood pressure during the observed period (F(2,57)=0.396, P=0.675).

In order to determine the existence of a statistically significant difference between the treatments, we compared their values over time. There was no statistically significant difference in diastolic blood pressure values between the groups (t=0.067, P=0.948).

Table 7 Heart rate by treatment duration and groups

Length of treatment	**Group**	**Mean**	**SD**	**N**
12 months	Bisoprolol and Carvedilol	76,7	17,9	32
	Other BB	69,9	13,4	16
	In total	74,4	16,7	48
24 months	Bisoprolol and Carvedilol	76,4	16,6	32
	Other BB	72,7	15,5	16
	In total	75,2	16,2	48
36 months	Bisoprolol and Carvedilol	75,0	15,6	32
	Other BB	76,9	15,3	16
	In total	75,6	15,3	48

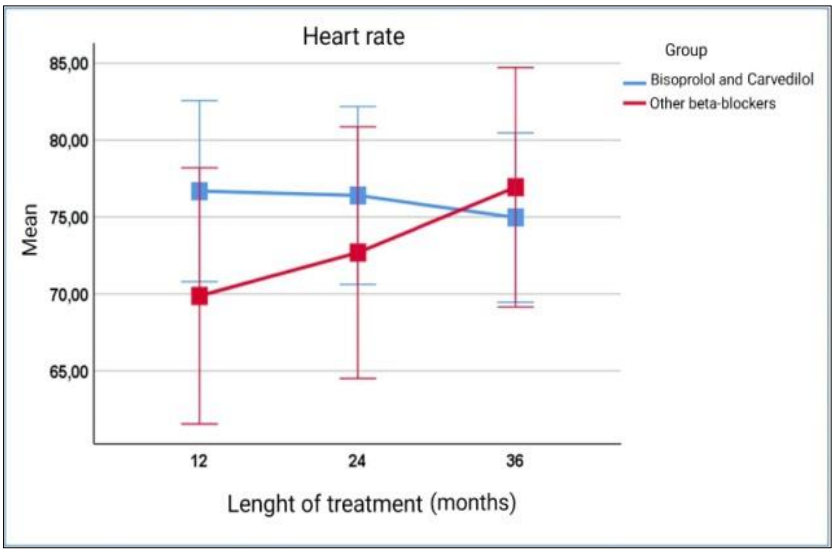

Figure 6 Mean values of heart rate (bpm). Vertical lines represent the 95% confidence interval (95% CI) of the mean

There was no statistically significant difference in heart rate values after 12, 24 and 36 months of treatment (F(2,45)=0.567, P=0.571).

Also, there was no statistically significant influence of the applied therapy on the change in heart rate value during the observed period (F(2,45)=1.480, P=0.239).

In order to determine the existence of a statistically significant difference between the treatments, we compared their values over time. There was no statistically significant difference in heart rate between the groups (t=0.663, P=0.511).

4. Discussion

No statistically significant difference was determined after 12, 24 and 36 months of treatment by monitoring the values of systolic and diastolic blood pressure as well as heart rate in patients using beta-blockers and other groups of antihypertensive drugs. Also, no statistically significant impact of the applied therapy on the change of these values was found during the observed period.

In order to determine the existence of a statistically significant difference between the treatments, we compared their values sorted by time. No statistically significant difference in systolic blood pressure and heart rate was found between the groups, but a statistically significant difference in diastolic blood pressure was found between the groups after 12 and 36 months of therapy.

By comparing the same values within the beta-blocker group (patients using bisoprolol and carvedilol and patients using other beta-blockers), no statistically significant difference was found in the values of systolic and diastolic blood pressure, as well as heart rate after 12, 24 and 36 months of treatment. Also, no statistically significant influence of the applied therapy on the change of these values during the observed period was found.

In order to determine the existence of a statistically significant difference between the treatments, we compared their values sorted by time. There was no statistically significant difference in the values of systolic and diastolic blood pressure and heart rate between the groups.

Also, the condition of patients who used beta-blockers in the treatment of hypertension did not require increasement of the dose in order to achieve the required parameters.

There have been several large clinical trials that have shown that beta-blockers are similar in antihypertensive efficacy to other major classes of antihypertensive drugs. Also, there is evidence to suggest that beta-1-selective blockers such as bisoprolol have a greater antihypertensive effect than non-selective blockers. (7)

Neutel et al conducted a study on a total of 659 patients that were treated with atenolol (50-100 mg) and bisoprolol (10-20 mg). After 24 h ambulatory blood pressure monitoring, a greater drop in diastolic blood pressure was demonstrated in patients who used bisoprolol (11.6 mmHg) than in those who used atenolol (8.7 mmHg), $p < 0.01$. (8)

In a further report, elderly patients that were treated using bisoprolol (n = 23) had a fall of 13/13 mmHg compared with patients that used atenolol (n = 30) of 4/6 mmHg. There was a small difference in the decrease of heart rate values by 16.3 and 13.8 ($p = 0.13$) in patients using bisoprolol and atenolol in therapy.

Likewise, evidence from the MRC study showed that in younger patients, β1-selective agents were more effective than thiazides. In the follow-up study, bisoprolol 5 mg (n = 151) produced a greater decrease in resting diastolic blood pressure than hydrochlorothiazide 25 mg (n = 133), 10.5 ± 0.5 mmHg and 8.5 ± 0.5 mmHg. , respectively ($p = 0.03$). (9)

Also, in a large study of 6,100 patients on different regimens in clinics, blood pressure control in patients using beta-blockers was 141.2/84.3 mmHg (n = 299) and it was very similar to blood pressure control in patients who used diuretics: 140.8/81.8 mmHg (n = 872). (10)

Comparative studies of atenolol inhibitors and ACE inhibitors were evaluated by McAinsh et al. Diastolic blood pressure was reduced by atenolol, enalapril and lisinopril to a similar degree, while systolic blood pressure was reduced more effectively by atenolol. (11)

A number of comparative studies suggest that beta-blockers generally lower blood pressure more than ACE inhibitors. After four years of therapy the drop in blood pressure in patients using acebutolol 400 to 800 mg/day (n = 126), by 13.9/11.5 mmHg was significantly different from placebo, in contrast to the reduction on fairly low doses of enalapril 5 to 10 mg /day (n = 119) by 11.3/9.7 mmHg in the TOMHS study (Treatment of Mild Hypertension Study). (12)

When it comes to calcium channel blockers, beta-blockers lower blood pressure similarly to nifedipine, diltiazem, and verapamil. However, 24-hour ambulatory monitored blood pressure showed that β1-selective bisoprolol (20 mg/day) more effectively lowered blood pressure than dihydropyridine-nitrendipine.

In the TOMHS study, the drop in blood pressure from amlodipine (n = 114) at 5 to 10 mg/day was 14.1/12.2 mmHg, similar to the drop in blood pressure seen in patients using acebutolol.

Trials with prazosin, trimazosin, and doxazosin have shown that alpha-blockers are less effective in lowering blood pressure than beta-blockers. In the TOMHS study, however, it was found that doxazosin in a dose of 2 to 4 mg/day (n = 121) led to a reduction in blood pressure by 13.4/11.2 mmHg, similar during use of acebutolol=13.9/11.5 mmHg.

Materson et al demonstrated that 54% of 183 patients treated with prazosin (2, 5, 10 mg) controlled diastolic blood pressure to less than 90 mmHg at the end of titration and less than 95 mmHg after one year of use, while with the use with atenolol (25, 50 and 100 mg) this figure was 60% (n = 215). (13)

There was a misconception that beta-blockers did not lower blood pressure as much as other groups of antihypertensives. Therefore, the meta-analysis "Blood Pressure Lowering Treatment Trialists' Collaboration" compared different classes of antihypertensive drugs (angiotensin-converting enzyme inhibitors, calcium antagonists, and beta-blockers and/or diuretics). In 8 trials involving 37,872 patients followed for 2-8 years, the difference in blood pressure between patients treated with different drug groups was minimal (systolic blood pressure 0-3 mmHg, diastolic blood pressure <1-2 mmHg). It is important to note that beta-blockers were combined with diuretics in the meta-analysis due to frequent simultaneous use, so the effects of beta-blockers used as monotherapy were not reported. (14)

However, large clinical trials that compared beta-blockers with diuretics showed no statistically significant difference between the treatments in terms of lowering blood pressure. In these trials approximately 3/4 of patients achieved a desired blood pressure by using any class of drugs. (15)

Bangalore, Sawhney and Messerli also studied an impact of beta-blockers on heart rate and their association with cardiovascular events. The average age of the patients in these trials was 58 years, and they were monitored for 3.5 years. The group of patients who used beta-blockers and the comparison groups were similar in terms of average age, duration of treatment, and initial values of systolic and diastolic blood pressure. In the beta-blocker group, systolic blood pressure decreased by 13.5% (166.2 ± 14.6 mmHg to 143.8 ± 10.6 mmHg; $p < 0.0001$), and diastolic blood pressure by 14.2 % (100.4 ± 6.8 mmHg to 86.1 ± 6.7 mmHg; $p < 0.0001$). Similarly, in the control group, mean systolic blood pressure decreased by 13.1% (166.7 ± 14.7 mmHg to 144.9 ± 17.3 mmHg; $p < 0.0001$), and diastolic blood pressure by 13. 3%

(100.4 ± 7.3 mmHg to 87 ± 7.7 mmHg; p <0.0001). Thus, there was no difference between the values of the finally achieved systolic and diastolic blood pressure between the beta-blockers and the control group. However, beta-blockers caused a significant reduction (12%) in heart rate, while in the control group this reduction was insignificant (1%, p <0.0001). (16).

5. Conclusion

There was a misconception that beta-blockers did not lower blood pressure as much as other groups of antihypertensive drugs. Despite these controversies surrounding their use, our research did not prove a worse effect of beta-blockers on blood pressure and heart rate compared to other antihypertensive drugs. The condition of patients who used beta-blockers in the treatment of hypertension did not require an increased dose in order to achieve the necessary parameters.

Also, within the group of beta-blockers, all drugs showed equal effectiveness.

Beta-blockers are extremely successful drugs in the therapy of arterial hypertension, and the danger of not treating arterial hypertension is much greater than the effect of various antihypertensives.

Compliance with ethical standards

Disclosure of conflict of interest

The authors confirm that there are no known conflicts of interest associated with this publication to be disclosed. The study was conducted independently by the authors without any influence or competing interests from anyone.

Statement of informed consent

Informed and written consent was obtained from all individual participants included in the study.

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