

## REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

# Fixed combination of bisoprolol and low-dose hydrochlorothiazide in arterial hypertension

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Beta-blockers showed better results in lowering elevated blood pressure in the younger age group of patients with higher renin plasma levels. Actual recommendations from the European Society of Cardiology for treatment of arterial hypertension from 2013 insist that heart rate should always be measured along with blood pressure. These recommendations point out the significance of resting heart rate as an independent predictor of cardiovascular morbidity and mortality in patients with arterial hypertension. Beta-blockers have a compelling indication for treatment of arterial hypertension in patients with coexistence of coronary artery disease, especially post myocardial infarction, as well as in patients with systolic heart failure. Bisoprolol, a highly selective beta-blocker with a long half-life and a prolonged antihypertensive effect, has shown consistent blood pressure control over a period of 24 hours.

It has been demonstrated in placebo-controlled studies that administration of thiazide diuretics, in addition to lowering blood pressure levels, had also been associated with a reduction of cardiovascular morbidity and mortality rates. It is evident that effectiveness of thiazide diuretics is dose-dependent; however, undesirable effects of drugs are also dose-dependent. Depending on the dose, they aggravate glucose intolerance, increase lipid levels, cause hypokalemia, hyponatremia, and hypomagnesemia, and increase levels of uric acid. Administration of very low doses of a thiazide diuretic is acceptable in combination with other antihypertensive drugs, because it potentiates the action of other drugs without causing undesirable metabolic effects. The effectiveness and safety of the combination of bisoprolol (in various doses) and a thiazide diuretic in a small dose has been proven in clinical trials.

**Keywords:** hypertension, drug therapy; antihypertensive agents; administration and dosage; beta-blockers; bisoprolol; thiazides

**INTRODUCTION**

The main treatment goal in patients with arterial hypertension is the normalization of blood pressure levels, prevention, stopping, or regression of the target organ damage, with the ultimate goal to decrease cardiovascular morbidity and mortality rate. Under normalization of blood pressure levels we consider a decrease to less than 140/90 mmHg, and to less than 140/85 mmHg in patients with diabetes mellitus. However, this goal is very difficult to achieve for most patients. According to results from Blood Pressure Control Rate and Cardiovascular Risk Profile study, in which 7,860 patients from Central and Eastern Europe treated for arterial hypertension were included, satisfactory control of blood pressure was achieved in only 27.1%. According to that study, target blood pressure levels were reached in 23.3% of patients in Serbia [1]. Possible reasons for treatment failure are physicians' inertia on the one hand, and patients' low awareness of the problem severity and significance of adherence to advised treatment on the other. Therapeutic inertia is reflected in satisfaction with achieved reduction without normalization of blood pressure values, and in insisting on monotherapy.

Administration of more than one antihypertensive agent is advised in international guidelines, for patients with systolic blood pressure that is 20 mmHg higher, and diastolic one that is 10 mmHg higher than border levels, as well as in patients with high level risk due to associated risk factors and subclinical damage to target organs, diabetes mellitus, associated cardiovascular or kidney disease. The best evidence in favor of benefits of combined therapy are the results of a meta-analysis in which 42 studies (10,968 patients) were included, and which showed that a combination of two antihypertensive agents lowered arterial blood pressure five times better than the maximal dose of a single drug [2]. It is possible to achieve the desired effectiveness by combining medicaments with different mechanisms of action due to their synergistic action. Fixed combinations of diuretics and renin-angiotensin-aldosterone system inhibitors or beta-blockers are useful, as they ensure numerous benefits, starting with better blood pressure control, a simplified dosage regime, and improvement of compliance with reduction of dose-dependent undesirable effects.

The objective of this paper is to summarize advantages of administering a fixed combination of bisoprolol and a low-dose thiazide diuretic.

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## BETA-BLOCKERS IN THERAPY OF ARTERIAL HYPERTENSION

A 10-year follow-up of 3,195 healthy persons with an average age of 48.5 years in the Framingham Heart Study has shown that overweight younger men, especially if they continue to further gain weight, predominantly develop diastolic arterial hypertension [3]. Isolated systolic hypertension in older patients was found more often in women, and usually occurred in persons with history of normal or high-normal blood pressure. It has been found that heart rate, as well as minute volume, and peripheral vascular resistance as well, were increased in proportion with body mass index and waist circumference [4]. Sympathetic neural activity in skeletal muscles, the index of sympathetic nervous system activation, increases in proportion with waist circumference and abdominal fat tissue mass [5]. Abdominal adipocytes cause sympathetic nervous system activation through leptin production. An increased sympathetic tone leads to an increase in renin and angiotensin II production, which in turn additionally activate sympathetic nervous system through feedback. Abdominal adipocytes stimulate an increase in interleukin 6 and tumor necrosis factor alpha through adipokines, and cause the development of increased insulin resistance. An increase in insulin level occurs with additional feedback activation of sympathetic nervous system. In this manner, central obesity and an increased leptin production increase catecholamines plasma levels with unfavorable effects on the heart and the blood vessels.

The increased sympathetic nervous system activation leads to an increase in heart rate and an increased strength of the myocardial contraction, and causes an increase in ventricular stroke volume and an increase in minute volume (minute volume is equal to the product of heart rate and stroke volume). The elevated adipokines, interleukin-6, and tumor necrosis factor alpha levels intensify oxidative stress and cause the development of endothelial dysfunction and inflammation [6]. The disorder of endothelial function is the underlying cause of inadequate vasodilatation of the arterioles in response to metabolic stimuli and an increased peripheral vascular resistance. In addition to the functional component, an anatomical substrate of an increased peripheral vascular resistance develops. Hypertrophy of small artery and arteriole media develops at the expense of lumen reduction; this is an anatomical change, which is the underlying cause of the development and progression of diastolic arterial hypertension and is referred to as eutrophic remodeling of small resistant arteries. The activation of the sympathetic nervous system causes the development and the progression of arterial hypertension through an increment of minute volume and peripheral vascular resistance. It has been demonstrated that in the treatment of arterial hypertension, beta-blockers showed better results in lowering elevated blood pressure in the younger-age group of patients with higher renin plasma levels [7]. Older patients with lower renin levels show a better therapeutic response to calcium antagonists [8]. It has been found that highly selective

beta-blocker bisoprolol, in a group of male patients, age between 35 and 60 years, and with moderate hypertension, showed better results after four weeks of treatment, compared to drugs from other groups of antihypertensive agents [9]. In these patients, monotherapy with bisoprolol with a daily dose of 5 mg showed a better efficacy in lowering both systolic and diastolic blood pressure compared to treatment with losartan 50 mg, amlodipine 5 mg, or hydrochlorothiazide 25 mg once a day. The strategy for arterial hypertension treatment in earlier guidelines was based on assessed sympathetic nervous system activity degree [10, 11, 12]. In younger patients with arterial hypertension and increased sympathetic tone and higher renin plasma levels, drugs with antiadrenergic effects were recommended for initiation of hypertension treatment: beta-blockers and angiotensin-converting-enzyme (ACE) inhibitors, or angiotensin receptor blockers. Diuretics and calcium antagonists (ABCD treatment strategy for arterial hypertension) were recommended as the initial therapy for elderly patients with lower renin levels.

While comparing antihypertensive effects of bisoprolol and atenolol in a single daily dose by using the method of ambulatory blood pressure monitoring, bisoprolol showed a better blood pressure control in 659 patients with mild to moderate hypertension during the entire period of twenty-four hours' follow-up. A greater efficacy of bisoprolol was exhibited especially in the last hours of the twenty-four-hour interval, in the morning of the following day, before the next scheduled dose of the drug [13]. For consistent blood pressure control during the period of twenty-four hours, it is necessary to use a medicament with longer elimination half-life and higher minimal-to-maximal effect ratio as a monotherapy. As opposed to atenolol, which has an average elimination half-life of six to seven hours and minimal-to-maximal effect ratio of 31%, the highly selective beta-blocker bisoprolol has an elimination half-life of 10–12 hours and minimal-to-maximal effect ratio of 78%. Under the current US Food and Drug Administration criteria for approval of a single daily dose drug for the treatment of arterial hypertension, minimal-to-maximal effect ratio over the period of 24 hours must be higher than 50%. Blood pressure values in the early morning hours, prior to taking the next dose for the following day, is of particular importance. At that time of the day, a pronounced increase in the sympathetic nervous system activity and an increased catecholamine level occur with awakening and beginning of daily activities. At that time, a sudden increase in heart rate and blood pressure is recorded, and increased frequency of ischemic episodes, both symptomatic and asymptomatic ones, is also registered in patients with coronary disease at that time. In the early morning hours, after awakening, a higher frequency of sudden cardiac death, as well as ischemic stroke, is recorded. Bisoprolol, a beta-blocker with a long half-life and a prolonged antihypertensive effect, and a consistent blood pressure control over the period of twenty-four hours, has shown a reduction of ischemic episodes in patients with coronary artery disease in the early morning hours [14].

## HEART RATE AND CARDIOVASCULAR MORTALITY

In a study with 2,037 men with untreated arterial hypertension, and a 36-year-long follow-up, it has been found that elevated resting heart rate at baseline increased the risk of mortality [15, 16]. It has been demonstrated that elevated resting heart rate increased the risk of mortality from coronary artery disease, the risk of cardiovascular mortality, but also the risk of overall mortality. It has been reported that resting heart rate higher than 84 beats per minute at baseline had been associated with an increased mortality, compared to lower heart rate levels. It has been confirmed in a study with elderly patients with arterial hypertension that elevated resting heart rate at baseline increased the risk of mortality. This has been demonstrated in both men and women [17]. Patients with arterial hypertension and resting heart rate over 79 beats per minute have a risk of mortality increased by 89%, in comparison to patients with heart rate under 79 beats per minute. It has been found, through a follow-up of 5,713 asymptomatic men over the period of 23 years, that elevated resting heart rate at baseline increased the risk of sudden cardiac death and the risk of mortality from myocardial infarction [18].

An analysis of risk factors has shown that in addition to classic risk factors for atherosclerosis, resting heart rate values in men had an independent significance as a predictor of mortality risk [19]. Heart rate higher than 80 beats per minute, along with classic risk factors – systolic and diastolic blood pressure, diabetes, smoking and age – indicate an increased risk of mortality. Actual recommendations from the European Society of Cardiology for treatment of arterial hypertension from 2013 insist that heart rate should be always measured along with blood pressure [20]. These recommendations point out the significance of resting heart rate as an independent predictor of cardiovascular morbidity and mortality in patients with arterial hypertension. [21].

An elevated heart rate increases the myocardial oxygen demand, and may cause occurrence of myocardial ischemic episodes in patients with coronary disease. It is less known that an elevated heart rate accelerates the progression of atherosclerosis, predisposes occurrence of a vulnerable atheroma rupture and the development of acute coronary syndrome. An increased activation of the sympathetic nervous system has unfavorable effects on the heart and stimulates hypertrophy of the left ventricle in patients with arterial hypertension. A sudden increase in the catecholamine plasma level may even lead to a direct toxic myocardial lesion, with an increase in markers of myocardial necrosis level. An excessive sympathetic stimulation may have initiation of apoptosis of myocardial cells as a result. An elevated sympathetic nervous system tone increases the frequency of disorders of heart rhythm and lowers the threshold for occurrence of malignant arrhythmias.

Secondary prevention with beta-blockers reduces cardiac mortality rate in patients with a history of myocardial infarction. A meta-analysis of 12 studies has shown that each 10-beat per minute reduction in heart rate reduce the

cardiac mortality rate by 26% on an annual basis [22]. It has been also demonstrated that an excessive neurohumoral stimulation had an unfavorable effect in patients with heart failure. An increased sympathetic activation accelerates the dilatation of the left ventricle, intensifies the remodeling of the ventricle, and aggravates heart failure. A meta-analysis of a larger number of studies with patients with heart failure has shown an unfavorable effect of elevated resting heart rate on an increased patient mortality rate [23]. Guidelines for treating systolic heart failure propose beta-blockers bisoprolol, carvedilol, and metoprolol succinate as chronic treatment. It has been demonstrated that these drugs exhibit a prognostic effect and reduce the mortality of patients with heart failure. It has been found that the risk from cardiovascular mortality in such patients had been decreased in proportion with reduction in resting heart rate [23].

ACE inhibitors, angiotensin receptor blockers, and calcium antagonists in therapy of arterial hypertension have shown a better effect on reduction of cardiovascular risk in a larger number of studies. In studies, the most common comparator from the beta-blocker group was atenolol, a moderately selective beta-blocker. Atenolol, with its shorter elimination half-life, in a single daily dose, could not maintain a consistent antihypertensive effect during the period of 24 hours. As opposed to highly selective beta-blockers and vasodilating beta-blockers, atenolol has shown a weaker effect and has had a lower efficacy in reduction of central arterial pressure in the population of advanced age patients. Because of this, some more recent guidelines from national and international cardiology associations have diminished the role of beta-blockers in initiation of treatment of uncomplicated arterial hypertension. The new American JNC 8 guidelines for the treatment of arterial hypertension emphasize that in making recommendations only the most recent clinical studies have been included [24]. Nowadays, widely used beta-blockers, with expired patents' protection, have not been studied in new meta-trials of arterial hypertension treatment, and it is required to limit treatment concerns to earlier comparators from the beta-blocker group, which were studied in the older trials. This is also the case with the current European Society of Cardiology guidelines for the treatment of arterial hypertension from the year 2013. In these recommendations, from the beta-blocker group, vasodilating beta-blockers and highly selective beta-blockers with a better blood pressure regulation profile, better metabolic effects, and more effective reduction of the cardiovascular risk, stand out [25].

## THE ADVANTAGES OF A LOW-DOSE THIAZIDE DIURETIC ADMINISTRATION

The use of thiazide diuretics started in the late 1950s. Since then, they have remained one of the most significant groups of drugs for lowering blood pressure due to their effectiveness and low cost. Their primary mechanism of action is the inhibition of Na-Cl cotransporter in the renal distal convoluted tubules and adjacent nephron segments. This inhibition initially leads to a diuretic effect,



which causes a reduction of plasma volume and decreased blood pressure. After the continuation of therapy, a partial restitution of blood volume occurs, and the vasodilating mechanism based on opening the ATP-sensitive potassium channels is responsible for the continuation of antihypertensive action.

The effectiveness of thiazide diuretics in blood pressure regulation is shown in comparison with placebo and other antihypertensive agents. It has been demonstrated in placebo-controlled studies that administration of thiazide diuretics, besides lowering blood pressure levels, had also been associated with a reduction of cardiovascular morbidity and mortality rates. A meta-analysis of these studies has proven that a low dose of a diuretic reduced the overall mortality rate by 10%, the stroke risk by 29%, decreased heart failure risk by 49%, and cardiovascular disease risk by 24% [26]. At the same time, it has been demonstrated that neither group of antihypertensive agents, with which they had been compared (beta-blockers, ACE inhibitors, potassium channel blockers, alpha-blockers, and AT1 receptor blockers), had not been significantly better than thiazide diuretics administered in low doses. Numerous randomized studies have determined that thiazide diuretics, in addition to efficient blood pressure regulation, also reduced the risk from coronary events, strokes, and heart failure in the elderly [27, 28]. The ALLHAT study has shown that a thiazide diuretic was equally efficient as an ACE inhibitor and a calcium channel blocker in coronary and cerebrovascular events prevention, and that it was more efficient than a calcium channel blocker in heart failure prevention, and more efficient than an ACE inhibitor in stroke prevention [29].

There are disagreements concerning the existence of differences in effectiveness of individual thiazide diuretics. In the MRFIT study, patients were treated with chlorthalidone or hydrochlorothiazide (HCTZ), depending on the clinical centers' experiences. After seven years, the Advisory Committee recommended chlorthalidone for use in all patients treated with a thiazide diuretic, based on an unfavorable mortality trend in patients treated with HCTZ in nine centers, in comparison to a favorable trend registered in patients treated with chlorthalidone in six centers [30]. A meta-analysis and a mini-study conducted in one centre, in which effectiveness of administered diuretics was studied during 24-hour ambulatory monitoring, confirmed the advantage of chlorthalidone in comparison with HCTZ [31, 32]. More complete data on the effectiveness of individual thiazide diuretics (bendrofluzide, cyclopentiazide, indapamide, hydrochlorothiazide, chlorthalidone, metolazone) were obtained in the Cochrane analysis [33]. Sixty double-blind placebo-controlled studies published until February 2014 were included in the stated analysis. The analysis comprised 11,282 patients with an average age of 55 years, out of which 53% were male. The mean blood pressure in the subjects was 158/99 mmHg. A similar effectiveness of studied thiazide diuretics was found. In general, systolic blood pressure was reduced by 9 mmHg, and diastolic by 4 mmHg in comparison with the placebo group. The most information about HCTZ was obtained from 35 random-

ized studies that included 6,725 patients. HCTZ was administered in daily doses of 6.25 mg, 12.5 mg and 25 mg. The dose of 6.25 mg showed a statistically significant better reduction of blood pressure levels in comparison with the placebo; however, in lowering systolic blood pressure, a clear dose-dependent response was registered. HCTZ dose of 12.5 mg lowered systolic pressure by 2.2 mmHg more than the dose of 6.25 mg, and the dose of 25 mg lowered systolic pressure by 2.7 mmHg more than the dose of 12.5 mg. The dose of 12.5 mg lowered diastolic pressure by 1.1 mmHg more than the dose of 6.25 mg, and the difference in effectiveness was only 1 mmHg for doses of 12.5 and 25 mg. The more efficient dose-dependent reduction of systolic, but not diastolic, blood pressure was also responsible for dose-dependent reduction in pulse pressure, which was up to 4–6 mmHg at maximal doses. Other groups of antihypertensive agents, such as ACE inhibitors and AT1 receptor blockers, lower pulse pressure independently of administered dose by 3 mmHg, and non-selective beta-blockers by 2 mmHg. It is obvious that the reduction in pulse pressure achieved by HCTZ administration in the lowest dose (6.25 mg) was bigger than the one achieved by other antihypertensive agents.

It is evident that effectiveness of thiazide diuretics is dose-dependent; however, undesirable effects of a drug are also dose-dependent. Depending on the dose, they aggravate glucose intolerance, increase lipid levels, cause hypokalemia, hyponatremia, and hypomagnesemia, and increase the levels of uric acid.

A meta-analysis of 22 studies has shown that the use of thiazide diuretics, in comparison with placebo and other antihypertensive agents, was associated with an increased risk of new-onset diabetes mellitus [34]. The mechanism of development of glucose intolerance and reduction in insulin sensitivity is not completely clear. According to the generally accepted assumption, thiazide-induced decreased level of potassium is responsible for the reduction in insulin secretion and the reduction in insulin-mediated glucose uptake in skeletal muscles with consequential reduction in insulin sensitivity, which leads to impaired glucose tolerance and hyperglycemia. This assumption is based on results from smaller studies, and it was reinforced in a post hoc analysis of the SHEP study, in which it was found that the risk of the new-onset diabetes mellitus was increased with each 0.5 mEq/L decrease in K level [35, 36]. Zillich et al. [37] have found a significant negative correlation between the potassium level and the glucose level ( $r = -0.28$ , 95% confidence interval  $-0.47$  to  $-0.07$ ,  $p < 0.01$ ). They have concluded that maintaining potassium levels above 4 mEq/L may reduce the risk of hyperglycemia development caused by treatment with thiazide diuretics. Obesity has been reported as a contributing factor to the development of this unfavorable effect of thiazide diuretics, as well as treatment duration of more than nine years, which may contribute to the development of diabetes mellitus [38].

In addition to individual risk assessment for each patient (existing disorder of glucose metabolism, obesity), as a preventive measure for diabetes mellitus development, administration of a thiazide diuretic in a low dose is reported.

A dose-dependent increase in total cholesterol, low-density lipoprotein and triglyceride levels may occur even after short-term administration of thiazide diuretics [39, 40]. These changes are more frequent in patients with diabetes mellitus. The mechanism of development of these changes is not clear, but it is associated with a decrease in insulin sensitivity and/or reflex activation of the sympathetic nervous system and renin-angiotensin-aldosterone system in diuretic-induced volume depletion. This increase is a reversible one – lipid levels return to the range prior to therapy initiation, a year after cessation of diuretics' administration [41]. Considering that a thiazide diuretic in a low dose does not induce a significant change in volume, it is expected that it will not have an impact on disorders of lipid status.

Hypokalemia (potassium level < 3.5 mEq/L) is often an adverse effect of thiazide diuretics [42]. In the first few days of therapy, thiazide diuretics cause the average of 0.6 mEq/L dose-dependent decrease in the potassium level (which is more than the decrease of 0.3 mEq/L caused by administering loop diuretics). An increased sodium intake, a decrease in chloride levels in the distal tubules, metabolic alkalosis, and secondary hyperaldosteronism contribute to the increase in flow-dependent potassium secretion.

Hypokalemia is, in addition to the aforementioned metabolic disorders, responsible for other disorders as well. In the MRFIT study, a significant inverse relationship between potassium concentrations and ventricular extrasystoles was found [30]. The risk of thiazide-induced hypokalemia and rhythm disorders is more significant in patients with existing hypertrophy of myocardium, heart failure, and ischemia; therefore, in such patients, greater caution should be exercised and the dosage of a thiazide diuretic should be lowered.

Hyponatremia is a rare but serious complication of diuretic therapy, with the remark that thiazide diuretics are more likely to cause it than loop diuretics. Possible hyponatremia has very rarely a degree that requires a correction [43]. Metabolic alkalosis is also a very rare complication of administering thiazide diuretics. Its occurrence is also dose-dependent, as are all listed adverse effects.

Thiazide diuretics, as well as loop diuretics, increase excretion of magnesium through urine, which may lead to a decrease in magnesium levels by 5–10%. Hypomagnesemia is found more often in the elderly and in those on high doses of diuretic therapy, and often coexists with hypokalemia, hyponatremia, and hypocalcemia. Hypomagnesemia is suspected when electrocardiography signs develop (prolonged QT and/or PR interval, a wide QRS complex, ST depression and low amplitude T wave along with supraventricular and ventricular arrhythmias), neurological changes (the change in mental status, and/or neuromuscular irritability such as tetany, tremor, muscle spasms). Parenteral supplementation of magnesium required due to the administration of thiazide diuretics is very rare, but oral supplementation should be considered when any of the listed symptoms occur [43].

A high dose of thiazide diuretics causes the increase in urates concentration by more than 35% due to their

clearance reduction. This reduction in clearance may be a consequence of an increased tubular reabsorption caused by diuretic-induced reduction of volume and/or competitive secretion of urates and thiazides since they have the same anion transporter. The occurrence of gout attacks requires temporary therapy cessation, and, if not acceptable, a drug should be administered in the lowest possible dose along with allopurinol [44].

The deleterious effect of thiazide and thiazide-like diuretics on male sexual function is not negligible. According to various studies, decreased libido, erectile dysfunction, and ejaculation problems are seen in 3–32% of patients [30].

In spite of all listed adverse effects of thiazide diuretics, the following Kaplan's [45] statement is undoubtedly acceptable: "... Appropriate use of diuretics can still be a safe and effective way to treat hypertension..." It is necessary to adapt the premise "appropriate use" to our midst, since only HCTZ and indapamide (which we have classified as thiazide-like diuretics) are registered. Having in mind the wide use of HCTZ, it is necessary to define the "low" dose that would be both effective in blood pressure control and have least adverse effects. It has been shown in the aforementioned Cochrane analysis that HCTZ administered in the dose of 6.25 mg achieves an antihypertensive effect. The administration of this very low dose of the thiazide diuretic is indeed acceptable in combination with other antihypertensive drugs, because it potentiates the action of other drugs without causing undesirable metabolic effects.

#### **THE IMPORTANCE OF A FIXED COMBINATION OF BISOPROLOL AND LOW-DOSE HIDROCHLORTHAZIDE**

The effectiveness and safety of a combination of bisoprolol (in various doses) and a thiazide diuretic in a small dose (6.25 mg) has been proven in experimental and clinical trials. It has been demonstrated in an animal model that this combination caused a reduction in blood pressure and heart rate, that it caused a lower renin activation compared to a thiazide diuretic alone, and that it caused a reduction of myocardial hypertrophy [46].

It has been demonstrated on the sample of 106 patients that an eight-week treatment with a combination of bisoprolol and a low-dose thiazide diuretic caused a successful reduction of systolic blood pressure from 157.4 mmHg to 137.3 mmHg, and of diastolic blood pressure from 98.8 mmHg to 87.4 mmHg [47]. The desired therapeutic response was achieved in 61% of the patients – normalization of blood pressure levels, with adverse effects occurring in 18.9%, out of which headache and fatigue were the most common ones. Disorders of glucose and lipid metabolism, potassium and uric acid levels were not recorded.

Even better results of blood pressure control in patients with mild to moderate hypertension have been obtained in a multicentric, randomized, double-blind, placebo-controlled study. A combination of bisoprolol and a thiazide diuretic reduced systolic blood pressure levels by

15.8 mmHg, and diastolic blood pressure by 12.6 mmHg, which was significantly more, compared to bisoprolol or a thiazide diuretic as monotherapy [48]. Normalization of blood pressure levels was achieved in 71% of the patients. A similar result has been obtained in another randomized, double-blind, placebo-controlled study. Using a combination of a low-dose bisoprolol (2.5 mg) and a thiazide diuretic (6.25 mg), a reduction of diastolic blood pressure was achieved in 61% of the patients with safety profile comparable to placebo [49]. In a randomized, double-blind, parallel study, the effectiveness of a combination of bisoprolol and a low-dose thiazide diuretic was compared to enalapril or amlodipine monotherapy [50, 51]. The desired therapeutic response was achieved in 71% of the patients treated with the combination, and in 69% and 45% of the patients treated with amlodipine and enalapril, respectively. Another similar randomized, double-blind, parallel study has shown that a low-dose combination of bisoprolol and a thiazide diuretic and amlodipine were equipotent, but it was more efficient compared to enalapril [52]. The same authors have shown, using efficacy analysis depending on race, that a combination of bisoprolol and a thiazide diuretic in non-black population led to more significant lowering of diastolic pressure compared to amlodipine, enalapril, or placebo [53]. The incidence of adverse effects has been similar in all treatment modalities,

but treatment cessation was rarer when using the combination of bisoprolol and a thiazide diuretic.

Papadopoulos and Papademetriou [54] have concluded in their review paper on effectiveness of a fixed low-dose combination of bisoprolol and a thiazide diuretic that the period in which a satisfactory response to therapy can be expected is about four weeks; after this period, in case of failure, a combination with a higher bisoprolol dose should be administered. A combination of bisoprolol and a low-dose of a diuretic showed both effectiveness and safety in treating isolated hypertension in elderly persons [55]. This combination has found its place in treatment of arterial hypertension in children [54].

## CONCLUSION

Bisoprolol, a highly selective beta-blocker with long half-life and a prolonged antihypertensive effect, has shown a consistent blood pressure control over a period of 24 hours. The administration of a very low dose of a thiazide diuretic is acceptable in combination with beta-blockers, because it potentiates antihypertensive action without causing undesirable metabolic effects. The effectiveness and safety of a combination of bisoprolol (in various doses) and a thiazide diuretic in a small dose has been proven in clinical trials.

## REFERENCES

- Grassi G, Cifkova R, Laurent S, Narkiewicz K, Redon J, Farsang C, et al. Blood pressure control and cardiovascular risk profile in hypertensive patients from central and eastern European countries: results of the BP-CARE study. *Eur Heart J*. 2011; 32(2):218–25.
- Wald DS, LawM, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med*. 2009; 122(3):290–300.
- Franklin SS, Pio JR, Wong ND, Larson MG, Leip EP, Vasan RS, et al. Predictors of new-onset diastolic and systolic hypertension: the Framingham Heart Study. *Circulation*. 2005; 111(9):1121–7.
- Drukteinis J, Roman MJ, Fabsitz RR, Lee ET, Best LG, Russell M, et al. Cardiac and systemic hemodynamic characteristics of hypertension and prehypertension in adolescents and young adults: the strong heart study. *Circulation*. 2007; 115(2):221–7.
- Joyner M, Charkoudian N, Wallin G. Sympathetic nervous system and blood pressure in humans: individualized patterns of regulation and their implications. *Hypertension*. 2010; 56(1):10–6.
- Cruickshank J. Are we misunderstanding beta-blockers. *Int J Cardiol*. 2007; 120(1):10–27.
- Bühler FR. Age and pathophysiology-oriented antihypertensive response to calcium antagonists. *J Cardiovasc Pharmacol*. 1988; 12(Suppl 8):S156–62.
- Tadic M, Ivanovic B, Celic V, Kocabay G. The impact of metabolic syndrome, recently diagnosed diabetes and hypertension on right ventricular remodeling. Is there difference between risk factors? *Clin Exp Hypertens*. 2014; 36(5):295–301.
- Hiltunen TP, Suonsyrjä T, Hannila-Handelberg T, Paavonen KJ, Miettinen HE, Strandberg T, et al. Predictors of antihypertensive drug responses: initial data from a placebo-controlled, randomized, cross-over study with four antihypertensive drugs (the GENRES study). *Am J Hypertens*. 2007; 20(3):311–8.
- Cruickshank JM. The modern role of beta-blockers in cardiovascular medicine. Shelton: PMPH-USA; 2011.
- Divac N, Naumović R, Ristić A, Milinković M, Brković V, Jovičić Pavlović S, et al. Patterns of antihypertensive medication use in kidney transplant recipients. *Herz*. 2017; 42(1):67–74.
- Vujan B, Kovačević D, Petrović M, Ivanov I, Panić G. Takotsubo cardiomyopathy in pregnancy. *Cent Eur J Med*. 2014; 9(1):49–53.
- Neutel JM, Smith DH, Ram CV, Kaplan NM, Papademetriou V, Fagan TC, et al. Application of ambulatory blood pressure monitoring in differentiating between antihypertensive agents. *Am J Med*. 1993; 94(2):181–7.
- Arnim T. Medical treatment to reduce total ischemic burden: Total ischemic burden bisoprolol study (TIBBS), a multicenter trial comparing bisoprolol and nifedipine. *J Am Coll Cardiol*. 1995; 25(1):231–8.
- Gillman MW, Kannel WB, Belanger A, D'Agostino RB. Influence of heart rate on mortality among persons with hypertension: the Framingham study. *Am Heart J*. 1993; 125(4):1148–54.
- Ivanovic B, Dincic D, Tadic M, Simic D. Arterial hypertension in the elderly. *Vojnosanit Pregl*. 2011; 69(9):779–85.
- Palatini P, Thijs L, Staessen JA, Fagard RH, Bulpitt CJ, Clement DL, et al. Predictive Value of clinic and ambulatory heart rate for mortality in elderly subjects with systolic hypertension. *Arch Intern Med*. 2002; 162(20):2313–21.
- Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med*. 2005; 352(19):1951–8.
- Janssen I, Katzmarzyk PT, Church TS, Blair SN. The Cooper Clinic Mortality Risk Index: clinical score sheet for men. *Am J Prev Med*. 2005; 29(3):194–203.
- Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. *Eur Heart J*. 2013; 34(28):2159–219.
- Ivanović B, Tadić M, Dinčić D. Heart rate – predictor of cardiovascular risk. *Vojnosanit Pregl*. 2012; 69(9):799–802.
- Cucherat M. Quantitative relationship between resting heart rate reduction and magnitude of clinical benefits in post-myocardial infarction: a meta-regression of randomized clinical trials. *Eur Heart J*. 2007; 28(24):3012–9.
- Dobre D, Borer JS, Fox K, Swedberg K, Adams KF, Cleland JG, et al. Heart rate as therapeutic target in heart failure. *Eur Heart J*. 1999; 1:H64–9.



24. James P, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014; 311(5):507–20.
25. Koračević G, Sakač D, Pavlović M, Ilić D, Tomašević M, Kostić T. Should we prescribe “vasodilating” beta-blockers in Marfan syndrome to prevent aortic aneurysm and dissection? *Vojnosanit Pregl*. 2012; 69(2):195–200 [DOI: 10.2298/VSP1202195K]
26. Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA*. 2003; 289(19):2534–44.
27. Ivanović B, Tadić M. When does low normal blood pressure become too low? The J-curve Phenomenon. *Acta Cardiol*. 2014; 69(2):121–9.
28. Aronow WS, Fleg JL, Pepine CJ, Artinian NT, Bakris G, Brown AS, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. *J Am Soc Hypertens*. 2011; 5(4):259–352.
29. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin converting enzyme inhibitor or calcium channel blocker vs. diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002; 288 (23):2981–97.
30. Multiple Risk Factor Intervention Trial Research Group. Mortality after 10½ years for hypertensive participants in the Multiple Risk Factor Intervention Trial. *Circulation*. 1990; 82(5):1616–28.
31. Roush GC, Holford TR, Guddati AK. Chlorthalidone compared with hydrochlorothiazide in reducing cardiovascular events: systematic review and network meta-analyses. *Hypertension*. 2012; 59(6):1110–7.
32. Ernst ME, Carter BL, Goerdt CJ, Steffensmeier JJ, Phillips BB, Zimmerman MB, et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office BP. *Hypertension*. 2006; 47(3):352–8.
33. Musini VM, Nazer M, Bassett K, Wright JM. Blood pressure-lowering efficacy of monotherapy with thiazide diuretics for primary hypertension. *Cochrane Database Syst Rev*. 2014; (5):CD003824.
34. Grossman E, Verdecchia P, Shamiss A, Angeli F, Reboldi G. Diuretic treatment of hypertension. *Diabetes Care*. 2011; 34(Suppl 2):S313–9.
35. Shafi T, Appel LJ, Miller ER, Klag MJ, Parekh RS. Changes in serum potassium mediate thiazide-induced diabetes. *Hypertension*. 2008; 52(6):1022–9.
36. Savage PJ, Pressel SL, Curb JD, Schron EB, Applegate WB, Black HR, et al. SHEP Cooperative Research Group. Influence of long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension. *Arch Intern Med*. 1998; 158(7):741–51.
37. Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension*. 2006; 48(2):219–24.
38. Mariosa LS, Ribeiro-Filho FF, Batista MC, Hirota AH, Borges RL, Ribeiro AB, et al. Abdominal obesity is associated with potassium depletion and changes in glucose homeostasis during diuretic therapy. *J Clin Hypertens*. 2008; 10(6):443–9.
39. Mantel-Teeuwisse AK, Kloosterman JM, Maitland-van der Zee AH, Klungel OH, Porsius AJ, de Boer A. Drug-induced lipid changes: a review of the unintended effects of some commonly used drugs on serum lipid levels. *Drug Saf*. 2001; 24(6):443–56.
40. Lakshman MR, Reda DJ, Materson BJ, Cushman WC, Freis ED. Diuretics and beta-blockers do not have adverse effects at 1 year on plasma lipid and lipoprotein profiles in men with hypertension. *Arch Intern Med*. 1999; 159(6):551–8.
41. Ernst ME, Carter BL, Zheng S, Grimm Jr RH. Meta-analysis of dose-response characteristics of hydrochlorothiazide and chlorthalidone: effects on systolic blood pressure and potassium. *Am J Hypertens*. 2010; 23(4):440–6.
42. Clayton JA, Rodgers S, Blakey J, Avery A, Hall IP. Thiazide diuretic prescription and electrolyte abnormalities in primary care. *Br J Clin Pharmacol*. 2005; 61(1):87–95.
43. Rob PM, Dick K, Bley N, Seyfert T, Brinckmann C, Höllriegel V, et al. Can one really measure magnesium deficiency using the short-term magnesium loading test? *J Intern Med*. 1999; 246(4):373–8.
44. Gurwitz JH, Kalish SC, Bohn RL, Glynn RJ, Monane M, Mogun H, et al. Thiazide diuretics and the initiation of anti-gout therapy. *J Clin Epidemiol*. 1997; 50(8):953–9.
45. Kaplan NM. The choice of thiazide diuretics. Why chlorthalidone may replace hydrochlorothiazide. *Hypertension*. 2009; 54(5):951–3.
46. Mougnot N, Mediani O, Lechat P. Bisoprolol and hydrochlorothiazide effects on cardiovascular remodeling in spontaneously hypertensive rats. *Pharmacol Res*. 2005; 51(4):359–65.
47. Luna RL, Oigman W, Ramirez JA, Mion D, Batlouni M, da Rocha JC, et al. Efficacy and tolerance of the bisoprolol/hydrochlorothiazide combination in arterial hypertension. *Arq Bras Cardiol*. 1998; 71(4):601–8.
48. Frishman WH, Bryzinski BS, Coulson LR, DeQuattro VL, Vlachakis ND, Mroczek WJ, et al. A multi-factorial trial design to assess combination therapy in hypertension. Treatment with bisoprolol and hydrochlorothiazide. *Arch Intern Med*. 1994; 154(13): 1461–8.
49. Frishman WH, Burris JF, Mroczek WJ, Weir MR, Alemayehu D, Simon JS, et al. First-line therapy option with low-dose bisoprolol fumarate and low-dose hydrochlorothiazide in patients with stage I and stage II systemic hypertension. *J Clin Pharmacol*. 1995; 35(2):182–8.
50. Tadic M, Ivanovic B. Why is functional capacity decreased in hypertensive patients? From mechanisms to clinical studies. *J Cardiovasc Med (Hagerstown)*. 2014; 15(6):447–55.
51. Prisant LM, Weir MR, Papademetriou V, Weber MA, Adegbile IA, Alemayehu D, et al. Low-dose drug combination therapy: an alternative first-line approach to hypertension treatment. *Am Heart J*. 1995; 130(2):359–66.
52. Papademetriou V, Prisant LM, Neutel JM, Weir MR. Efficacy of low-dose combination of bisoprolol/hydrochlorothiazide compared with amlodipine and enalapril in men and women with essential hypertension. *Am J Cardiol*. 1998; 81(11):1363–5.
53. Prisant LM, Neutel JM, Ferdinand K, Papademetriou V, DeQuattro V, Hall WD, et al. Low-dose combination therapy as first-line hypertension treatment for blacks and nonblacks. *J Natl Med Assoc*. 1999; 91(1):40–8.
54. Papadopoulos DP, Papademetriou V. Low-dose fixed combination of bisoprolol/hydrochlorothiazide as first line for hypertension: a review of the rationale and clinical evidence. *Angiology*. 2009; 60(5):601–7.
55. Benetos A, Consoli S, Safavian A, Dubanchet A, Safar M. Efficacy, safety, and effects on quality of life of bisoprolol/hydrochlorothiazide versus amlodipine in elderly patients with systolic hypertension. *Am Heart J*. 2000; 140:623–9.

## Фиксна комбинација бисопролола и хидрохлортиазида у малој дози у лечењу артеријске хипертензије

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### САЖЕТАК

Бета-блокатори имају бољи учинак у смањењу повећаног крвног притиска код млађих болесника са вишим нивоом ренина у плазми. Актуелне препоруке Европског удружења кардиолога за лечење артеријске хипертензије из 2013. године предлажу да се увек уз мерење крвног притиска одређује и срчана фреквенција. Ове препоруке истичу значај срчане фреквенције у мировању, као независног предиктора кардиоваскуларног морбидитета и морталитета болесника са артеријском хипертензијом. Посебан разлог за увођење бета-блокатора у терапију артеријске хипертензије представља постојање придружене коронарне болести, као и систолне срчане инсуфицијенције. Бисопролол је високоселективни бета-блокатор са дугим полуживотом у плазми и продуженим антихипертензивним учинком, који показује сталну контролу крвног притиска у току двадесет четири сата.

У плацебо контролисаним студијама показано је да је примена тиазидних диуретика, поред редукције висине артеријског притиска, повезана са смањењем кардиоваскуларног морбидитета и морталитета. Очито је ефикасност тиазидних диуретика дозно зависна, међутим дозно зависни су и нежељени ефекти лека. Они дозно-зависно погоршавају интолеранцију глукозе, повећавају ниво липида, узрокују хипокалемију, хипонатремију и хипомагниемију и повећавају ниво мокраћне киселине. Примена веома ниске дозе тиазидног диуретика је прихватљива у комбинацији са другим антихипертензивима зато што она потенцира деловање других лекова без изазивања нежељених метаболичких ефеката. Ефикасност и сигурност комбинације бисопролола (у различитим дозама) и тиазидног диуретика у малој дози доказани су у клиничким студијама.

**Кључне речи:** хипертензија, лечење; антихипертензивни лекови, ординирање; бета-блокатори; бисопролол; тиазиди