

# Effect of amlodipine on the manifestations of chronic insomnia in hypertensive patients with type 2 diabetes mellitus

Ganna Isayeva <sup>1</sup>, Olena Buriakovska <sup>1</sup>, Anna Shalimova <sup>1,2</sup>

<sup>1</sup>Government Institution 'L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine', Kharkiv, Ukraine

<sup>2</sup>Kharkiv National Medical University, Kharkiv, Ukraine

## Abstract

**Background:** The aim of the study was to assess the association between antihypertensive therapy and the manifestations of insomnia in patients with arterial hypertension (AH) and type 2 diabetes mellitus (T2DM).

**Material and methods:** The study included 120 hypertensive patients with and without T2DM (among them there were 60 patients with insomnia). The study consisted of three stages. The first stage was conducted as a cross-sectional study, during which an association was established between different antihypertensive products and the presence of insomnia in the study population. The second and third stages were a prospective study, during which a modification of the therapy to reduce the manifestations of insomnia was performed.

**Results:** It was found that patients receiving amlodipine in the combination antihypertensive therapy had insomnia manifestations much less frequently as compared to indapamide. A statically significant decrease in blood pressure (BP) and a higher proportion of patients with target BP were observed in both groups. Replacement of indapamide with amlodipine was shown to improve sleep quality. Thus, the number of patients with insomnia significantly decreased in both groups. After correction of antihypertensive therapy after 12 months, all patients were assessed for sleep disorders. The incidence of insomnia was found to be significantly reduced in both groups after changing therapy from indapamide to amlodipine.

**Conclusions:** Correction of antihypertensive therapy, namely the replacement of indapamide with amlodipine, contributes to an improvement in BP, quality of life, and a reduction in the proportion of patients with insomnia.

**Key words:** insomnia; arterial hypertension; type 2 diabetes mellitus; amlodipine

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## Introduction

The association between insomnia and cardiovascular diseases has been proven in a large number of works [1–4]. According to Taylor [5], 40% of patients with diseases of the cardiovascular system have problems with the quality or duration of sleep. A high prevalence of insomnia among patients with hypertension

and its effect on the course of hypertension was demonstrated in a systemic review of Jarrin [6]. Li [7] found that difficulties in maintaining sleep and early morning awakenings significantly increased the risk of developing hypertension. Fernandez-Mendoza [8] confidently demonstrated that insomnia was an independent risk factor for developing hypertension. A higher risk of developing hypertension in people

**Address for correspondence:** Prof. Anna Shalimova, Department of Internal Medicine No 1, Kharkiv National Medical University, Kharkiv, Ukraine; e-mail: anna.shalimova83@gmail.com

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with insomnia was also found in study of Lin [9]. For instance, according to these authors, patients with insomnia have a 21% higher risk of developing hypertension compared with those who have quality sleep [9]. At the same time, Wang [10] found that insomnia is much more common in patients with hypertension (36.35%) compared with the general population (28.9%). Similar data were presented in a study of Bathgate [11], who found that almost 36.9% of patients with hypertension had some form of insomnia. A study, which included 21,678 patients with a medical history of stroke, demonstrated that those with hypertension were more likely to take sleeping pills [12]. The presented literature data show that insomnia is both a risk factor for hypertension and often accompanies it. It should be noted that a patient with both diseases can live quite a long time and there is a problem of finding the optimal therapy for this group of patients.

At the same time, data on the effect of antihypertensive therapy on the quality and duration of sleep are scarcely presented in the modern literature.

The aim of the study was to assess the association between antihypertensive therapy and the manifestations of insomnia in patients with hypertension and type 2 diabetes mellitus.

## Material and methods

### General characteristics and design of the study

The study consisted of three stages. The first stage was conducted as a cross-sectional study, during which an association was established between different antihypertensive products and the presence of insomnia in the study population. The second and third stages were a prospective study, during which a modification of the therapy to reduce the manifestations of insomnia was performed. The study design is presented in Figure 1.

The inclusion criteria were age over 45 years, presence of hypertension. The diagnosis of hypertension was established according to the 2018 ESC/ESH Guidelines for the management of arterial hypertension [13]. The diagnosis of type 2 diabetes mellitus was established according to the Unified Clinical Protocol of Primary and Secondary (Specialized) Medical Care: Type 2 Diabetes (Order of the Ministry of Health No. 1118 of 21.12.2012) [14].

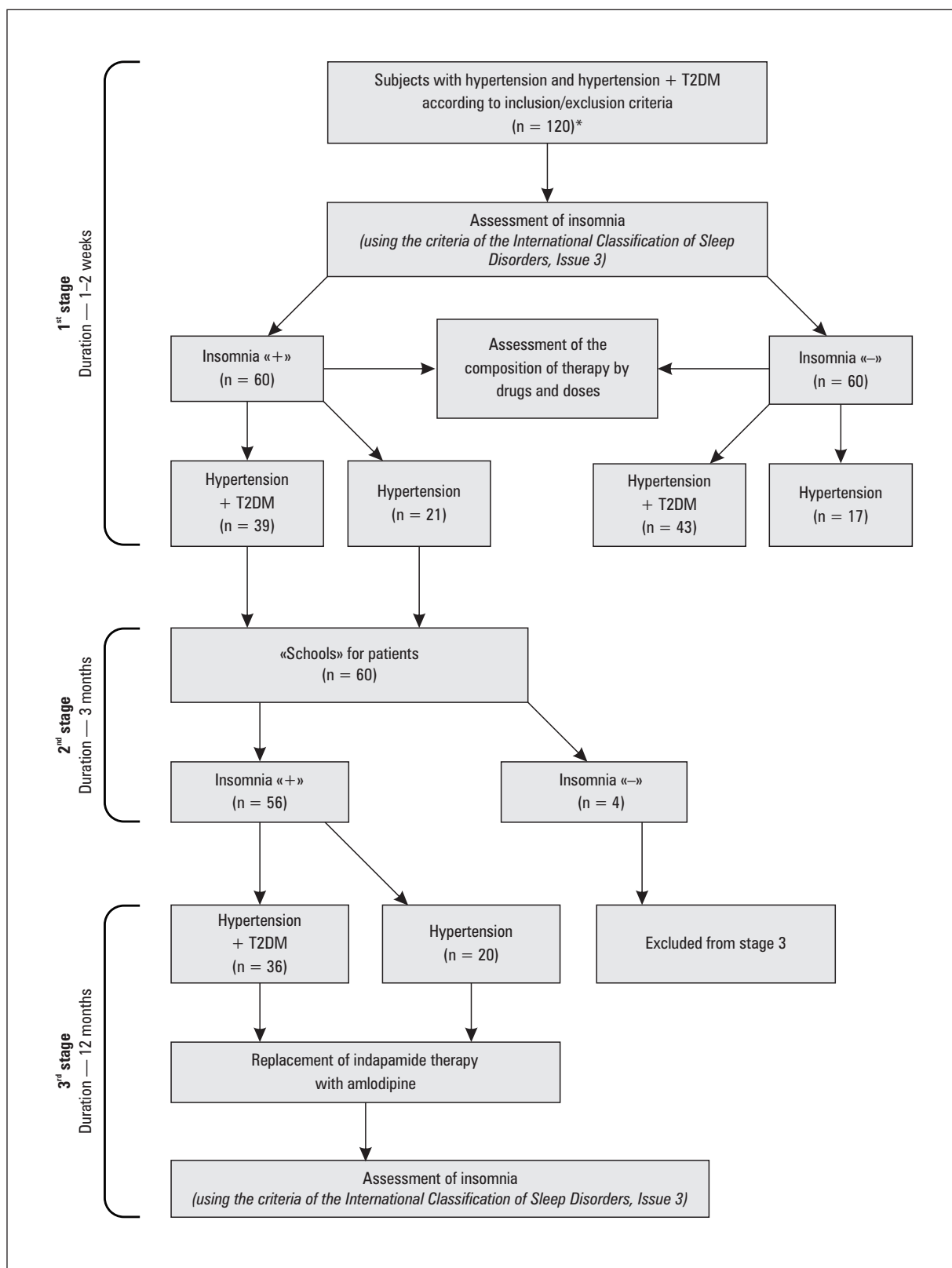
The study did not include patients who had cardiovascular events (myocardial infarction, stroke), patients with heart failure or with an ejection fraction of less than 45%, with resistant arterial hypertension, thyroid gland dysfunction, gastric ulcer

and duodenal ulcer in the exacerbation phase, with concomitant diseases affecting the quality of life, patients with obesity grade III, with concomitant any active cancer, with depressive states (organic depressive disorder (F 06.32), recurrent depressive disorder (F 33.0–3) or a depressive episode of any severity (F 31.3–5, F 32.0–3), also a mixed anxiety and depressive disorder (F 41.2) according to the criteria of the International Classification of Diseases 10th revision (ICD-10), with insomnia as a symptom of any mental illness, with concomitant therapy with glucocorticosteroids, antihypertensive drugs of central action (moxonidine, reserpine), beta-blockers, hypnotics, patients who confirmed eating at night, patients with obstructive sleep apnea syndrome.

During stage 2, all patients, who were diagnosed with sleep disorders, were enrolled in “Health Schools” for 3 months, after which the following were assessed: sleep disorders, quality of life, anthropometric, hemodynamic, and biochemical parameters. After finishing the “Health Schools”, there were 56 patients with symptoms of insomnia in the general group, among whom 36 patients had combined hypertension and type 2 diabetes mellitus, and 20 of them had isolated hypertension. A detailed analysis of the antihypertensive therapy showed that in the group of combined hypertension and diabetes mellitus with insomnia symptoms, indapamide was taken by 78% of patients, while amlodipine by 22% ( $p = 0.05$ ). The same trend was observed in the group of isolated hypertension with insomnia: indapamide was taken by 70.6% of patients, while amlodipine by 29.4% ( $p = 0.05$ ). Due to the fact that insomnia was less common among patients in both groups receiving amlodipine, indapamide therapy was replaced by amlodipine. Patients received this therapy for 12 months. Then, sleep disorders, quality of life index, hemodynamic parameters were re-assessed and the percentage of patients who reached the target blood pressure was calculated (Fig. 1).

### Assessment of sleep disorders

The presence of insomnia was assessed using the criteria of the International Classification of Sleep Disorders, 3<sup>rd</sup> Edition, which was developed by the International Academy of Sleep Disorders, 2014 [15]. The diagnosis of insomnia was established in the presence of the following criteria: 1 — difficulty falling asleep or staying asleep continuously; 2 — availability of adequate sleeping conditions; 3 — day consequences of poor sleep quality [15]. The night apnea syndrome was detected by night monitoring with the use of a SOMNOcheck micro CARDIO device (2013, Germany).



**Figure 1.** Design of the study. \* «+» Insomnia is present; «-» Insomnia is absent. T2DM — type 2 diabetes mellitus

### Instrumental examination

Blood pressure was measured in accordance with the current recommendations of the European Society of Cardiology [13].

### Assessment of achievement of target indicators

Achievement of target blood pressure levels and lipid metabolism values was assessed in accordance with current recommendations of the European Society of Cardiology [13].

### Therapy

Patients were initially treated with an ACE inhibitor (ramipril) or sartan (valsartan), a diuretic (indapamide) and a calcium antagonist (amlodipine). All patients received atorvastatin as a lipid-lowering therapy and metformin as an antidiabetic therapy.

### Statistical data processing

Statistical analysis was performed with the use of SPSS, version 17.0 (Chicago, IL, USA). The type of data distribution was assessed using the Kolmogorov-Smirnov method. With the normal distribution of continuous values, the data are presented as mean values (M) and standard deviation (SD), for quantitative values — the number (n) and frequency (%). Data which did not meet the requirements of normal distribution were presented as medians and 25% and 75% quartiles. The Student's t-test was used for comparing two independent samples corresponding to normal distribution. If the dependent samples did not meet the requirements of normal distribution, the comparison was performed using the Mann-Whitney test. Differences were considered as statistically significant if  $p < 0.05$ .

### Ethic aspects

The study was approved by the Commission on Ethics and Deontology of the State Institution “L.T. Malaya National Institute of Therapy of the National Academy of Medical Sciences of Ukraine” on April 28, 2017. All participants of the study signed an informed consent, the aim and objectives of the study were previously clearly explained to them.

### Results

Patients receiving amlodipine were found to have insomnia manifestations much less frequently (Fig. 2).

The therapy in groups after replacement of indapamide with amlodipine is shown in Figure 3.

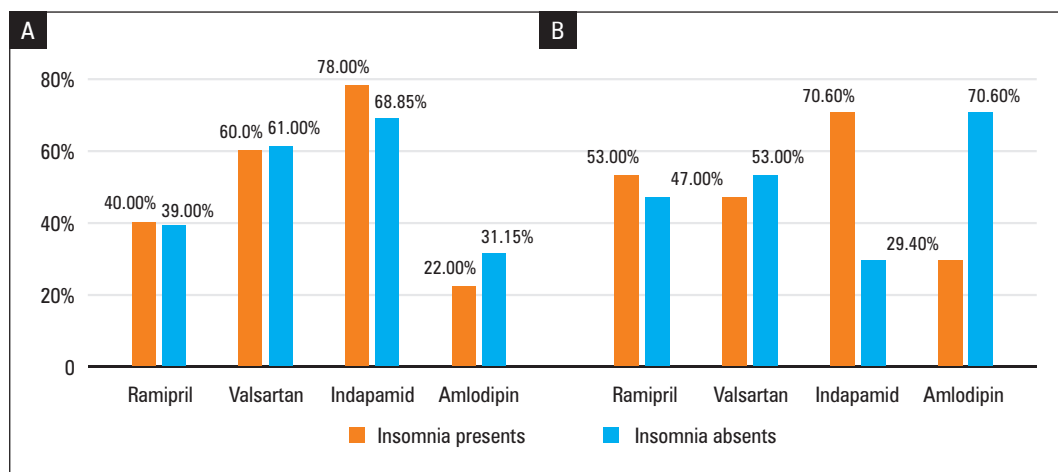
A statically significant decrease in blood pressure (Tab. 1) and a higher proportion of patients with target blood pressure were observed in both groups (Fig. 4 and 5).

Replacement of indapamide with amlodipine was shown to improve sleep quality. Thus, the number of patients with insomnia significantly decreased in both groups.

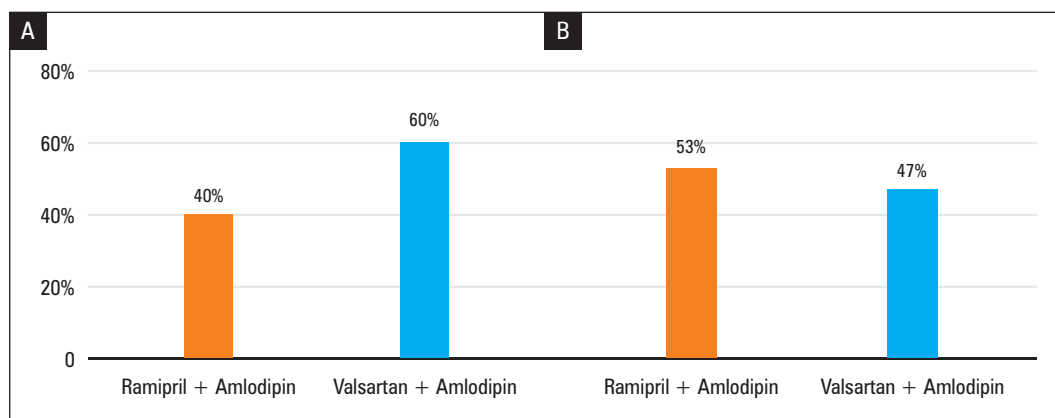
After correction of antihypertensive therapy after 12 months, all patients were assessed for sleep disorders. The incidence of insomnia was found to be significantly reduced in both groups after changing therapy from indapamide to amlodipine ( $p = 0.05$ ) (Fig. 7).

### Discussion

Although insomnia is quite common in patients with essential hypertension and type 2 diabetes mellitus,



**Figure 2.** Medical therapy in groups with and without insomnia. **A.** Patients with hypertension + diabetes mellitus type 2. **B.** Patients with hypertension. Data presented as a proportion of patients (%) treated with particular drug

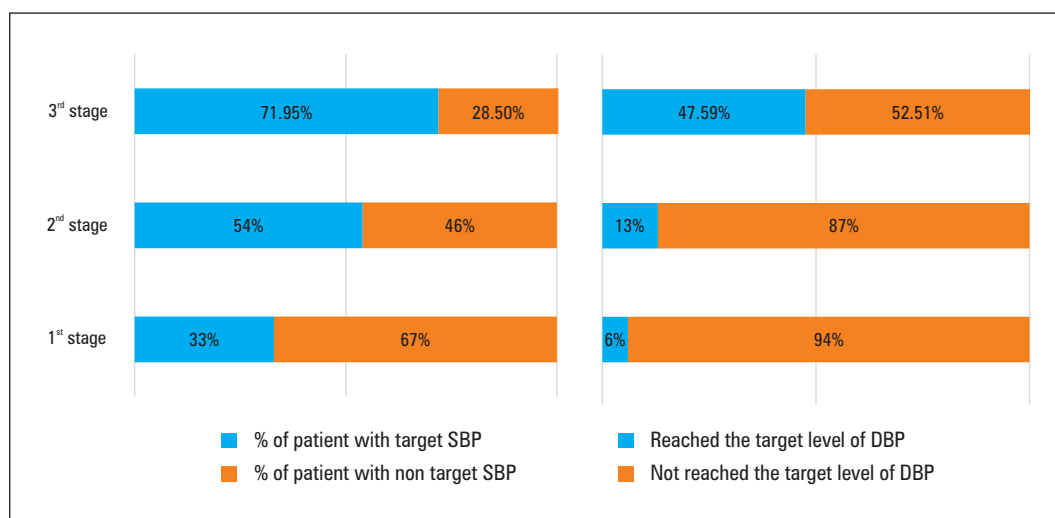


**Figure 3.** Medical therapy during third period of study (after replacement of indapamid to amlodipine). **A.** Patients with hypertension + type 2 diabetes mellitus. **B.** Patients with hypertension. Data presented as a proportion of patients (%) treated with particular drug

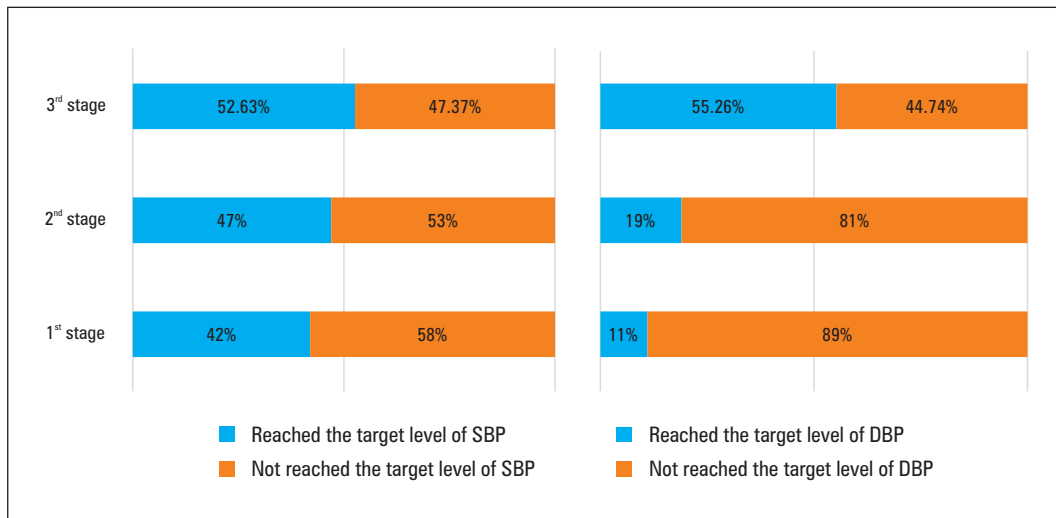
**Table 1.** Dynamics of hemodynamic parameters of patients in groups with symptoms of insomnia before and after correction of therapy\*

Index	Group 1 (hypertension + T2DM) (n = 36)				Group 2 (hypertension) (n = 20)			
	1 stage	2 stage	3 stage	p	1 stage	2 stage	3 stage	p
SBP [mm Hg]	142.14 ± 12.25	138.71 ± 7.25	129.16 ± 4.35	$p^{1-2} = 0.136$ $p^{1-3} = 0.001$ $p^{2-3} = 0.001$	140.75 ± 7.46	137.35 ± 14.16	128.76 ± 6.16	$p^{1-2} = 0.336$ $p^{1-3} = 0.001$ $p^{2-3} = 0.014$
DBP [mm Hg]	92.87 ± 8.72	88.87 ± 7.62	85.07 ± 7.12	$p^{1-2} = 0.342$ $p^{1-3} = 0.001$ $p^{2-3} = 0.027$	88.52 ± 10.17	85.72 ± 7.36	78.67 ± 5.43	$p^{1-2} = 0.272$ $p^{1-3} = 0.003$ $p^{2-3} = 0.001$
Heart rate (per minute)	77.62 ± 7.03	74.90 ± 7.91	75.12 ± 5.75	$p^{1-2} = 0.116$ $p^{1-3} = 0.087$ $p^{2-3} = 0.886$	71.82 ± 8.70	68.62 ± 6.13	70.17 ± 4.76	$p^{1-2} = 0.175$ $p^{1-3} = 0.536$ $p^{2-3} = 0.140$

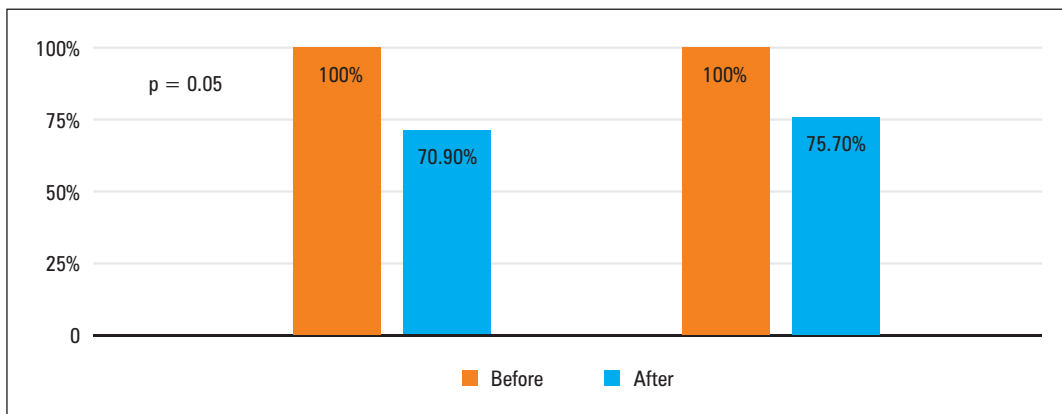
T2DM — type 2 diabetes mellitus; SBP — systolic blood pressure; DBP — diastolic blood pressure. \*Data presented in the view of the middle value and the standard deviation ( $M \pm \sigma$ )



**Figure 4.** Number of patients with target systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients with hypertension and type 2 diabetes mellitus



**Figure 5.** Number of patients with target systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients with hypertension



**Figure 6.** The proportion of patients with insomnia in the groups of combined hypertension with type 2 diabetes mellitus and isolated hypertension after third period of study

there are very little data in the literature on the causes for the development of such a sleep disorder in this group of patients.

Certainly, the development of insomnia in patients with hypertension and type 2 diabetes mellitus is based on several general mechanisms of pathogenesis. First of all, the possible activation of the sympathoadrenal system underlying both the pathogenesis of hypertension and always accompanying insomnia should be taken into account [16, 17]. Markers of systemic inflammation were found to increase both in chronic insomnia as well as in hypertension and type 2 diabetes mellitus. An increase in the production and release of aldosterone was found in patients with insomnia. Also, there are studies demonstrating endothelial dysfunction in chronic sleep disorders. An important factor contributing to the development of insomnia in patients with hypertension and diabetes

mellitus is increased anxiety and depression, which also often accompany both conditions. Certainly, the most interesting for the practicing physician is the question: can antihypertensive therapy contribute to the development of insomnia or, on the contrary, reduce the risk of this condition. When searching the PubMed, Clinicaltrials.org, MedLine, SCOPUS databases, we did not find clinical randomized trials that take into account the risk of developing insomnia in hypertensive patients under the influence of antihypertensive therapy. Quite interesting is the paper of Tanabe [18], which is a pharmacoeconomic study. The authors demonstrated that the risk of developing insomnia in patients with hypertension is increased in the highest degree by therapy with alpha- and beta-blockers. So, according to the study by Tanabe [18] the risk of developing insomnia with the administration of alpha-blockers was  $OR = 2.38$ ;

95% confidence interval (CI): 1.14–4.98, and in the case of  $\beta$ -blockers — OR = 1.54; 95% CI: 0.99–2.39. In comparison, the risk of developing insomnia with calcium antagonist therapy was 0.67; 95% CI: 0.47–0.96. ACE inhibitor therapy was not associated with the risk of developing insomnia. According to the authors' data, insomnia, as a rule, manifested itself by the 5<sup>th</sup> week of therapy and in more than 50% of cases manifested itself as “difficulty falling asleep” [18]. A study by Chang [19] also confirmed the ability of beta  $\beta$ -blockers to induce insomnia and this effect depended on the degree of  $\beta(1)$ -receptor selectivity and lipophilicity of the drug. Interesting results are presented by Finnish scientists. Haaramo [20] showed that antihypertensive therapy could contribute to the development of insomnia symptoms: OR = 1.57, 95% CI: 1.23–2.00. John W Winkelman [21] demonstrated that diuretic therapy can negatively affect sleep quality. There are also data in literature, which demonstrates an increase in the risk of developing insomnia in the case of using ACE inhibitors through the possibility of developing such an adverse effect as a cough [22]. Nevertheless, the described works are non-systemic and are not prospective studies. Although the abovementioned literature data confirm the presence of a connection between antihypertensive therapy and the risk of developing insomnia, our results demonstrate that the risk of developing insomnia can be reduced by replacing the diuretic indapamide with amlodipine. Our study was conducted as a prospective one with a quite long follow-up period — 12 months.

It should be noted that a decrease in insomnia itself contributes to a decrease in blood pressure [11, 23]. Therefore, a search for relationships between antihypertensive therapy and the risk of developing sleep disorders will allow developing an individualized approach to patients with hypertension and insomnia.

## Conclusion

Correction of antihypertensive therapy, namely the replacement of indapamide with amlodipine, contributes to an improvement in blood pressure, quality of life, and a reduction in the proportion of patients with insomnia.

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