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Therapeutic approaches to the Rational Use of triple combination therapy with a fixed combination of amlodipine, indapamide and perindopril arginine (TRIPLE COMBINATION) in patients with hypertension who do not control blood pressure on conventional treatment. (Description and main results of the TRIO program)

Aim — To study tactics of outpatient physicians in choosing the treatment when the previous double antihypertensive therapy (AHT) fails and to analyze the effectivity of an amlodipine/indapamide/perindopril arginine triple combination (TC).

Material and methods — The program included 1252 patients with arterial hypertension (AH); the TC group consisted of 992 (79.23%) patients (38.3% males; age, 61.6 [55.0; 67.9]); the control group included 260 (20.77%) patients (37.7% males; age, 60.6 [53.3; 67.4]). The main inclusion criteria were essential AH, age 18–79 years, insufficient response to previous AHT (clinical systolic blood pressure (SBP) >140–179 mm Hg). The study duration was three months. The following parameters were evaluated: dynamics of clinical and ambulatory BP (BP self-monitoring (BPSM); frequency of achieving the first goal of <140/90 mm Hg and the goal of <130/80 mm Hg); and changes in glomerular filtration rate (GFR) and quality of life (QoL). Responses to TC were analyzed in groups with different ranges of increased baseline SBP in patients with AH and diabetes mellitus (DM)/impaired glucose tolerance (IGT), overweight or obesity, and chronic kidney disease (CKD, reduced estimated GFR (eGFR <60 ml/min/1.73 m^2). Safety was evaluated based on records of adverse events (AEs).

Results — The TC group had a more severe condition at baseline by clinical parameters and history and had higher baseline BP, which made difficult the intergroup comparison. Nevertheless at three months, the decrease in clinical SBP was more pronounced in the TC group (from 162.1 to 126.8 mm Hg, Δ=35.7 mm Hg) than in the control group (from 157.8 to 128.4 mm Hg, Δ=29.4 mm Hg). 87.8% of patients in the TC group and 81.9% (p=0.012) in the control group achieved the first BP goal of <140/90 mm Hg; 34.3% and 28.2% of patients, respectively, achieved the BP goal of <130/80 mm Hg (p=0.055). The more effective SBP control in the TC group was associated with a pronounced BP decrease with higher BP values at baseline, which was also confirmed by an analysis in subgroups with SBP 140–160, 160–180, and >180 mm Hg. The TC treatment was associated with a pronounced antihypertensive effect with respect of BPSM values, improved QoL, and renal function. Significant decreases in BP and achievement of BP goals by a vast majority of patients receiving TC were also observed in subgroups with DM or IGT, overweight and/or obesity, and CKD. AEs were observed during the treatment only in 8 patients (0.64%), which confirmed good tolerability and high safety of the therapy.

Conclusion — The study results demonstrated a therapeutic effect of the amlodipine/indapamide/perindopril arginine fixed-dose combination (Triplixam®). This effect was evident as control of clinical BP with any baseline BP level, including different ranges of increased SBP, in AH combined with DM, IGT, obesity, and CKD, which offers advantages over a subjective choice of AHT. TC improved BPSM values, QoL indexes, provided nephroprotection, and was well tolerated.

Keywords — Arterial hypertension; amlodipine/indapamide/perindopril arginine fixed-dose triple combination

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Despite progress in the treatment of hypertension, it is still the top contributor to mortality and disability in the Russian Federation, significantly outpacing other common known risk factors [1]. The prevalence of hypertension in adults of diverse countries is 30–45% [2]. In Russia, there was an increase from 33.9 to 43.3% during 1998–2017 [3].

The effectiveness of blood pressure (BP) control among patients with hypertension in Russia remains low [3, 4] due to the use of mainly medium-duration antihypertensive drugs, insufficient doses, and long-term single-drug treatment. In 2010, the Russian National Guidelines on Hypertension stressed the use of initial two-drug combination therapy for patients with blood pressure (BP) ≥160/100 mm Hg and who were exposed to high and very high cardiovascular risk and for whom transition to three or more drugs was without effect [5]. In the updated European Guidelines, the primary strategy for treatment of patients with uncomplicated hypertension is to administer a stable, triple combination (TC), i.e., «the one pill concept,» of an angiotensin-converting enzyme inhibitor (ACE inhibitor) or an angiotensin II receptor blocker (ARB) plus a calcium channel blocker (CCB) plus a diuretic, if a starting, preferably combined, two-drug treatment, is ineffective [6]. The recent Russian Guidelines also recommend multiple antihypertensive drugs, preferably combined, to improve adherence to treatment [7].

TC of amlodipine/indapamide/perindopril arginine (Triplixam®) is distinguished by an extensive range of doses, which allows using it in a wide range of patients [8–13]. The concept of TC is exceptional due to the combination of properties of each component for inhibition of the renin-angiotensin-aldosterone system (RAAS) and inflammatory processes, protection of endothelium, necessary cardio-, vaso- and nephroprotection, and diuretic function [12, 14–17]. Antihypertensive efficacy and beneficial effects on metabolic performance and good tolerance of amlodipine/indapamide/perindopril arginine TC were demonstrated in several foreign (PETRA, PAINT, PIANIST, TRIUMF) and national (EVIDENCE) studies [18–22].

However, real-life implementation of the aforementioned, step-by-step treatment algorithms continues to be a pressing challenge for outpatient physicians. The situation is aggravated if prior antihypertensive therapy was ineffective. Due to outdated thinking, it is easier for the physician to increase doses of individual drugs, which increases the risk of side effects [23].

The study of the efficacy and safety of fixed-dose combination therapy in different categories of patients with hypertension is also of high priority. The objective of the observational program TRIO (Therapeutic Approaches to the Rational Use of Triple Combination Treatment with the Fixed Combination of Amlodipine, Indapamide, and Perindopril Arginine [TRIPLE COMBINATION] in Patients with Hypertension Who Do Not Control BP During Conventional Treatment) was to study the disease management in the outpatient setting in terms of choosing triple combination treatment (perindopril arginine, amlodipine, indapamide) if the prior antihypertensive therapy was not successful.

The objectives of this study were:

- Study the efficacy of the combination of amlodipine, indapamide, and perindopril arginine if the prior two-drug combination treatment was ineffective.
- Estimate the achievement of target BP levels based on changes in office BP and self-monitoring of BP, depending on the approach to treatment correction.
- Assess quality of life (QOL).
- Evaluate tolerability and safety of the treatment.

Material and Methods

The TRIO study is a post-marketing, observational, open-label, multi-center program. The study was approved by the relevant ethics committee. The researchers were outpatient primary care physicians or cardiologists. A total of 265 physicians from 69 Russian cities took part in the study.

Diagnosis of essential hypertension and determination of the degrees were carried out following the 2015 Guidelines for Diagnosis and Treatment of Hypertension [24].

Inclusion criteria were:

- 1) Essential hypertension.
- 2) Age 18–79 yrs.
- 3) Insufficient efficacy of prior antihypertensive therapy (clinical SBP >140–179 mm Hg).
- 4) Signed informed consent form.

Exclusion criteria were:

- 1) Symptomatic (secondary) forms of hypertension.
- 2) Myocardial infarction, unstable angina, or cerebrovascular accident within the previous 12 mos.
- 3) Functional class III–IV chronic heart failure (CHF).
- 4) Type 1 diabetes mellitus (DM) or decompensated type 2 DM.
- 5) Diseases with severe visceral dysfunction (e.g., liver failure, kidney failure, etc.).
- 6) Contraindications or known intolerance of dihydropyridine calcium channel blockers (including amlodipine) and/or indapamide and/or ACE inhibitors (including perindopril) or other antihypertensive drugs to be prescribed by the physicians.
- 7) Inability to understand the essence of the program and follow the recommendations.

The total duration of the study was 3 mos. Clinic visits were made after the inclusion visit at 2 wks, 1 mo, and 3 mos. The physician corrected ineffective, two-drug, fixed-dose combination, antihypertensive therapy based on his/her own experience and standard clinical practice. Patients were divided into two groups depending on the treatment:

- 1) Control group (any change in treatment except for the combination of amlodipine, indapamide, perindopril arginine).
- 2) Treatment group using amlodipine, indapamide, perindopril arginine as a TC, if the physician deemed it necessary to use such TC, or as a combination of single components or as two-drug fixed-dose combinations and single components.

After achieving the desired effect with a non-fixed-dose combination of amlodipine, indapamide, perindopril arginine, the physician at his/her discretion could transfer the patient to fixed-dose TC, i.e., Triplixam®, a combination of amlodipine, indapamide, perindopril arginine.

The patient's condition was evaluated four times. At the baseline visit, patients were assessed for eligibility according to the inclusion/exclusion criteria, a history was taken, body weight and height were measured, body mass index was calculated, BP, and heart rate (HR) were measured. QOL was also analyzed using the extended SF-36 questionnaire [25]. Samples were collected for laboratory tests, and the patient's diary was distributed for self-monitoring of BP.

All patients were directed to perform self-monitoring of BP using a standard method [26], including a week before a visit to the physician. Patients measured BP at home using an automatic or semi-automatic sphygmomanometer. Measurements were made in the morning before taking antihypertensive drugs and in the evening before going to bed. Patients recorded BP measurements in their self-monitoring diary.

All patients underwent clinical and instrumental examinations, including the target organs. Data from the previous three months were taken into account, and the following procedures were done: ECG, echocardiographic examination, ophthalmological examination, calculation of glomerular filtration rate (GFR). GFR was calculated using the Cockcroft-Gault formula. During interim visits, the patient's clinical status (BP, HR) was assessed, the BP self-monitoring diary and the rate of adverse events (AEs) were analyzed, and the antihypertensive drugs and doses were corrected, if necessary, based on the data obtained. At the final visit, the final evaluation of all the above listed variables was made.

The target levels of clinical and outpatient BP were <140/<90 and <135/<85 mm Hg, respectively. The achievement of the target values of clinical BP <130/<80 mm Hg was evaluated. The criteria of treatment efficacy were:

- 1) Changes in clinical systolic (SBP) and diastolic BP (DBP), and the number of patients who achieved the target BP levels;
- 2) Changes in SBP and DBP, and the number of patients who achieved the target BP levels as shown by the self-monitoring of BP;
- 3) Changes in patients' quality of life according to the SF-36 questionnaire.

The occurrence of AEs and the rate of AEs, including serious AEs, recorded during the study at each visit were the evaluation criteria of treatment tolerability. Within the program, an additional analysis of subgroups with different ranges of baseline SBP was performed: <140, 140–160, 160–180, and >180 mm Hg in the TC group in patients with hypertension and DM or impaired glucose tolerance (IGT); with hypertension and overweight or obesity; with hypertension and chronic kidney disease (CKD), as indicated by GFR less than 60 ml/min/1.73 m^2.

Descriptive statistical methods were used for the statistical analysis of the data. Quantitative variables are described as the mean and standard deviation (μ and σ) or the median (1^{st} quartile; 3^{rd} quartile). Qualitative variables are described as rates and percentages. Changes in efficacy and safety variables are presented relative to the baseline. The level for significance was p=0.05 (5%), and the test power was 0.8 (80%). The paired Student's t-test was used to compare changes in all variables (SBP, DBP, HR, test results, QOL components according to the SF-36 questionnaire) evaluated during the treatment. For normally distributed data, the Student's t-test for dependent samples was used to compare interval study results within the same group, and for non-normally distributed data, the non-parametric Wilcoxon test or the non-parametric Friedman test was used. Qualitative data were compared with Fisher's exact test.

Results

The program included 1,252 outpatients of both sexes with essential hypertension and an age of 23 or more years (Table 1). The analysis identified a group of patients with SBP more than 179 mm Hg at inclusion. Patients with SBP >180 mm Hg did not meet the inclusion criteria, but it was decided to include all patients who took the medications in the analysis, i.e, intention-to-treat group. Initially, the TC group consisted of 992 (79.2%) patients, and the control group consisted of 260 (20.8%) patients. During the study, 15 (1.5%) patients in the TC group and 1 (0.4%) patient the control group discontinued participation in the study. A total of 1,236 (98.7%) patients completed the program according to the protocol: 977 (98.5%) in the TC group and 259 (99.6%) in the control group.

The analysis population included more female patients. The history of hypertension, mainly of grade 2, was 10.9 years. Almost 50% of the patients had concomitant CHF, and 20% of the patients had angina pectoris (Table 1). 15.2% of the patients had been hospitalized for any reason within the previous 12 mos. 10.9% of the patients had been previously hospitalized due to hypertensive crisis. 22.3% had had more than two visits to a physician due to hypertension within the previous 3 mos. More than 40% of patients were overweight, and a similar percentage were overweight and obese. The study population was characterized by preserved myocardial systolic function. Almost

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50% of the patients had left ventricular hypertrophy and diastolic dysfunction, and the majority had hypertension fundopathy (Table 2).

Characteristics of patients in the triple-drug combination treatment and control groups

The baseline clinical and demographic characteristics of patients are shown in Table 1. Significant differences should be noted between the groups in terms of the duration of hypertension, the number of patients with grade 3 hypertension, mean SBP, and the history of hospitalizations during the previous 12 mos, hospitalizations due to hypertensive crisis, the number of visits to a physician over the past 3 mos, with higher values in the TC group.

The values of body mass index and the number of obese patients were significantly higher in the TC group than those in the control group. The number of patients with diastolic dysfunction was also higher in the TC group, but the percentage of patients with hypertension fundopathy was the same. The number of patients with proteinuria was higher in the control group (Table 2).

Table 1. Baseline characteristics of the total population, TC treatment group, and control group

Variable	All patients, n=1,252	TC group, n=992	Control group, n=260	p (TC vs control)
Age, years, Me [Q1; Q3]	61.3 [54.6; 67.9]	61.6 [55.0; 67.9]	60.6 [53.3; 67.4]	ns
Sex, m/f, n (%)	478 (38.2)/774 (61.8)	380 (38.3)/612 (61.7)	98 (37.7)/162 (62.3)	ns
Employment: working, n (%) retired, n (%)	 573 (45.8) 362 (28.9)	 437 (44.1) 294 (29.6)	 136 (52.3) 68 (26.2)	 0,017 нд
Marital status: married, n (%)	918 (73.3)	727 (73.3)	191 (73.5)	ns
Smoking, n (%)	191 (15.3)	153 (15.4)	38 (14.6)	ns
Family history of early CV events, n (%)	325 (25.9)	266 (26.8)	59 (22.7)	ns
Duration of hypertension >5 years, μ (σ)	10.9 (7.4)	10.9 (7.6)	9.5 (6.2)	0.002
Hypertension: Grade 1, n (%) Grade 2, n (%) Grade 3, n (%)	 102 (8.2) 853 (68.1) 271 (21.7)	 87 (8.8) 650 (55.5) 235 (23.7)	 15 (5.8) 203 (78.1) 36 (13.6)	 ns <0.001 <0.001
Comorbidities:				
CHF, n (%)	546 (46)	464 (46.8)	112 (43.1)	ns
FC I/II, n (%)	206 (16.5)/292 (23.3)	161 (16.2)/245 (24.7)	45 (17.3)/47 (18.1)	ns/0.025
Angina pectoris, n (%)	284 (22.7)	223 (22.5)	61 (23.5)	ns
History of AMI, n (%)	95 (7.6)	74 (7.5)	21 (8.1)	ns
History of CVA, n (%)	64 (5.1)	55 (5.5)	9 (3.5)	ns
CVD, n (%)	54 (4.3)	37 (3.7)	17 (6.5)	0.047
Type 2 DM, n (%)	173 (13.8)	143 (14.4)	30 (11.5)	ns
IGT, n (%)	123 (9.8)	96 (9.7)	27 (10.4)	ns
Hospital admissions within 12 mos, all causes, n (%)	191 (15.2)	166 (16.7)	24 (9.2)	0.013
Hospitalizations due to hypertensive crisis, n (%)	137 (10.9)	123 (12.4)	14 (5.4)	0.001
More than two visits to the physician due to hypertension in the past 3 mos, n (%)	289 (22.3)	253 (25.5)	36 (13.9)	<0.001
BMI, kg/m^2, μ (σ)	29.6 (4.7)	29.8 (4.7)	28.9 (4.8)	0.003
Overweight, n (%)	515 (41.1)	394 (39.7)	121 (46.5)	0.047
Obesity, n (%)	527 (42.1)	436 (44)	91 (35)	0.009
HR (according to ECG), bpm, μ (σ)	73.6 (9.1)	73.5 (9.0)	74.2 (9.7)	ns
SBP, mm Hg, μ (σ)	161.4 (11.9)	162.1 (12.2)	158.7 (10.3)	0.001
DBP, mm Hg, μ (σ)	93.22 (8.6)	93.16 (8.4)	93.44 (9.3)	ns

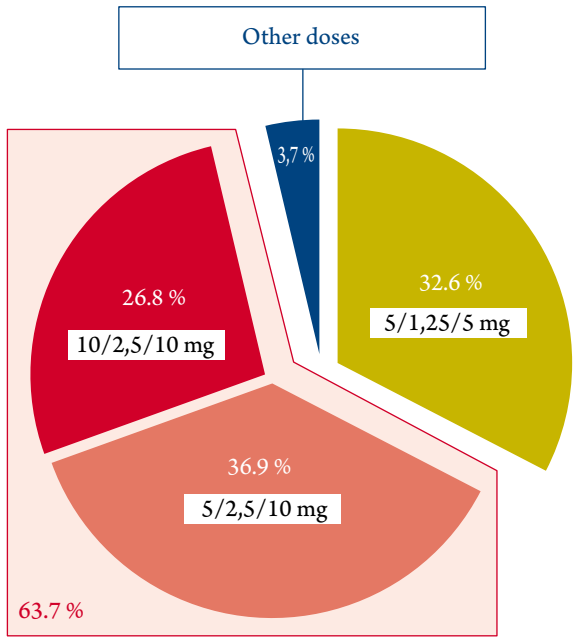
TC, triple combination; CV, cardiovascular; CHN, chronic heart failure; FC, functional class; AMI, acute myocardial infarction; CVA, cerebrovascular accident; CVD, cerebrovascular disease; DM, diabetes mellitus; IGT, impaired glucose tolerance; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; ns, not statistically significant. The data are expressed as: n (%), number (percentage of the total number in the group); Me [Q1; Q3], median [1st quartile; 3rd quartile]; μ (σ), mean value (standard deviation).

Table 2. Baseline condition of the target values in the entire population, the TC treatment group, and the control group

Variable	All patients, n=1,252	TC group, n=992	Control group, n=260	p (TC vs control)
Echocardiography: LVH, n (%) DD, n (%)	 644 (51.4) 522 (41.7)	 511 (51.5) 428 (43.2)	 133 (51.2) 94 (36.2)	 ns 0.042
LVEF, %, μ (σ)	62 (6.5)	61.9 (6.3)	62.3 (7.3)	ns
Proteinuria, n (%)	153 (12.2)	111 (11.2)	42 (16.5)	0.030
Hypertensive fundopathy, n (%)	850 (67.9)	690 (69.6)	160 (61.5)	0.014

TC, triple combination; LVH, left ventricular hypertrophy; DD, diastolic dysfunction; LVEF, left ventricular ejection fraction.
The data are expressed as: n (%), the number of patients (percentage of the total number of patients in the group), μ(σ), mean value (standard deviation); ns, not statistically significant.

Figure 1. Triplaxam dose prescribed at the baseline visit



Characteristics of antihypertensive therapy at the time of inclusion

Table 3 shows that the number of patients receiving RAAS blockers did not differ between the subgroups, though ACE inhibitors were prescribed more often before inclusion in the program in the TC group than in the control group (p=0.005), and ARBs were administered less often (p=0.026). The percentage of patients taking CCBs in the TC group was significantly higher (p <0.001). There were no differences between the groups in the number of patients who took beta-blockers, diuretics, and moxonidine.

The percentage of patients who received drugs of two antihypertensive groups before being included in the protocol was significantly lower in the TC group than in the control group (p <0.001). Moreover, the number of patients who took three or more than three antihypertensive drugs was significantly higher in the TC group compared to the control group (p<0.001, p=0.002, respectively) (Table 3). Those differences were due to the more severe baseline clinical and anamnestic status of patients in the TC group.

Minimal doses of the amlodipine/indapamide/perindopril TC 5/1.25/5 mg was prescribed in 32.6% of patients, 5/2.5/10 mg in 36.9% of patients, and the maximum dose of 10/2.5/10 mg in 26.8% of patients. Thus, the TC combinations containing the optimal dose of perindopril 10 mg were used in most patients (63.7%) (Figure 1). The other 27 (3.7%) patients used other doses and were not included in the final analysis. In the control group, the amlodipine/indapamide/perindopril TC was not prescribed to anyone at the beginning of the study. At the same time, it was used in 20 (7.7%) patients at the end of the study.

Antihypertensive therapy during the study period

During the study, patients in both groups received complimentary antihypertensive therapy. In the TC group, the following medications were administered additionally:

- 1) beta-blockers in 242 (24.8%) patients, +28 patients by the end of the study for a total of 270 (27.6%) patients;
- 2) diuretics in 15 (1.5%) patients +8 patients by the end of the study for a total of 23 (2.4%) patients;
- 3) moxonidine in 22 (2.3%) patients +7 patients by the end of the study for a total of 29 (3%) patients.

The TC group patients received an average of 3.2 antihypertensive drugs. By the end of the study, 257 (99.3%) patients in the control group received RAAS blockers:

- 1) ACE inhibitors, 151 (58.3%) patients;
- 2) ARBs, 106 (41%) patients;
- 3) CCBs 158 (61%) patients;
- 4) beta-blockers 103 (39.8%) patients;
- 5) diuretics, 175 (67.6%) patients;
- 6) moxonidine 20 (7.7%) patients.

The control group patients also received an average of 3.2 antihypertensive drugs.

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Table 3. Baseline antihypertensive therapy

Drug group	All patients, n=1236	TC group, n=977	Control group, n=259	p (TC vs control)
ACE inhibitors, %	63.2	65.1	55.8	0.005
ARBs,%	30.5	29.0	36.1	0.026
RAAS blockers, %	93.7	94.1	91.9	ns
CCBs,%	38.1	41.7	24.2	<0.001
Beta-blockers, %	34.9	35.5	32.8	ns
Diuretics, %	58.1	59.2	54.2	ns
Moxonidine,%	3.3	4.8	3.1	ns
Number of medications				
Single drug therapy, %	6.0	5.1	9.2 (Δ= +4.1%*)	0.013
Two-drug treatment, %	63.1	59.8	75.8 (Δ= +16%*)	<0.001
Triple drug treatment, %	23.6	26.4	13.1 (Δ= –13.3%**)	<0.001
More than three, %	6.4	7.6	1.5 (Δ= –6.1%**)	0.002
Unknown. %	0.9	1.1	0.9	ns

*, percentage increase versus the TC group; **, percentage decrease versus the TC group. TC, triple combination; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; RAAS, renin-angiotensin-aldosterone system; CCBs, slow calcium channel blockers; ns, not statistically significant.

Table 4. Changes in the BP levels identified by self-monitoring of BP in the TC and control groups.

Variable	TC group, n=375			Control group, n=107		
	2 wks	1 mo	3 mos	2 wks	1 mo	3 mos
SBP in the morning, mm Hg	140.9±14.1	131.6±15.8*	125.4±9.2*	140.6±12.7	130.5±9.8*	127.4±8.7*
p=0.040 (between groups at 3 mos)						
DBP in the morning, mm Hg	83.6±8.1	79.3±6.8*	76.9±6.0*	84.1±7.8	80.0±6.9*	78.4±6.8*
p=0.044 (between groups at 3 mos)						
SBP in the evening, mm Hg	140.2±13.1	131.6±10.5*	126.9±7.9*	139.4±12.2	132.0±8.7*	128.9±7.7*
p=0.021 (between groups at 3 mos)						
DBP in the evening, mm Hg	83.0±8.1	79.4±6.5*	77.5±5.9*	83.3±7.3	80.2±6.0*	79.2±6.1*
p=0.010 (between groups at 3 mos)						

*, p <0.001 versus the previous visit, intra-group. BP, blood pressure; TC, triple combination; SBP, systolic blood pressure; DBP, diastolic blood pressure. Data are expressed as mean value±standard deviation.

Changes in clinical BP during the study

During the study, both groups showed significant decreases in clinical SBP (Figure 2). At every successive visit, significant (p <0.001) inter-group differences were observed in decreases of SBP. For the TC and control groups, these decreases were 21 vs. 17 mm Hg at 2 wks, 29.6 vs. 25.1 mm Hg at 1 mo, and 35.3 vs. 29.4 mm Hg at the final visit, respectively. The baseline SBP was higher in the TC group (p <0.001). However, at the final visit, the situation was reversed, with SBP of the TC group lower than that of the control group (p=0.008).

Most patients in both groups achieved the target BP levels, and this number was higher at the final visit in the TC group. 87.8% vs. 81.8% (p=0.012). The difference between the groups in the number of patients who achieved the target BP <130 mm Hg was 6.3% (p=0.045). During the study, significant decreases in HR were observed from 74.7±8.7 to 68.4±5.6 bpm the TC group (p <0.001), and from 75.1±8.8 to 68.4±5.5 bpm in the control group (p <0.001); there were no significant inter-group differences.

Changes in the BP levels according to self-monitoring of BP during the study

The analysis of outpatient BP self-monitoring was performed for 482 patients, 375 in the TC group and 107 in the control group (Table 4). Other patients did not perform BP self-monitoring. In patients included in the analysis, significant decreases in morning and evening SBP and DBP were observed from visit to visit in both groups (p <0.001). At the final visit, there were statistically significant differences in the morning and evening SBP and DBP between the groups, with lower values in the TC group. Target values of BP <135/85 mm Hg were achieved by 32.5% of patients in the TC group and by 32.7% of patients in the control group at the second visit. Target values were achieved by 61.6 and 64.5% of

these groups at the third visit, and by 81.07 and 75.7% at the fourth visit, respectively. There were no differences between the groups.

Evaluation of efficacy of the triple-drug combination therapy in the patient subgroups depending on baseline levels of SBP

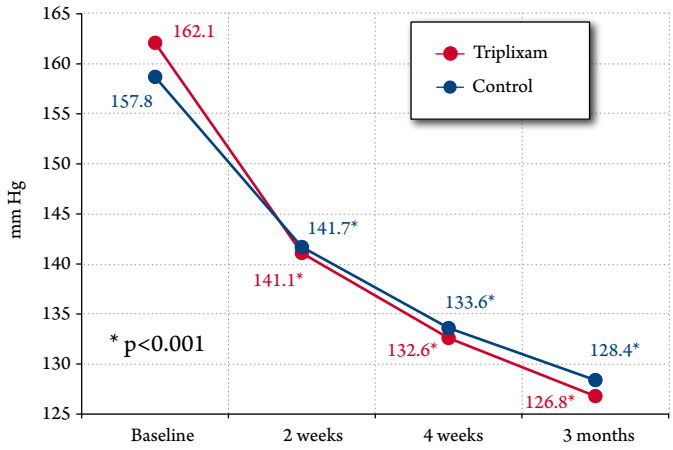
The subgroup of patients with SBP <140 mm Hg included 15 patients from the TC group and 7 patients from the control group. In this subgroup, the decrease in BP during the follow-up period was insignificant, 10.8/8.0 mm Hg in TC patients and 9.0/7.7 mm Hg control patients.

The subgroup of patients with SBP 140–160 mm Hg included 314 patients from the TC group and 109 patients from the control group. In this subgroup, TC therapy decreased SBP and DBP significantly throughout the study. By the end of the program, the decrease in BP was 26/12.5 in the TV group and 23.5/11.4 mm Hg in the control group. At the final visit, the difference between the groups was significant (p=0.003). More patients in the TC group achieved the target BP values than in the control group (92.7 vs. 85.3%, p=0.022).

The subgroup of patients with SBP 160–180 mm Hg included 582 patients from the TC group and 135 patients from the control group. During the follow-up period, BP decreased significantly by 38.8/17 and 35.7/14.8 mm Hg in the TC and control groups, respectively, and at the final visit, BP was lower in the TC group than in the control group (p=0.014 for SBP; p=0.006 for DBP). More patients in the TC group achieved the target BP values than in the control group (88.3 vs. 79.3%, p=0.005).

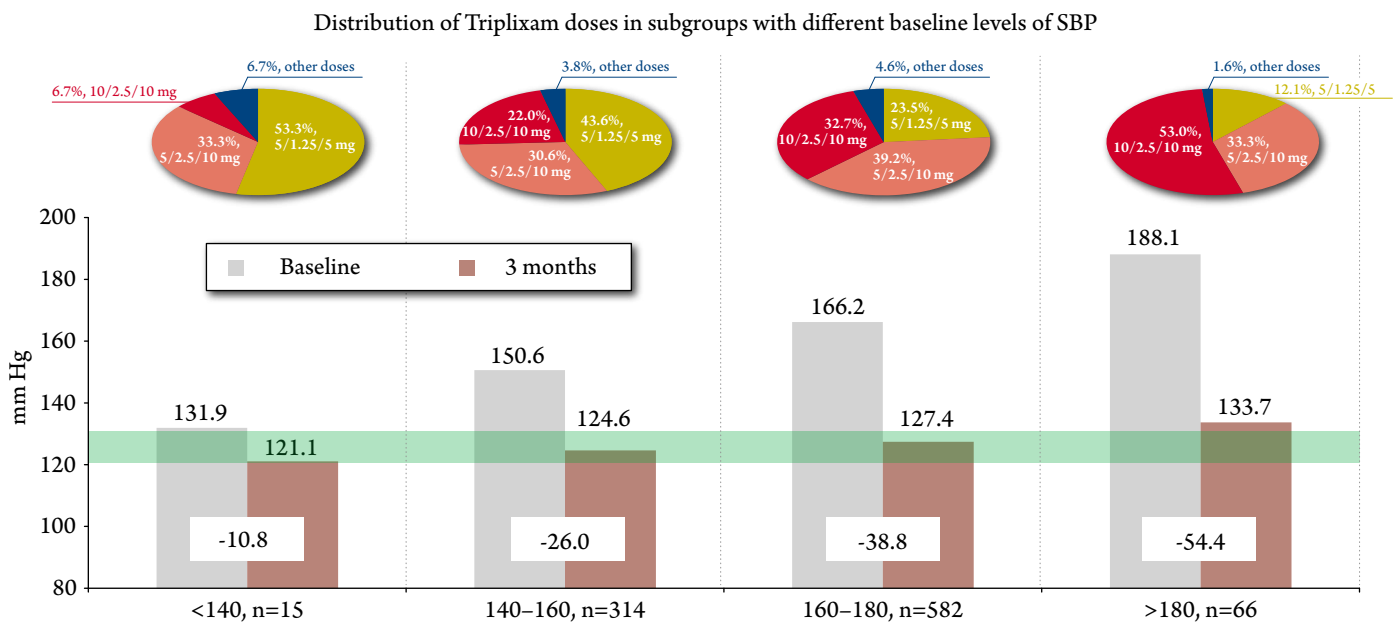
The subgroup of patients with SBP >180 mm Hg included 66 patients from the TC group and 8 patients from the control group. During the follow-up period, BP decreased significantly by 54.4/19.6 mm Hg in the TC group, and 62.5% of patients achieved the target values of BP. The changes of SBP in subgroups depending on the baseline levels of SBP and the administered doses of the fixed-dose TC treatment are shown in Figure 3.

Figure 2. Changes in the mean clinical SBP in the groups within three months of treatment



At the end of the study, the dose of TC 5/1.25/5 mg was more common in patients with SBP <140 mm Hg; 8 (53.3%) patients received this dose. It was administered in 137 (43.6%) patients with grade 1 hypertension and SBP 140–160 mm Hg. The distribution of doses in patients with grade 2 hypertension and SBP 160–180 mm Hg was such that the majority of patients (n=228 (39.2%)) received 5/2.5/10 mg, and in the subgroup of SBP >180 mm Hg, 35 (53%) patients received the dose 10/2.5/10 mg. In most cases, the TC treatment normalized SBP to within the recommended range of 120–

Figure 3. Changes in the clinical SBP during the use of Triplixam depending on the baseline BP levels



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ГАРМОНИЯ
артериального давления

Нолипрел® А Би–форте

Индапамид + периндоприл

130

80

Нолипрел® А, Нолипрел® А форте, Нолипрел® А Би-форте

СОСТАВ*. Нолипрел А 0,625 мг/2,5 мг таблетки: индапамид 0,625 мг и периндоприл 2,5 мг. Нолипрел А форте 1,25 мг/5 мг таблетки: индапамид 1,25 мг и периндоприл 5 мг. Нолипрел А Би-форте 2,5 мг/10 мг таблетки: индапамид 2,5 мг и периндоприл 10 мг. **ПОКАЗАНИЯ К ПРИМЕНЕНИЮ***. Нолипрел А 0,625/2,5 и Нолипрел А форте 1,25/5: эссенциальная гипертензия. У пациентов с артериальной гипертензией и сахарным диабетом 2 типа для снижения риска развития микрососудистых осложнений (со стороны почек) и макрососудистых осложнений от сердечно-сосудистых заболеваний. Нолипрел А Би-форте 2,5/10: эссенциальная гипертензия (пациентам, которым требуется терапия периндоприлом в дозе 10 мг и индапамидом в дозе 2,5 мг). **СПОСОБ ПРИМЕНЕНИЯ И ДОЗЫ***. Внутрь, 1 таблетка 1 раз в сутки, утром, перед приемом пищи. *Пациенты пожилого возраста.* Нолипрел А 0,625/2,5 и Нолипрел А форте 1,25/5: назначать лечение после контроля функции почек и АД. Нолипрел А Би-форте 2,5/10: клиренс креатинина (КК) рассчитывают с учетом возраста, массы тела и пола. Почечная недостаточность. Необходим регулярный контроль концентрации креатинина и калия в плазме крови. Пациентам с КК ≥60 мл/мин, коррекции дозы не требуется. Нолипрел А 0,625/2,5 и Нолипрел А форте 1,25/5: для пациентов с умеренно выраженной почечной недостаточностью (КК 30–60 мл/мин) рекомендуется начинать терапию с необходимых доз препаратов (в виде монотерапии), входящих в состав Нолипрела А/ Нолипрела А форте; противопоказан пациентам с тяжелой почечной недостаточностью (КК менее 30 мл/мин). Нолипрел А Би-форте: противопоказан пациентам с умеренной и тяжелой почечной недостаточностью (КК ≤60 мл/мин). **ПРОТИВОПОКАЗАНИЯ***. Повышенная чувствительность к периндоприлу и другим иАПФ, индапамиду, другим сульфонамидам, а также к вспомогательным веществам. Ангионевротический отек (отек Квинке) в анамнезе на фоне приема ингибиторов АПФ (см. «Особые указания»). Наследственный/идиопатический ангионевротический отек. Одновременное применение с алискиреном и лекарственными препаратами, содержащими алискирен, у пациентов с сахарным диабетом и/или умеренными или тяжелыми нарушениями функции почек (скорость клубочковой фильтрации (СКФ) менее 60 мл/мин/1,73м² площади поверхности тела). Гипокалиемия. Тяжелая почечная недостаточность (КК ≤30 мл/мин) для Нолипрел А 0,625/2,5 и Нолипрел А форте 1,25/5. Умеренная и тяжелая почечная недостаточность (КК ≤60 мл/мин) для Нолипрел А Би-форте 1,25/5. Одновременное применение с АРА II у пациентов с диабетической нефропатией. Печеночная энцефалопатия. Тяжелая печеночная недостаточность. Одновременное применение с неантиаритмическими средствами, способными вызвать полиморфную желудочковую тахикардию типа «пируэт» (см. раздел «Взаимодействие с другими лекарственными средствами»). Беременность и период грудного вскармливания. Из-за отсутствия достаточного клинического опыта препарат не следует применять у пациентов, находящихся на гемодиализе, а также у пациентов с нелеченой декомпенсированной сердечной недостаточностью. Возраст до 18 лет. Наличие лактазной недостаточности, галактоземия или синдром глюкозо-галактозной мальабсорбции, непереносимость лактозы. **ОСОБЫЕ УКАЗАНИЯ***. Совместное применение с препаратами лития, калийсберегающих диуретиков, солей калия. Двойная блокада РААС посредством сочетания ингибитора АПФ с АРА II или алискиреном не рекомендуется, так как имеются данные об увеличении риска возникновения артериальной гипотензии, гиперкалиемии и нарушений функции почек (включая острую почечную недостаточность). Применение ингибиторов АПФ в сочетании с антагонистами рецепторов АРА II противопоказано у пациентов с диабетической нефропатией и не рекомендуется у других пациентов. *Нейтропения/агранулоцитоз/тромбоцитопения/анемия:* у пациентов с системными заболеваниями соединительной ткани, на фоне приема иммунодепрессивных средств, аллопуринола рекомендуется периодически контролировать количество лейкоцитов в крови. *Повышенная чувствительность/ангионевротический отек:* прием препарата должен быть прекращен, а пациент должен наблюдаться до полного исчезновения признаков отека. Ангионевротический отек, сопровождающийся отеком гортани, может привести к летальному исходу. *Одновременное применение ингибиторов mTOR (мишени рапамицина млекопитающих) (например, сиролимус, эверолимус, темсиролимус):* может повышаться риск развития ангионевротического отека (в том числе отека дыхательных путей или языка с/без нарушения функции дыхания). *Анафилактоидные реакции при проведении десенсибилизации:* имеются отдельные сообщения о развитии длительных, угрожающих жизни анафилактоидных реакций у пациентов с отягощенным аллергическим анамнезом или склонностью к аллергическим реакциям, проходящих процедуры десенсибилизации. Ингибиторы АПФ необходимо применять с осторожностью у склонных к аллергическим реакциям пациентов и избегать назначения пациентам, получающим иммунотерапию. Реакции можно избежать путем временной отмены ингибитора АПФ не менее чем за 24 часа до начала процедуры. *Анафилактоидные реакции при проведении афереза ЛПНП:* следует временно прекращать терапию ингибитором перед каждой процедурой афереза. В редких случаях при проведении афереза ЛПНП с использованием декстрана сульфата развивались угрожающие жизни анафилактоидные реакции. Следует временно прекращать терапию ингибитором АПФ перед каждой процедурой афереза. *Гемодиализ:* при проведении гемодиализа с использованием высокопроточных мембран были отмечены анафилактоидные реакции. Желательно использовать мембрану другого типа или применять антигипертензивное средство другой фармакотерапевтической группы. *Печеночная энцефалопатия:* следует прекратить терапию. *Фоточувствительность:* следует прекратить лечение. *Нарушение функции почек:* у некоторых пациентов без предшествующего очевидного нарушения функции почек могут появиться лабораторные признаки функциональной почечной недостаточности. Лечение следует прекратить. В дальнейшем можно возобновить комбинированную терапию, используя низкие дозы препаратов, либо применять только один из препаратов. Необходим регулярный контроль уровня калия и креатинина в сыворотке крови — через 2 недели после начала терапии и в дальнейшем каждые 2 месяца. *Двусторонний стеноз почечных артерий или наличие одной функционирующей почки:* не показан. *Печеночная недостаточность:* при появлении желтухи или значительном повышении активности печеночных ферментов следует прекратить прием препарата. В редких случаях на фоне приема ингибиторов АПФ возникает холестатическая желтуха. При прогрессировании этого синдрома возможно развитие фульминантного некроза печени, иногда с летальным исходом. *Транзиторная функциональная почечная недостаточность:* лечение следует прекратить. В дальнейшем можно восстановить комбинированную терапию, используя низкие дозы препаратов, либо использовать препараты в режиме монотерапии. Необходим регулярный контроль уровня калия и креатинина в сыворотке. *Реноваскулярная гипертензия:* начинать лечение с низкой дозы препарата в условиях стационара. *Риск артериальной гипотензии и/или почечной недостаточности (у пациентов с исходно низким АД, у пациентов с сердечной недостаточностью, со стенозом почечных артерий, нарушением водно-электролитного баланса, с циррозом печени с отеком и асцитом и т.д.):* применять препарат в более низкой дозе и затем постепенно увеличивать дозу. *Артериальная гипотензия и нарушение водно-электролитного баланса:* необходим регулярный контроль уровня электролитов плазмы крови. После восстановления ОЦК и АД можно возобновить терапию, используя низкие дозы препаратов, либо использовать препараты в режиме монотерапии. *Пациенты с тяжелой сердечной недостаточностью (IV стадия):* лечение начинать с низких доз и под тщательным врачебным контролем. *Аортальный стеноз/митральный стеноз/гипертрофическая кардиомиопатия:* с осторожностью пациентам с обструкцией выносящего тракта левого желудочка. *Атеросклероз:* у пациентов с ишемической болезнью сердца и недостаточностью мозгового кровообращения лечение следует начинать с низких доз. Кашель. *Содержание ионов калия в плазме крови:* необходим регулярный контроль. *Гиперкалиемия: на фоне регулярного контроля содержания ионов калия в сыворотке крови у пациентов с факторами риска:* почечная недостаточность, нарушение функции почек, пожилой возраст (старше 70 лет), сахарный диабет, некоторые сопутствующие состояния (дегидратация, острая декомпенсация сердечной деятельности, метаболический ацидоз), одновременный прием калийсберегающих диуретиков (таких, как спиронолактон, эплеренон, триамтерен, амилорид), а также препаратов калия или калийсодержащих заменителей пищевой соли. Гиперкалиемия может привести к серьезным, иногда фатальным нарушениям ритма сердца. *Гипокалиемия: группа высокого риска:* пациенты пожилого возраста, истощенные пациенты (как получающие, так и не получающие сочетанную медикаментозную терапию), пациенты с циррозом печени (с отеками и асцитом), ишемической болезнью сердца, хронической сердечной недостаточностью, пациенты с увеличенным интервалом QT. Необходим регулярный контроль содержания ионов калия в плазме крови. Способствует развитию тяжелых нарушений сердечного ритма, особенно аритмии типа «пируэт», которая может быть фатальной. *Содержание ионов натрия в плазме крови:* необходимо определить до начала лечения. Более частый контроль показан пациентам с циррозом печени и лицам пожилого возраста. *Содержание ионов кальция в плазме крови:* перед исследованием функции паращитовидной железы следует отменить прием диуретических средств. *Мочевая кислота:* может увеличиваться частота возникновения приступов подагры. *Хирургическое вмешательство/общая анестезия:* рекомендуется прекратить прием препарата за сутки до хирургической операции. *Пациенты с лактазной недостаточностью, галактоземией или синдромом глюкозо-галактозной мальабсорбции, непереносимостью лактозы:* противопоказан. *Пациенты с сахарным диабетом:* необходимо контролировать концентрацию глюкозы в крови, особенно при наличии гипокалиемии. *Этнические различия:* явно менее выраженное гипотензивное действие у пациентов негроидной расы. *Спортсмены:* препарат может дать положительную реакцию при проведении допинг-контроля. *Острая миопия и вторичная закрытоугольная глаукома:* как можно скорее прекратить прием лекарственного препарата. В случае если внутриглазное давление продолжает оставаться высоким, может потребоваться немедленное терапевтическое или хирургическое лечение. **ВЗАИМОДЕЙСТВИЕ С ДРУГИМИ ЛЕКАРСТВЕННЫМИ ПРЕПАРАТАМИ***. *Одновременное применение противопоказано:* алискирен и лекарственные препараты, содержащие алискирен у пациентов с сахарным диабетом и/или умеренной или тяжелой почечной недостаточностью (СКФ <60 мл/мин/1,73 м² площади поверхности тела). *Комбинации, не рекомендуемые к применению:* алискирен у пациентов, не имеющих сахарного диабета или нарушения функции почек, препараты лития, калийсберегающие диуретики, препараты калия, одновременное назначение ингибиторов АПФ и АРА II, эстрамустин, калийсберегающие диуретики (например, триамтерен, амилорид) и соли калия. *Комбинации, требующие особого внимания:* баклофен, нестероидные противовоспалительные препараты (НПВП), включая высокие дозы ацетилсалициловой кислоты, гипогликемические средства, препараты, способные вызвать аритмию типа «пируэт», препараты, способные вызывать гиперкалиемию, лекарственные препараты, вызывающие гиперкалиемию, калийнесберегающие диуретики, сердечные гликозиды, рацекадотрил, ингибиторы mTOR (мишени рапамицина млекопитающих) (например, сиролимус, эверолимус, темсиролимус). *Комбинации, требующие внимания:* трициклические антидепрессанты, антипсихотические средства (нейролептики), гипотензивные средства и вазодилататоры, аллопуринол, цитостатические и иммуносупрессивные средства, кортикостероиды (при системном применении) и прокаинамид или тетракозактид, средства для общей анестезии, глиптины, симпатомиметики, препараты золота, метформин, йодсодержащие контрастные вещества, соли кальция, циклоспорин, такролимус. **БЕРЕМЕННОСТЬ И ПЕРИОД ГРУДНОГО ВСКАРМЛИВАНИЯ***. Противопоказан. **ВЛИЯНИЕ НА СПОСОБНОСТЬ УПРАВЛЯТЬ АВТОМОБИЛЕМ ИЛИ МЕХАНИЧЕСКИМИ УСТРОЙСТВАМИ***. В ответ на снижение АД могут развиваться различные индивидуальные реакции. Способность управлять автотранспортом или другими механизмами может быть снижена. **ПОБОЧНОЕ ДЕЙСТВИЕ***. *Часто:* гиперчувствительность (в основном кожные реакции, у пациентов с предрасположенностью к аллергическим и астматическим реакциям), головокружение, головная боль, парестезии, нарушение вкусового восприятия, нарушения зрения, вертиго, звон в ушах, артериальная гипотензия, кашель, боль в животе, запор, диарея, диспепсия, тошнота, рвота, кожная сыпь, кожный зуд, макулопапулезная сыпь, спазмы мышц, астения. *Нечасто:* эозинофилия, гипогликемия, гиперкалиемия, гипонатриемия, лабильность настроения, нарушение сна, сонливость, обморок, ощущение сердцебиения, тахикардия, васкулит, бронхоспазм, сухость слизистой оболочки полости рта, крапивница, ангионевротический отек, пурпура, повышенное потоотделение, реакция фоточувствительности, пемфигоид, артралгия, миалгия, почечная недостаточность, эректильная дисфункция, боль в грудной клетке, недомогания, периферические отеки, лихорадка, повышение концентрации мочевины в крови, повышение концентрации креатинина в крови, падения. *Редко:* обострение псориаза, повышенная утомляемость, гипербилирубинемия, повышение активности печеночных ферментов. *Очень редко:* ринит, агранулоцитоз, апластическая анемия, панцитопения, тромбоцитопения, лейкопения, нейтропения, гемолитическая анемия, гиперкальциемия, спутанность сознания, инсульт, возможно, вследствие чрезмерного снижения АД у пациентов из группы высокого риска, стенокардия, нарушения ритма сердца (в том числе брадикардия, желудочковая тахикардия и фибрилляция предсердий), инфаркт миокарда, возможно, вследствие избыточного снижения АД у пациентов группы высокого риска, эозинофильная пневмония, панкреатит, нарушение функции печени, многоформная эритема, холестатическая желтуха, гепатит цитолитический или холестатический, мультиформная эритема, токсический эпидермальный некролиз, синдром Стивенса–Джонсона, острая почечная недостаточность, снижение гемоглобина и гематокрита. *Неуточненной частоты:* снижение содержания калия и гипокалиемия, особенно значимая для пациентов, относящихся к группе риска, печеночная энцефалопатия у пациентов с печеночной недостаточностью, миопия, нечеткость зрения, полиморфная желудочковая тахикардия типа «пируэт» (возможно, со смертельным исходом), возможно обострение уже имеющейся системной красной волчанки, повышение концентрации мочевой кислоты и глюкозы в крови, удлинение QT-интервала на ЭКГ. **ПЕРЕДОЗИРОВКА***. **СВОЙСТВА***. Нолипрел А/форте/Би-форте – комбинированный препарат, содержащий периндоприла аргинин, ингибитор фермента, превращающего ангиотензин I в ангиотензин II, и индапамид, который относится к группе сульфонамидов и по фармакологическим свойствам близок к тиазидным диуретикам. Комбинация периндоприла аргинина и индапамида усиливает антигипертензивное действие каждого из них. **ФОРМА ВЫПУСКА**. Нолипрел А/форте/Би-форте: таблетки, покрытые пленочной оболочкой. 2,5 мг + 0,625 мг/5 мг + 1,25 мг/10 мг + 2,5 мг (флакон) 14/29/30х1 (пачка картонная). Регистрационное удостоверение: ЛСР-010489/08, ЛСР-010490/08, ЛСР-008847/10.

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130 mm Hg, irrespective of the baseline BP. The effect of TC was more evident in patients with higher baseline BP.

Effect of antihypertensive therapy on quality of life

The mean mood score increased from 3.83±0.90 to 5.20±0.73 (p <0.001) in the TC group and from 4.03±0.95 to 5.00±0.78 (p <0.001) in the control group during the follow-up period. Compared to the control group, the TC group had a lower value at the baseline visit (p=0.002), but this value was higher (p <0.001) by the end of the study. The increase was 1.37 points in the TC group and 0.97 points in the control group. There were no significant changes in other QOL variables in both groups.

Evaluation of tolerability and safety of antihypertensive therapy

The analysis of tolerability and safety of antihypertensive therapy was carried out for the entire patient population (n=1,252). AEs were reported only in 8 (0.64%) patients in the TC group. One (0.2%) patient had a serious AE with decreased BP, dizziness, headache, and gait instability.

This event was clinically significant and associated with the use of Triplixam®. Other AEs were not serious and were reported in 7 (0.54%) patients. These AEs were one case of enlargement of submandibular lymph nodes, two cases of hypotension, three cases of cough, and one case of gastrointestinal symptoms. In all of these cases, an association with Triplixam® was suspected.

In all cases the outcome was favorable. As BP normalized, the dose of Triplixam® was decreased. The number of cases of hypotension during TC treatment was 3 (0.3%).

Changes in renal function during antihypertensive therapy within the study period

654 patients in the TC group and 180 patients in the control group were monitored to assess the dynamics of the GFR calculated by the Cockroft – Gault formula. In this subsample, creatinine was 85.5±14.3 μmol/l at the beginning of the study and 83.7±13.8 μmol/l at the end of the study (p <85.3) in the TC group. Likewise, there were no change in the control group (85.1±16.2μmol/l at the beginning of the study and 85.1±14.4 μmol/l at the end of the study). GFR in the TC group increased from 89.2±28.8 to 90.7±29.9 ml/min/1.73 m^2 (the increase was 1.5 ml/min/1.73 m^2, p=0.035), but there were no significant change in the control group (from 91.1±30.1 to 90.4±29.3 ml/min/1.73 m^2, the difference was 0.7 ml/min/1.73 m^2). There were no significant differences between the groups during the follow-up period.

Evaluation of the TC efficacy in subgroups of patients with hypertension and DM or IGT, overweight and/or obesity, CKD

The analysis was performed in patient subgroups of the TC group with hypertension and with DM or IGT (n=232), or with overweight and/or obesity (n=817), or with CKD (GFR <60 ml/min/1.73 m^2) (n=173). Results showed a decrease in SBP and DBP by 35.1/16.0 mm Hg, 35.2/15.6 mmHg, and 37.7/17.1 mm Hg for these three subgroups, respectively. The target BP values were achieved in 191 (82.3%), 711 (87%) and 143 (82.7%) of these patients, respectively. At the final visit, the dose of TC 5/1.25/5 mg was received by 26.3% of patients with and DM/IGT, 27.3% of patients with overweight and/or obesity, and 26.01% of patients with CKD. TC 5/2.5/10 mg was received by 35.8% of patients with DM or IGT, by 37.1% of patients with overweight and/or obesity, and by 31.2% of patients with CKD. TC 10/2.5/10 mg was received by 35.3% of patients with DM or IGT, by 31.3% of patients with overweight and/or obesity, and by 36.4% of patients with CKD.

Discussion

The primary objective of the TRIO study was to investigate the tactics of outpatient physicians when choosing triple-drug combination treatment after ineffective prior two-drug antihypertensive therapy, as well as the efficacy of various treatment approaches in patients with essential hypertension.

The characteristics of the total patient sample corresponded to similar national and foreign studies with two-drug and triple-drug combination therapy [18–20, 22, 27, 28]. The baseline analysis showed that the TC group was more severe than the control group in many variables, which, on one hand, violated the inclusion criteria, and on the other hand, clearly proved the validity of using TC in such patients. As for the antihypertensive therapy, 337 (34%) patients in the TC group and 38 (14.6%) patients in the control group had already received three or more groups of medications at the time of inclusion in the program, which contradicted the primary inclusion criteria. However, the baseline mean BP in both groups at the beginning of the program demonstrated the absence of BP control, despite a significantly higher number of patients using ACE inhibitors and CCBs in the TC group before being included in the program. The distribution of TC doses, which remained stable except for slight variations throughout the study period, is highly illustrative and is comparable to other studies [18–20, 22, 28].

With TC therapy, BP decreased by 35.3/15.6 mm Hg, and significantly more patients (87.8%) achieved the target BP levels versus the control group. More effective control of SBP during TC therapy was accompanied by a significant decrease in the cases with higher baseline values. Thus, in patients with SBP >180 mm Hg, the decrease was 54.4/19.6 mm Hg.

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Lately, there has been much debate about the usefulness of achieving the target BP levels. The findings of a large-scale meta-analysis in 2016 showed a positive effect on the predicted decrease in SBP for every 10 mm Hg within the baseline level of 130–139 mm Hg [29]. Another meta-analysis showed a reduced risk of major cardiovascular outcomes when SBP less than 130 or DBP less than 80 mm Hg was achieved as compared to a less pronounced decrease [30]. In the SPRINT study, patients with hypertension at the age of 75 yrs and older in the group of SBP <120 mm Hg were compared with the group with the standard target value <140 mm Hg. A significant improvement was identified in both the primary endpoint (the rate of nonfatal myocardial infarction, acute coronary syndrome, non-fatal strokes, acute decompensated heart failure) and the secondary endpoint (all-cause mortality) [31]. In the Russian EVIDENCE program, the use of TC was associated with the achievement of BP <130/80 mm Hg in 25.4% of patients [22]. In the TRIO program, 34.5% of patients taking TC achieved the target BP level of <130/80 mm Hg.

Each component of TC, both individually and in combination, is known to have proven renal protective effects (NESTOR, ADVANCE, PREMIER, ACCOMPLISH, Chukaeva et al., 2013). In the TRIO program, almost 66% of patients in the TC group had CKD. Kidneys have a critical role as both an activator of local renal RAAS in hypertension and as a target organ for its action. Thus, the effect of antihypertensive therapy on the regression of nephropathy is crucial [32]. In this regard, the significant result was a positive effect of TC on kidney function, which was expressed as a decrease in the creatinine levels, an increase in GFR, and a reduced number of patients with GFR <60 ml/min/1.73 m^2.

The latest clinical guidelines for the management of hypertension of the Russian Society of Cardiology recommend starting treatment of all patients with hypertension and DM/CKD with the combination of a RAAS blocker and a CCB or a thiazide/thiazide-like diuretic. This recommendation is due to a more beneficial effect of these combinations on the rate of achieving the target BP and on reducing cardiovascular risk and due to the renal protection potential of RAAS blockers [7]. In the TRIO study, an additional analysis of the use of TC was carried out in the subgroups of patients with hypertension and DM/IGT, overweight and/or obesity, or CKD markers. This analysis identified a good antihypertensive effect of a significant decrease in both SBP and DBP and achievement of target BP in the majority of patients.

Triple-drug combination therapy of hypertension allows achieving the most potent vasoprotective effect, which reduces the risk of cardiovascular complications and improves the prognosis. The effect of ACE inhibitors is mainly associated with the improvement of endothelial dysfunction. CCBs reduce smooth muscle tone and hypertrophy. Indapamide reduces sodium excretion and the degree of sodium-hydrogen exchange, which reduces vascular wall stiffness. In the comparison study with careful 24-hour monitoring of BP (ABPM), TC (amlodipine/indapamide/perindopril arginine 10/2,5/10 mg) reduced BP more effectively than the two-drug combination (indapamide/perindopril arginine, Noliprel® A Bi-forte (2.5/10 mg), by 6.7 mm Hg (clinical BP) and 5 mm Hg (24-hour ABPM) [33]. However, central BP also decreased significantly by 4.5 mm Hg, augmentation index was reduced by 2.4%, and pulse-wave velocity decreased by 0.13 m/s within 24 hrs [33]. Reducing vascular remodeling during TC therapy is more important than an additional reduction in BP. Thus, the additional analysis in the ADVANCE study identified that the triple-drug combination therapy (Noliprel® + CCB) reduced BP as effectively as the two-drug combination therapy (Noliprel®), but an additional 14% reduction in the risk of death was observed only in the triple-drug combination treatment [11]. The SPRINT study should be mentioned once again, in which the TC therapy with antihypertensive drugs not only decreased BP more than the two-drug combination treatment but also reduced the risk of death by 27% [34].

Moreover, triple-drug combination treatment has been shown to reduce significantly the risk of cognitive impairment and dementia, which has a direct effect on QOL of patients with hypertension [35]. In the TRIO study, a significant finding was confirmation of the positive effect on QOL of TC versus the control group. Despite the elderly age and high comorbidity of patients, our findings on the safety profile show good tolerability of triple-drug combination therapy.

Conclusion

In the majority of cases, physicians chose a fixed-dose TC therapy to ensure more reliable 24-hour BP control. Our findings show the therapeutic efficacy of the fixed-dose TC of amlodipine/indapamide/perindopril arginine. This efficacy involves the control of clinical BP in various ranges of the baseline increase in SBP in cases of hypertension and concomitant DM/IGT, obesity, CKD, and, in addition, advantages over the subjective choice of antihypertensive therapy. The TC therapy improves self-monitoring of BP, QOL, renal protection, and is well tolerated and accompanied by higher adherence to treatment. Thus, the treatment of hypertension with fixed-dose drug combinations, such as aml odipine/indapamide/perindopril arginine, is one of the most promising methods of improving the prognosis for patients in the 21st century.

Limitations of the study

The observational nature of the study does not allow making conclusions about the comparative efficacy of the fixed-dose triple-drug combination studied. However, findings

of our observational study carried out in the real-world clinical setting confirm previous conclusions made in other large-scale observational programs [18,19,21,22].

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