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Study of the effect of different drug treatment strategies in patients with hypertension

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Abstract: *fixed combinations of antihypertensive medications can improve blood pressure (BP) control, reduce complications and increase life expectancy. The objective of our study was to analyze the efficiency of fixed, free and not traditional combinations of antihypertensive medications in the management of patients with arterial hypertension. 396 patients with hypertension with various degrees of its severity were examined. The inclusion criteria were the age of patients older than 18 years and the level of office BP greater than 140/90 mm Hg. Patients were in three observational groups: traditional free combinations, traditional fixed combinations, and not traditional free combinations. 91 patients received an unfixed combination of ramipril and hydrochlorothiazide. 132 patients received an unfixed combination of metoprolol-retard and hydrochlorothiazide. 50 patients were assigned to group with studying the effect of fixed traditional double and triple combinations of antihypertensive medications. The last 123 patients with hypertension comprised the group of studying the effect of dihydropyridine and non-dihydropyridine calcium blockers on the degree of BP reduction and the development of adverse events. The use of metoprolol-retard 100-300 mg per day in patients with mild to moderate hypertension provided a significant decrease in office BP: SBP/ DBP – 32/18 mm Hg, heart rate (HR) – 18 bpm, ABPM: 24SBP/DBP – 21/13 mm Hg and HR – 7 bpm. Achievement of the target BP 93.6% office BP and in 84,9% – ABPM. The use of ramipril 10 mg in combination with hydrochlorothiazide 25 mg in patients with mild and moderate arterial hypertension provided a reliable reduction of both office SBP/DBP – 36,6/17,2 mm Hg and ABPM 24SBP/DBP – 18,9/7,0 mm Hg. The prescribed monotherapy of lercanidipine 20 mg or a low-dose combination of lercanidipine 10 mg and diltiazem 120 mg were most effectively tolerated treatment. Combined treatment based on lercanidipine and diltiazem had similar efficiency as treatment based on monotherapy with lercanidipine, according to both office and ABPM measurements. Patients taking fixed triple combination of valsartan/hydrochlorothiazide/ amlodipine had decrease 24SBP/DBP – 23.8/20.7 mmHg ($p<0,05$). This improvement of BP on this combination was also observed during the day and night period – 27.4/22.6 mmHg and 20.5/18.2 mm Hg, respectively ($p<0.05$). Achieved the target blood pressure during ABPM was 77.3% in the group of fixed double therapy valsartan/amlodipine and 95.2% in the triple combination valsartan/amlodipine/ hydrochlorothiazide. The triple fixed combination of valsartan/ hydrochlorothiazide /amlodipine was the most effective in lowering blood pressure according to data of office measurement and 24 hours monitoring. It contributed to the achievement of target blood pressure levels at office measurement – 95.7% and at ABPM – 95.2%.*

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Keywords. Amlodipine, Blood Pressure, Diltiazem, Drug Combinations, Hydrochlorothiazide, Hypertension, Metoprolol, Ramipril, Valsartan, lercanidipine.

Introduction

Treatment of arterial hypertension (AH) is one of the most important issues of modern cardiology. This is due to the high prevalence of hypertension in Ukraine, as well as a large number of its complications. Since the discovery of propranolol, beta-blockers have widely entered the practice of treating cardiovascular diseases, including hypertension (Kjekshus, 1988; Task Force Members for 2013 ESH/ESC Guidelines, 2013).

The use of beta-blockers has a beneficial effect to sinus tachycardia and supraventricular arrhythmias, coronary heart disease, heart failure (HF) etc. (Luomanmäki et al., 1992; Task Force Members for 2013 ESH/ESC Guidelines, 2013). Beta-blockers mainly suppress the effects of the sympathetic nervous system. Its activation causes peripheral vasoconstriction and reduces kidneys sodium excretion, which in turn leads to an increase in volume and pressure within heart ventricles. Today, there are enough prospective multicenter studies on the proven effectiveness of beta-blockers on hypertension. Metoprolol succinate has a long period of half-life, which allows to prescribe it once a day.

Multicenter studies CAPPP, STOP-Hypertension-2, ALLHAT showed that ACE inhibitors in patients with hypertension are as effective in reducing mortality from cardiovascular pathology as thiazide diuretics and beta-blockers (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002; Hansson, 2000; Hansson, et al., 1999). The last two named groups of antihypertensive drugs have proven ability to improve cases (Task Force Members for 2013 ESH/ESC Guidelines, 2013). Long-term therapy with ACE inhibitors reduced the incidence of new cases of diabetes mellitus (DM) (CAPPP, HOPE) (Hansson, et al., 1999; Sleight, 2000; Task Force Members for 2013 ESH/ESC Guidelines, 2013). The HOPE trial evaluated the clinical effectiveness of using ACE inhibitors in preventing vascular catastrophes in patients with cardiovascular diseases and reducing a high risk of complications in cases of preserved left ventricle (LV) systolic function. For 4.5 years, patients received ramipril at a dose of 10 mg/day or placebo in addition to therapy by aspirin, beta-blockers and calcium channel blockers. The addition of ramipril to such therapy reduced the combined incidence of cardiovascular death and nonfatal myocardial infarction (MI) and stroke compared to placebo by 19%, including cardiovascular death by 26%, MI by 20%, accompanied by a reduction in total mortality by 17% and the risk of developing HF by 22% (Task Force Members for 2013 ESH/ESC Guidelines, 2013).

According to current guidelines for the treatment of hypertension, most patients require two or more antihypertensive medications to achieve target BP levels (Task Force Members for 2013 ESH/ESC Guidelines, 2013). Such conclusions were made because of the results of large clinical studies that demonstrated the necessity for combined therapy (Matsui et al., 2009; Philipp et al., 2007; Sison, Assaad-Khalil et al., 2014; Task Force Members for 2013 ESH/ESC Guidelines, 2013). The fixed combination reduces the number of pills a patient has to take and by that improves its compliance. A meta-analysis of 9 studies that compared the use of a fixed combination with monotherapy in the treatment of patients with diabetes mellitus (DM) and AH showed improvement in 26% of compliance to treatment with fixed combination (Pogue et al., 2009; Sawada et al., 2009).

Aim

The objective of our study was to analyze the effectiveness of fixed, free and not traditional combinations of antihypertensive medications in the treatment of patients with AH.

Materials and methods

396 patients with AH with various degrees of severity were examined. The inclusion criteria were the age of patients older than 18 years and the level of office BP greater than 140/90 mm Hg. Patients were in three observation groups: traditional free combinations, traditional fixed combinations, and not traditional free combinations. 91 patients

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received an unfixed on the effect on lowering blood pressure, tolerability and side effects combination of ramipril and hydrochlorothiazide. 132 patients received an unfixed on the effect on blood pressure, tolerability and development of adverse reactions combination of metoprolol-retard and hydrochlorothiazide. 50 patients were assigned to group with studying the effect of fixed traditional double and triple combinations of antihypertensive medications. The last 123 patients comprised the group of studying the effect of free not traditional combination dihydropyridine and non-dihydropyridine calcium channel blockers (CCB) on the degree of BP reduction and the development of adverse reactions. Exclusion criteria were patients older than 80 years, with HF more severe than NYHA II, a permanent form of atrial fibrillation, stroke, MI, mental disorders, cases of anaphylactic reactions to therapy components in the past 6 months.

All patients underwent office BP measurement, ambulatory 24 hours blood pressure monitoring (ABPM) and a biochemical blood test.

Statistical analysis

Statistical processing of the results was made after creating databases in Microsoft Excel systems. The mean numbers of examined patients were determined using the analysis package in the Microsoft Excel system. All other statistical calculations were performed using the SPSS 21.0. The normality of the ranges was determined using the Shapiro-Wilk test. With a normal distribution the reliability of the difference in means at the stages of treatment was determined using a paired sample test. The reliability of the difference between groups was determined using an independent t-test for means after determining the nature of the distribution of measurements. The efficiency in groups and the difference in groups by distribution of presence of one or another characteristic were evaluated by a dichotomous variable with using the $\chi 2$ criteria.

Results

396 patients with hypertension were examined. We conducted a study of the antihypertensive effectiveness of metoprolol-retard used as monotherapy or combination with hydrochlorothiazide and ramipril as monotherapy or in combination with hydrochlorothiazide to identify the most effective combinations in the treatment of hypertension and its use in the further treatment of patients with hypertension. The use of the retard form of metoprolol in patients with mild and moderate hypertension once a day for 8 weeks with sufficient antihypertensive efficacy had good tolerability and safety. According to ABPM data, it allowed effective reducing level of BP during the day. With the use of the such therapy a significant decrease in both maximum of systolic blood pressure (SBP) and degree of its increase in the morning hours was observed. The use of long-acting metoprolol in a dose of 100-300 mg per day in patients with mild and moderate hypertension provided a significant decrease in office SBP – by 32 mm Hg, diastolic BP (DBP) – by 18 mm Hg, HR – by 18 bpm, as well as 24SBP/DBP – by 21/13 mm Hg and HR – at 7 bpm. (Table 1). First results were presented earlier (Sirenko & Rekovets, 2006). In patients with mild to moderate AH, long-acting metoprolol in a dose of 100-300 mg (alone or in combination with hydrochlorothiazide) contributed to the achievement of the target BP in 93.6% of patients – office measurement, and 84,9% of patients according to ABPM. There was a significant decrease in the variability of SBP and DBP according to ABPM during treatment with long-acting metoprolol, as well as percent time elevation (PTE) and hyperbaric area index (HBI), mean 24-hours period BP, mean day and night BP. (Table 2). Therapy with long-acting metoprolol (alone or in combination with hydrochlorothiazide) was safe and well tolerated by patients. The use of long-acting metoprolol once a day in patients with mild and moderate hypertension provided a reliable and equable decrease in SBP and DBP throughout the day, including the morning hours. It contributed to a reliable decrease in the maximum level of SBP by 29 mm Hg ($p<0.001$) and the degree of its increase in the morning hours from 60.9 ± 1.9 to 50.5 ± 1.7 mm Hg ($p<0.05$). The dynamics of the decrease in the rate of maximum SBP increase in the morning hours (11.21 ± 0.85 and 11.15 ± 1.02) was unreliable. The absence of a decrease in the speed of the morning blood pressure rise in our study can be explained by the fact that the its initial mean value was not high.

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Table 1. Dynamics of mean office SBP, DBP and HR during taking metoprolol-retard both monotherapy and in combination with hydrochlorothiazide (M ± m).

	Initiation	10 days	20 days	30 days	60 days
SBP, mm Hg	161,4 ± 0,9	143,1 ± 1,2*	135,3 ± 1,0*	130,9 ± 0,9*	129,4 ± 0,7*
DBP, mm Hg	97,5 ± 0,7	86,7 ± 0,9*	83,2 ± 0,7*	81,3 ± 0,6*	79,2 ± 0,5*
HR, bpm	82 ± 1,2	70,5 ± 0,9*	67 ± 0,8*	65,1 ± 0,7*	63,8 ± 0,6*

Notes: * – reliability of difference between groups P<0,05; SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate, bpm – beats per minute.

Table 2. Dynamics of numbers of ABPM BP and HR during raking metoprolol-retard (M ± m)

Indicator	Measurement units	Initially n=118	After 60 days n=118
24SBP	mm Hg	145,4 ± 1,2	124,2 ± 1,04*
24DBP	mm Hg	86,9 ± 1,1	74,1 ± 0,82*
24HR	bpm	75,7 ± 0,9	68,4 ± 0,76*
24SBP SD	mm Hg	16,3 ± 0,4	12,4 ± 0,34*
24DBP SD	mm Hg	13,3 ± 0,3	13,3 ± 1,74
24SBP DI	%	10,6 ± 0,6	10,0 ± 0,6
24DBP DI	%	15,4 ± 0,7	15,2 ± 0,77
24SBP HIdx	%	66,3 ± 1,9	26,2 ± 2,11*
24DBP HIdx	%	46,5 ± 2,5	18,8 ± 1,82*
24SBP HIpt	mm Hg x h.	302,6 ± 17,9	79,8 ± 9,86*
24DBP HIpt	mm Hg x h.	140,7 ± 11,6	39,0 ± 4,7*
Day SBP	mm Hg	149,9 ± 1,2	127,3 ± 1,12*
Day DBP	mm Hg	90,2 ± 1,1	78,1 ± 0,83*
Day HR	bpm	79,6 ± 1,0	72,2 ± 0,77*
Day SBP SD	mm Hg	16,1 ± 0,4	12,2 ± 0,24*
Day DBP SD	mm Hg	12,6 ± 0,3	10,5 ± 0,3
Day SBP HIdx	%	64,5 ± 2,1	22,0 ± 2,18*
Day DBP HIdx	%	49,7 ± 2,7	18,6 ± 1,79*
Day SBP HIpt	mm Hg x h	277,4 ± 17,3	65,0 ± 9,21*
Day DBP HIpt	mm Hg x h	151,9 ± 12,3	41,4 ± 5,62*
Night SBP	mm Hg	135,4 ± 1,5	114,6 ± 1,17*
Night DBP	mm Hg	77,4 ± 1,2	65,8 ± 0,88*
Night HR	bpm	68,4 ± 0,9	62,9 ± 0,84*
Night SBP SD	mm Hg	14,2 ± 0,4	11,1 ± 0,31*
Night DBP SD	mm Hg	11,4 ± 0,3	9,1 ± 0,3
Night SBP HIdx	%	70,2 ± 2,3	32,9 ± 2,55*
Night DBP HIdx	%	39,1 ± 2,8	17,3 ± 2,06*
Night SBP HIpt	mm Hg x h	322,2 ± 25,1	96,0 ± 12,63*
Night DBP HIpt	mm Hg x h	107,2 ± 12,2	34,2 ± 4,53*

Notes: * – reliability of difference between groups P<0,05, 24 – measured throughout full 24 hours period, Day – measured throughout day, Night – measured throughout night, SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate, SD – standard deviation, bpm – beats per minute, HIdx – percent time BP elevation, HIpt – hypertonic area index.

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The use of ramipril (10 mg) in combination with hydrochlorothiazide (25 mg) in patients with mild and moderate hypertension provided a reliable reduction of both office SBP/DBP – by 36,6/17,2 mm Hg, and also 24SBP/DBP – by 18.9/7.0 mm Hg respectively (P<0.001) (Table 3). In patients with mild and moderate hypertension, the target BP was reached in 85.7% of cases according to office measurement data, and in 74% of cases according to ABPM data. According to the ABPM data there was a significant decrease in HIdx and HIpt for SBP and DBP, both during the 24 hours period and during the day and night periods, during treatment with ramipril in combination with hydrochlorothiazide. First results were presented earlier (Sirenko, Andriyevskaya, et al., 2007).

We used a fixed-combination study to identify the efficacy of hypertension treatment and exploration of its effect on BP. 50 patients with moderate and severe hypertension were included in the study. The mean age of the patients was 54.9 ± 1.8 (in range 25-75) years. The mean body weight was 92.4 ± 2.6 kg. The average body mass index (BMI) was 31.2 ± 0.7 kg/m^2. The mean numbers of office SBP and DBP at the beginning of the study were 161.7 ± 1.8 mm Hg and 98.5 ± 1.4 mm Hg respectively. The mean HR was 70.7 ± 1.4 bpm. Initially, 25 patients (50%) received a double fixed combination of valsartan/amlodipine 5/160 mg once a day and 25 patients (50%) received a triple fixed combination of valsartan/amlodipine/hydrochlorothiazide at a dose of 5/160/12.5 mg once a day. First results was presented earlier (Rekovets, Sirenko, Torbas, Kushnir, & Primak, 2020).

During taking valsartan/amlodipine therapy the decrease in office SBP at the 1 month, 2 months, and 3 months was 19, 34 and 35 mm Hg respectively, p<0.05 for all values. During taking triple combined therapy of valsartan/amlodipine/hydrochlorothiazide, the reduction of office SBP at the 1 month, 2 months, and 3 months was 15, 34, 42 mm Hg respectively, p<0,05 for all values. In the group of taking double therapy, the target office BP was achieved in 90.9% of patients, in the group of taking triple combination – in 95.7% of patients. While we analyzed the dynamics of BP during ABPM in patients taking the double combination of valsartan/amlodipine in comparison with the triple combination of valsartan/amlodipine/hydrochlorothiazide, we found a reliable significant decrease in ABPM SBP/DBP during taking valsartan/amlodipine therapy – 18.0/16.1 mm Hg, (p<0,05) and during the day and night periods – 19.4/17.8 mm Hg and 17.0/12.1 mm Hg, respectively, p<0,05 for all values. More prominent findings were observed during taking triple combined therapy of valsartan/amlodipine/hydrochlorothiazide. Thus, the reduction of ABPM SBP/DBP after 3 months of therapy was 23.8/20.7 mm Hg, and the reduction of BP during the day and night periods was 27.4/22.6 mm Hg and 20.5/18.2 mm Hg, respectively, p<0.05 for all values (Figure 1).

Achieving the target BP level during ABPM was 86% in the group as a whole. In the group of taking dual therapy valsartan/amlodipine, the achievement of target ABPM BP was 77.3%. In the group of taking triple combination valsartan/amlodipine/hydrochlorothiazide – 95.2% of patients. Therefore, the triple fixed combination was more effective in reducing BP at office measurement and at ABPM after 3 months of treatment.

Table 3. Dynamics of office BP during taking ramipril (M ± m), (n=91)

	Initiation	1 day	14 days	30 days	60 days
SBP, mm Hg	163,44 ± 0,96	165,41 ± 0,98	145,86 ± 0,97*	136,27 ± 1,05*	128,79 ± 0,82*
DBP, mm Hg	95,70 ± 1,16	96,42 ± 1,18	86,63 ± 0,75*	82,98 ± 0,73*	79,21 ± 0,58*
HR, bpm	74,28 ± 0,71	74,69 ± 0,68	71,49 ± 0,72*	70,20 ± 0,76*	71,04 ± 0,78*

Note: * – difference is reliable compared with first day of observation P<0.001.

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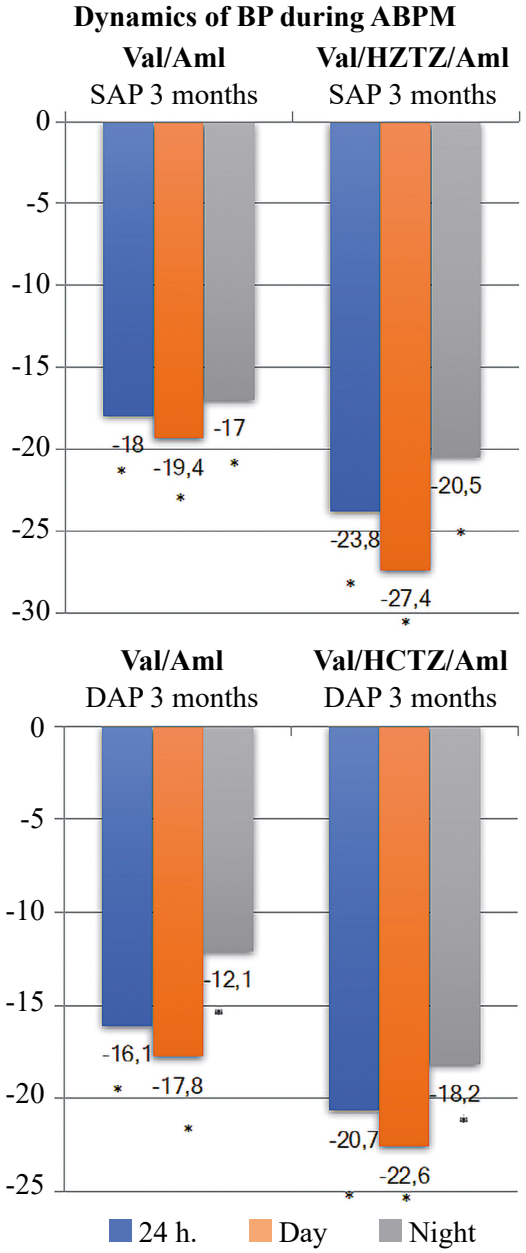

Figure 1. Dynamics of ABPM BP during taking fixed double or triple combination of antihypertensive medications valsartan/amlodipine (Val/Aml) and valsartan/hydrochlorothiazide/ amlodipine (Val/HCTZ/Aml).

Notes: BP – blood pressure, ABPM – ambulatory 24 hours blood pressure monitoring, SBP – systolic blood pressure, DBP – diastolic blood pressure.

123 patients with mild and moderate hypertension (mean level of SBP/DBP – 149.12/91.92 ± 1.42/0.93 mm Hg) were included in group of defining influence of free not traditional combinations of dihydropyridine and non-dihydropyridine CCB (Table 4). Patients were divided into six groups. A total number of 102 patients (59 men, 43 women) underwent complete initial and followed-up examination during taking therapy. The mean age of the patients was 52.37 ± 0.97 years, the mean duration of hypertension was 5.49 ± 0.30 years, and the treatment period was 1 month. According to office BP measurement, combined treatment based on lercanidipine and diltiazem was as effective as treatment based on monotherapy with lercanidipine or diltiazem respectively. In the group of taking diltiazem 240 mg, office SBP/DBP significantly decreased by 9.94/9.89 mm Hg. In the group of taking lercanidipine 20 mg is decreased by 12.35/8.18 mm Hg, in the group of taking combination of lercanidipine 20 mg/ diltiazem 240 mg – by 12.75/8.19 mm Hg, in the group of taking combination of lercanidipine 10 mg/diltiazem 240 mg – by 11.60/8.33 mm Hg, in the group taking lercanidipine 10 mg/diltiazem 120 mg – by 11.68/9.84 mm Hg, in the group taking lercanidipine 20 mg/ diltiazem 120 mg – by 13.88/9.76 mm Hg (Table 5). That means all selected treatment options were equally effective in reducing office BP. First results it was presented earlier (Sirenko, Rekovets, & Dobrokhod, 2016).

The same result was obtained according to the data of ABPM. According to it, combined treatment based on lercanidipine and diltiazem was as effective as treatment based on monotherapy with lercanidipine or diltiazem respectively. In the group of taking diltiazem 240 mg group, ABPM SBP/DBP was significantly decreased by 11.92/7.22 mmHg, in the group of taking lercanidipine 20 mg – by 8.65/9.06 mm Hg, in the group of taking combination lercanidipine 20 mg/diltiazem 240 mg – by 6.10/6.94 mm Hg, in the group of taking combination lercanidipine 10 mg/diltiazem 240 mg – by 8.96/5.54 mm Hg, in the group taking lercanidipine 10 mg/diltiazem 120 mg combination – by 7.21/5.47 mm Hg, in the group taking lercanidipine 20 mg/diltiazem 120 mg combination – by 6.81/7.89 mm Hg. That means all selected treatment options were equally effective in terms of reducing daily BP. Achieving target levels of office BP and BP measured by ABPM was similar in all treatment groups. In the group of taking diltiazem 240 mg, both office BP and BP

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measured with ABPM were achieved in 72.23% of patients. In the group of taking lercanidipine, both office BP and ABPM BP were achieved in 76.47% of patients. In the group of taking lercanidipine 20 mg/diltiazem 240 mg combination, the target office BP was achieved in 56.25% of patients, and the target ABPM BP – in 62.50% of patients. In the group of taking lercanidipine 10 mg/diltiazem 240 mg combination, the target office BP was achieved in 66.67% of patients, and the target ABPM BP – in 73.34% of patients. In the group of taking lercanidipine 10 mg/diltiazem 120 mg combination, the target office BP was achieved in 52.63% of patients, and the target ABPM BP – in 78.95% of patients. In the group of taking lercanidipine 20 mg/diltiazem 120 mg combination, the target office BP was achieved in 82.35% of patients, while the target ABPM BP – in 52.94% of patients. There was no negative effect of all treatment options on the levels of the blood lipid spectrum. There was no significant effect of either monotherapy with diltiazem, monotherapy with lercanidipine or their combinations on changes in HR variability. The prescribed treatment was most effectively tolerated by patients in cases of taking monotherapy with lercanidipine 20 mg or a low-dose combination of lercanidipine 10 mg and diltiazem 120 mg.

Table 4. Clinical and demographic characteristics of examined taking not traditional combinations patients, n=102, (M ± m, n, %)

Indicator	Value
Men, n (%)	59 (57,84%)
Women, n (%)	43 (43,16%)
Height, m	1,72 ± 0,01
Weight, kg	85,86 ± 1,20
Age, years	52,37 ± 0,97
BMI, kg/m2	29,14 ± 0,36
Duration of hypertension, years	5,49 ± 0,30
Smoking, n (%)	22 (21,57%)
Alcohol use, n (%)	45 (44,12%)
Office SBP, mm Hg	150,37 ± 0,89
Office DBP, mm Hg	91,91 ± 0,68
Office HR, bpm	67,78 ± 1,00
ABPM SBP, mm Hg	139,08 ± 0,60
ABPM DBP, mm Hg	84,29 ± 0,85
ABPM PBP, mm Hg	54,96 ± 0,81
ABPM HR, bpm	68,76 ± 0,96
HRV (LF/HF during 24 hours)	2,74 ± 0,18
HRV (LF/HF during day)	3,19 ± 0,21
HRV (LF/HF during night)	2,37 ± 0,14
Cholesterol, mmol/l	6,22 ± 0,12
Triglycerides, mmol/l	1,77 ± 0,13
HDL cholesterol, mmol/l	1,24 ± 0,02
LDL cholesterol, mmol/l	4,14 ± 0,10
VLDL cholesterol, mmol/l	0,80 ± 0,06
AI	4,15 ± 0,15
Normal weight – n (%)	10 (9,80%)
Overweight – n (%)	57 (55,88%)
Obesity, class I – n (%)	28 (27,45%)
Obesity, class II – n (%)	7 (6,86%)

Notes: BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, PBP – pulse blood pressure, HR – heart rate, bpm – beats per minute, ABPM – ambulatory 24 hours blood pressure monitoring, HRV – heart rate variability, HF – higher frequencies, LF – lower frequencies, AI – atherogenic index, HDL – high-density lipoprotein, LDL – low-density lipoprotein, VLDL – very low-density lipoprotein.

21 patients (17.07%) were excluded from the study of not traditional combinations due to the development of adverse reactions. In the group of taking diltiazem monotherapy, 2 patients (1.63%) withdrew due to the development of headache. In the group taking lercanidipine monotherapy reasons of withdrawing of 3 patients (2.44%) were the following: palpitations and facial flushing in 2 of them, and edema of the lower extremities in 1 patient. In the group of taking combination of 20 mg lercanidipine and 240 mg diltiazem, withdrawal was observed in 6 patients (4.88%): 3 of them developed headache and facial redness, 2 – swelling of the lower extremities, and 1 – skin itching. In the group of taking combination of 10 mg lercanidipine and 240 mg diltiazem, withdrawal was observed in 5 patients (4.06%): 3 of them developed headache and facial redness, 2 – edema of the lower extremities and skin itching. In the group of taking combination of 10 mg lercanidipine and 120 mg diltiazem, withdrawal due to headache was observed in 2 patients (1.63%). In the group of taking combination of 20 mg lercanidipine and 120 mg diltiazem,

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Table 5. Dynamics of numbers of office BP and HR in groups of taking not traditional combinations, (M ± m)

	Initiation of treatment	End of treatment
Diltiazem 240 mg (N=18)		
Office HR, bpm	73,17 ± 2,21	68,44 ± 2,20
Office SBP, mm Hg	149,17 ± 1,73	139,22 ± 2,03**
Office DBP, mm Hg	91 ± 1,44	81,11 ± 2,27**
Lercanidipin 20 mg(N=17)		
Office HR, bpm	63 ± 2,28	65,65 ± 2,47
Office SBP, mm Hg	149,59 ± 1,94	137,24 ± 3,84**
Office DBP, mm Hg	91,76 ± 1,48	83,59 ± 2,64**
Lercanidipin 20 mg Diltiazem 240 mg (N=16)		
Office HR, bpm	67,31 ± 1,93	68,13 ± 1,758
Office SBP, mm Hg	150,81 ± 2,4	138,06 ± 3,1**
Office DBP, mm Hg	90,69 ± 0,77	82,5 ± 1,3**
Lercanidipin 10 mg Diltiazem 240 mg (N=15)		
Office HR, bpm	74,73 ± 2,81	71,13 ± 1,99
Office SBP, mm Hg	150,93 ± 1,62	139,33 ± 1,82**
Office DBP, mm Hg	92,2 ± 1,32	83,87 ± 1,53**
Lercanidipin 10 mg Diltiazem 120 mg (N=19)		
Office HR, bpm	66,26 ± 1,52	65,26 ± 1,14
Office SBP, mm Hg	151,84 ± 2,57	140,16 ± 1,82**
Office DBP, mm Hg	93,42 ± 2,03	83,58 ± 1,72**
Lercanidipin 20 mg Diltiazem 120 mg (N=17)		
Office HR, bpm	62,88 ± 2,67	64,29 ± 2,3
Office SBP, mm Hg	149,88 ± 2,62	136 ± 2,49**
Office DBP, mm Hg	92,24 ± 2,37	82,47 ± 2,36**
Total (N=102)		
Office HR, bpm	67,78 ± 1	67,04 ± 0,82
Office SBP, mm Hg	150,37 ± 0,89	138,36 ± 1,05**
Office DBP, mm Hg	91,91 ± 0,68	82,83 ± 0,82**

Notes: SAP – systolic blood pressure, DAP – diastolic blood pressure, HR – heart rate, bpm – beats per minute, *– p<0,05 reliability of findings compared with initiation of treatment, ** – p<0,01 reliability of findings compared with initiation of treatment.

withdrawal was observed in 3 patients (2.44%): they experienced headache, palpitations, and facial flushing. Our study for the first time demonstrated the possibility of a combination of dihydropyridine and non-dihydropyridine calcium blockers in the treatment of hypertension.

Common side effects of diltiazem include dizziness, headache and swelling. The most common skin reactions include exanthematous and urticarial lesions, erythema multiforme, Stevens-Johnson syndrome and acute generalized exanthematous pustulosis. Photodistributed hyperpigmentation is a rare side effect of diltiazem with fewer than twenty cases reported in the literature. It is most often associated with extended-release forms of diltiazem and can appear months or years after starting the drug. Its most common localization is face, neck, forearms and chest. The

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pattern of hyperpigmentation can be one-piece or reticulated. Diltiazem-associated photodistributed hyperpigmentation is more common in patients with Fitzpatrick skin phototypes V and VI than in patients with lighter skin types, also more frequently in women than men. The mean age at the time of application is 65 years. Patients with post-treatment hyperpigmentation may report a history of itching, burning, redness, or other rash prior to hyperpigmentation. The pathogenesis of diltiazem-associated photodistributed hyperpigmentation is unknown, but is thought to involve the absorption of solar radiation by diltiazem, leading to the formation of free radicals, the binding of reactive intermediates to cellular proteins and DNA, and the release of erythrogenic and pigment mediators. Discontinuation of diltiazem is important in the management of diltiazem-related photodistributed hyperpigmentation. Hyperpigmentation has not been reported with other calcium channel blockers such as nifedipine and verapamil. Such a unique side effect was not detected in our study.

Discussion

Obtained results reveal effectiveness of the therapy taken by patients. It can be compared with the data of other researchers. Thus, according to a 4-week multicenter, randomized, double-blind study, ramipril at a dose of 2.5 mg once a day reduced office BP by 26.9/14.8 mm Hg, and mean ABPM SBP and DBP by 10/7 mm Hg (Dahlöf, Hansson, et al., 1993; Dahlöf, Lindholm, et al.,1991). Slightly larger numbers of BP reduction in our observation can be explained by the higher dose of used ramipril. The low incidence of adverse reactions (5.5%) in our study was comparable to other data in the literature, where it was 3.1–6.2% of cases, also in some studies it was comparable to placebo (DREAM Trial Investigators, 2006; Johannesson, et al, 1993; Mallat, Itani, & Tanios, 2013). The high efficacy and safety of prescribing low doses of ramipril (2.5–5 mg) during the treatment of hypertension was confirmed in the large-scale (n=8261) CARE study, where general practitioners prescribed this medication for 8 weeks. 86% of patients in the general group achieved a DBP of less than 90 mm Hg, and 70.4% of patients with isolated systolic hypertension had SBP reduced to less than 140 mm Hg (Kaplan, 2006). In the RACE study with using ramipril at a dose of 2.5 mg/day the same antihypertensive efficacy was noted as with using atenolol 50 mg once a day (Dahlöf, Hansson, et al., 1993; Dahlöf, Lindholm, et al., 1991). Basic studies on the antihypertensive effectiveness and safety of ramipril in patients with mild and moderate hypertension proved its feasibility as optimal medication in such patients (Burris determined the 24-hour BP profile when ramipril was prescribed; Koenig compared the effectiveness of ramipril and lisinopril; Nami compared the effectiveness of using different doses of ramipril and lisinopril, enalapril and quinapril; in CARE research there was studied the effectiveness of using ramipril in clinical practice; in RACE, HYCAR, PART-2 researches there was studied the effect of ramipril on left ventricular hypertrophy) (Dahlöf, Hansson, et al., 1993; Kaplan, 2006; Marre et al., 2004; Pogue, et al., 2009; Task Force Members for 2013 ESH/ESC Guidelines, 2013).

Therefore, the use of ramipril at a dose of 10 mg as monotherapy or in combination with hydrochlorothiazide 25 mg/day in patients with mild and moderate hypertension during 2 months of treatment provided notable antihypertensive efficacy of the treatment, which is well tolerated and convenient for single administration. Effective control of BP and a high level of achievement of target BP numbers with using ramipril together with good tolerability of treatment and its once-a-day administration confirm the feasibility of prescribing ramipril as a drug of first choice in the treatment of patients with mild and moderate hypertension (Dahlöf, Hansson, et al., 1993; Task Force Members for 2013 ESH/ESC Guidelines, 2013).

It should be emphasized that according to both office and ABPM BP findings the effect of metoprolol-retard therapy increased throughout the study period. On the one hand, this is explained by the fact that the dose of the drug increased during titration. On the other hand, there is a slow release of the medication due to the unique structure of the tablet, which results in increase of the effectiveness during the first 4-12 weeks of treatment during long-term therapy. The addition of hydrochlorothiazide to metoprolol-retard significantly improved BP control and increased the number of patients who achieved BP targets.

It is known that BP control in the morning can provide additional benefits in the treatment of

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patients with hypertension: it can reduce the risk of developing cardiovascular complications (Assaad-Khalil, & Nashaat, 2016; Genth-Zotz, et al., 2000; Johannesson, et al, 1993; Sawada et al., 2009; White, 2001). It is important to emphasize that the longer the duration of action of the antihypertensive drug, the better the level of BP will be controlled in the morning hours. One of the mechanisms responsible for the morning increase in BP is an increase in the activity of the sympathetic nervous system, so the use of long-acting beta-blockers for this objective is pathogenetically justified (Boggia et al., 2007; Kjekshus, 1988; LaPalio, Schork, Glasser, & Tifft, 1992).

Not all antihypertensive medications planned by manufacturers for once-a-day administration provide optimal BP control in the morning hours. Received data convincingly prove that the use of the studied retard medication metoprolol 1 time per day made possible reducing the level of BP in the period from 6 to 12 hours (a day after taking the drug) to the same level as mean during the 24 hours or in the active and the passive period (Kjekshus, 1988; LaPalio, Schork, Glasser, & Tifft, 1992). In addition, the reduction of the maximum SAP peak in the morning hours by an average of 29 mm Hg made possible reducing its mean numbers in the group to 144.8 mm Hg. That is only 5 mm Hg above the limit level of BP. Important finding, in our understanding, is decreasing in the level of SBP increase in the morning hours by more than 10 mm Hg, which also indicates the reliable influence of the studied medication on the possible pathogenetic mechanisms of this process – the activation of the sympatho-adrenal system (Khan, et al. 2014; LaPalio, Schork, Glasser, & Tifft, 1992; Lash et al., 2006; Lins, et al., 2011; Luomanmäki, et al. 1992).

Thus, the use of the extended-release form of metoprolol in patients with mild and moderate hypertension once a day for 8 weeks with sufficient antihypertensive efficacy had good tolerability and safety. According to ABPM data it allowed to effectively reduce the level of BP throughout 24 hours, as in daytime as well as in the morning. During taking such therapy a significant decrease in the maximum level of SBP and the degree of its increase in the morning hours was observed (LaPalio, et al., 1992; Philipp, et al., 2007).

In the randomized, prospective, open-label study VALISH (Valsartan in Elderly Isolated Systolic Hypertension; n = 3260, mean follow-up 3.07 years), it was shown that in elderly patients (age 70-84 years, mean age 76.1 years) with isolated systolic hypertension valsartan in a daily dose of 40-80 mg in monotherapy or in combination with other hypotensive agents (calcium blockers, diuretics) allows to ensure effective BP control and is quite safe (Assaad-Khalil, & Nashaat, 2016; Ogihara, et al., 2010; Oparil, et al., 2011; Sawada et al., 2009). According to W.C. Cushman et al. the combination of valsartan and hydrochlorothiazide provides better BP control in elderly patients with isolated systolic hypertension than each component alone (Khan, et al., 2014; Krio, et al., 2017; Matsui, et al., 2009).

Similar results were obtained in the randomized, double-blind ValVET trial. It was established that in elderly patients with systolic arterial hypertension the combination of valsartan with hydrochlorothiazide (160 / 12.5 mg) more effectively reduces BP after 4 weeks of therapy than the use of each of the this components as monotherapy (Duprez, et al., 2011; Kafrawy et al., 2014; Sison, Vega, Dayi, Bader, & Brunel, 2018).

The efficacy of a fixed double valsartan/amlodipine combination has been extensively studied in many randomized trials. Therefore, 13 large studies were conducted involving more than 60,000 patients in 26 countries of the world (Alleman, et al., 2008; Baser, Andrews, Wang, & Xie, 2011; Boggia, et al., 2007; Boutouyrie, Achouba, Trunet, & Laurent, 2010; Calhoun, Crikelair, Yen, & Glazer, 2009; Calhoun, Lacourcière, Crikelair, Jia, & Glazer, 2013; Destro, Luckow, Samson, Kandra, & Brunel, 2008; Flack, et al., 2009). The effectiveness of the triple fixed combination of valsartan/amlodipine/hydrochlorothiazide in one tablet has been proven in 5 large randomized trials including 1500 patients with elderly age, obesity, diabetes and ethnical diversion. There were also 2 large studies (EXCITE and SIMPLIFY) of a fixed combination of valsartan/amlodipine/hydrochlorothiazide in one tablet in 14 countries of the world in 8000 patients (Mayer-Hamblett, et al., 2023; Schrader, et al., 2006; Sison, Assaad-Khalil, et al., 2014; Waeber, & Ruilope, 2009; Weycker, 2008; White, 2001).

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In our study the achievement of the target level of BP during taking fixed triple combination was more than 95% both with its office measurement and ABPM. Thereby, our study showed the high efficiency of fixed combinations in the treatment of patients with hypertension.

Conclusions

1. The triple fixed combination of valsartan/HCTZ/amlodipine was more effective in reducing BP according to its office measurement and ABPM after 3 months of treatment, contributing to the achievement of target BP levels at office measurement – in 95.7%, at ABPM – in 95.2% of patients.

2. The best tolerability and effectiveness was in patients who received monotherapy with lercanidipine 20 mg and a low-dose combination of lercanidipine 10 mg and diltiazem 120 mg, so such therapy can be recommended for use.

3. The use of long-acting metoprolol in a dose of 100-300 mg once a day in patients with hypertension ensured a reliable and equable decrease in SBP and DBP throughout the day, including the morning hours.

Limitations of study

Study is single-centered.

Perspective

Further studies of treatment strategies for patients with hypertension with different fixed combinations and multicenter studies.

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Conflict of interests

There are no conflicts of interests.

Consent to publication

All authors have read the text of the article and gave consent to its publication.

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REFERENCES:

Allemann, Y., Fraile, B., Lambert, M., Barbier, M., Ferber, P., & Izzo, J. L., Jr (2008). Efficacy of the combination of amlodipine and valsartan in patients with hypertension uncontrolled with previous monotherapy: the Exforge in Failure after Single Therapy (EX-FAST) study. Journal of clinical hypertension (Greenwich, Conn.), 10(3), 185–194. https://doi.org/10.1111/j.1751-7176.2008.07516.x

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (2002). 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, 288(23), 2981–2997. https://doi.org/10.1001/jama.288.23.2981

Assaad-Khalil, S. H., & Nashaat, N. (2016). Real-life Effectiveness and Safety of Amlodipine/Valsartan Single-pill Combination in Patients with Hypertension in Egypt: Results from the EXCITE Study. Drugs – real world outcomes, 3(3), 307–315. https://doi.org/10.1007/s40801-016-0082-5

Baser, O., Andrews, L. M., Wang, L., & Xie, L. (2011). Comparison of real-world adherence, healthcare resource utilization and costs for newly initiated valsartan/amlodipine single-pill combination versus angiotensin receptor blocker/calcium channel blocker free-combination therapy. Journal of medical economics, 14(5), 576–583. https://doi.org/10.3111/13696998.2011.596873

Boggia, J., Li, Y., Thijs, L., Hansen, T. W., Kikuya, M., Björklund-Bodegård, K., Richart, T., Ohkubo, T., Kuznetsova, T., Torp-Pedersen, C., Lind, L., Ibsen, H., Imai, Y., Wang, J., Sandoya, E., O'Brien, E., Staessen, J. A., & International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO) investigators (2007). Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. Lancet (London, England), 370(9594), 1219–1229. https://doi.org/10.1016/S0140-6736(07)61538-4

Boutouyrie, P., Achouba, A., Trunet, P., Laurent, S., & EXPLOR Trialist Group (2010). Amlodipine-valsartan combination decreases central systolic blood pressure more effectively than the amlodipine-atenolol combination: the EXPLOR study. Hypertension (Dallas, Tex. : 1979), 55(6), 1314–1322. https://doi.org/10.1161/HYPERTENSIONAHA.109.148999

Calhoun, D. A., Crikelair, N. A., Yen, J., & Glazer, R. D. (2009). Amlodipine/valsartan/hydrochlorothiazide triple combination therapy in moderate/severe hypertension: Secondary analyses evaluating efficacy and safety. Advances in therapy, 26(11), 1012–1023. https://doi.org/10.1007/s12325-009-0077-7

ISSN 2786-6661
eISSN 2786-667X

Calhoun, D. A., Lacourcière, Y., Crikelair, N., Jia, Y., & Glazer, R. D. (2013). Effects of demographics on the antihypertensive efficacy of triple therapy with amlodipine, valsartan, and hydrochlorothiazide for moderate to severe hypertension. Current medical research and opinion, 29(8), 901–910. https://doi.org/10.1185/03007995.2013.803057

Dahlöf, B., Hansson, L., Lindholm, L. H., Scherstén, B., Ekbom, T., & Wester, P. O. (1993). Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) analyses performed up to 1992. Clinical and experimental hypertension (New York, N.Y. : 1993), 15(6), 925–939. https://doi.org/10.3109/10641969309037082

Dahlöf, B., Lindholm, L. H., Hansson, L., Scherstén, B., Ekbom, T., & Wester, P. O. (1991). Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). Lancet (London, England), 338(8778), 1281–1285. https://doi.org/10.1016/0140-6736(91)92589-t

Destro, M., Luckow, A., Samson, M., Kandra, A., & Brunel, P. (2008). Efficacy and safety of amlodipine/valsartan compared with amlodipine monotherapy in patients with stage 2 hypertension: a randomized, double-blind, multicenter study: the EX-EFFeCTS Study. Journal of the American Society of Hypertension : JASH, 2(4), 294–302. https://doi.org/10.1016/j.jash.2008.01.004

DREAM Trial Investigators, Bosch, J., Yusuf, S., Gerstein, H. C., Pogue, J., Sheridan, P., Dagenais, G., Diaz, R., Avezum, A., Lanas, F., Probstfield, J., Fodor, G., & Holman, R. R. (2006). Effect of ramipril on the incidence of diabetes. The New England journal of medicine, 355(15), 1551–1562. https://doi.org/10.1056/NEJMoa065061

Duprez, D. A., Weintraub, H. S., Cushman, W. C., Purkayastha, D., Zappe, D., Samuel, R., & Izzo, J. L., Jr (2011). Effect of valsartan, hydrochlorothiazide, and their combination on 24-h ambulatory blood pressure response in elderly patients with systolic hypertension: a ValVET substudy. Blood pressure monitoring, 16(4), 186–196. https://doi.org/10.1097/MBP.0b013e32834944e9

Flack, J. M., Calhoun, D. A., Satlin, L., Barbier, M., Hilkert, R., & Brunel, P. (2009). Efficacy and safety of initial combination therapy with amlodipine/valsartan compared with amlodipine monotherapy in black patients with stage 2 hypertension: the EX-STAND study. Journal of human hypertension, 23(7), 479–489. https://doi.org/10.1038/jhh.2008.153

Genth-Zotz, S., Zotz, R. J., Sigmund, M., Hanrath, P., Hartmann, D., Böhm, M., Waagstein, F., Treese, N., Meyer, J., & Darius, H. (2000). MIC trial: metoprolol in patients with mild to moderate heart failure: effects on ventricular function and cardiopulmonary exercise testing. European journal of heart failure, 2(2), 175–181. https://doi.org/10.1016/s1388-9842(00)00078-7

Hansson L. (2000). Results of the STOP-Hypertension-2 trial. Blood pressure. Supplement, 2, 17–20.

Hansson, L., Lindholm, L. H., Niskanen, L., Lanke, J., Hedner, T., Niklason, A., Luomanmäki, K., Dahlöf, B., de Faire, U., Mörlin, C., Karlberg, B. E., Wester, P. O., & Björck, J. E. (1999). Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet (London, England), 353(9153), 611–616. https://doi.org/10.1016/s0140-6736(98)05012-0

Johannesson, M., Dahlöf, B., Lindholm, L. H., Ekbom, T., Hansson, L., Odén, A., Scherstén, B., Wester, P. O., & Jönsson, B. (1993). The cost-effectiveness of treating hypertension in elderly people--an analysis of the Swedish Trial in Old Patients with Hypertension (STOP Hypertension). Journal of internal medicine, 234(3), 317–323. https://doi.org/10.1111/j.1365-2796.1993.tb00749.x

Kafrawy, Nabil & Rashwan, Magdy & Lion, Khaled & Khedr, Kawkab & Nashaat, Nashwa. (2014). Effectiveness and tolerability of fixed dose combination of amlodipine/valsartan in treatment of hypertension in the real-life setting among Egyptian patients. The Egyptian Heart Journal, 66(1):30–35. https://doi.org/10.1016/j.ehj.2013.12.033

Kaplan N. M. (1996). The CARE Study: a postmarketing evaluation of ramipril in 11,100 patients. The Clinical Altace Real-World Efficacy (CARE) Investigators. Clinical therapeutics, 18(4), 658–670. https://doi.org/10.1016/s0149-2918(96)80216-5

Kario, K., Tomitani, N., Kanegae, H., Ishii, H., Uchiyama, K., Yamagiwa, K., Shiraiwa, T., Katsuya, T., Yoshida, T., Kanda, K., Hasegawa, S., & Hoshide, S. (2017). Comparative Effects of an Angiotensin II Receptor Blocker (ARB)/Diuretic vs. ARB/Calcium-Channel Blocker Combination on Uncontrolled Nocturnal Hypertension Evaluated by Information and Communication Technology-Based Nocturnal Home Blood Pressure Monitoring - The NOCTURNE Study. Circulation journal : official journal of the Japanese Circulation Society, 81(7), 948–957. https://doi.org/10.1253/circj.CJ-17-0109

Khan, W., Moin, N., Iktidar, S., Sakrani, J., Abid, R., Afzal, J., Maheshwary, N., Kumar, K., Siddiqi, A., & Qadir, M. (2014). Real-life effectiveness, safety, and tolerability of amlodipine/valsartan or amlodipine/valsartan/hydrochlorothiazide single-pill combination in patients with hypertension from Pakistan. Therapeutic advances in cardiovascular disease, 8(2), 45–55. https://doi.org/10.1177/1753944714525496

Kjekshus J. K. (1988). According to MIAMI and ISIS-I trials, can a general recommendation be given for beta blockers in acute myocardial infarction? Cardiovascular drugs and therapy, 2(1), 113–119. https://doi.org/10.1007/BF00054261

LaPalio, L., Schork, A., Glasser, S., & Tifft, C. (1992). Safety and efficacy of metoprolol in the treatment of hypertension in the elderly. Journal of the American Geriatrics Society, 40(4), 354–358. https://doi.org/10.1111/j.1532-5415.1992.tb02134.x

ISSN 2786-6661
eISSN 2786-667X

Lash, J. P., Wang, X., Greene, T., Gadegbeku, C. A., Hall, Y., Jones, K., Kusek, J. W., Sika, M., Unruh, M., & African American Study of Kidney Disease and Hypertension Trial Study Group (2006). Quality of life in the African American Study of Kidney Disease and Hypertension: effects of blood pressure management. American journal of kidney diseases : the official journal of the National Kidney Foundation, 47(6), 956–964. https://doi.org/10.1053/j.ajkd.2006.02.175

Lins, R., Aerts, A., Coen, N., Hermans, C., MacDonald, K., Brié, H., Lee, C., Shen, Y. M., Vancayzeele, S., Mecum, N., & Abraham, I. (2011). Effectiveness of amlodipine-valsartan single-pill combinations: hierarchical modeling of blood pressure and total cardiovascular disease risk outcomes (the EXCELLENT study). The Annals of pharmacotherapy, 45(6), 727–739. https://doi.org/10.1345/aph.1P663

Luomanmäki, K., Inkovaara, J., Hartikainen, M., Helin, M., Viikari, J., Kataja, M., Ekman, K., & Harjula, K. (1992). Efficacy and tolerability of isradipine and metoprolol in treatment of hypertension: the Finnish Isradipine Study in Hypertension (FISH). Journal of cardiovascular pharmacology, 20(2), 296–303. https://doi.org/10.1097/00005344-199208000-00016

Mallat, S. G., Itani, H. S., & Tanios, B. Y. (2013). Current perspectives on combination therapy in the management of hypertension. Integrated blood pressure control, 6, 69–78. https://doi.org/10.2147/IBPC.S33985

Mancia, G., Fagard, R., Narkiewicz, K., Redón, J., Zanchetti, A., Böhm, M., Christiaens, T., Cifkova, R., De Backer, G., Dominiczak, A., Galderisi, M., Grobbee, D. E., Jaarsma, T., Kirchhof, P., Kjeldsen, S. E., Laurent, S., Manolis, A. J., Nilsson, P. M., Ruilope, L. M., Schmieder, R. E., … Task Force Members (2013). 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Journal of hypertension, 31(7), 1281–1357. https://doi.org/10.1097/01.hjh.0000431740.32696.cc

Marre, M., Lievre, M., Chatellier, G., Mann, J. F., Passa, P., Ménard, J., & DIABHYCAR Study Investigators (2004). Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). BMJ (Clinical research ed.), 328(7438), 495. https://doi.org/10.1136/bmj.37970.629537.0D

Matsui, Y., Eguchi, K., O'Rourke, M. F., Ishikawa, J., Miyashita, H., Shimada, K., & Kario, K. (2009). Differential effects between a calcium channel blocker and a diuretic when used in combination with angiotensin II receptor blocker on central aortic pressure in hypertensive patients. Hypertension (Dallas, Tex. : 1979), 54(4), 716–723. https://doi.org/10.1161/HYPERTENSIONAHA.109.131466

Mayer-Hamblett, N., Ratjen, F., Russell, R., Donaldson, S. H., Riekert, K. A., Sawicki, G. S., Odem-Davis, K., Young, J. K., Rosenbluth, D., Taylor-Cousar, J. L., Goss, C. H., Retsch-Bogart, G., Clancy, J. P., Genatossio, A., O'Sullivan, B. P., Berlinski, A., Millard, S. L., Omlor, G., Wyatt, C. A., Moffett, K., … SIMPLIFY Study Group (2023). Discontinuation versus continuation of hypertonic saline or dornase alfa in modulator treated people with cystic fibrosis (SIMPLIFY): results from two parallel, multicentre, open-label, randomised, controlled, non-inferiority trials. The Lancet. Respiratory medicine, 11(4), 329–340. https://doi.org/10.1016/S2213-2600(22)00434-9

Ogihara, T., Saruta, T., Rakugi, H., Matsuoka, H., Shimamoto, K., Shimada, K., Imai, Y., Kikuchi, K., Ito, S., Eto, T., Kimura, G., Imaizumi, T., Takishita, S., Ueshima, H., & Valsartan in Elderly Isolated Systolic Hypertension Study Group (2010). Target blood pressure for treatment of isolated systolic hypertension in the elderly: valsartan in elderly isolated systolic hypertension study. Hypertension (Dallas, Tex. : 1979), 56(2), 196–202. https://doi.org/10.1161/HYPERTENSIONAHA.109.146035

Oparil, S., Giles, T., Ofili, E. O., Pitt, B., Seifu, Y., Hilkert, R., Samuel, R., & Sowers, J. R. (2011). Moderate versus intensive treatment of hypertension with amlodipine/valsartan for patients uncontrolled on angiotensin receptor blocker monotherapy. Journal of hypertension, 29(1), 161–170. https://doi.org/10.1097/HJH.0b013e32834000a7

Philipp, T., Smith, T. R., Glazer, R., Wernsing, M., Yen, J., Jin, J., Schneider, H., & Pospiech, R. (2007). Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. Clinical therapeutics, 29(4), 563–580. https://doi.org/10.1016/j.clinthera.2007.03.018

Pogue, V., Rahman, M., Lipkowitz, M., Toto, R., Miller, E., Faulkner, M., Rostand, S., Hiremath, L., Sika, M., Kendrick, C., Hu, B., Greene, T., Appel, L., Phillips, R. A., & African American Study of Kidney Disease and Hypertension Collaborative Research Group (2009). Disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease. Hypertension (Dallas, Tex. : 1979), 53(1), 20–27. https://doi.org/10.1161/HYPERTENSIONAHA.108.115154

Rekovets O., Sirenko Yu., Torbas O., Kushnir S., Primak G. The use of fixed double and triple combinations in achieving the target level of blood pressure during daily monitoring in patients with arterial hypertension. Bukovynskyi Medychnyi Visnyk. 2020, № 2 (94), c. 102-112. https://doi.org/10.24061/2413-0737. XXIV.2.94.2020.50

Sawada, T., Yamada, H., Dahlöf, B., Matsubara, H., & KYOTO HEART Study Group (2009). Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high cardiovascular risks: KYOTO HEART Study. European heart journal, 30(20), 2461–2469. https://doi.org/10.1093/eurheartj/ehp363 (Retraction published Eur Heart J. 2013 Apr;34(14):1023)

ISSN 2786-6661
eISSN 2786-667X

Schrader, J., Lüders, S., Kulschewski, A., Hammersen, F., Züchner, C., Venneklaas, U., Schrandt, G., Schnieders, M., Rangoonwala, B., Berger, J., Dominiak, P., Zidek, W., & MARPLE Study Group (2006). Microalbuminuria and tubular proteinuria as risk predictors of cardiovascular morbidity and mortality in essential hypertension: final results of a prospective long-term study (MARPLE Study)*. Journal of hypertension, 24(3), 541–548. https://doi.org/10.1097/01.hjh.0000209991.48928.c4

Sirenko Yu., Rekovets O., Andriyevskaya S., Babak O., Govorova O., Rudyk Yu. Antihypertensive efficacy of ramipril in patients with mild and moderate arterial hypertension (results of the multicenter study RASH – Ramipril Study in patient with arterial Hypertension). Ukrayinsky cardiologichnyi journal. – 2007. – №1. – С. 41-47

Sirenko Yu., Rekovets O., Dobrokhod A. Evaluation of the effect of mono- and combined antihypertensive therapy with dihydropyridine and non-dihydropyridine calcium antagonists on office blood pressure and blood pressure during daily monitoring in patients with mild and moderate arterial hypertension "Arterialna hypertensia" 1 (45) 2016, С. 45 – 66.

Sirenko Yu., Rekovets O. The influence of metoprolol-retard on the morning rise in blood pressure in patients with mild and moderate arterial hypertension according to 24-hour blood pressure monitoring. Ukrayinsky cardiologichnyi journal. – 2006. – № 3. – С. 73-77

Sison, J., Assaad-Khalil, S. H., Najem, R., Kitchlew, A. R., Cho, B., Ueng, K. C., Shete, A., & Knap, D. (2014). Real-world clinical experience of amlodipine/valsartan and amlodipine/valsartan/hydrochlorothiazide in hypertension: the EXCITE study. Current medical research and opinion, 30(10), 1937–1945. https://doi.org/10.1185/03007995.2014.942415

Sison, J., Vega, R. M. R., Dayi, H., Bader, G., & Brunel, P. (2018). Efficacy and effectiveness of valsartan/amlodipine and valsartan/amlodipine/hydrochlorothiazide in hypertension: randomized controlled versus observational studies. Current medical research and opinion, 34(3), 501–515. https://doi.org/10.1080/03007995.2017.1412682

Sleight P. (2000). The HOPE Study (Heart Outcomes Prevention Evaluation). Journal of the renin-angiotensin-aldosterone system : JRAAS, 1(1), 18–20. https://doi.org/10.3317/jraas.2000.002

Waeber, B., & Ruilope, L. M. (2009). Amlodipine and valsartan as components of a rational and effective fixed-dose combination. Vascular health and risk management, 5(1), 165–174. https://doi.org/10.2147/vhrm.s3134

Weycker, D., Keskinaslan, A., Levy, D. G., Edelsberg, J., Kartashov, A., & Oster, G. (2008). Effectiveness of add-on therapy with amlodipine in hypertensive patients receiving valsartan. Blood pressure. Supplement, 2, 5–12. https://doi.org/10.1080/08038020802316536

White W. Blood pressure monitoring in cardiovascular medicine and therapeutics. – New Jersey: Humana Press, 2001. – 308 p.

Вивчення впливу різних стратегій медикаментозного лікування у пацієнтів із артеріальною гіпертензією

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Анотація: *використання фіксованих комбінацій антигіпертензивних препаратів може покращити контроль АТ та зменшення ускладнень і збільшення тривалості життя. Метою нашого дослідження було проаналізувати ефективність фіксованих, вільних та нетрадиційних комбінацій антигіпертензивних препаратів у лікуванні пацієнтів із АГ. Обстежено 396 пацієнтів із артеріальною гіпертензією різного ступеня тяжкості. Критеріями включення були вік пацієнтів старше 18 років та рівень офісного АТ більше 140/90 мм рт ст. Пацієнти були в трьох групах спостереження: традиційні вільні комбінації, традиційні фіксовані комбінації та нетрадиційні вільні комбінації. 91 пацієнт з АГ, що отримували нефіксовану комбінацію раміприлу*

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та гідрохлортіазиду; 132 пацієнти з АГ, що отримували нефіксовану комбінацію метопрололу-ретард та гідрохлортіазид; 50 пацієнтів для вивчення впливу фіксованих традиційних подвійних та потрійних комбінацій антигіпертензивних препаратів; 123 пацієнти з АГ в групу вивчення впливу дигідропіридинових і недигідропіридинових антагоністів кальцію на ступінь зниження артеріального тиску та розвиток побічних реакцій. Використання метопрололу пролонгованої дії в дозі 100-300 мг на день у хворих на м'яку та помірну артеріальну гіпертензію забезпечувало достовірне зниження як офісного САТ – на 32, ДАТ – на 18 мм рт.ст., ЧСС – на 18 уд.хв., так і середньодобового САТ – на 21, ДАТ – на 13 мм рт.ст. та ЧСС – на 7 уд.хв та сприяло досягненню цільового АТ 93,6% – за даними офісного вимірювання, а за даними ДМАТ – 84,9%. Використання раміприлу (10 мг) у комбінації з гідрохлортіазидом (25 мг) у хворих з м'якою та помірною артеріальною гіпертензією забезпечувало достовірне зниження як офісного САТ – на 36,6 та ДАТ – на 17,2 мм рт.ст. так і САТ24 – на 18,9 і ДАТ24 – на 7,0 мм рт.ст. Призначене лікування найбільш ефективно переносилося хворими, що приймали монотерапію лерканідіпіном 20 мг або низькодозову комбінацію лерканідіпін 10 мг та дилтіазем 120 мг. За даними офісного та добового моніторуваннявимірювання АТ комбіноване лікування на основі лерканідіпіну і дилтіазему було таке ж ефективне, як і лікування на основі монотерапії лерканідіпіном і дилтіаземом. На фоні фіксованої потрійної комбінації валсатан/ГХТЗ/амлодипін зниження 24САТ/ДАТ склало – 23,8/20,7 мм рт.ст., а зниження АТ за денний та нічний періоди становило – 27,4/22,6 мм рт ст., та – 20,5/18,2 мм рт ст відповідно (p<0,05) для усіх значень. Досягнення цільового рівня АТ при добовому моніторуванні склало в групі фіксованої подвійної терапії валсартна/амлодипін – 77,3%, в групі потрійної комбінації валсартна/амлодипін/гідрохлортіазид – 95,2% пацієнтів. Потрійна фіксована комбінація валсартан/ГХТЗ/амлодипін була самою ефективною в зниженні АТ при офісному вимірюванні та при добовому моніторуванні, що сприяло досягненню цільових рівнів АТ при офісному вимірюванні – 95,7%, при ДМАТ – 95,2%.

Ключові слова. Амлодипін, артеріальна гіпертензія, валсартан, гідрохлортіазид, дилтіазем, комбінована терапія, лерканідипін, метопролол-ретард, раміприл.