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Research Article

Efficacy of fixed dose of triple combination of perindopril-indapamide-amlodipine in obese patients with moderate-to-severe arterial hypertension: an open-label 6-month study

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ABSTRACT

Background: Arterial hypertension (AH) remains the most common cardiovascular (CV) risk factor worldwide. **Methods:** Seventy five moderate-to-severe hypertensive patients with abdominal obesity aged from 48 to 66 years (45/30 men and women respectively) were selected from the entire cohort (n = 375) according to the inclusion and exclusion criteria. The patients were divided into two subgroups depending on the arm of antihypertensive therapy lines. The first subgroup of patients (n = 36) received a non-fixed combination of oral antihypertensive agents: perindopril (4–8 mg daily), indapamide (1.25–2.5 mg daily) and amlodopine (5–10 mg daily). The second subgroup of patients (n=39) received fixed-dosed combination of these antihypertensive agents aforementioned in the ranged doses (4 mg/1.25mg/5 mg; 4 mg/1.25mg/10 mg; 8 mg/2.5 mg/5 mg; 8 mg/2.5mg/10 mg) in the same manner. The examinations of the clinical status, office, and ambulatory blood pressure values were carried out at baseline in 3 and 6 months after study entry. **Results:** The frequencies of BP target levels after treatment were higher in the fixed-dose combination group than in the non-fixed combination (at 3 months: 80% versus 58%, p<0.05 and at 6 months: 85% versus 53%, p<0.05). The adherence to triple fixed-dose combination was also higher in comparison with one to non-fixed combination (at 3 months: 82% versus 64%, p<0.05 and at 6 months: 87% versus 61%, p<0.05). It has been established that low-dose of perindopril/indapamide/amlodopine (4mg/1.25/10mg and 8mg/2.5/5mg) were used frequently in fixed-dose combination cohort of patients than in non-fixed combination (15% versus 0%, P<0.05, and 33% versus 19%, p<0.05, respectively). At the same time, maximum doses of these agents (8mg/2.5mg/10mg) were required for achieving target BP levels in a significantly lower proportion of patients receiving fixed-dose combination as compared to patients receiving non-fixed combination (52% versus 81%, p<0.05). Additionally, the triple fixed-dose combination has proved to be better in restoring ambulatory blood pressure monitoring profile than non-fixed combination. **Conclusion:** Achievement of target blood pressure levels in patients with uncontrolled arterial hypertension and abdominal obesity was possible at lower doses of perindopril, indapamide, and amlodipine when used as a fixed-dose combination rather than non-fixed (free) combination.

Key words: abdominal obesity, antihypertensive therapy, arterial hypertension, fixed-dose combination of antihypertensive agents, non-fixed combination of antihypertensive agents

INTRODUCTION

Arterial hypertension (AH) is the most common cardiovascular (CV) risk factor worldwide[1,2]. Prevalence of AH in European countries fluctuates from 20% to 50% of the adult population[3,4]. AH is frequently associated with various metabolic diseases including abdominal obesity (AO)[5,6]. In fact, at least 60% of AO patients were reported having mild-to-moderate AH[7] and 15-20% of them had severe–to-refractory AH[8]. Moreover, endothelial dysfunction, dyslipidaemia, insulin resistance (IR), increased serum uric acid (SUA) - hypeuricemia (HUE), microvascular inflammation, which are accompanied to both AH and AO, can accelerate atherosclerosis, mediate pro-coagulation state and sufficiently elevate a risk of CV complications[9–11]. In this context, tight control for systolic and diastolic blood pressures (BP) at target levels (generally <140/90 mm Hg) is considered a useful tool for improving survival and preventing life-threatening events[12,13]. Unfortunately,

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double and triple combined anti-hypertensive therapy did not correspond to achieve target level of BP in many cases in patients with AO [14]. Previous studies have shown that more than half of patients needed double therapies to achieve full control in BP, while 20–30% of patients required triple combination and ever more [15–17]. It has been postulated that poor adherence to antihypertensive treatment, respectively high frequency of adverse effects and low tolerability could be the main causes to withdraw from the therapy [18]. Early prescription of triple fixed-dose combination could improve patient response to the treatment and consequently decrease CV risk. Substantiated triple fixed-dose combinations of angiotensin-converting enzyme (ACE) inhibitor perindopril (P), thiazide-like diuretic (TLD) indapamide (Ind), and long-acting dihydropyridine calcium channel blocker (CCB) amlodipine (Aml) is considered most promising to achieve high efficacy and superiority in safety when compared with the same non-fix dose combination [19]. The study aimed to investigate the efficacy of triple fixed-dose versus the non-fixed combination of P + Ind + Aml in obese patients with moderate-to-severe AH.

METHODS

Seventy-five moderate-to-severe hypertensive patients with AO aged from 48 to 66 years (45 men and 30 women) were selected from the entire cohort (n=375) according to the inclusion and exclusion criteria (**Figure 1**). Inclusion criteria were patients with uncontrolled hypertension (systolic and/or diastolic BP levels > 140/90 mm Hg despite previous anti-hypertensive treatment with double drugs combination) at the study entry, age > 18 years and with written informed consent to participation in the study. Non-inclusion criteria includes patients with an acute coronary syndrome, acute myocardial infarction, heart failure, type 2 diabetes mellitus, angina pectoris, severe chronic renal failure, acute and chronic inflammatory diseases, severe liver insufficiency, chronic obstructive pulmonary disease, bronchial asthma, pregnancy, malignancy, and disability to know the reason of informed consent.

Study Design

This is an open-label, randomized, parallel-group and controlled study.

After the initial examination, the patients were divided into two subgroups depending on the arm of anti-hypertensive therapy lines. The first subgroup of patients (n=36) received a non-fixed combination of -anti-hypertensive agents, which include ACE inhibitor P (4–8 mg daily orally), TLD Ind (1.25–2.5 mg daily orally) and dihidroperidine CCB Aml (5–10 mg daily orally) non-fasting in the morning. The second subgroup of patients (n=39) received fixed-dosed combination of these anti-hypertensive agents mentioned above in the ranged doses (4 mg/1.25mg/5 mg; 4 mg/1.25mg/10 mg; 8 mg/2.5 mg/5 mg; 8 mg/2.5mg/10 mg) in the same manner. The examinations of the clinical status, office BP value was carried out at baseline, and in 3 and 6 months after the study entry, and ambulatory BP value was carried out at baseline and at 6 months after treatment. For target, BP levels systolic and diastolic BP <140/90 mm Hg were taken. All patients received recommendations about life-style modifications, and they were treated with atorvastatin 20 mg daily as a concomitant medication due to high-to very high CV risk.

Ethical declaration

The study was approved by the local Ethical Committee (Government Institution "L.T. Malaya Therapy National Institute of the National Academy of Medical Science of Ukraine," date of approval was 18.01.2018). All patients have given their voluntary informed consent to participate in the study.

Determination of AH

AH was diagnosed if systolic blood pressure (SBP) was >140 mm Hg, and/or diastolic blood pressure (DBP) >90 mm Hg, according to European guideline on diagnostics and treatment of arterial hypertension (2018) [5], or a self-reported history of hypertension, and/or the use of anti-hypertensive medications.

Determination of risk factors and comorbidities

Determination of dyslipidemia

Dyslipidemia was diagnosed if total cholesterol (TC) level was above 5.2 mmol/L, and/or low density lipoproteid cholesterol (LDL) level was above 3.0 mmol/L, and/or triglyceride (G) level was above 1.7 mmol/L according to with European Cardiology Society dyslipidemia guideline (2016) [20], or use of lipid-lowering medication.

Determination of AO

AO was defined as a body mass index (BMI) $\geq$30 kg/m^2, waist circumference $\geq$90 cm in men or $\geq$80 cm in women [21].

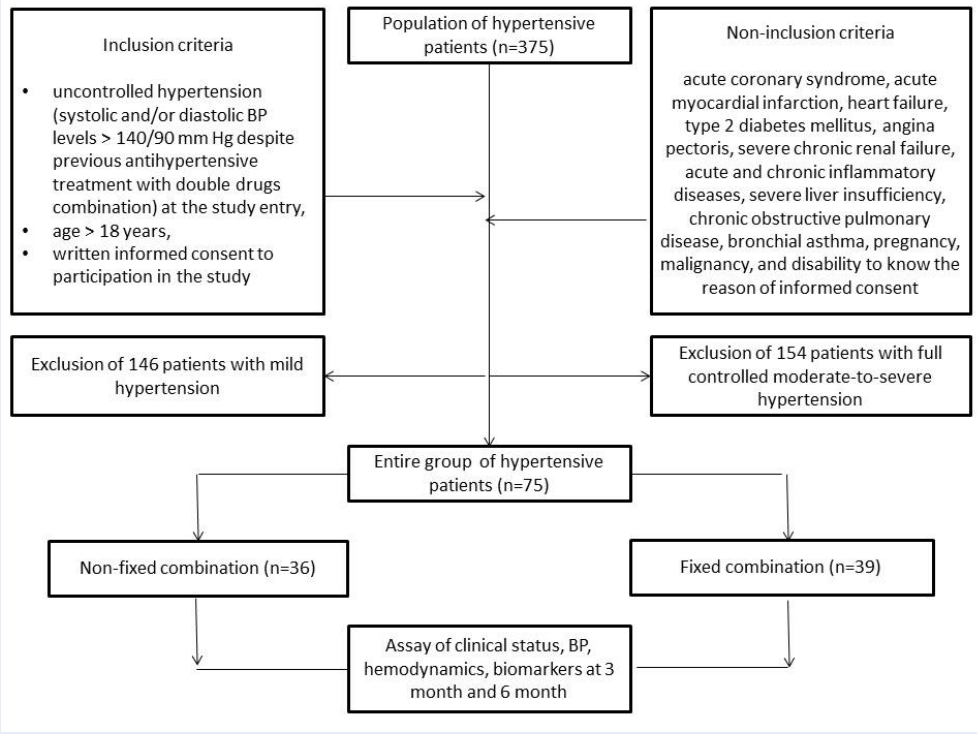

Figure 1: Flow chart with including/excluding criteria of the study.

Determination of metabolic syndrome(MetS)

MetS was diagnosed based on the National Cholesterol Education Program Adult Treatment Panel III criteria[22]. Patients were enrolled in the MetS cohort when at least three of the following components were defined: waist circumference ≥90 cm in men or ≥80 cm in women; high density lipoprotein (HDL) cholesterol <1.03 mmol/L in men or <1.3 mmol/L in women; triglyceride levels ≥1.7 mmol/L; blood pressure ≥130/85 mmHg or current exposure of antihypertensive drugs; fasting plasma glucose ≥5.6 mmol/L.

Determination of HUE

HUE was diagnosed when blood serum levels of uric acid were found to be higher than 360 μmol/L.

Determination of family history of coronary artery disease (CAD)

A family history of CAD was defined if a first degree relative of any age was diagnosed with CAD, as mentioned in the self-report questionnaire.

Smoking status

Current smoking was defined as consumption of one cigarette daily for three months[23].

Anthropometric measurements

Anthropometric measurements (weight, height, body mass, body mass index [BMI], waist circumference, and waist-to-hip ratio) were made using standard procedures[24]. Height and weight were measured by professional health staff, with the participants standing without shoes and heavy outer garments with a wall-mounted stadiometer (OMRON, Japan). BMI was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured at the level midway between the lower rib margin and the iliac crest, with participants in a standing position without heavy outer garments, with emptied pockets and breathing out gently. Hip circumference was recorded as the maximum circumference over the buttocks.

Adherence to the treatment

Adherence to the treatment was measured as a percentage of the patients, who were not dropped out

from the treatment arm due to several reasons including low tolerability, lowed compliance or lost for follow-up.

BP measure

Office BP was measured with the conventional method using a sphygmomanometer (Microlife BP AG 1-10, Hungary).

ECG recording

Standard 12-lead electrocardiography was performed at rest according to the conventional method with a three-channel FX-326U ECG recorder (Fukuda, Japan).

Ambulatory blood pressure monitoring (ABMP)

ABPM was performed according to contemporary protocol[5] with AVRM-02/0 machine (Meditech, Hungary). Traditional parameters, such as SBP(24), average daily systolic BP; DBP(24), average daily diastolic BP; SBP(D), average daytime systolic BP; DBP(D), average daytime diastolic BP; SBP(N), average night-time systolic BP; DBP(N), average night-time diastolic BP; TISBP(24), time-index 24-hour SBP TIDBP(24), time-index 24-hour DBP; DNSBPR, degree of night-time SBP reduction; DNDBPR, degree of night-time DBP reduction; SBPV(24), average daily SBP variability; DBPV(24) and average daily DBP variability, were calculated and interpreted.

Echocardiography

Echocardiography was conducted in M- and B-modes with a 2.5 MHz phased probe using a medical diagnostic ultrasound complex SSD 280 LS (Aloka, Japan). The left ventricular myocardial mass (LVMM) and the LVMM index (LVMMI) were calculated by the formula of the American Society of Echocardiography. Left ventricular hypertrophy (LVH) was diagnosed when LVMMI increased to more than 50 g/m^2 in men and 47 g/m^2 for women[5].

B-mode vascular ultrasound

B-mode common carotid artery (CCA) ultrasound examination was performed with a 7.5 MHz linear array probe using colour flow mapping by ultrasound scanner (LOGIQ-5, Japan). Thickness of intima-media segment (IMT) was measured according to conventional method[25] Carotid IM values $\leq$ 0.9 mm were considered to be normal, IM was registered when its value was more than 0.9 mm, atheromatous plaques were registered when IMT value was >1.5 mm, or when carotid artery was locally thickened by 0.5 mm, or when IMT segment was up to 50% thicker than surrounding segments[5].

Calculation of glomerular filtration rate (GFR)

GFR was calculated using CKD-EPI formula[26].

Blood sampling

Blood samples were drawn immediately before study entry and at 6 months of investigation. Blood samples were centrifuged, serum was isolated within 30 min of sample acquisition and then freezed at -70^{0}C and stored in plastic tubes until being shipped to the laboratory of immune-chemical and molecular-genetic researches of Government Institution "L.T. Malaya Therapy National Institute of the National Academy of Medical Science of Ukraine".

Biomarker assay

The levels of plasma glucose, serum urea, creatinine, and uric acid were determined by enzymatic method using Humareazer 2000 analyzer (HUMAN GmbH, Germany).

Total cholesterol (TC), low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride levels (TG) were measured by direct method on Humareazer 2106 analyser (HUMAN GmbH, Germany).

Hemoglobin A1c (HbA1c) were determined by high-pressure liquid chromatography method.

Fasting insulin level was measured by double-antibody sandwich immunoassay using commercial kits produced by DRG (Germany).

IR was assessed by the homeostasis model assessment for insulin resistance (HOMA-IR)[27] using the following formula:

HOMA-IR (mmol/L $\times$ μU/mL) = fasting glucose (mmol/L) $\times$ fasting insulin (μU/mL) / 22.5.

IR was arbitrarily defined as HOMA-IR value above the 75th percentile of normal glucose tolerance, equal 2.45 mmol/L $\times$ μU/mL.

Statistics

Statistical analysis of the obtained results was performed in the SPSS system for Windows, Version 22 (SPSS Inc, Chicago, IL, USA). The data were presented as mean (M) and standard deviation ($\pm$SD) or 95% confidence interval (CI). To compare the main parameters of patient cohorts, a two-tailed Student t-test or Mann-Whitney U-test were used. To compare categorical variables between cohorts, the Chi2

test ($\chi 2$) and Fisher F exact test were performed. The three consequent comparisons for variables between each other and baseline were analysed using post-hoc ANOVA method with the Duncan test. A two-tailed probability value of <0.05 was considered as significant.

RESULTS

The characteristics of the entire patient study population and both treatment arm cohorts are reported in **Table 1.** Among all groups of patients, moderate hypertension (2nd stage of hypertension) was found in 37 (49%) patients, severe hypertension (stage 3) — in 38 (51%), stage I AO found in 50 (67%) patients, stage II — in 25 (33%) patients. In the group of patients who were included in the study, a family history of hypertension was detected in 43 patients (78%). The following metabolic disorders were found: 67 (89%) patients with dyslipidaemia; 26 patients (35%) with fasting hyperglycemia (FHG), 53 (71%) patients with IR (HOMA-IR $\geq$2.77) and 20 (27%) patients with HUE. Occurrence of asymptomatic hypertension-mediated organs damage among examined patients was as follows: pulse BP (PBP) increase (PBP$\geq$60 mm Hg) was diagnosed in 29 (39%) patients, LVH - in 57 (76%) patients, carotid IMT >0.9 mm and/or atheromatous plaques - in 40 (53%) patients, and reduced to 45–59 ml/min/1.73 m^2 GFR (stage IIIa chronic kidney disease (CKD) was found in 13 (170%) patients.

Figure 2 reports frequencies of BP target levels among all groups of patients. At 3 months and at 6 months of treatment, there were significant differences between numbers of patients in the groups having a target level of BP. Indeed, lower frequencies of BP target levels have appeared in patients treated with non-fixed triple combination in comparison with individuals taking triple fixed-does combination (p<0.05). However, 53% and 85% in moderate-to-severe hypertensive patients treated with non-fixed and fixed-does combination were found as those who have achieved BP<140/90 mm Hg after 6 months of treatment.

Additionally, 3-month and 6-month adherence to triple fixed-dose combination were higher (82% and 87%, respectively) in comparison with one to non-fixed combination (64% and 61%, respectively) (p<0.05) (**Figure 3**). While in the subgroup of patients treated with non-fixed combination of drugs adherence to therapy in 6 months tended to decrease compared to the rate of adherence in 3 months, in the group of patients who used fixed-dose combination of these drugs, adherence to treatment tended to increased with the continuation of treatment from 3 to 6 months from 82% to 87%.

For both cohorts, step-by step elevation of doses among all compounds embedded onto fixed and non-fixed combinations was specified (**Table 2**). It has been established that low-dosed triple fixed combination (4mg/1.25/10mg and 8mg/2.5/5mg) were used frequently in the second cohort to the first cohort to achieve target blood pressure. Moreover, 39% of patients, who were transferred to non-fixed combination, did not adhere to the given recommendations, and took only two medications (perindopril 8 mg daily and amlodipine 5 mg daily), or took medications irregularly or did not take any.

For individuals in the first and second cohorts with successful BP control, maximal doses of the agents (perindopril/indapamide/amlodipin: 8mg/2.5mg/10mg) were required in 81% and 52% respectively (p<0.05) (**Table 3**). Conversely, minimum and average doses of these agents were more commonly used by patients who were treated with fixed-dose combination, and reached target BP levels than by patients who were treated with non-fixed combination, and also reached target BP levels. It should be especially noted that 15% of patients with AH and AO treated with fixed-dose combination reached target BP levels after 6 months with minimum doses of these agents (perindopril/indapamide/amlodipin: 4mg/1.25/10mg). At the same time, such doses used in a non-fixed variation were not effective in patients to reach target levels of BP.

Ambulatory BP monitoring

6-month ABPM has shown that both triple non-fixed and triple fixed-dose combinations have driven a significant decrease in average daily systolic BP (SBP(24)), average daytime systolic BP (SBP(D)), time-index 24-hour SBP (TISBP(24)) and time-index 24-hour DBP (TIDBP(24)) (**Table 4**). However, the triple fixed-dose combination has been proved to be much better in restoring the ABPM profile. Additionally, triple fixed-dose combinations' patients have exhibited significant decrease in average daily diastolic BP (DBP(24)), average daytime diastolic BP (DBP(D)), average night-time systolic BP (SBP(N)) and average night-time diastolic BP (DBP(N)). Patients also showed significant increase in a degree of night-time SBP reduction (DNSBPR) and degree of night-time DBP reduction (DNDBPR) and significant decrease in average daily SBP variability (SBPV(24)) and average daily DBP variability

Table 1: Basic characteristics of patient study population

Parameters	Entire group (n=75)	First cohort (n=36)	Second cohort (n=39)	p value
Age, years	55.9±13.8	53.6±13.3	59.4±14.1	NS
Male, n (%)	45 (60%)	22 (61%)	23 (59%)	NS
Female, n (%)	30 (40%)	14 (39%)	16 (41%)	NS
Moderate arterial hypertension (2^{nd} stage of arterial hypertension), n (%)	37 (49%)	18 (50%)	19 (49%)	NS
Severe arterial hypertension (3^{rd} stage of arterial hypertension), n (%)	38 (51%)	18 (50%)	20 (51%)	NS
Abdominal obesity stage 1, n (%)	50 (67%)	23 (64%)	27 (69%)	NS
Abdominal obesity stage 2, n (%)	25 (33%)	13 (36%)	12 (31%)	NS
Dyslipidaemia, n (%)	67 (89%)	32 (89%)	35 (90%)	NS
Metabolic syndrome, n (%)	72 (96%)	34 (94%)	38 (97%)	NS
LV hypertrophy, n (%)	57 (76%)	27 (75%)	30 (77%)	NS
Carotid IMT >0.9 mm, n (%)	40 (53%)	18 (50%)	22 (57%)	NS
LV mass index, g/m^2 (male)	60.6±11.3	57.2±11.7	63.8±10.9	NS
LV mass index, g/m^2(female)	54.5±11.3	53.2±11.7	56.8±10.9	NS
Fasting glucose, mmol/L	5.1±1.3	5.0±1.4	5.2±1.5	NS
Creatinine, μmol/L	90.4±21.1	92.1±19.6	89.3±22.4	NS
SUA, μmol/L	316.6±87.5	307.9±82.3	326.6±89.1	NS
HOMA-IR, unit	2.98±0.6	2.86±0.55	3.16±0.64	NS
GFR, ml/min/1.73 m^2	76.7±18.7	79.2±19.3	73.5±17.6	NS
Total cholesterol, mmol/L	5.92±1.21	5.57±1.17	6.14±1.23	NS
LDL cholesterol, mmol/L	3.97±0.82	3.66±0.79	4.24±0.83	NS
HDL cholesterol, mmol/L (male)	0.85±0.27	0.96±0.26	0.73±0.28	NS
HDL cholesterol, mmol/L (female)	1.12±0.27	1.15±0.26	1.03±0.28	NS
Triglycerides, mmol/L	2.33±0.38	2.18±0.37	2.54±0.41	NS

Abbreviations: SUA: serum uric acid, LV: left ventricular, IMT: intima-media thickness, GFR: glomerular filtration rate, HDL: cholesterol, high-density lipoprotein cholesterol, LDL: cholesterol, low-density lipoprotein cholesterol; NS: not significant
Notes: *p* values were calculated between the first and the second cohorts

(DBPV(24)) (**Table 4**). Moreover, degrees of average daily systolic BP (SBP(24)), average daily diastolic BP (DBP(24)) and average night-time systolic BP (SBP(N)) reduction were sufficiently higher in triple fixed-dose combination patients compared to triple non-fixed combination individuals.

It was noted that there were no significant changes in SUA, serum uric and creatinine levels, estimating GFR, HOMA-IR, fasting glucose levels and BMI in both cohorts. Therefore, we did not find significant changes in LV mass index and carotid IMT for both cohorts.

DISCUSSION

It was established that neither one of the patients received a fixed-dose combination of anti-hypertensive agents before inclusion in the study. The largest proportion of patients (80%) received two-component non-fixed combination of anti-hypertensive agents as a pre-study therapy. There was 47% of patients,

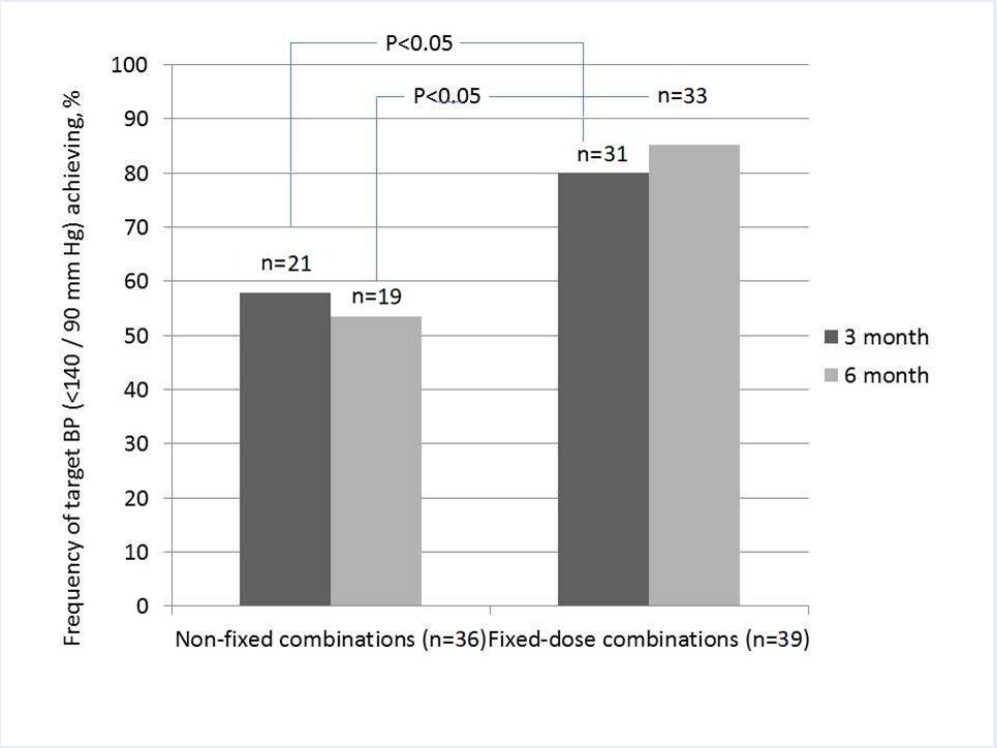

Figure 2: **The frequencies of blood pressure target level achieving in both patient cohorts.** There are significant differences between the numbers of the patients having target level of BP in 3 month and 6 month (P<0.05 for all cases). The BP target level has been achieved in 53% and 85% in moderate-to-severe hypertensive patients treated with non-fixed and fixed-does combination respectively at 6 months of observation period.

Table 2: Proportionof patients in both cohorts who has been treated with different types offixed and non-fixed triple combinations at 6 month

	Non-fixed triple combination (n=36)		Fixed-dose triple combination (n=39)		p-value
	n	%	n	%	
Perindopril/indapamide/amlodipin: 4mg/1.25mg/10mg	0	0	6	15	=0.001
Perindopril/indapamide/amlodipin: 8mg/2.5mg/5mg	2	5	14	36	=0.044
Perindopril/indapamide/amlodipin: 8mg/2.5mg/10mg	20	56	19	49	NS
8 mg Perindopril + 5 mg Amlodipin (free combination)	6	17	0	0	=0.012
Took the medication irregularly	5	14	0	0	=0.01
Didn't take any medications	3	8	0	0	>0.05

Abbreviation: NS: not significant
Notes: *p* values were calculated between patients treated with fixed and non-fixed triple combinations

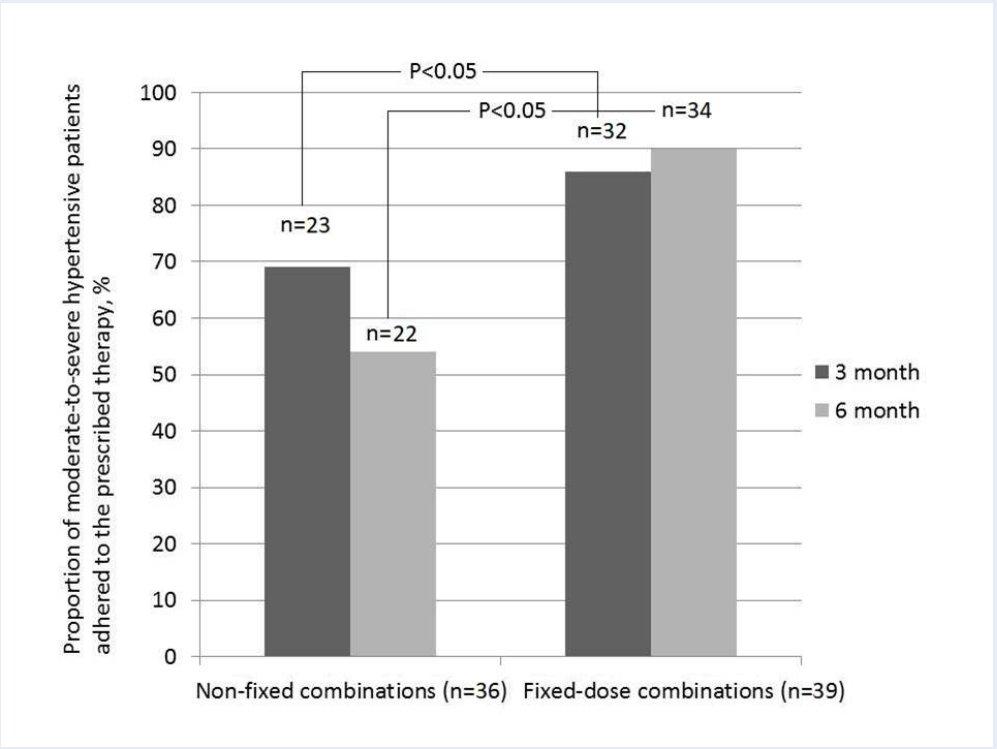

Figure 3: **Proportion of patients who were adherent to the prescribed therapy at 3 month and 6 month.** There were significantly higher 3-month and 6-month adherence to triple fixed-dose combination than non-fixed combination (p<0.05 for all cases).

Table 3: Proportion of patients with full control BP at 6 month who has been treated with different types of fixed and non-fixed triple combinations

	Non-fixed triple combination (n=21)		Fixed-dose triple combination (n=33)		p value
	n	%	n	%	
Perindopril/indapamide/amlodipin: 4mg/1.25mg/10mg	0	0	5	15	=0.046
Perindopril/indapamide/amlodipin: 8mg/2.5mg/5mg	4	19	11	33	=0.044
Perindopril/indapamide/amlodipin: 8mg/2.5mg/10mg	17	81	17	52	=0.044

Notes: *p* values were calculated between patients treated with fixed and non-fixed triple combinations

who received combination of an ACE inhibitor or an angiotensin II receptor blocker (ARB) and a thiazide or thiazide-like diuretic, 24% of patients received combination of an ACE inhibitor or an ARB and a long-acting dihydropyridine CCB, and 9% of patients received combination of a beta-blocker and a thiazide-like diuretic. 20% of patients received a three-component combination of anti-hypertensive agents before inclusion in the study: ACE inhibitor or an ARB and a long-acting dihydropyridine CCB. However, 60% of these patients received treatment irregularly and not in sufficiently optimal daily doses. Both subgroups of patients who were transferred to non-fixed and fixed-dose combinations did not differ significantly by the types of the described pre-study therapy.

Consequently, transferring patients with uncontrolled AH and AO to non-fixed and fixed-dose three-component anti-hypertensive therapy with perindopril, indapamide and amlodipine significantly in-

Table 4: The results of ABPM in hypertensive patients with abdominal obesity treated with non-fixed and fixed-dose combinations of perindopril, indapamide and amlodipine

Variables	Triple non-fixed combination (n=36)			Triple fixed-dose combination (n=39)		
	Baseline	6 month	Deviation from baseline	Baseline	6 month	Deviation from baseline
SBP(24), mm Hg	151.31±10.67	136.35±11.09 p<0.001	-14.96±1.29	155.69±10.87	128.12±12.26 P<0.05	-22.93±1.54 P1<0.05
DBP(24), mm Hg	92.50±12.75	84.69±10.95	-6.8±2.95	94.79±10.49	77.93±10.99 p<0.001	-15.86±1.12 p1<0.05
SBP(D), mm Hg	160.27±12.18	140.62±10.88 p<0.001	-20.65±2.38	162.59±10.66	134.76±11.15 P<0.001	-28.83±3.56 p1=0.05
DBP(D), mm Hg	94.23±10.46	86.23±11.85 NS	-7.15±1.91	99.79±10.59	82.69±12.61 p<0.001	-16.86±3.32 p1=0.05
SBP(N), mm Hg	135.10±11.52	128.35±10.46	-7.15±1.42	137.69±12.69	119.53±10.66 p<0.001	-17.86±1.78 p1<0.05
DBP(N), mm Hg	86.38±12.70	73.73±10.75	-8.65±2.40	88.62±11.71	69.13±10.89 p<0.001	-18.62±3.83 p1=0.05
TISBP(24), %	83.89±16.88	33.38±13.53 P<0.001	-50.51±10.91	86.55±14.37	23.20±8.45 p<0.001	-63.36±10.29 p1=0.05
TIDBP(24), %	62.65±12.91	31.27±9.59 P=0.01	-31.38±6.84	65.53±13.77	22.28±6.90 p<0.001	-42.26±10.12 p1=0.05
DNSBPR,%	11.52±1.90	16.88±1.44 p>0.05	5.37±1.06	9.16±1.64	18.34±1.35 p<0.001	9.19±1.75 p1=0.05
DNDBPR,%	8.45±1.59	11.78±1.38 p>0.05	3.33±0.74	7.66±0.22	15.47±1.59 p<0.001	8.81±0.56 p1=0.05
SBPV(24), mm Hg	17.54±1.44	12.62±1.22 NS	-4.92±0.74	20.10±1.35	9.34±0.92 p<0.001	-10.34±1.43 p1=0.05
DBPV(24), mm Hg	15.62±1.36	10.42±1.21 p>0.05	-5.19±0.36	17.55±1.37	8.31±0.92 p<0.01	-8.24±0.45 p1=0.05

Abbreviations: BP: blood pressure; SBP(24): average daily systolic BP; DBP(24): average daily diastolic BP; SBP(D): average daytime systolic BP;DBP(D): average daytime diastolic BP; SBP(N): average night-time systolic BP; DBP(N): average night-time diastolic BP; TISBP(24): time-index 24-hour SBP, TIDBP(24): time-index 24-hour DBP; DNSBPR: degree of night-time SBP reduction; DNDBP:, degree of night-time DBP reduction; SBPV(24): average daily SBP variability; DBPV(24): average daily DBP variability; NS: not significant.

Notes: variables are given mean (M) and standard deviation (SD); p values were calculated between means of baseline and 6-month; p^1 values were calculated between means in patients treated with fixed and non-fixed triple combinations

creased treatment efficacy. However, the use of a fixed-dose combination of these agents is significantly more effective than the use of the non-fixed combination.

One of the main reasons for achieving the higher and more stable effect of fixed-dose combination than non-fixed one was the better adherence to treatment in patients, who were treated with the fixed-dose combination of anti-hypertensive drugs [16,19].

Of great clinical significance are the data obtained on complete normalization of the daily BP profile under the influence of the fixed-dose combination of perindopril, indapamide, and amlodipine, than that of under the influence of non-fixed combination [5]. It should be noted that the fixed-dose combination of these agents is useful in normalizing not only daily average and daytime average but also night-time average values of the daily BP profile.

An important result of this study was the absence of negative influence of the use of variants of non-fixed and fixed-dose combinations of perindopril, indapamide and amlodipine on metabolic parameters of patients with AH and AO [5,15]. The study showed that both non-fixed and fixed-dose combinations of these agents did not reduce efficacy of hypolipidemic therapy with average atorvastatin doses and contributed to significant decrease of dyslipidemia occurrence in patients with AH and AO. Moreover, it was found that when these patients were treated with the fixed-dose combination, their BMI occurrence values were significantly lower.

Both variants of combined therapy allowed slowing down the progression of cardiovascular and kidney diseases, inhibit the increase of LVH levels, stiffness and vascular wall remodeling (PBP elevation and carotid IMT and/or growth, or appearance of new atheromatous plaques in CCA), and slow down GFR reduction.

One of the most considerable results of the study was that lower doses of perindopril, indapamide and amlodipine are required for achieving target BP levels in patients with uncontrolled AH and AO if these agents are used as a fixed-dose combination.

It was found that maximum doses of perindopril, indapamide, and amlodipine were required for achieving target BP levels in a significantly lower proportion of patients receiving fixed-dose combination as compared to patients receiving a non-fixed combination of specified products.

Overall, it should be noted that combining agents of three anti-hypertensive drug groups, such as an ACE inhibitor, a TLD and a long-acting dihydropyridine CCB in one tablet contributes to significant increase of anti-hypertensive efficacy compared to non-fixed combination of these agents in patients with uncontrolled AH and AO [4,15,18]. An influential result of this study was also confirming better adherence of patients with hypertension and AO to fixed-dose combination of perindopril, indapamide, and amlodipine than to non-fixed combination of these agents. According to modern beliefs, better adherence to therapy is one of the most critical factors determining the possibility of achieving optimal control of hypertension in the population [5,16].

Thus, this study has shown feasibility and perspectivity of a fixed-dose three-component combination of perindopril, indapamide and amlodipine use in patients with uncontrolled AH and AO. This is confirmed by findings of a number of published studies conducted in different groups of patients with AH and, most importantly, in patients with insufficiently controlled hypertension.

STUDY LIMITATIONS

The main limitation of our study is the small number of patients. Because of this, it was not possible to perform subgroup analyses of the fixed-dose combination of perindopril, indapamide and amlodipine versus non-fixed combination within different subgroups (*e.g.*, gender, age, hypertension, and obesity severity. Another potential limitation is that the post-baseline ABPM evaluation was done only at 6 months. Despite these limitations, the findings show the higher anti-hypertensive efficacy and more complete restoring of daily blood pressure profiles of the fixed-dose combination of perindopril, indapamide, and amlodipine in comparison with the non-fixed combination of these agents.

CONCLUSIONS

In conclusion, we found that the efficacy of the fixed-dose combination of perindopril, indapamide and amlodipine is significantly higher than non-fixed combination of these agents in patients with uncontrolled hypertension affected by AO. Using a fixed-dose combination of perindopril, indapamide and amlodipine in patients with uncontrolled hypertension and AO allow to significantly increase patients' adherence to therapy by 26% compared to using the non-fixed combination. Patients with uncontrolled hypertension and AO receiving a fixed-dose combination of perindopril, indapamide, and amlodipine showed more complete normalization of the daily BP profile than patients receiving non-fixed combination. It was established that achievement of target BP

levels in patients with uncontrolled AH and AO was possible at lower doses of perindopril, indapamide, and amlodipine when used as a fixed-dose combination rather than non-fixed (free) combination. Maximum doses of these agents were required for achieving target BP levels in a significantly lower proportion of patients, who received fixed-dose combination when compared to patients receiving a non-fixed combination of these products.

ABBREVIATIONS

ABPM: Ambulatory Blood Pressure Monitoring
ACE: angiotensin-converting enzyme
AH: arterial hypertension
Aml: amlodipine
AO: abdominal obesity
BMI: body mass index
BP: blood pressure
CAD: coronary artery disease
CCB: calcium channel blocker
CI: confidence interval
CV: cardiovascular
DBP: diastolic blood pressure
DBP(N): average night-time diastolic blood pressure
DBPV(24): average daily diastolic blood pressure variability
DNDBPR: degree of night-time diastolic blood pressure reduction
DNSBPR: degree of night-time systolic blood pressure reduction
GFR: glomerular filtration rate
HDL: high density lipoprotein cholesterol
HOMA-IR: homeostasis model assessment for insulin resistance
HUA: hyperuricemia
IMT: carotid intima-media segment thickness
Ind: indapamide
IR: insulin resistance
LDL: low density lipoprotein cholesterol
LVH: left ventricular hypertrophy
LVMMI: left ventricular myocardial mass index
MetS: metabolic syndrome
P: perindopril
SBP: systolic blood pressure
SBP(N): average night-time systolic blood pressure
SBPV(24): average daily systolic blood pressure variability
SUA: serum uric acid
TC: total cholesterol
TG: triglycerides
TIDBP(24): time-index 24-hour diastolic blood pressure
TISBP(24): time-index 24-hour systolic blood pressure
TLD: thiazide-like diuretic

COMPETING INTERESTS

Not declared.

FINANCIAL DISCLOSURE

There has been no significant financial support for this work that could have influenced its outcome.

AUTHORS' CONTRIBUTIONS

S.M. Koval initiated the hypothesis and designed the study protocol. I.O. Snihurska enrolled the patients; collected and analyzed the data reviewed the source documents. T.G. Starchenko and M.Y. Penkova contributed to enroll the patients in the study and collected the data. O.V. Mysnychenko and K.O. Yushko performed of blood collection and interpreted of the obtained results. O.M. Lytvynova and O.V. Vysotska contributed to collect, analyze and interpret the data, and performed statistical analysis. A.E. Berezin performed statistical analysis, wrote the manuscript and approved final version of the paper. All authors read the manuscript before submitting and agree with final version of the paper.

STATEMENT OF ORIGINALITY

The authors do hereby declare that all materials used herein are original. This study is not under consideration for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

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