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# **Combined therapy's antihypertensive** efficacy and influence on metabolic parameters in patients with arterial hypertension and diabetes mellitus

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## Summary

### Objective

*To compare three regimen of long-term combined antihypertensive therapy in order to reach target levels of blood pressure (BP), dynamics of daily BP profile and metabolic parameters in patients with arterial hypertension (AH) associated with diabetes mellitus, type 2 (DM-2).*

### Materials and methods

*69 patients with the combination of AH and DM-2 completed the treatment course (male/female 22/47; average age 57,1±6,5 years). Target BP <130/80 mm Hg. in the group №1 (n=22) was achieved using the combination of perindopril arginine, indapamide retard and amlodipine, in the group №2 (n=25) it was reached with the combination of valsartan, indapamide retard and amlodipine, and in the group №3 (n=22)– using the combination of amlodipine, indapamide retard and metoprolol succinate. Body weight and the levels of office BP, 24 hour ambulatory BP monitoring, parameters of lipid and carbohydrate metabolism were measured before prescription of drugs and 30-32 weeks after and HOMA index was quantified.*

### Results

*The degree of office BP levels reduction didn't differ in all three groups of patients. Values of systolic BP (SBP) and diastolic BP (DBP) "load" for 24 were higher in the patients of the group №3 comparing with the group №1, and achieved levels of night SBP were higher than in the group №1 and the group №2. The treatment based on*

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*perindopril arginine and amlodipine and not the combination of valsartan and amlodipine led to decrease of body weight and HbA1c serum levels. Patients of groups №1 and 2 were united into one common group of therapy based on renin-angiotensin-aldosterone system (RAAS) blockers, and after the treatment increased levels of high density lipids cholesterol (HDL cholesterol) levels (from 1,29±0,2 to 1,45±0,3 mmol/L, p=0,006) and improved glycemic control (expressed as HbA1c levels reduction from 8,1±2,2% to 7,0±2,3% (p=0,01)) were detected, and it was present in case of unchanged glucose-lowering therapy and was realized in case of three-component regimen (after addition of amlodipine). Combination of metoprolol succinate, indapamide retard and amlodipine was considered as metabolically neutral in patients with DM-2.*

**Conclusion**

*Although all three antihypertensive therapy regimens allow to reach target BP levels in the majority of patients with AH+DM-2, the value of night AH correction and metabolic effects of this therapy re not equal.*

**Key words**

*Arterial hypertension, diabetes mellitus, combined therapy, circadian rhythm, metabolic effects.*

## Introduction

The number of Russian patients suffering from diabetes mellitus type 2 (DM-2) is drastically increasing, and it goes along with worldwide tendency [1]. Strict control of blood pressure (BP) is a necessary condition to improve cardiovascular and renal prognosis of patients with diabetes, and for the majority of DM-2 patients combined antihypertensive therapy (AHT) is recommended since the beginning of treatment because arterial hypertension pathogenesis involves many components in case of associated pathology [2]. Although according with modern guidelines, it is possible to choose any drug that allows achieving target BP levels, and rennin-angiotensin-aldosterone system (RAAS) blockers are considered preferable only in case of present albuminuria/proteinuria [2, 3], it is not possible to exclude that they can have advantages over other antihypertensive drugs (AHD) in patients with DM-2 due to their high organoprotective potential and favorable metabolic effects. ß-blockers administration (ß-B) in patients with diabetes is reasonable due to hyperactivation of sympathetic nervous system, but they are known to cause unfavorable metabolic shifts, due to it their combination with dihydropyridine calcium receptor blockers (CB) seem to be more promising. Up to nowadays it is still unclear if the dynamics of 24-hours BP profile characteristics differs after achievement of target levels in different therapeutic schemes of combined AHT, and possible advantages of RAAS blockers and metabolic effects of different AGD combinations in patients with DM-2 require further investigation.

The **objective** of this study – is to perform comparative estimation of three regimen of long combined AHT based on two variants of RAAS blockers and other AGD in relation to reaching target BP levels, dynamics of daily BP profile and metabolic parameters in patients with AH+DM-2.

## Materials and methods

Open, randomized, comparative in parallel groups trial included patients with AH associated with DM-2. Patients with symptomatic AH, acute vascular complications that occurred less than one year before inclusion into study, unstable angina, arrhythmias requiring special treatment, chronic heart failure > than 2 functional class (NYHA), evident peripheral atherosclerosis, DM type 1, clinically apparent diabetic nephropathy, severe concomitant diseases, absolute contraindications to investigated drugs. Target BP level at the moment of the beginning of this study was defined as BP < 130/80 mm Hg. according with the previous issue of guideline dedicated to AH diagnostics and treatment [4]. After patients signed informed consent about participation in this study, all their previous AHT except of "emergency" drugs was cancelled for the period of 2-3 weeks, and after it patients underwent examination Then patients were randomized into three groups, in which AHT started from perindopril, valsartan or amlodipine respectively. AHT intensity increased in stepwise way: in the beginning of treatment patients were administered with 5 mg of perindopril arginine (n=23), 80 mg of valsartan (n=25) and 5 mg of amlodipine (n=23). After three weeks of treatment if the target levels of PB had not been achieved, indapamide retard (IR) in the dose of 1.5 mg (in the morning, on an empty stomach) was added to the therapy. After every three weeks if the target levels still had not been achieved therapy was augmented with: increased daily dose of perindorpil up to 10 mg, valsartan - up to 160 mg, amlodipine - up to 10 mg; addition of amlodipine 5mg/day to the therapy with RAAS inhibitors and then increase of

Table 1. **Clinical characterization of patients completed the therapy (n=69)**

| Characteristic | Group 1 (n=22) | Group 2 (n=25) | Group 3 (n=22) |
|---|---|---|---|
| Gender (male, female) | 5 (22.7%)/ 17 (77.3%) | 11 (44%)/ 14 (66%) | 6 (27.3%)/ 16 (72.7%) |
| Average age, (years) | 57.1±6.1 | 58.04±6.9 | 56.1±6.8 |
| AH duration, years | 10 (5–15) | 16 (9–30)# | 9 (5–15) |
| DM duration, years | 4 (3–8) | 9 (3–12) | 4 (2–10) |
| Body mass index, kg/m$^2$ | 33.3±4.3 | 32.4±4.4 | 33.4±4.6 |
| Fasting glucose levels, mmol/L | 7.4±2.0 | 7.7±2.0 | 7.6±2.1 |
| $HbA_1c$, % | 7.8±2.0 | 8.3±1.8 | 8.2±1.8 |
| Office SBP, mm Hg | 148.3±8.4 | 150.3±14.3 | 149.6±12.3 |
| Office DBP, mm Hg | 90.5±7.1 | 89.0±8.6 | 89.9±8.9 |
| SBP 24h, mm Hg | 136.9±9.9 | 132.3±10.8 | 138.1±14.7 |
| DBP 24h, mm Hg | 82.4±7.5 | 78.0±6.9# | 81.7±11.8 |
| Smoking | 3 (13.6) | 4 (16%) | 4 (18.2%) |

Comment: — p<0.05: — for comparison of group 1 and 2

its ose up to 10 mg per day; addition of metoprolol succinate to amlodipine, starting from 50 mg per day and, if necessary, increasing its dose up to 100 mg. Thus, patients of the first group received perindopril arginine in combination with IR and amlodipine, patients of the second group – valsartan, IR and amlodipine, patients of the third group – amlodipine, IR and metoprolol succinate. This study included 71 patients, and 69 patients (male/female – 22/47, average age 57,1±6,5 years) – their clinical characterization is present in Table 1. Therapy of one female patient was cancelled due to development of dry cough, one adverse effects of perindopril monotherapy. Therapy of another female patient was terminated because of shin edema, adverse effect of amlodipine monotherapy. Body weight, office BP values, results of 24-hours outpatient BP monitoring, lipid, carbohydrate and insulin metabolism characteristics and HOMA index value were obtained before drug prescription and 30-32 weeks after the beginning of therapy.

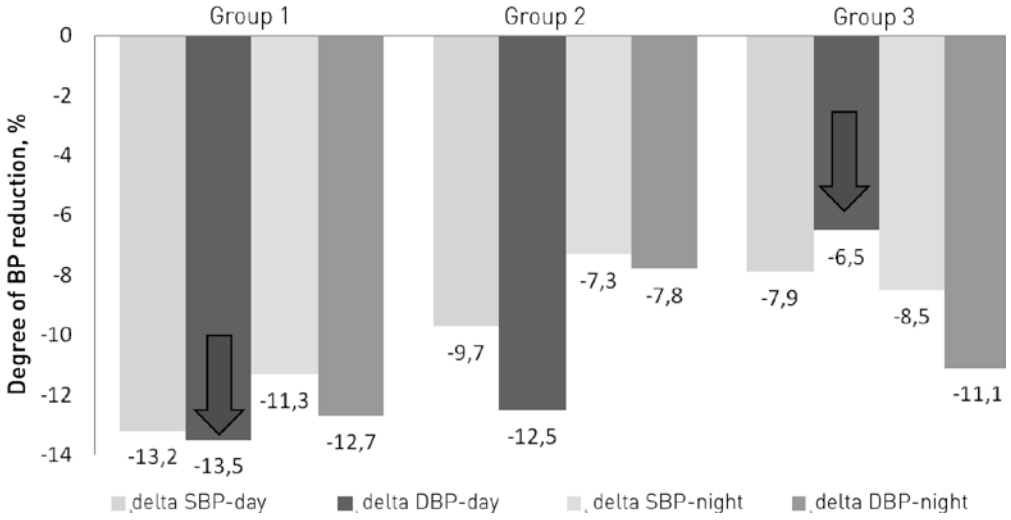
Statistical analysis was performed using Statistica 6.0 software (StatSoft Inc, USA). Kolmogorov-Smirnov test was used to check the normality of selection. Results are present as M±m where M is mean value, m – error of mean, or median (Me) or interquantile range (Q25-Q75), where Q25 is the 25$^{th}$ quartile, Q75 is the 75$^{th}$ quartile. Significance of differences was controlled with Mann-Whitney test. p=0,05 was taken as the critical significance level for hypothesis testing

## Results

Degree of office BP reduction and reached levels did not differ in all three groups, BP levels after treatment were 124,5±6,5/76,5±4,9**,** 125,0±9,2/77,0±4,8 and 126,5±6,2/76,2±5,7 in groups 1, 2 and 3, respectively). Percentage of patients who reached target BP levels was: for therapy based on perindopril arginine -95,5%, for therapy based on valsartan – 80%, for therapy based on amlodipine – 86,4% (differences are not significant).

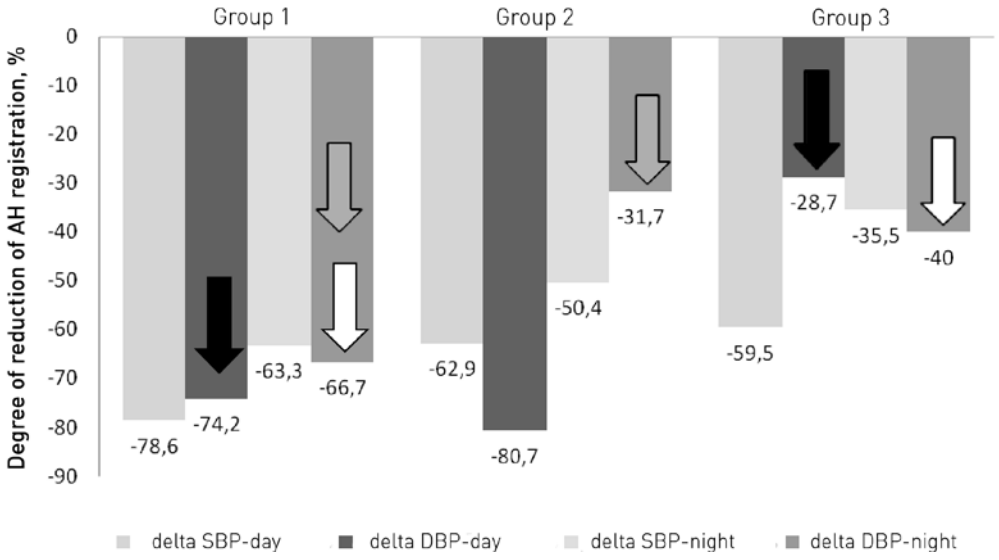
If RAAS blockers were not present in therapy scheme, 24 hours systolic BP (SBP) reduction was not enough, especially at night time: patients of the 3$^{rd}$ group had higher levels of night SBP comparing with its levels after therapy based on RAAS inhibitors; the degree of day SBP reduction was more evident in the 1$^{st}$ group (-11,6 (-16,2; -7,9)%) comparing with the 3$^{rd}$ group (8,3 (-10,3; -4,2)%, p=0,05). It is worth to mention that reached levels of night SAD in case of therapy based on amlodipine, IR and metoprolol succinate combination were higher than its target levels (<120 mm Hg). So, night SAD levels in the 3$^{rd}$ group were 120,2±10,9 mm Hg., whereas its levels in groups 1 and 2 were 113,9±8,9 и 112,8±13,8 mm Hg, respectively. Images 1 and 2 demonstrate the degree of day diastolic BP (DBP) reduction (p=0,03) and reduction of DBP loads during all studied periods in this group were less evident than in the 1$^{st}$ group. More than that, comparing groups 1 and 3, we found that the frequency of "double" AHT administration in the group 1 was higher (59,1% vs 27,3%, p<0,05), and the frequency of "triple" therapy in the group 1 was lower (39,1% vs 63,6%, p=0,07). So, in case of two drugs combination reaching of target BP levels was more likely for RAAS blocker and IR combination comparing with IR and CB combination that required addition of the third drug for adequate BP control.

At the same time, therapeutic regimen based on perindopril and amlodipine combination had advantages over the combination of valsartan and amlodip-




Comment: arrows indicate the differences between the degree of delta-DBP-day reduction in groups 1 and 3 (p<0,05).

**Image 1.** Comparison of BP reduction degree (%) in different therapeutic schemes of combined AHT in patients with AH+DM-2.




Comment: black and white arrows indicate the differences between the degree of reduction of diastolic AH duration at daytime and night in groups 1 and 3 (p<0,05), blue arrows indicate the differences between the degree of reduction of night diastolic AH duration in groups 1 and 2 (p<0,05)

**Image 2.** Comparison of the degree of AH duration reduction (%) with different schemes of combined AHT in patients with AH+DM-2

ine, because it caused better night diastolic AH correction: duration of diastolic AH at night time was significantly more reduced in the group 1 comparing with the group 2 (p=0,02). The percentage of patients who received amlodipine and its average dose didn't differ significantly between two groups: 39,1% in group 1 vs 48% in group2 and 6,3±3,5 mg/day. vs 6,5±3,3 mg/day, respectively. It was also documented that antihypertensive effect of the therapy based on angiotensin receptor type II antagonists (ARAII) and CB was associated with higher heart rate (HR) at night time, comparing to the combination of angiotensin-converting enzyme (ACE) inhibitors and CB. Individual analysis demonstrated that the highest level of HR during sleep after treatment was between the patients with less prominent degree of 24 hours SBP reduction: –6,9 (–10,8; –2,7)% vs –15,9 (–21,5; –8,6)% (p<0,05).

During estimation of impact of different schemes of compined AHT on metabolic characteristics we identified that only patients of group1 demonstrated significant weight loss from 87,8±11,9 to 85,8±11,4 kg (p<0,05) and glycated hemoglobin levels (HbA1c) from 7,8±2,0% to 7,2±1,9% (p<0,05) in absence of any changes of glucose-lowering therapy, whereas there was no such dynamics in other two groups. There was only the tendency to HOMA index of insulin resistance reduction in the 2nd group from 5,44 (3,4-6,8) to 3,8 (2,3-5,2) (p=0,07).

To perform sub-analysis that aimed to estimate metabolic effects of combined therapy based on RAAS blockers, we united the patients who received ACE inhibitor and ARAII into one common group (n=47) and analyzed the dynamics of lipid and carbohydrate metabolism characteristics in this group of patients.

Combined AHT that included RAAS blockers caused improvement of glycemic control that was reflected in HbA1c levels reduction from 7,9±2,0 to 7,2±2,0% (p=0,01), although there were no changes of glucose-lowering therapy, and there was also a tendency to reduction of initially high median values of HOMA insulin resistance index from 4,1 (2,7-5,9) to 3,8 (2,3-5,2) (p=0,08). More than that, we identified positive changes of lipid-transporting blood components that was expressed as a tendency to increase of high density lipids (HDL) cholesterol concentration in serum from 1,26±0,2 to 1,32±0,3 mmol/L (p=0,08). These favorable metabolic changes were realized through the group of patients who received "triple" therapy with addition of amlodipine. Table 2 demonstrates that there were no statistically significant changes of carbohydrate and lipid metabolism characteristics in patients receiving RAAS blockers combined with IR, whereas patients who received RAAS blocker together with IR and amlodipine demonstrated such evident positive metabolic changes like reduction of HbA1c serum levels from 8,1±2,2% to 7,0±2,3% (p=0,01), change of ratio of low density lipids (LDL) cholesterol/HDL cholesterol from 2,4±0,9 to 2,3±1,0 (p=0,05) and increase of HDL cholesterol concentration from 1,29±0,2 to 1,45±0,3 mmol/L (p=0,006).

## Discussion

Diabetes mellitus is an important predictor of bad clinical prognosis. Its association with AH goes along with early atherosclerosis development, coronary heart disease, high frequency of vascular catastrophes, cardiac failure and impaired kidney function, and because of it the problem of rational AHT and organoprotective therapy in this category of patients is very important [1, 2]. It is known that modern guildelines allow prescription of any AHD for reaching target BP levels in patients with DM, and RAAS blockers are considered preferable only in case of present albuminuria/proteinuria [3]. At the same time there are many evidences that RAAS blockers have potential advantages particularly in patients with diabetes due to the presence of high potential of organ protection and favorable metabolic effects [2-4]. Nowadays RAAS blockers and their combination have the biggest amount of evidences proving the presence of organoprotective properties that do not depend on their antihypertensive action and ability to improve cardiovascular prognosis in general population of patients with AH and diabetes [2-13]. The most promising approaches to improve the prognosis of patients with AH+DM-2 are combinations of RAAS blockers with dihydropyridine CB or thiazide-like diuretic IR, that have synergic antihypertensive, organoprotective and metabolic effects and good base of evidences of their efficacy in reduction of cardiovascular morbidity and mortality [5-10]. It is known that indapamide drug form with prolonged release demonstrated metabolic neutrality in patients with DM [14]. Combination of dihydropyridine CB and ß-B in patients with DM is more reasonable from pathogenetic point of view but at the same time much less studied.

Table 2. **Biochemical characteristic dynamics in different schemes of AHT**

| Characteristic | RAAS blockers+IR (n=26) (n=26) | | RAAS blockers+IR+amlodipine (n=20) | |
|---|---|---|---|---|
| | Before treatment | After treatment | Before treatment | After treatment |
| Fasting glycemia, mmol/L | 7,6±2,0 | 7,2±1,9 | 7,3±2,1 | 7,5±1,9 |
| Postprandial glycemia, mmol/L | 9,5±3,5 | 9,1±3,0 | 8,6±3,2 | 8,3±3,1 |
| Insulin, basal, μU/mL | 11,6 (11,0–16,3) | 10,9 (9,2–15,2) | 13,7 (9,7–19,1) | 13,7 (7,9–19,1) |
| Insulin, posprandial, μU/mL | 37,8 (21,8–52,3) | 32,6 (19,8–55,2) | 29,5 (23,4–43,7) | 32,4 (18,1–39,8) |
| C-peptide, basal, μU/mL | 2,8 (2,5–3,4) | 2,9 (2,3–3,4) | 2,9 (2,3–3,8) | 3,9 (2,6–4,3) |
| C-pepdide, postprandial, μU/mL | 7,0 (4,5–8,9) | 6,1 (4,3–9,4) | 7,7 (5,3–8,9) | 6,8 (5,6–7,9) |
| HbA1c, % | 7,9±1,9 | 7,6±1,8 | 8,1±2,2 | 7,0±2,3* |
| Total cholesterol, mmol/L | 4,9±0,9 | 4,8±0,9 | 5,2±1,2 | 5,5±1,5 |
| Triglycerides, mmol/L | 1,8±0,7 | 1,8±0,7 | 2,0±0,7 | 1,9±0,7 |
| LDL cholesterol, mmol/L | 2,8±0,8 | 2,7±0,7 | 3,0±1,1 | 3,2±1,3 |
| HDL cholesterol, mmol/L | 1,24±0,3 | 1,21±0,3 | 1,29±0,2 | 1,45±0,3** |
| LDL cholesterol/HDL cholesterol, standard units | 2,4±0,8 | 2,4±0,8 | 2,4±0,9 | 2,3±1,0* |

Comment: * — p<0,05: significance of differences between characteristic values achieved with treatment and their initial levels показателями; ** -p<0,05: significance of differences between characteristic values achieved with treatment in 2 subgroups.

This study aimed to perform comparative estimation of efficacy of three therapeutic regimens of long AHT based on two RAAS block variants or dihydropyridine CB in relation to reaching target BP levels, dynamics of night AH and metabolic characteristics in patients with DM-2. It was demonstrated that, although there was no significant difference between the frequency of reaching office BP target levels in three groups of patients, the percentage of patients who received combination of two AHD was significantly higher in the group which received combined therapy based on ACE inhibitor, comparing with the group where patients did not receive RAAS blockers. We identified that adequate correction of night AH was impossible in absence of RAAS inhibitors. Activity of intrarenal RAAS under dihydropyridine CB [15] and less prominent antihypertensive action of ß-blockers at night hours due to naturally impared adrenergic activity during sleep can be considered as possible reasons of this BP reduction [16]. More evident decrease of the frequency of night diastolic AH in patients of the 1st group comparing with the 2nd group can be explained with additional impact of ACE inhibitors on kallicrein-kinin system that allows the drugs of this class to have more prominent and more stable during daytime and night time influence on neurohumoral systems and BP regulation [17]. Antihypertensive effect of therapy based on combination of ARAII and CB was accompanied with increased HR at night time, especially in patients with less evident reduction of 24-hours SBP, that can reflect some activation of sympathoadrenal system under amlodipine influence that was not compensated with valsartan action.

These results indicate of metabolic neutrality of CB, IR and ß-B combination in patients with diabetes, since no negative changes of carbohydrate, insulin or lipid metabolism were detected. At the same time, combined administration of ACE inhibitor, IR and amlodipine caused favorable metabolic shifts: statistically significant improvement of glycemic control and weight loss. Results of meta-analysis performed by Sharma A., et al. (2001) go along with our data, it has been reported that patients who received ACE inhibitors lost 0,3-5,3 kg of weight during therapy [18]. More evident influence of the therapy based on ACE inhibitor and CB combination on HbA1c comparing with combined use of ARAII and CB can be explained with this possible mechanism: ACE inhibitors potentiate endogenous kinins' effects and cause secondary stimulation of prostaglandins in different organs including pancreas [19], that increases transmembrane transport of glucose into cells.

It is necessary to understand which exactly AHD combination was responsible for detected improvement of glycemic control and weight loss in patients who received ACE inhibitor, IR and amlodipine, and to identify if RAAS blockers by themselves have benignant influence on metabolic characteristics in patients with DM-2. To answer this question we analyzed metabolic effects of two-component (without amlodipine addition) and three-component (with addition of amlodipine) therapy in united group of patients who received perindopril and valsartan. We found out significant improvement of glycemic control, tendency to increase of antiatherogenic part of blood cholesterol and reduced insulin resistance index in the common group of RAAS blockers that was realized because of patients who received combination of amlodipine with RAAS blockers and IR, whereas in absence of amlodipine no significant change of lipid and carbohydrate metabolism was detected. Observations of synergic positive metabolic effects of RAAS blockers and amlodipine go along with existing ideas of clinical benefits of this combination.

Rubio A.F., et al. found out that normotensive patients with DM who received combination of ACE inhibitor and CB for nephroprotection achieved better glycemic control than the same patients who received monotherapy with ACE inhibitors [20]. The study of Fogari R., et al. (2010) demonstrated that valsartan and amlodipine combination improves insulin sensitivity of tissues better than separate therapy with each drug [21], and after this it was proposed that combined administration of RAAS blocker and CB can play an important role in metabolic control of DM patients due to antihypertensive action of these drugs.

## Conclusion

Our results demonstrate that although all three therapeutic regimen of long AHT allow to reach target BP levels in majority of patients with AH+DM-2, their degree of night AH correction and metabolic effects are not equivalent. Therapeutic scheme based on amlodipine, IR and metoprolol succinate combination is less effective in correction of night systolic AH than combination of RAAS blocker, IR and amlodipine. Combined administration of ACE inhibitor, IR and amlodipine has advantages over combined therapy with ARAII, IR and amlodipine in majority of patients with DM-2, it promotes weight loss and reduction of HbA1c levels. Increased levels of HDL cholesterol and favor-

able dynamics of glycemic control in case of combined therapy with RAAS blocker, IR and amlodipine can be explained with their synergic metabolic effects and they can be realized after addition of amlodipine to the therapy.

## Study's limitations

This study has several limitations. First of all, target levels of glycated hemoglopin at the moment of inclusion into the study have not been achieved in patients of all three groups. At second, only half of patients did not receive lipid-lowering therapy with statins at the moment of inclusion into the study and did not take it constantly during the study that can have an impact on estimation of AHT influence on metabolic characteristics.

**Conflict of interest:** None declared

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