International Heart and Vascular Disease Journal
Volume 5, Number 15, September 2017

Journal of the Cardioprogress Foundation



# Circadian variability of blood pressure in untreated middle-aged patients with arterial hypertension

**Kochetkov A.I.[1], Borisova E.V.[2], Piksina G. F.[3], Orlov A.V.[3], Ostroumova O.D.[1, 4]***

[1] Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, Moscow, Russia
[2] City Clinical Hospital named after E.O. Mukhin, Moscow, Russia
[3] National Research Nuclear University MEPhI (Moscow Engineering Physics Institute), Moscow, Russia
[4] I.M. Sechenov First Moscow State Medical University, Moscow, Russia

## Authors

**Alexei I. Kochetkov,** M.D., assistant professor of the department of internal medicine and occupational diseases, Moscow State University of Medicine and Dentistry named after A. I. Evdokimov, Moscow, Russia.
**Ekaterina V. Borisova,** M.D., cardiologist of the department of cardiology № 1, City Clinical Hospital named after E.O. Mukhin, Moscow, Russia.
**Galina F. Piksina,** M.D., Ph.D., cardiologist, head of the department of cardiology № 1, City Clinical Hospital named after E.O. Mukhin, Moscow, Russia.
**Artemii V. Orlov,** head of students' laboratory of the department № 65, National Research Nuclear University MEPhI (Moscow Engineering Physics Institute), Moscow, Russia.
**Olga D. Ostroumova,** M.D., Ph.D., doctor of sciences, professor of the department of internal medicine and occupational diseases, Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, professor of the department of clinical pharmacology and propedeutics, I.M. Sechenov First Moscow State Medical University, Moscow, Russia.

## Summary

### Objective

*(1) Evaluate the parameters of circadian variability of blood pressure (BP) in untreated patients aged 45–65 years with 1–2 grade, II stage arterial hypertension (AH) comparing with healthy individuals of comparable age and gender; (2) compare the influence of fixed combination (FC) of amlodipine/lisinopril (FC A/L) and FC bisoprolol/hydrochlorothiazide (FC B/H) on circadian variability of BP in these patients.*

* Corresponding author. Tel.: +7903-169-68-28; E-mail: ostroumova.olga@mail.ru

## Materials and methods

*At the first stage of this study we observed 44 healthy individuals (21 males, 23 females, average age 51.5±1.0 years) and 60 untreated patients with AH 1–2 grade, II stage (31 males, 29 females, average age 53.6±0.8 years). At the second stage of this study we randomized the patients with AH into two subgroups. The patients of the first subgroup (average age 52.7±1.1 years) received FC A/L starting from 5mg/10mg per day, and the patients of the second subgroup (average age 54.6±1.0 years) received FC B/H starting from 2.5mg/6.25 mg per day. FC dose was adjusted every 14 days until the target levels of BP below 140/90 mm Hg had been reached, after it patients continued to receive these doses of drugs for 12 weeks.*

## Results

*Patients with AH had significantly higher (p<0.001) variability of systolic BP (SBP) and diastolic BP (DBP) at night (12.1±0.4 and 9.8±0.4 mm Hg, respectively) comparing with the control group (9.3±0.4 и 6.9±0.3 mm Hg, respectively). FC therapy led to significant reduction of office SBP, DBP, pulse BP (PBP), average daytime SBP, DBP, and PBP, average nighttime SBP and DBP. Both drug combinations resulted in significantly (p<0.05) reduced daytime SBP variability, and FC A/L had significantly more evident effects comparing with FC B/H (–2.7±0.7, –0.9±0.3 mm Hg, respectively). FC A/L subgroup was characterized with significant reduction of SBP variability (p<0.05) at night and DBP variability at daytime and night (–1.2±0.5, –0.7±0.3, –1.4±0.6 mm Hg, respectively).*

## Conclusions

*Untreated patients aged 45–65 years with 1–2 grade, II stage AH have higher variability of SBP and DBP at night comparing with healthy individuals of comparable age and gender. 12 week therapy with FC A/L has more evident antihypertensive effects and reduces circadian BP variability better comparing with FC B/H) in these patients.*



## Key words

*Arterial hypertension, circadian variability of blood pressure, 24h blood pressure monitoring, amlodipine, lisinopril, bisoprolol, hydrochorothiazide, fixed combination*


## Introduction

Arterial hypertension (AH) is the most common and significant risk factor (RF) for cardiovascular disease (CVD) development that significantly increases population mortality and disability and due to it represents one of the most important healthcare problems in all over the world including the Russian Federation [1].

At the same time it has been proved that not only blood pressure (BP) levels but also excessive fluctuations of BP — its increased variability — are associated with target organ lesions (TOL) [2]. Nowadays BP variability has been recognized as a new RF of CVD and brain stroke (BS). Numerous studies [3–10] demonstrated independent impact of short-term (time periods from several minutes to several days) and long-term (during months) BP variability on increase of mortality and on development of TOL not only in patients with AH but also in patients with diabetes mellitus and chronic kidney disease [2]. Several studies [11] demonstrated that BP variability reflects the stiffness of major arteries thus influencing the risk of complications. Some other studies [12, 13] revealed the significance of increased BP variability during daytime and night time for the risk of BS and myocardial infarction development in case of AH. Night systolic BP (SBP) variability was identified to be the RF of BS and myocardial infarction development, whereas night diastolic BP (DBP) variability appeared to be myocardial infarction RF [14].

Consequently, it is necessary to take into consideration the efficacy of antihypertensive agents (AHA) for reduction of BP variability in case of treatment of patients with AH from the point of view of reduction of fatal and not fatal cardiovascular and cerebrovascular complications. It is necessary to highlight that according to the guidelines of the Russian Medical Society on AH [1] and the European guidelines on diagnostics and treatment of AH [15] patients with high and very high risk should receive combined antihypertensive therapy since the start of the treatment, and fixed drug combinations (FC) of AHA should be prescribed in the first instance. According to this, nowadays the problem of AHA FC becomes relevant not only due to their direct antihypertensive effect but also because of effective reduction of BP variability.

It is worth to notice that the influence of selected AHA on BP variability has been evaluated in several studies [16–18], but in available databases there are no comparative studies that would have analyzed the ability of various AHA FC to reduce BP variability.

Investigation of influence of various AHA FC looks very relevant, taking into account all above-mentioned facts. The objectives of our study were: (1) evaluation of parameters of BP variability within 24h in untreated patients aged 45–65 years with arterial hypertension (AH), II stage, 1–2 grade without concomitant CVD comparing with healthy individuals of comparable age and gender; and (2) comparative analysis of FC amlodipine/lisinopril (FC A/L) and FC bisoprolol/hydrochlorthiazide (FC B/H) on these parameters in above-mentioned category of patients with AH.

## Materials and methods

At the first stage of this study we observed 44 healthy individuals (control group) (21 males, 23 females, average age 51.5±1.0 years) with normal BP levels and without CVD and 60 untreated patients with AH 1–2 grade, II stage (31 males, 29 females, average age 53.6±0.8 years) who were admitted to the City clinical hospital named after E.O. Mukhin.

Inclusion criteria for patients with AH: patients with AH II stage, males and females aged 45–65 years, office SBP 140–179 mm Hg and/or office DBP 90–109 mm Hg; no history of pharmacological antihypertensive therapy or irregular administration of hypotensive drugs during at least 12 months before involvement in the study.

Inclusion criteria for the control group: almost healthy adult men and women aged 45–65 years; absence of AH.

Exclusion criteria: patient's refusal of participation in the study, III grade obesity [19]; age below 45 or above 65 years; pregnancy, lactation, BP levels ≥ 180/110 mm Hg; clinically significant heart diseases (including cardiogenic shock and acute cardiac failure, history of myocardial infarction, angina, AV block II and III degree without artificial pacemaker, SA block, sick sinus syndrome, hypertrophic cardiomyopathy, aortal and mitral stenosis, chronic heart failure); liver and kidney disorders (severe chronic kidney disease [glomerular filtration rate < 30 ml/min/1.73 $m^2$ quantified with CKD-EPI], hemodialysis, anuria), respiratory and digestive system disorders, clinically significant immunological disorder including systemic lupus erythematosus, clinically significant endocrinological disorder including diabetes mellitus and secondary AH; gout, mental disorders, dementia, addiction to pharmacological agents, drugs, and alcohol; severe disorders of peripheral circulation including Reynaud syndrome; metabolic acidosis, refractory hypokalemia; clinically significant neurological disorders (including any history of acute cerebral circulatory insufficiency and transient ischemic attack); surgical operation performed up to 3 months before the study (excluding dental and cosmetic surgery); increased sensitivity to lisinopril/amlodipine, bisoprolol/hydrochlorthiazide and other thiazides, sulfonamides and/or other angiotensin-converting enzyme (ACE) inhibitors/dihydropyridine derivatives; increased sensitivity to other components of combined fixed dose medicines; any history of angioedema; history of sultopride administration or of any pharmacological agent (including regular AHA administration) that could have influenced the results of the study within 12 weeks before its initiation, at the moment of inclusion and before the end of this study.

This study was approved by Inter-institutional ethic committee, and all participants of the study signed informed consent.

All patients underwent clinical examination that included measurement of office BP, heart rate (HR), height, weight, waist circumference (WC), body mass index (BMI) quantification, 24h BP monitoring (24hBPM) (MnSDP-2 BPLAB monitor, Limited liability company «Pyotr Telegin», Russia) according to the European Society of Hypertension recommendations on 24hBPM [21, 22]; transthoracic echocardiography (Vivid 7 Dimension GE Vingmed Ultrasound A/S, Horten, Norway equipment) according to the American Society of Echocardiography on quantitative estimation of heart chambers' structure and function (2015) [23]; biochemical blood test (lipid spectrum characteristics, glucose and creatinine levels). Left ventricular mass index (LVMI) was quantified using ASE formula [23]. LVMI values above 115 g/$m^2$ and above 95 g/$m^2$ were considered as criteria of left ventricular hypertrophy (LVH) in men and women respectively [23].

At the second stage of this study we randomized the patients with AH into two subgroups each one of which included 30 persons. The patients of the first subgroup (16 males; average age 52.7±1.1 years, 12 smokers (40%), 14 persons with obesity 1–2 grade [46.7%]) received FC A/L starting from 5mg/10mg per day, and the patients of the second subgroup (15 males, average age 54.6±1.0 years, 10 smokers (33.3%), 18 persons with obesity 1–2 grade [60.0%]) received FC B/H starting from 2.5 mg/6.25 mg per day.

If two weeks after the start of the therapy BP was ≥ 140/90 mm Hg [1, 15], FC dose was increased: FC A/L was prescribed as 5/20 mg once per day, and FC B/H was adjusted as 5/6.25 mg once per day in

the morning. If BP levels were ⩾ 140/90 mm Hg even after this change, FC were increased once more: FC A/L was administered as 10/20 mg once per day, and FC B/H was prescribed as 10/6.25 mg once per day in the morning. If two weeks after patient did not manage to achieve BP target levels < 140/90 mm Hg we excluded him from the study. Patients used to buy the medicines on their own. After the target levels of BP below 140/90 mm Hg had been reached, patients continued to receive selected doses of drugs for 12 weeks, and it was followed by repeated 24hBPM.

Statistical analysis of the results was performed using Microsoft Excel 2010 and SPSS Statistics 20 software and PC with Windows 7 operation system. Normality of parameters' distribution was evaluated using Kolmogorov-Smirnov test. Significance of difference was estimated using one-way ANOVA dispersion analysis for quantitative variables and contingency tables ($\chi^2$) for categorical variables. Non-parametric Mann-Whitney U-test and Wilkoxon signed-rank test were used for analysis of not normally distributed data. Correlation analysis was used to evaluate paired connections between two and more continuous variables. 95% confidence interwal was considered for correlation analysis. Qualitative variables are shown as average values (M) ± standard error of the mean (m). Results were considered statistically significant if p-value was < 0.05.

## Results

**The first stage of the study.** Characteristics of the study population are present in Twable 1. There were no differences in age, gender, smoking status between the control group and the group of patients with AH (Table 1). Height, weight, BMI, WC were significantly (p<0.001) higher in the group of patients with AH. Also the levels of triglycerides (p<0.001), glucose (p<0.05), and creatinine (p<0.05) were significantly higher in this group (Table 1).

Table 1. **Initial characteristics of the control group and the group of patients with AH**

| Characteristic / Group | Control group (n=44) | Patients with AH (n=60) |
|---|---|---|
| Age, years | 51,5±1,0 | 53,6±0,8 |
| Smokers, n (%) | 8 (18,2) | 22 (36) |
| BMI, kg/m$^2$ | 26,5±0,6 | 31,0±0,5[c] |
| Waist circumference in men, cm | 92,8±2,1 | 109,4±1,5[c] |
| Waist circumference in women, cm | 87,9±2,3 | 101,9±2,6[c] |
| AH, 1 grade, n (%) | - | 33 (55) |
| AH, 2 grade, n (%) | - | 27 (45) |
| Total cholesterol, mmol/L | 5,8±0,2 | 5,9±0,1 |
| HDL cholesterol, mmol/L | 1,5±0,1 | 1,2±0,1[b] |
| LDL cholesterol, mmol/L | 3,6±0,1 | 3,9±0,1 |
| Triglycerides, mmol/L | 1,2±0,1 | 2,1±0,2[c] |
| Glucose, mmol/L | 5,2±0,1 | 5,5±0,1[a] |
| Creatinine, μmol/L | 86,6±1,9 | 91,9±1,8[a] |
| GFR, quantified with CKD-EPI formula, mL/min/1,73 m$^2$ | 84,0±2,4 | 87,1±1,7 |

Comment: The results are shown as M±m
[a] — differences are significant (p<0,05) comparing with the control group,
[b] — differences are significant (p<0,01) comparing with the control group,
[c] — differences are significant (p<0,001) comparing with the control group,
BMI — body mass index; HDL — high density lipoproteins, LDL — low density lipoproteins; GFR — glomerular filtration rate; AH — arterial hypertension.

Characteristics of SBP and DBP variability at night time were significantly higher in the group of patients with AH (Figure 1). SBP and DBP variability at day time in the control group (13.7±0.7 and 10.4±0.6 mm Hg, respectively) and in the group of patients with AH ГБ (15.4±0.5 and 11.4±0.4 mm Hg, respectively) did not differ significantly.

**Results of the second stage of the study: comparative analysis of FC A/L and FC B/H on circadian BP variability.**

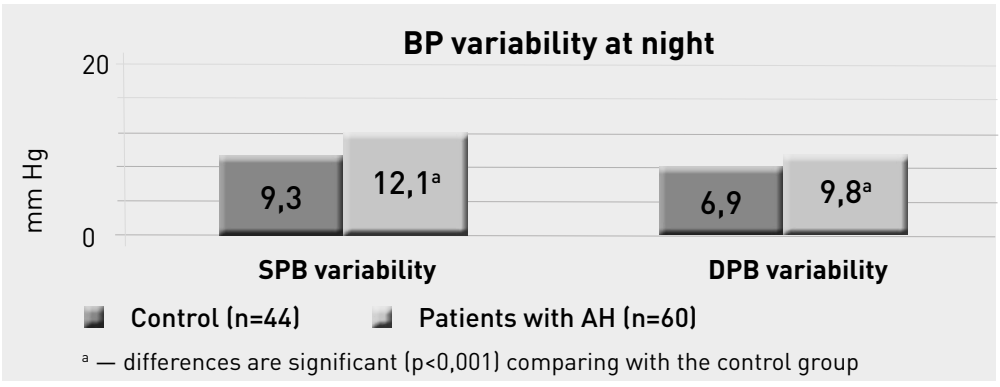


**Figure 1.** BP variability at nighttime in the group of patients with AH and in the control group during the first stage of the study.
Comment. BP — arterial pressure; SBP — systolic BP; DBP — diastolic blood pressure.

Table 2. **Initial levels and office BP and HR dynamics during the therapy with FC A/L and FC B/H**

| Group / Characteristic | FC A/L (n=30) | | FC B/H (n=30) | |
|---|---|---|---|---|
| | Initially | In the end of observation period | Initially | In the end of observation period |
| SBP, mm Hg | 154.4±2.7 | 130.6±1.2[c] | 150.6±2.7 | 134.0±0.5[c] |
| DBP, mm Hg | 96.5±1.3 | 83.0±0.6[c] | 95.8±1.1 | 84.6±0.4[b] |
| PBP, mm Hg | 58.0±1.9 | 47.6±0.9[b] | 54.8±2.1 | 49.4±0.4[a] |
| HR, beats per minute | 72.5±1.6 | 72.0±1.6 | 74.5±1.7 | 66.2±0.8[c] |

**Comment:** The results are shown as M±m.
[a] — p<0.05 comparing with the initial values;
[b] — p<0.01 comparing with the initial values;
[c] — p<0.001 comparing with the initial values.
BP — blood presure; HR — heart rate; FC — fixed combination; A/L — amlodipine/lisinopril; B/H — bisoprolol/hydrochlorothiazide; SBP — systolic blood pressure; DBP — diastolic blood pressure; PBP — pulse blood pressure.

Table 3. **Dynamics of average daily, average daytime, and average night SBP, DBP, and PBP during treatment with FC A/L and FC B/H**

| Group / Characteristic | FC A/L (n=30) | | FC B/H (n=30) | |
|---|---|---|---|---|
| | Initially | In the end of observation period | Initially | In the end of observation period |
| Average daily SBP, mm Hg | 148.8±2.3 | 127.5±0.9[b] | 150.6±2.6 | 131.9±1.4[b] |
| Average daily DBP, mm Hg | 93.1±1.2 | 77.9±0.7[b] | 92.9±1.5 | 77.3±0.9[b] |
| Average daily PBP, mm Hg | 56.3±1.9 | 49.6±1.0[b] | 56.9±1.6 | 54.7±1.0[a] |
| Average daytime SBP, mm Hg | 153.7±2.4 | 134.7±0.8[b] | 155.0±2.5 | 137.9±1.3[b] |
| Average daytime DBP, mm Hg | 96.9±1.3 | 84.4±0.5[b] | 96.5±1.5 | 85.3±0.6[b] |
| Average daytime PBP, mm Hg | 56.8±1.7 | 50.3±0.8[b] | 58.6±1.6 | 52.6±1.0[b] |
| Average nighttime SBP, mm Hg | 139.3±2.6 | 119.4±1.2[b] | 143.9±3.0 | 125.7±1.6[b] |
| Average nighttime DBP, mm Hg | 85.1±1.7 | 70.7±1.1[b] | 86.5±1.9 | 69.1±1.3[b] |
| Average nighttime PBP, mm Hg | 53.9±1.9 | 48.8±1.5[b] | 57.5±2.0 | 56.5±1.0 |

**Comment:** The results are shown as M±m.
[a] — p<0,01 comparing with the initial values;
[b] — p<0,001comparing with the initial values. FC — fixed combination; A/L — amlodipine/lisinopril; B/H — bisoprolol/hydrochlorothiazide; SBP — systolic blood pressure; DBP — diastolic blood pressure; PBP — pulse blood pressure.

By the end of the observation period all 60 patients (100%) had reached target levels of office BP (<140/90 mm Hg). In the group of FC A/L10 patients (33.3%) reached it using 5/10 mg dose, and 8 (26.7%) and 12 patients (40%) achieved it using 5/20 mg and 10/20 mg doses, respectively, whereas in the group of FC B/H 13 patients (43.3%) achieved target levels of office BP using 2.5/6.25 mg dose, 11 patients (36.7%) and 6 patients (20%) reached it using 5/6.25 mg dose and 10/6.25 mg dose, respectively. Both drug combinations were well-tolerated. Cough in the FC A/L group was registered in 6.7% of cases; patients of both group episodically reported weakness, vertigo, headache, but these adverse effects were rare, did not influence patients' life quality and did not require drug withdrawal or dose reduction. No swollen ankles and feet, bradycardia or other adverse effects have been registered. Dynamics of office BP characteristics and HR during therapy is present in Table 2.

Office values of SBP, DBP, pulse BP (PBP) were significantly reduced in both groups. The FC B/H group demonstrated also significant reduction of HR (Δ — 8.37±0.99%, p<0.001). Office levels of SBP and PBP got more evident reduction in the group of FC A/L comparing with the group of FC B/H.

BP dynamics registered with 24h BPM are present in Table 3.

Both groups demonstrated significant reduction of average daytime SBP, DBP, PBP and average night SBP and DBP (Table 4). More than that, significant reduction of night BPB values was registered in the group of FC A/L and not in the group of FC B/H (Figure 2).

SBP variability at daytime significantly decreased after treatment with FC A/L and FC B/H, and this reduction was more evident in the group of FC A/L (Table 4). More than that, the group of FC A/L was characterized with significant reduction of SBP variability at night, and DBP variability at daytime and at night.

## Discussion

According to known evidences [24], BP variability has prognostic significance for development of cardiovascular and cerebrovascular complications and it is also associated with TOL.

In particular, K. Eguchi et al [25] demonstrated the role of SBP and DBP variability during sleep as the in-

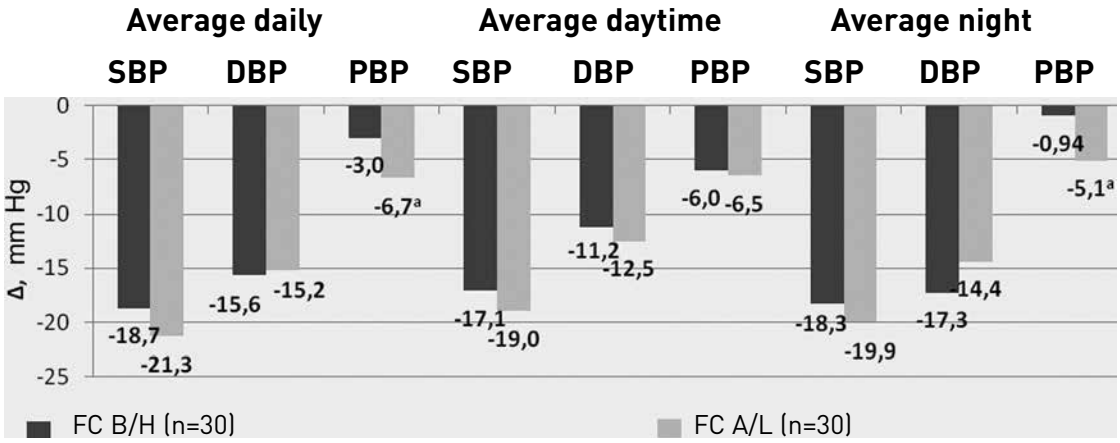


**Figure 2.** Dynamics of average daily, average daytime, and average night SBP, DBP and PD during treatment with FC A/L and FC B/H.
**Comment:** [a] — p<0,05 comparing with the initial values; FC — fixed combination; A/L — amlodipine/lisinopril; B/H — bisoprolol/hydrochlorothiazide; SBP — systolic blood pressure; DBP — diastolic blood pressure; PBP — pulse blood pressure.

Table 4. **SBP and DBP variability during treatment with FC A/L and FC B/H**

| Group / Parameter, mm Hg | FC A/L (n=30) | | | FC B/H (n=30) | | |
|---|---|---|---|---|---|---|
| | Initially | After treatment | Δ | Initially | After treatment | Δ |
| SBP variability at daytime | 15.4±0.9 | 12.7±0.5[c] | –2.7±0.7 | 15.2±0.6 | 14.5±0.5[b] | –0.9±0.3[d] |
| SBP variability at night | 11.8±0.7 | 10.7±0.5[a] | –1.2±0.5 | 12.5±0.4 | 12.3±0.4 | –0.1±0.3[e] |
| DBP variability at daytime | 11.0±0.6 | 10.3±0.5[a] | –0.7±0.3 | 11.9±0.5 | 11.9±0.6 | 0.1±0.4[d] |
| DBP variability at night | 9.4±0.6 | 8.0±0.4[c] | –1.4±0.6 | 10.1±0.4 | 10.3±0.4 | 0.1±0.3[f] |

Comment: The results are shown as M±m.
[a] — p<0.05 comparing with the initial values;
[b] — p<0.01 comparing with the initial values;
[c] — p<0.001 comparing with the initial values;
[d] — p<0.05 between groups;
[e] — p<0.01between groups;
[f] — p<0.001between groups.
FC — fixed combination; A/L — amlodipine/lisinopril; B/H — bisoprolol/hydrochlorothiazide; SBP — systolic blood pressure; DBP — diastolic blood pressure; PBP — pulse blood pressure.

dependent predictor of cardiovascular complications like fatal BS, non-fatal MI, and sudden death. More than that, the number of unfavorable cardiovascular outcomes in the group of patients with increased SBP variability at night time (12.2 mm Hg and more according to study protocol) was significantly higher. Systematic review and meta-analysis performed by S.L. Stevens et al [26] demonstrated that elevated SBP variability at daytime and within 24h correlates with the risk of general and cardiovascular mortality, and increased SBP variability during sleep was related to the risk of unfavorable cardiovascular events development.

Correlation between elevated circadian BP variability and TOL is reported by numerous studies [4, 7, 8, 10, 27–45]. Particularly, it's known that increased circadian BP variability during sleep and awakening correlates with LVH [27–32], and with global longitudinal LV 2D strain (LV GLS) [33–35], parameter characterizing deformational and elastic capacity of LV. It is worth to mention that nowadays LV GLS is recognized as a new RF predicting cardiovascular morbidity and mortality in general population [46]. In addition to this, increased SBP and DBP variability identified with 24hBPM is associated with increased left atrium dimensions and its remodeling [36, 37]. Interrelation between circadian BP variability and kidney (AH target organ) lesions [27, 28, 38, 39] including albuminuria [27, 28] has been identified. The correlation between BP variability and vascular lesions has been established [4, 7, 30, 40–42]. For example, the ELSA study (European Lacidipine Study on Atherosclerosis) [4] demonstrated highly significant correlation (p<0.001) between SBP and PBP circadian variability and number of atherosclerotic plaques in carotid arteries and intima-media thickness. Similar results have been obtained in other studies [7, 40–42]. G. Schillaci et al [8] performed multivariance analysis in their study and established significant correlation between circadian BP variability and carotid-femoral pulse wave velocity (CFPWV) that is the «golden standard» of magistral arteries' stiffness. Another study [30] identified correlation between BP variability measured with 24hBPM and arterial stiffness (CFPWV, cardio-ankle

vascular index (CAVI), ankle-brachial index (ABI), and biological age of arteries). The last study demonstrated the role of elevated BP variability in lesions of the brain as a target organ of AH. Thus, apart from the above-mentioned [12, 13] role of this parameter as the BS predictor, its correlation with the presence of small cerebral vascular lesions in patients with AH I (independently from BP levels and various clinical RF) [43, 44] and its association with cognitive disorders [10, 44, 45] have been demonstrated in several works.

Evaluating parameters of BP variability measured with 24 BPM during the first stage of the study, we identified significantly ($p<0.001$) higher variability of SBP and DBP at nighttime in the group of patients with AH. It is necessary to point out once more that BP variability has been recognized as a new RF for patients with AH, and, as it has been shown by some studies [11], it reflects the stiffness of major arteries thus influencing the risk of complications. It has been shown that average daytime and average night SBP and DBP variability parameters can be independent predictors of development of both cardiac and cerebrovascular events [12, 14]. Taking into account the fact that in our study we detected significantly higher SBP and DBP variability at night time in the group of patients with AH, it is possible to talk about elevated risk of cardiovascular complications (CVC) even at early stages of AH in patients with relatively short duration of the disease.

At the second stage of our study we demonstrated that FC A/L and FC B/H have high antihypertensive activity, since all 60 patients (100 %) who received these drugs had reached target levels of office BP. Our results go along with the other studies [47–53]. Together with this, FC A/L reduced office SBP significantly higher comparing with FC B/H. It is necessary to point out that several works [54–58] demonstrated the prevalence of SBP impact on CVC development.

We also noticed that the group of FC A/L was characterized with significantly higher reduction of office and average night PBP comparing with the group of FC B/H ($p<0.05$). These data correspond to the results of the CAFÉ (Conduit Artery Functional Endpoint, sub-study in the frame of the ASCOT-BPLA study) — the largest trial performed in patients with AH tat evaluated reduction of central (aortal) BP [59]. The CAFÉ study involved 2073 patients from 5 centers, and by the moment of inclusion into sub-study all of them had reached target BP levels. According to the results of the above-mentioned sub-study, SBP and PBP in aorta was significantly lower in the group of patients who received amlodipine and ACE inhibitors [59]. Another study [51] evaluated antihypertensive effects of FC B/H in patients with firstly diagnosed or untreated AH 1–2 grade (13 patients with AH 1 stage, 19 patients with AH 2 stage; average AH duration was 5.1±0.4 years). In the end all 32 patients reached target BP levels < 140/90 mm Hg (routine measurement) and achieved significant reduction of SBP, DBP and HR. According to 24hBPM results, patients who received stable doses of FC B/H for 12 weeks had significantly lower SBP, DBP, and PBP levels at daytime, at night and within 24h. It is important to point out that PBP has high prognostic significance for CVC development. In the SHEP (Systolic Hypertension in the Elderly Program) study BS risk in elderly patients with isolated systolic AH correlated with initially elevated PBP levels independently from average BP values [60]. Correlation between PBP levels and parameters of cardiovascular and coronary mortality was evaluated in one major population study performed in patients aged 40–69 years in France [61]. Results of observation on 12631 persons with normal BP (<140/90 mm Hg) and 6824 patients with AH (SBP>160 mm Hg and/or DBP>95 mm Hg) were analyzed. Characteristics of total and cardiovascular mortality were significantly higher in the subgroups of patients with higher PBP in men (independently from initial BP levels) and women with AH. PBP>50 mm Hg was associated with elevation of cardiovascular mortality by 40 % in men with normal BP and by 48 % in male patients with AH.

In our study we found out that, although both FC reduced significantly SBP and DBP variability at daytime and at night, FC A/L influenced BP variability at daytime and at night significantly better than FC B/H.

It is worth to point out that according to the results of the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm) [11], BP variability (in particular SBP) is considered to be a strong independent predictor of development of myocardial infarction and BS independently from SBP changes during all study period (around 5 years) and from patients' age and gender. More than that, increased BP variability at daytime and at night turned out to be important for BS development in AH.

I.R. Ersh et al [53] investigated clinical efficacy of 1 and 2 month therapy with FC A/L in outpatients with AH in observation study. This study included two groups of patients. The first one consisted of 34 patients (16 men and 18 women, average age 47±6.8

years, AH duration 12.6 ± 6.2 years) with AH 1–2 grade who regularly received FC A/L for one year. The control group included 33 patients (15 women and 18 men, average age 48 ± 6.3 years, AH duration 13.4 ± 5.8 years) who took AHA including FC A/L irregularly in case of BP elevation or in case of deterioration of their well-being. This group of patients was used just for the analysis of annual results. Average initial SBP and DBP values in both groups of patients were 171.1 ± 1.8 mm Hg and 98.2 ± 2.3 mm Hg, respectively. The majority of patients had additional CVC RF and/or associated clinical conditions: coronary heart disease, stable angina (I–II functional class), impaired glucose tolerance, dyslipidemia, and smoking. In this study it was found that significant decrease of BP variability measured with 24hBPM occurred after 6 months of regular therapy with FC A/L, and with time these changes became even more evident.

It is worth to highlight the X–CELLENT (The Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients) [62], that investigated the influence of candesartan, amlodipine and indapamide on BP reduction and BP circadian variability measured with 24hBPM in 577 patients during 3 months. All 3 drugs effectively reduced BP, but only amlodipine and indapamide significantly lowered circadian BP variability. Several other studies [16, 18] demonstrated the capacity of calcium channel blockers to significantly reduce BP variability.

## Conclusion

Taking into account the results of our study, we can conclude that the use of FC A/L comparing with FC B/H contributes to more significant decrease of coronary and cerebrovascular events' risk through the mechanisms modulating BP variability at daytime and at night.

**Conflict of interest**: None declared

## References

1. Chazova I.E., Ratova L.G., Boitsov S.A., Nebieridze D.V. Recommendations for the management of arterial hypertension Russian Medical Society of Arterial Hypertension and Society of Cardiology of the Russian Federation. Sistemnye gipertenzii, 2010;3:5–26. Russian
2. Höcht C. Blood Pressure Variability: Prognostic Value and Therapeutic Implications. ISRN Hypertension 2013; vol.2013: article ID 398485.
3. Parati G., Pomidossi G., Albini F., Malaspina D, Mancia G. Relationship of 24-hour blood pressure mean and variability to severity of target-organ damage in hypertension. Journal of Hypertension 1987;5 (1): 93–98.
4. Mancia G., Parati G., Hennig M. et al. Relation between blood pressure variability and carotid artery damage in hypertension: baseline data from the European Lacidipine Study on Atherosclerosis (ELSA). Journal of Hypertension 2001;19 (11): 1981–1989.
5. Sega R., Corrao G., Bombelli M. et al. Blood pressure variability and organ damage in a general population: results from the PAMELA study. Hypertension 2002;39 (2): 710–714.
6. McMullan C.J., Bakris G.L., Phillips R.A., Forman J.P. Association of BP variability with mortality among African Americans with CKD. Clinical Journal of the American Society of Nephrology 2013;8 (5): 731–738.
7. Kawai T., Ohishi M., Kamide K. Differences between daytime and nighttime blood pressure variability regarding systemic atherosclerotic change and renal function. Hypertension Research 2013;36:232–239.
8. Schillaci G., Bilo G., Pucci G. et al. Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: findings from 2 large databases. Hypertension 2012;60:369–377.
9. Schutte A.E., Schutte R., Huisman H.W. et al. Blood pressure variability is significantly associated with ECG left ventricular mass in normotensive Africans:The SABPA Study. Hypertension Research 2011;34 (10): 1127–1134.
10. Sakakura K., Ishikawa J., Okuno M., Shimada K., Kario K. Exaggerated ambulatory blood pressure variability is associated with cognitive dysfunction in the very elderly and quality of life in the younger elderly. American Journal of Hypertension 2007;20 (7): 720–727.
11. Dahlöf B., Sever P.S., Poulter N.R., Wedel H., Beevers D.G., Caulfield M., Collins R., Kjeldsen S.E., Kristinsson A., McInnes G.T., Mehlsen J., Nieminen M., O'Brien E., Ostergren J.; ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA): a multicentre randomized controlled trial. Lancet 2005;366:895–906.
12. Parati G., Ulian L., Santucciu C., Omboni S., Mancia G. Blood pressure variability, cardiovascular risk and antihypertensive treatment. Journal of Hypertension 1995;3:S27-S34.
13. Frattola A., Parati G., Cuspidi C., Albini F., Mancia G. Prognostic value of 24-hour blood pressure variability. J Hypertens 1993;11 (10): 1133–1137.
14. Verdecchia P., Angeli F., Gattobigio R., Rapicetta C., Reboldi G. Impact of blood pressure variability on cardiac and cerebrovascular complications in hypertension. Am J Hypertens. 2007;20 (2): 154–161.
15. Mancia G., Fagard R., Narkiewicz K., Redon J., Zanchetti A., Bohm 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., Sirnes P., Sleight P., Viigimaa M., Waeber B., Zannad F. 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). J Hypertens 2013;31:1281–1357.

16. Mancia G., Parati G., Bilo G., Maronati A., Omboni S., Baurecht H., Hennig M., Zanchetti A. Assessment of long-term antihypertensive treatment by clinic and ambulatory blood pressure: data from the European Lacidipine Study on Atherosclerosis. J Hypertens 2007;25:1087–1094.
17. Ichihara A., Kaneshiro Y., Takemitsu T. et al. Effects of amlodipine and valsartan on vascular damage and ambulatory blood pressure in untreated hypertensive patients.J. Hum. Hypertens 2006;20 (10): 787–794.
18. Pringle E., Phillips C., Thijs L., Davidson C., Staessen J.A., de Leeuw P.W., Jaaskivi M., Nachev C., Parati G., O'Brien E.T., Tuomilehto J., Webster J., Bulpitt C.J., Fagard R.H.; Syst-Eur investigators. Systolic blood pressure variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population. J Hypertens 2003;21 (12): 2251–2257.
19. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000;894:1–253.
20. Levey A.S., Stevens L.A., Schmid C.H., Zhang Y.L., Castro A.F. 3rd, Feldman H.I., Kusek J.W., Eggers P., Van Lente F., Greene T., Coresh J.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612.
21. O'Brien E., Parati G., Stergiou G., Asmar R., Beilin L., Bilo G., Clement D., de la Sierra A., de Leeuw P., Dolan E., Fagard R., Graves J., Head G.A., Imai Y., Kario K., Lurbe E., Mallion J.M., Mancia G., Mengden T., Myers M., Ogedegbe G., Ohkubo T., Omboni S., Palatini P., Redon J., Ruilope L.M., Shennan A., Staessen J.A., van Montfrans G., Verdecchia P., Waeber B., Wang J., Zanchetti A., Zhang Y.; European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension position paper on ambulatory blood pressure monitoring. J Hypertens 2013;31 (9): 1731–1768.
22. Parati G., Stergiou G., O'Brien E., Asmar R., Beilin L., Bilo G., Clement D., de la Sierra A., de Leeuw P., Dolan E., Fagard R., Graves J., Head G.A., Imai Y., Kario K., Lurbe E., Mallion J.M., Mancia G., Mengden T., Myers M., Ogedegbe G., Ohkubo T., Omboni S., Palatini P., Redon J., Ruilope L.M., Shennan A., Staessen J.A., van Montfrans G., Verdecchia P., Waeber B., Wang J., Zanchetti A., Zhang Y.; European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. J Hypertens 2014;32 (7): 1359–1366.
23. Lang R.M., Badano L.P., Mor-Avi V., Afilalo J., Armstrong A., Ernande L., Flachskampf F.A., Foster E., Goldstein S.A., Kuznetsova T., Lancellotti P., Muraru D., Picard M.H., Rietzschel E.R., Rudski L., Spencer K.T., Tsang W., Voigt J.U. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28 (1): 1–39.e14.
24. Ostroumova O.D., Borisova E.V., Ostroumova T.M., Kochetkov A.I. The 24-hours blood pressure variability: prognostic value, evaluation methods and the effect of antihypertensive drugs. Kardiologija 2017;57 (12): 62–72. Russian.
25. Eguchi K., Hoshide S., Schwartz J.E., Shimada K., Kario K. Visit-to-visit and Ambulatory Blood Pressure Variability as Predictors of Incident Cardiovascular Events in Patients with Hypertension. Am J Hypertens. 2012;25 (9): 10.1038/ajh.2012.75.
26. Stevens S.L., Wood S., Koshiaris C., Law K., Glasziou P., Stevens R.J., McManus R.J. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. BMJ 2016;354:i4098.
27. Zhang Q.Q., Zhang X.J., Chang B.B., Qiu B.Y., Zhang Y., Li J., Zeng Z. [Blood pressure variability correlates with target-organ damage in elderly patients with hypertension]. [Article in Chinese]. Sichuan Da Xue Xue Bao Yi Xue Ban 2011;42 (2): 252–255.
28. Tatasciore A., Renda G., Zimarino M., Soccio M., Bilo G., Parati G., Schillaci G., De Caterina R. Awake Systolic Blood Pressure Variability Correlates With Target-Organ Damage in Hypertensive Subjects. Hypertension. 2007;50:325–332.
29. Ozawa M., Tamura K., Okano Y., Matsushita K., Ikeya Y., Masuda S., Wakui H., Dejima T., Shigenaga A., Azuma K., Ishigami T., Toya Y., Ishikawa T., Umemura S. Blood pressure variability as well as blood pressure level is important for left ventricular hypertrophy and brachial-ankle pulse wave velocity in hypertensives. Clin Exp Hypertens. 2009;31 (8): 669–679.
30. Kastanayan A.A., Zheleznyak E.I., Hagush A.K., Demidova A.A., Kartashova E.A., Zhulitov A.Yu. The relationship between blood pressure variability and cardiovascular remodeling in hypertension developed in the elderly. Atrerial'naya gipertenziya 2016;22 (4): 389–400. Russian
31. Juhanoja E.P., Niiranen T.J., Johansson J.K., Puukka P.J., Jula A.M. Agreement between ambulatory, home, and office blood pressure variability. J Hypertens 2016;34 (1): 61–67.
32. Madden J.M., O'Flynn A.M., Fitzgerald A.P., Kearney P.M. Correlation between short-term blood pressure variability and left-ventricular mass index: a meta-analysis. Hypertens Res 2016;39 (3): 171–177.

33. Shin S.M., Shim W.J., Park S.M. Early changes of left ventricular function in young adults with never-treated hypertension and no left ventricular hypertrophy: relationships to ambulatory blood pressure monitoring. Clin Exp Hypertens. 2014;36 (7): 517–523.
34. Tsai W.C., Lee W.H., Liu Y.W. Effects of blood pressure variability on layer-specific longitudinal strain in hypertension. Eur Heart J Cardiovasc Imaging. 2016;17 (suppl_2): ii270-ii276.
35. Ciobanu A.O., Gherghinescu C.L., Dulgheru R., Magda S., Dragoi Galrinho R., Florescu M., Guberna S., Cinteza M., Vinereanu D. The Impact of Blood Pressure Variability on Subclinical Ventricular, Renal and Vascular Dysfunction, in Patients with Hypertension and Diabetes. MAEDICA — a Journal of Clinical Medicine 2013;8 (2): 129–136.
36. Cipollini F., Arcangeli E., Seghieri G. Left atrial dimension is related to blood pressure variability in newly diagnosed untreated hypertensive patients. Hypertens Res. 2016;39 (8): 583–587.
37. Tadic M., Cuspidi C., Ilic I., Suzic-Lazić J., Zivanovic V., Jozika L., Celic V. The relationship between blood pressure variability, obesity and left atrial phasic function in hypertensive population. Int J Cardiovasc Imaging. 2016;32 (4): 603–612.
38. Parati G., Ochoa J.E., Bilo G. Blood pressure variability, cardiovascular risk, and risk for renal disease progression. Curr Hypertens Rep 2012;14 (5): 421–431.
39. Manios E., Tsagalis G., Tsivgoulis G., Barlas G., Koroboki E., Michas F. et al. Time rate of blood pressure variation is associated with impaired renal function in hypertensive patients. J Hypertens. 2009;27 (11): 2244–2248.
40. Chen Y., Xiong H., Wu D., Pirbhulal S., Tian X., Zhang R. et al. Relationship of short-term blood pressure variability with carotid intima-media thickness in hypertensive patients. Biomed Eng Online 2015;14:71.
41. Shintani Y., Kikuya M., Hara A., Ohkubo T., Metoki H., Asayama K., Inoue R., Obara T., Aono Y., Hashimoto T., Hashimoto J., Totsune K., Hoshi H., Satoh H., Imai Y. Ambulatory blood pressure, blood pressure variability and the prevalence of carotid artery alteration: the Ohasama study. J Hypertens 2007;25 (8): 1704–1710.
42. Ichihara A., Kaneshiro Y., Takemitsu T., Sakoda M., Hayashi M. Ambulatory blood pressure variability and brachial–ankle pulse wave velocity in untreated hypertensive patients. Journal of Human Hypertension 2006;20:529–536.
43. Filomena J., Riba-Llena I., Vinyoles E., Tovar J.L., Mundet X., Castane X. et al. Short-term blood pressure variability relates to the presence of subclinical brain small vessel disease in primary hypertension. Hypertension 2015;66 (3): 634–640.
44. Yamaguchi Y., Wada M., Sato H., Nagasawa H., Koyama S., Takahashi Y., Kawanami T., Kato T. Impact of Ambulatory Blood Pressure Variability on Cerebral Small Vessel Disease Progression and Cognitive Decline in Community-Based Elderly Japanese. American Journal of Hypertension 2014;27 (10): 1257–1267.
45. Kanemary A., Kanemary K., Kuwajima I. The effects of Short-Term blood pressure variability and nighttime blood pressure levels on cognitive function. Hypertens Res 2001;24:19–24.
46. Biering-Sørensen T., Biering-Sørensen S.R., Olsen F.J., Sengeløv M., Jørgensen P.G., Mogelvang R., Shah A.M., Jensen J.S. Global Longitudinal Strain by Echocardiography Predicts Long-Term Risk of Cardiovascular Morbidity and Mortality in a Low-Risk General Population: The Copenhagen City Heart Study. Circ Cardiovasc Imaging. 2017;10 (3): e005521.
47. Dzyak G.V., Kolesnik T.V., Kolesnik Je.L. Dynamics of the arterial wall stiffness parameters on the background of combination antihypertensive therapy. Ukrainskij medicinskij zhurnal. Aktual'nye voprosy klinicheskoj praktiki 2011;5 (85) IX–X:57–59. Russian
48. Donskaja A.A., Morozov S.N., Morozova E.A. Evaluation of the impact of monotherapy with the Equator on hemodynamic parameters in persons with arterial hypertension. Kardiovaskulyarnaya terapiya i profilaktika 2008;№ 4 (4), Suppl.2:37. Russian
49. Kakhramanova S.M., Bahshaliev A.B. Antihypertensive and cardioprotective efficacy of the Equator in patients with essential hypertension. «Russian National Congress of Cardiologists. Improving the quality and availability of cardiac care (Congress materials)». Kardiovaskulyarnaya terapiya i profilaktika 2008;7 (6) b Suppl. 1:173. Russian.
50. Morozov S.N., Donskaja A.A., Morozova E.A. The effectiveness of the equator treatment of patients with arterial hypertension (evidence from Yakutsk). Yakutskij medicinskij zhurnal 2008;4 (24): 9–12. Russian
51. Ostroumova O.D., Smolarchuk E.A. Reznikova K.U. Morning Elevations of Blood Pressure: Clinical Significance, Methods of Calculation and Perspectives of Correction with Lodoz. Lechebnoe delo 2011;3:42–49. Russian.
52. Nedogoda S.V., Chumachek E.V., Ledyaeva A.A., Tsoma A.V., Salasyuk A.S. Comparative effectiveness of fixed-dose combinations of lisinopril/amlodipine and enalapril/hydrochlorothiazide. Kardiovaskulyarnaya terapiya i profilaktika 2013;12 (2): 25–29. Russian.
53. Ersh I.R. Zaicev V.I., Romanchuk E'.V., Kugach V.V., Zareckij P.L., Matvejchik A.I., Myatleva I.A. Efficacy of long-term therapy with the Equator in patients with arterial hypertension in ambulatory conditions. Mezhdunarodnye obzory: klinicheskaya praktika I zdorov'e 2014;2 (8): 74–86. Russian
54. Stokes J. 3rd, Kannel W.B., Wolf P.A., D'Agostino R.B., Cupples L.A. Blood pressure as a risk factor for cardiovascular disease. The Framingham study: 30 years of follow-up. Hypertension 1989;13 (suppl. 1): I13–I18.
55. Stamler J., Vaccaro O., Neaton J.D., Wentworth D., for the Multiple Risk Factor Intervention Trial Research Group.

Diabetes, other risk factors, and 12year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993;16:434–444.

56. Kannel W. Risk stratification in hypertension: new insights from the Framingham Study. Am. J. Hyper. 2000;13 (Pt. 2): S3–S10.
57. Kannel W., Gordon T., Schwartz M. Systolic versus diastolic blood pressure and risk of coronary heart disease. The Framingham study. Am. J. Cardiol. 1971;27:335–346.
58. Multiple Risk Factor Intervention Trial Research Group: relationship between baseline risk factors and coronary heart disease and total mortality in the Multiple Risk Factor Intervention Trial. Prev Med 1986;15:254–273.
59. Williams B., Lacy P.S., Thom S.M., Cruickshank K., Stanton A., Collier D., Hughes A.D., Thurston H., O'Rourke M.; CAFE Investigators; Anglo-Scandinavian Cardiac Outcomes Trial Investigators; CAFE Steering Committee and Writing Committee. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006;113 (9): 1213–1225.
60. Domanski M.J., Davis B.R., Pfeffer M.A., Kastantin M., Mitchell G.F. Isolated systolic hypertension: prognostic information provided by pulse pressure. Hypertension 1999;34:375–380.
61. Benetos A., Safar M., Rudnichi A., Smulyan H., Richard J.L., Ducimetière P., Guize L. Pulse pressure. Hypertension 1997:30 (6); 1410–1415.
62. London G., Schmieder R., Calvo C., Asmar R. Indapamide SR versus candesartan and amlodipine in hypertension: the X–CELLENT Study. Am J Hypertens. 2006;19 (1): 113–121