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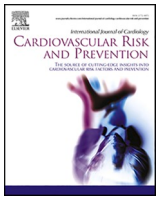

"The impact of statins addind to the fixed combination antihypertensive therapy on the arterial stiffness in patients with moderate and severe hypertension"

Yuriy Sirenko *, Oksana Rekovets

National Scientific Center "The M.D. Strazhesko Institute of Cardiology, Clinical and Regenerative Medicine of the National Academy of Medical Science of Ukraine", Ukraine

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ABSTRACT

Aim: The objective of this study was the evaluation of the arterial stiffness, which changed after adding statins to the guidelines recommended dual or triple fixed combination antihypertensive therapy in patients with moderate to severe arterial hypertension.

Materials and methods: It was included 99 patients in total being diagnosed with moderate and severe arterial hypertension (2nd and 3rd stages of arterial hypertension) without diabetes. Those patients were divided into 2 groups. The first group (n = 59) was assigned to the dual or triple fixed combination antihypertensive therapy plus including statins.

Patients in the second group (n = 40) received only the dual or triple fixed combination antihypertensive treatment following the recommended guidelines without any statins. The CAVI index was performed in order to measure in all participants before and at the end of the follow-up period. Furthermore, the Office (Clinic BP) Blood Pressure (BP) was monitored in assigned participants as well as the Ambulatory Blood Pressure Monitoring (ABPM). The laboratory investigations also took place such as the standard blood test, the urine and biochemistry analysis and the estimated Carotid Intima-Media Thicknesses with Ultrasound. The study-duration was 6 months.

Results: Office BP and ABPM had decreased significantly and equally in both treatment groups. The total cholesterol (TC) and LDL cholesterol had decreased significantly in the statin group on 1,76 mmol/l (30%, $p < 0,05$) and 1,51 mmol/l (41%, $p < 0,05$) respectively. In the group without statin therapy, there was no changes in the level of TC and LDL cholesterol. In the group without statins, it was noted a significant decrease in the level of BP, however, the CAVI index level was shown the growth to +0,9 units on the right side and +1,0 units on the left.

In the group without statin's treatment, the CAVI index was changed from $7.73 \pm 0.17/7.62 \pm 0.19$ units to $8.63 \pm 0.22/8.62 \pm 0.12$ units on the right/left site after treatment ($p < 0,05$). It means there was an increase in the stiffness of the arterial wall in terms of cardio-vascular index CAVI in the group without added statin after 6 months of the therapy. In the group with added statin after 6 months of the therapy, the CAVI had not have any changes. It can be seen from the observed figures: the CAVI on the right/left site was $8.32 \pm 0.16/8.33 \pm 0.19$ initially and $8.44 \pm 0.16/8.24 \pm 0.15$ units treatment ($p > 0,05$) afterwards.

We did not note any impact of statin therapy on the BP level. However, a significant correlations was found between the CAVI index with age and the serum level of blood Triglycerides before treatment, including LDL Cholesterol and HDL Cholesterol, duration of hypertension, the blood glucose level, the Potassium level and the Maximum Thickness of Intima-Media of Carotid Arteries in the statins group.

Conclusion: The adding of the statin to the current fixed dual or triple combination of the antihypertensive therapy could prevent the progression of arterial stiffness in patients with 2nd and 3rd stages of arterial hypertension.

* Corresponding author.
E-mail address: sirenkoyu@gmail.com (Y. Sirenko).

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1. Introduction

According to the current scientific data, about 70% of patients with arterial hypertension (AH) require combined antihypertensive therapy. The most effective fixed combinations of antihypertensive drugs include blocker of the Renin-Angiotensin-Aldosterone system in combination with Calcium Antagonists and/or Diuretics [1].

Arterial stiffness is one of the earliest and reliable biomarker for increased CVD risk and it can be considered as an important predictor for the development of subclinical target organ damage and cardiovascular dysfunction [2]. The arterial stiffness begins with structural changes in the vascular wall prior to the appearance of a plaque or thrombus. The gold standard for assessing the arterial stiffness is the measurement of a pulse wave velocity (PWV) in arteries of the elastic and muscular type. and It is also may be a surrogate marker of atherosclerosis. However, these parameters could be affected by the level of systemic arterial blood pressure (BP) and could vary from the operator skill when some type of devices are in use. The invention of the new method for measuring of the arterial stiffness with the cardio-ankle vascular index (CAVI) shows the correlation between others cardiovascular risk factors reflecting the degree of atherosclerotic changes. This relationship especially noticed in patients with type 2 diabetes and for the patients with atherosclerotic lesions or on hemodialysis [3,4].

The CAVI reflects the stiffness of the aorta, femoral artery, and tibial artery as a whole, and also CAVI is not related to the BP level. In patients with the high level of cardiovascular risk, the prognostic value of CAVI was established for the long-term prediction of cardio-vascular events in comparison with other parameters of atherosclerosis [5,6]. The CAVI has been correlated with coronary stenosis, diabetes and metabolic syndrome [7]. Is an extremely important that the information mentioned above regarding the CAVI data was received in patients from Asian region and there was the only multicenter study performed in Caucasians called The Triple A study [8].

In the available literature, no data were found regarding the impact of statin therapy on the CAVI index in the Caucasians patients with the 2nd an3rd stages of hypertension.

The objective of the study was the evaluation of the arterial stiffness being changed after adding (introducing) of statins to the dual or triple fixed combined antihypertensive therapy in patients with moderate to severe arterial hypertension.

2. Materials and methods

Patients with diagnosed 2nd and 3rd degree of hypertension were included in this study [1]. They underwent inpatient or outpatient treatment in the department of secondary and pulmonary hypertension of the National Scientific Center "The M.D. Strazhesko Institute of Cardiology, Clinical and Regenerative Medicine of the National Academy of Medical Science of Ukraine". This study was not registered in any clinical trials' registry.

The inclusion criteria of the study were the following: patients aged 25–75 years, essential hypertension stage II - III, level of systolic (SBP) and/or diastolic (DBP) blood pressure $>$ 160/100 mm Hg. Appropriately designed consent form was signed by all participants in this study and in the following 7 days period of the withdrawal of all antihypertensive drugs. Moreover, not only the lack of exclusion criteria was evaluated but also the patient's ability to cooperate adequately.

The following exclusion criteria included the blood pressure level $>$ 220/140 mm Hg; secondary and malignant forms of hypertension and the presence of diabetes mellitus. Also, the presence in the patients' history the following complications: myocardial infarction, revascularization procedures, cerebro-vascular events; heart rhythm disorders (persistent or long standing forms of atrial fibrillation, frequent ventricular or supraventricular extrasystoles, atrioventricular block II and III degrees, sinus weakness syndrome); heart failure II-IV functional class (NYHA); angina pectoris of II-IV functional class; pulmonary embolism; severe chronic renal failure (GFR $<$ 30 ml/min); decompensated liver damage; mental disorders; oncological diseases; pregnancy or lactation; a history of increased sensitivity to antihypertensive or statin therapy components.

The study was decided to cease (stop) in case of individual's intolerance of the drug or severe, including suddenly appeared, adverse reactions. Additionally, the study stopped, if participants faced a significant deterioration of the general condition during this study period or once changes in laboratory parameters were noted leading to indication of a potential threat to patients. In case of dissatisfaction for any reason by patient or researcher, this research was discontinued as well.

It was an investigator driven study. The study protocol was approved by the Local Ethical Committee of the National Scientific Center "The M. D. Strazhesko Institute of Cardiology, Clinical and Regenerative Medicine of the National Academy of Medical Science of Ukraine" as a part of the investigations in our Scientific Center. All patients signed informed consent form concerning including their data in our Institute's database. We performed the retrospective analysis of patients' database of the Department of Secondary and Pulmonary Hypertension of the National Scientific Center "The M.D. Strazhesko Institute of Cardiology, Clinical and Regenerative Medicine of the National Academy of Medical Science of Ukraine".

According to the protocol, all patients underwent the following examinations: diseases history, measurement of body weight and height with a body mass index (BMI) calculation, objective examination, standard measurement of the office systolic and diastolic BP (SBP and DBP) with the validated professional device and heart rate (HR), general clinical blood and urine, biochemical blood tests.

The main assessment criteria in this sub-study was some changes in vascular wall stiffness according to CAVI indicators. These changes of the arterial stiffness were evaluated with using the CAVI measured by VaSera 1500 device (Fukuda Denshi, Japan) according to the apparatus' instruction.

The formula for its calculation is:

$$CAVI = a[(2\rho/\Delta P) \cdot In(SBP/DBP) \cdot PWV^2] + b,$$

Where a and b are scale conversion constants, PWV = pulse wave velocity from valve orifice to ankle, SBP = systolic blood pressure; DBP = diastolic blood pressure; ΔP = change in blood pressure; ρ = blood density [9]. Blood pressure is measured in a supine position automatically. This formula helps to minimize the influence of the "functional" component of arterial stiffness, when blood extends on the arterial wall at high pressure [10].

The normal value of CAVI was mean $<$ 8.0 [11,12]. Increased arterial stiffness was considered as an early asymptomatic hypertension mediated target organ damage. We accepted CAVI value $\geq$ 8 as an indicator of abnormal systemic arterial stiffness.

A biochemical blood test was included: the serum level of creatinine, electrolytes (potassium and sodium), glucose, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) measured by an automatic photometer (Cormay Livia Chemistry Analyzer, Lublin, Poland). GFR (glomerular filtration rate), was calculated by the CKD-EPI (Chronic kidney disease Epidemiology) 2021 formula.

All patients underwent Carotid Ultrasonography of the common carotid artery, internal and external carotid arteries on the both sides according to the recommendations of the protocol recommended by Society of Radiologists at the Ultrasound Research Conference [13]. The presence of atherosclerotic plaques in the carotid arteries was measured according to the standard method using the ultrasound diagnostic device "Imagic Agile" (Kontron Medical, France) with determination of the intima-media thickness (IMT) of the carotid arteries. The maximum thickness of the intima-media thickness (IMT) was measured in the area of the bifurcation of the common carotid artery (CCA).

Also, in all patients we performed the ambulatory blood pressure monitoring (ABPM) with ABPM-4 device (Meditech, Hungary) according to ESH recommendations [1]. All measurements were performed before and after 6 months of the follow-up period.

Patients were prescribed a fixed triple combination of Val/Amlo/HCT tablets. The drugs were prescribed as 1 tablet (160 mg valsartan/5 mg amlodipine/12.5 mg hydrochlorothiazide) once a day, at the morning before meal for 1 month. As an alternative, patients received a double fixed combination of the drug Valsartan/Amlodipine by a similar scheme: 1 tablet (160 mg valsartan/5 mg amlodipine) once a day at the morning before meal for 1 month. If necessary, in case when the target level of office BP (less than 140/90 mm Hg) was not achieved, the dose was titrated to a daily dose of the fixed triple combination 320/10/12.5 mg (valsartan/amlodipine/hydrochlorothiazide) and to 320/10 mg (valsartan/amlodipine) was used the double fixed combination.

Patients were divided into 2 groups. Participants in groups was divided as sealed opaque envelope system. In one group, atorvastatin was added to the double or triple fixed combination of antihypertensive drugs in a dose (20–40 mg) per day during 6 months of treatment. We studied the addition of a known statin molecule to a guidelines' recommended three-component in single pill known antihypertensive therapy on parameters of arterial stiffness. All measurements were performed before and at the end of follow-up period.

2.1. Statistical analysis

Statistical analysis of the results was performed on a personal computer after creating databases in Microsoft Excel systems. Statistic Package for Social Sciences (IBM SPSS Statistics, version 21.0, SPSS Inc, Armonk, New York, USA) was used for statistical analyses. The ANOVA one way test was used for normally distributed continuous variables. ANOVA to calculate the following parameters: the arithmetic mean value – M, the SD from the arithmetic mean value of – m; significance coefficient – p. The Student's t-test of mean values was used for comparisons between the two groups. The difference was considered reliable at a value of $p < 0.05$. The Levene's test was performed before the Student's *t*-test. The reliability of the difference between the groups was determined by the independent *t*-test for the mean. Correlation analysis was performed after determining the character of the distribution for Spearman. The Spearman correlation coefficients were calculated between the systemic artery stiffness parameters and the main patient characteristics. The univariate and multivariable binary logistic analyses were performed to indicate the parameters associated with abnormal CAVI level (≥8). All the tests were two-tailed. The data were considered significant at $p < 0.05$.

3. Results

As it was indicated above, 99 patients with diagnosed 2nd and 3rd degree of hypertension were included in this study according with the 2018-ESC/ESH classification. 11 patients were not included due to not matching eligible criteria. Among them, 6 had heart failure II grade, 2 had history myocardial infarction, 1 had history of stroke, 1 had severe chronic renal failure and 1 had secondary arterial hypertension. The average age of the patients was 54.82 ± 1.25 (25–75) years. The average BMI was 31.21 ± 0.48 kg/m^2. The average levels of office SBP/DBP at the beginning of the study were 161.69 ± 1.25/98.55 ± 0.97 mm Hg respectively. The average office heart rate was 70.81 ± 0.96 bpm. The main clinical and demographic indicators of the patients included in the study in comparison groups are presented in Table 1.

The levels of office BP and 24-h monitoring were the same in both compared groups.

The double or triple fixed dose combination antihypertensive therapy led to the significant and equal decrease in office BP in patients with moderate and severe arterial hypertension during next months. The office SBP/DBP decreased to 35/19 mm Hg ($p < 0.05$) and 42/26 mm Hg. ($p < 0.05$) on the double and triple combination, respectively. After 6 months of the antihypertensive treatment in the double therapy subgroup the target office BP (<140/90 mm Hg) was achieved in 90.9%, in the triple combination group - in 95.7% of patients (the difference was NS). Office BP and ABPM decreased significantly and equally in both treatment groups and there was no difference in achieved BP levels in the both comparison groups. In addition, no significant dynamics of laboratory and biochemistry parameters were noticed during 6 months of treatment except cholesterol related variables. We observed the non-statistically significant elevation of glucose level in statin (+) group on 0,13 mmol/l.

Table 1
Clinical-demographic characteristics for the patients of both groups at the beginning of the study (M ± m).

Indicator	Statin (−), (n = 40)	Statin (+), (n = 59)	P
Women/Men, n,%	12/28 (30,0/70,0%)	29/28 (52,5/47,5%)	NS
Duration of AH, years	7,00 ± 0,96	9,60 ± 0,82	NS
Age, years	50,05 ± 2,30	58,05 ± 1,28	<0,05
BMI, kg/m2	30,13 ± 0,57	31,94 ± 0,70	NS
Smoking, n,%	2/5	4/6,78	NS
Alcohol intake, n, %	6/15	17/28,18	NS
Office SBP mm Hg	160,85 ± 2,18	162,25 ± 1,53	NS
Office DBP mm Hg	100,30 ± 1,64	97,36 ± 1,20	NS
Office HR, b.p.m.	71,90 ± 1,74	70,07 ± 1,14	NS
24SBP, mm Hg	141,80 ± 1,32	141,21 ± 1,10	NS
24DBP, mm Hg	86,65 ± 1,33	85,63 ± 1,11	NS
24HR, b.p.m.	73,38 ± 1,82	70,37 ± 1,22	NS
GFR CKD-EPI, ml/min/1,72m^2	83,87 ± 2,05	76,30 ± 2,10	NS
uric acid, μmol/l	348,02 ± 13,64	361,44 ± 12,14	NS
Cholesterol, mmol/l	5,19 ± 0,15	5,86 ± 0,20	NS
LDL Cholesterol, mmol/l	3,22 ± 0,11	3,71 ± 0,17	NS
IMT max (mm)	1,22 ± 0,03	1,42 ± 0,05	NS
(CAVI) right, units	7,73 ± 0,17	8,32 ± 0,16	NS
(CAVI) left, units	7,62 ± 0,19	8,33 ± 0,19	NS

Abbreviations: Statin (−) – group without adding statin, Statin (+) – group with adding statin to the therapy; AH – arterial hypertension, AHT – antihypertensive therapy, BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate, 24SBP - systolic blood pressure during ambulatory blood pressure monitoring, 24DBP - diastolic blood pressure during ambulatory blood pressure monitoring, 24HR – heart rate during ambulatory blood pressure monitoring, CAVI – cardio-ankle vascular index, IMT – intima-media thickness, b.p.m. – beats per minute, GFR CKD-EPI - calculated glomerular filtration rate, LDL – low density lipoproteins.
Initially patients in statin group were significantly older than patients in statin (−) group on 8 years ($p < 0,05$). Also, they have some evidence to prolong AH duration, increase BMI, TC and LDL-C levels, a rise max IMT in carotid arteries as well as the CAVI levels without any statistical significance.

The dynamic of investigated parameters in both groups are presented in Table 2.

It has been noticed the impact of the statins on BP level. The total cholesterol and LDL cholesterol significantly decreased in statin group on 1,76 mmol/l (30%, $p < 0,05$) and 1,51 mmol/l (41%, $p < 0,05$) respectively what was the appropriate to the used atorvastatin doses. In the group without statin therapy we did not noted the changes of those parameters.

In the statin group the CAVI level remained still unchanged and did not show statistically significant growth at the end of the follow-up period. In spite of BP decreasing, the level of CAVI was shown a statistically significant growth in the group without statins +0,9 right and 1,0 left. The CAVI level on the right/left site changed from 7.73 ± 0.17/7.62 ± 0.19 units to 8.63 ± 0.22/8.62 ± 0.12 units after treatment ($p < 0,05$). Those changes meant can be explained by the increase of the stiffness of the arterial wall in terms of cardio-vascular index CAVI in the group without added statin after 6 months of the therapy.

It was analyzed how many patients in groups had pathological CAVI index ≥ 8 before and after 6 months treatment. In statin group, the

Table 2
Dynamics of the investigated parameters in the comparison groups.

Indicator	Statin (−) (n = 40)			Statin (+) (n = 59)		
	Baseline	6 month	p	Baseline	6 month	p
Office SBP mm Hg	160,85 ± 2,18	125,53 ± 1,08	<0,05	162,25 ± 1,53	126,56 ± 1,38	<0,05
Office DBP mm Hg	100,30 ± 1,64	78,53 ± 0,74	<0,05	97,36 ± 1,20	80,84 ± 0,97	<0,05
Office HR, b.p.m.	71,90 ± 1,74	67,18 ± 1,03	NS	70,07 ± 1,14	64,33 ± 0,79	<0,05
24SBP mmHg	141,80 ± 1,32	120,76 ± 0,90	<0,05	141,21 ± 1,10	124,13 ± 1,09	<0,05
24DBP mmHg	86,65 ± 1,33	71,94 ± 1,39	<0,05	85,63 ± 1,11	74,89 ± 1,29	<0,05
24HR b.p.m.	73,38 ± 1,82	68,34 ± 1,51	<0,05	70,37 ± 1,22	68,29 ± 0,83	NS
Glucose, mmol/l	5,64 ± 0,14	5,57 ± 0,14	NS	5,90 ± 0,14	6,03 ± 0,16	NS
GFR CKD-EPI, ml/min/1,72m^2	83,87 ± 2,05	82,09 ± 1,24	NS	76,30 ± 2,10	76,30 ± 2,10	NS
Uric acid, μmol/l	348,02 ± 13,64	315,73 ± 9,18	NS	361,44 ± 12,14	345,25 ± 6,22	NS
Total cholesterol, mmol/l	5,19 ± 0,15	5,24 ± 0,21	NS	5,86 ± 0,20	4,17 ± 0,18	<0,05
LDL Cholesterol, mmol/l	3,22 ± 0,11	3,38 ± 0,17	NS	3,71 ± 0,17	2,27 ± 0,13	<0,05
(CAVI) right	7,73 ± 0,17	8,63 ± 0,22	<0,05	8,32 ± 0,16	8,44 ± 0,16	NS
(CAVI) left	7,62 ± 0,19	8,62 ± 0,12	<0,05	8,33 ± 0,19	8,24 ± 0,15	NS
(CAVI) right≥8, n, %	16 (40%)	15 (37,5%)	NS	32 (54,2%)	28 (47,5%)	NS
(CAVI) left≥8, n, %	14 (35%)	15 (37,5%)	NS	28 (47,5%)	18 (30,5%)	NS

Abbreviations: Statin (−) – group without adding statin, Statin (+) – group with adding statin to the therapy; AHT – antihypertensive therapy, SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate, 24SBP - systolic blood pressure during ambulatory blood pressure monitoring, 24DBP - diastolic blood pressure during ambulatory blood pressure monitoring, 24HR – heart rate during ambulatory blood pressure monitoring, CAVI – cardio-ankle vascular index, b.p.m. – beats per minute, GFR CKD-EPI - calculated glomerular filtration rate, LDL – low density lipoproteins.

number of patients with pathological CAVI decreased compared with non-statin group. In statin group the CAVI right was declined slightly from 54,2% to 47,5% and left from 47,5% to 30,5%. Nevertheless, some positive changes were taking place in non-statin group that presented in the table above (Table 2).

Thus, the progression of arterial stiffening in patients with 2nd and 3rd stages of AH on the antihypertensive therapy without statins and retardation of the further stiffens arteries in the same patients after adding of statin. It is known that the CAVI index does not depend on the BP level. In our study, it was shown the impact of statin therapy on the CAVI index in the Caucasian patients with hypertension when added it to the guidelines recommended antihypertensive therapy and found a prevention of the arterial stiffness progression.

In the next part of this study, the Spearmen correlation of patients' parameters with the CAVI was analyzed. These data have been presented in Table 3. In patients taking atorvastatin was found statistically significant correlations of the CAVI index with age, the levels of serum Potassium, TG, LDL-Cholesterol and HDL-Cholesterol prior to treatment. Also, the same pattern regarding correlation was noted during the hypertension history, the blood glucose level and the maximum IMT in Carotid Arteries.

Table 3
Correlations of the CAVI index with other patients parameters in statin (+) group.

Parameter	CAVI	
Age, years	r = 0,716	P< 0,001
Weight, kg	r = - 0,375	P = 0,029
Duration AH, years	r = 0,384	P = 0,036
Statins added	r = 0,538	P = 0,002
IMT max, mm	r = 0,576	P< 0,01
Glucose, mmol/l	r = - 0,386	P = 0,035
K+, mmol/l	r = - 0,469	P = 0,014
HDL-cholesterol, mmol/l	r = 0,505	P = 0,008
TG, mmol/l	r = - 0,344	P = 0,046
LDL-cholesterol, mmol/l	r = 0,402	P = 0,042

Abbreviations: AH – arterial hypertension, CAVI – cardio-ankle vascular index, IMT – intima-media thickness, K + - serum potassium level, LDL – low density lipoproteins, LDL – low density lipoproteins.

On performing a regression analysis, there was a relationship between the CAVI index and the use of statins b = 0.403, p = 0.043; the level of total cholesterol before treatment b = 0.426, p = 0.041; the level of blood triglycerides before treatment b = 0.417, p = 0.046; and age b = 0.548, p = 0.008. In group without statin, it was clear that the only correlation with the CAVI was age: CAVI b = 0.327, p = 0.036.

Thus, guidelines recommended antihypertensive therapy based on the double or triple fixed combinations of valsartan/amlodipine and valsartan/amlodipine/hydrochlorothiazide with the adding of atorvastatin leading to a significant control the progression of arteries stiffness and prevention the organ damage. Also, there were no negative effects on metabolic parameters.

4. Discussion

This study is the first pilot investigation in which the CAVI index was used to assess target organ damage in white patients with 2nd and 3rd grade of AH. Adding statins to the recommended guidance of double and triple antihypertensive therapy leading to a retardation of the arterial stiffening progression in this category of patients.

Measurement of the arterial stiffness in routine medical practice is important for the assessment of the progression of the arterial wall damage and atherosclerosis development. Many parameters have been proposed that quantitatively represent arterial stiffness. Among them, PWV is the most often used in clinical practice due to its simplicity, non-invasively and affordability. However, PWV level substantially depends on the BP at the time of the measurement and the BP lowering per sec reduces the PWV. Therefore, PWV is not suitable for the assessment of the real changes of the arterial stiffness, especially in the studies with the substantial changes in the BP level. In 2006, K. Shirai with coworkers proposed the CAVI as a new arterial wall stiffness parameter and it is almost independent from the BP changes. They invented a proper device that also is independent from the operator skill [14].

Because the CAVI index does not depend from the BP level in the moment of the measurement, it can be used for the more accurate assessment of the real impact of the antihypertensive treatment on the changes of arterial wall stiffness. It has been shown that a fixed combination of losartan/hydrochlorothiazide reduced the CAVI level in hypertensive patients with diabetes mellitus [7]. However, the mono therapy of thiazide did not have any changes on it.

In our study, patients with severe hypertension were strongly recommended to be prescribed the double or triple fixed combination. This treatment did not have any influence on the reduction of arterial stiffness during 6 months, according to the CAVI index. Despite the fact, that the BP was reduced significantly, we noted the significant increase of this parameter.

G.Uehara et al. compared impact of candesartan, telmisartan and losartan on CAVI, and reported that candesartan among compared drugs reduced the CAVI index mostly [7]. Bukuda et al. [15] studied effects of

candesartan comparison with the calcium channel blockers. They showed a significant level of the BP decline equally in both groups, including the CAVI levels remained nearly equal in two observed groups. In contrast, in Miyashita et al. study compared the effect of amlodipine and olmesartan on the level of BP and the CAVI index. As a result of their study, the BP level reduced equally but the CAVI was significantly reduced only in the olmesartan group in comparison to the amlodipine group [16].

According to some resent studies, it was shown the positive effect of angiotensin II receptor blockers on some parameters of the vascular elasticity [17,18,19,20]. However, in our study, we did not notice any significant positive dynamic of the CAVI index after 6 months of treatment with fixed double or triple combinations based on valsartan without statins therapy.

The CAVI index was studied as a non-invasive marker of arterial stiffness in some metabolic disorders [15,21,22]. It is widely known that the CAVI was significantly elevated among the patients with metabolic syndrome and the weight loss reduced the CAVI significantly in obese patients [23].

Regarding carotid artery wall changes, several researchers found strong correlations between CAVI and carotid TIM, but the presence of the atherosclerotic plaque appeared to show a much stronger correlation with CAVI [3,4,24,16,17,20]. Correlations of CAVI and TIM may be an important predictor of cerebral thrombosis in patients with high risk of atherosclerosis [20,25]. Cholesterol-lowering drugs such as pitavastatin, ezetimibe, and triglyceride-lowering drugs, eicosapentaenoic acid, have been reported to reduce CAVI [26]. In the study of T. Yamaguchi et al., compared the effect of bezafibrate with eicosapentaenoic acid on vascular stiffness measured by the CAVI in patients with diabetes and hypertriglyceridemia. The researchers showed a direct significant positive effect of bezafibrate on the arterial stiffness (due to a decrease in the CAVI index) after 12 weeks of treatment and did not note the such effect of eicosopentaenoic acid [25]. There were a significant decrease in the serum triglycerides level, the improvement in the glycemic profile of the patients with diabetes due to the effect of the insulin resistance. In our study we did not include patients with diabetes, there were no significant changes in glucose levels in both treatment groups.

XiaoXiao Zhao et al. studied the correlation of the CAVI index with dyslipidemia and cardiovascular risk factors [27]. They showed that CAVI among patients with AH was higher in comparison with the patients without hypertension. The CAVI index in this study was associated with age, BP, level of total cholesterol, triglycerides and LDL. In this study the authors didn't notice any associations between the CAVI index and the use of statins as well as between smokers and non-smokers and the presence of diabetes.

In our study, we found a significant relationship between the CAVI index and the use of statins in patients with hypertension who received double or triple fixed combination of antihypertensive drugs. These patients didn't have the diabetes or previous cardiovascular complications in the study performed. However, in our study the CAVI correlated with age, weight, duration of AH, glucose and cholesterol level.

As it was mentioned above, the most of current studies express their concerns with regard to the relationship between CAVI and the development of atherosclerosis, cognitive impairment and metabolic syndrome which were conducted in Japan and China [13,15,21,28–32,20].

A.Aminuddin et al. analyzed information on arterial stiffness and the relationship to dyslipidemia, inflammation and hypertension being taken from various PubMed publications and Scopus database. All of them were published in available sources. The authors found that inflammation measured by increased level of C reactive protein (CRP) contributes to increase of arteries stiffness in patients with dyslipidemia and this increase can contribute the development of hypertension. In patients with dyslipidemia, the inflammation was associated with a high rate of pulse wave velocity [33].

J.Yin et al. studied relationship between the arterial stiffness and atherosclerosis being measured as atherogenic index in patients with hypertension in 4744 Chinese patients with hypertension. Arterial stiffness was measured with PWV. The authors identified the atherogenic index as ratio of plasma triglycerides to the high-density lipoprotein cholesterol level. This study concluded that in patients with hypertension the arterial stiffness strongly correlated with atherogenic index [34].

Recently G. Chang et al. was evaluated the prognostic value of PWV for the cardio vascular disease progression in 630 hospitalized patients with hypertension in China in 2007–2008 years. Authors found the strong association between the arterial stiffness measured as PWV with the atherosclerotic cardiovascular disease (ASCVD) risk. Authors indicated that PWV 12.45 m/s was a good predictor of high CVD risk [35].

A Cicero et al. evaluated added statins to ACE inhibitors on CVD outcomes in Brisighella Heart Study (8-year follow-up). Authors concluded that combined treatment with ACE inhibitors and atorvastatin in hypertensive patients significantly reduce the risk of developing CVD in compared with treatment with ACE inhibitors alone [36].

A Cicero et al. commented interesting results X Zhang et al. and agree that a great idea about self-management for control BP in patients with AH [37]. X Zhang et al. analyzed cost-effectiveness of different hypertension management strategies in a community setting. Thay explore whether the Chinese Health Literacy Scale (CHLSH) can be used to screen for appropriate patients with hypertension for self-management and to evaluate the clinical effectiveness and health economic evaluation of three hypertension management schemes. It was prospective study which performed from March 2017 to July 2017 in consecutive patients with primary hypertension and of 50–80 years of age [38]. Author concluded that the CHLSH can be used as a tool for screening patients with hypertension for self-management. The cost-effectiveness of self-management was optimal.

A Sofogianni, K Tziomalos commented the results of the study by Kim et al. [39] which evaluate the efficacy and safety of a fixed-dose combination of amlodipine/rosuvastatin in patients with dyslipidemia and hypertension. Sofogianni A, Tziomalos K. concluded that provide additional evidence regarding the safety and efficacy of fixed-dose combinations of statins and antihypertensive agents. Authors concluded that improved adherence to fixed-dose combination will possibly better control of both hypertension and hypercholesterolemia and greater reductions in cardiovascular morbidity [40].

Our study was a pilot study in which we evaluated impact of an additional treatment by statin on the CAVI index. The changes of this index was analyzed during modern guidelines recommended fixed combination antihypertensive therapy in Caucasian patients with 2nd and 3rd grade of AH. It is clear that the adding of atorvastatin (20–40 mg) to the modern double and triple fixed antihypertensive combination based on valsartan resulting in a retardation of the progression of arterial stiffening according to the CAVI index, while in the group without statin the progression was evident.

The limitations of this study were following: a single center study without any blinding to the adding of atorvastatin and the absence of the total and LDL cholesterol target levels.

5. Conclusion

In moderate and severe hypertensive patients (2nd and 3^{d} stages) the modern guided recommended combination therapy did not the prevent the progression of arterial stiffness according to the CAVI data. Adding of atorvastatin (20–40 mg) led to retardation in the progression of the arterial stiffness.

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CRediT authorship contribution statement

Yu Sirenko: Conceptualization, Methodology, Investigation, Supervision, Project administration, Writing – review & editing. **O. Rekovets:** Methodology, Investigation, Formal analysis, Visualization, Writing – original draft.

Declaration of competing interest

No.

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