Privalova E. A., Belenkov Yu. N., Danilogorskaya Yu. A.,
Zheleznykh E. A., Kozhevnikova M. V., Zektser V. Yu., Lishuta A. S., Ilgisonis I. S.
I. M. Sechenov First Moscow Medical University (Sechenov University), Moscow, Russia

To study the dynamics of serum levels of vascular remodeling in patients with hypertension, including in combination with type 2 diabetes mellitus during 12-month therapy with perindopril A

Aim	To study the dynamics of serum markers for vascular remodeling in patients with arterial hypertension (AH), including AH associated with type 2 diabetes mellitus (DM2) during the 12-month treatment with the angiotensin-converting enzyme (ACE) inhibitor, perindopril A.
Material and methods	The study included patients with grade 1–2 AH with or without type 2 DM (30 and 32, respectively). Perindopril A 10 mg/day was administered for the outpatient correction of previous, ineffective antihypertensive therapy. The following biomarkers were measured for all patients at baseline and at 12 months: matrix metalloproteinase-9 (MMP-9), tissue inhibitor of metalloproteinase-1 (TIMP-1), E-selectin, endothelin 1, transforming growth factor β-1 (TGF-β1), and von Willebrand factor (WF). Laboratory tests were performed with enzyme immunoassay.
Results	After 12 months of the perindopril A (perindopril arginine) 10 mg/day treatment, both groups achieved the goal blood pressure. Evaluation of biomarker dynamics during the perindopril A treatment showed significant decreases in MMP-9, TIMP-1, and endothelin 1 in the AH group; then the level of TIMP-1 returned to normal values ($p<0.05$). In the AH+DM2 group, the MMP-9 concentration was significantly decreased ($p<0.05$); the other values did not show any significant differences. In both groups, MMP-9 was significantly decreased (28.6% ($p=0.01$) in group 1 and 33.2% ($p=0.00$) in group 2. Notably, in none of these groups, did this index reach normal values. Also, there were no significant differences in this index between the groups ($p=0.66$). It should be noted that the decreases in TIMP-1 were significantly different between the groups ($p=0.001$). Thus, this biomarker did not significantly decrease in patients with AH and DM2 ($p=0.26$) whereas in group 1 (AH without DM2), the level of TIMP-1 decreased by 39.3% and reached the normal range ($p=0.005$).
Conclusion	Concentrations of biomarkers were decreased in both groups. However, in the AH group, there were statistically significant decreases in the markers that reflect processes of fibrosis and vasoconstriction. At the same time in the AH+DM2 group, there was no significant dynamics of the biomarkers, which was most likely due to more pronounced damage of blood vessels. However, the decrease in MMP-9 may indicate an alleviation of fibrotic processes in arterial walls. These results allow a conclusion that the long-term treatment with the ACE inhibitor, perindopril A, may reverse remodeling of the vascular changes that are called «early vascular ageing».

Keywords	Biomarkers; type 2 diabetes mellitus; arterial hypertension; endothelial dysfunction; perindopril
For citations	Privalova E.A., Belenkov Yu.N., Danilogorskaya Yu.A., Zheleznykh E.A., Kozhevnikova M.V., Zektser V.Yu. et al. To study the dynamics of serum levels of vascular remodeling in patients with hypertension, including in combination with type 2 diabetes mellitus during 12-month therapy with perindopril A. Kardiologiia. 2022;62(1):24–31. [Russian: Привалова Е.А., Беленков Ю.Н., Данилогорская Ю.А., Железных Е.А., Кожевникова М.В., Зекцер В.Ю. и др. Оценка динамики уровня сывороточных маркеров ремоделирования сосудистого русла у больных артериальной гипертензией, в том числе в сочетании с сахарным диабетом 2-го типа, на фоне 12-месячного лечения периндоприлом А. Кардиология. 2022; 62(1):24–31]

Corresponding author	Privalova E.A. E-mail: e_a_privalova@bk.ru

If the already high prevalence of arterial hypertension (AH) and diabetes mellitus (DM) in Russia continues to increase, it may soon reach pandemic proportions. With only 14% of male patients and 30% of female patients achieving the target levels of blood pressure (BP), the percentage of patients with AH reaches 45% of the adult population [1, 2]. Out of over 425 million people diagnosed with DM so far, about 90% have DM type 2 [3]. The high prevalence of DM is due to significant changes in the contemporary lifestyle: easily available high-calorie food and lack of physical activity, as well as a lack of treatment efficacy due to poor adherence. According to the World Health Organization (WHO), the percentage of patients with AH will continue to increase, amounting to 15–20% by 2025 [4]. Thus, in order to develop

ISSN 0022-9040. Kardiologiia. 2022;62(1). DOI: 10.18087/cardio.2022.1.n1890

and improve the existing diagnostic algorithms, it is of immediate relevance to study these groups of patients, taking into consideration many emerging opportunities including the evaluation of biological markers [5].

The concept of early vascular aging, first defined by the European Society of Cardiology in 2017, is now one of the leading concepts explaining the cardiovascular continuum. Not only is the vascular wall a target for many diseases, but it also serves as a touchstone for determining the severity of abnormalities [6]. Thus, a detailed study of molecular processes accompanied by an increase or decrease in the levels of various biomarkers can significantly improve the efficacy of treatment [7, 8]. In this way, a prognosis is determined for patients with AH and DM not only by BP and blood glucose, but also the activity of biomarkers that change during modulation of endothelial function and vascular remodeling [9].

Along with smoking and hyperlipidemia, AH and DM are well-established risk factors for endothelial dysfunction (ED). ED is seen as a complex of interrelated changes, with the leading role taken by the regulatory mechanisms of biomarkers that affect vascular wall remodeling.

The main biomarkers actively involved in the development of ED are as follows:

1) factors derived from the endothelium and released from the cells in the basolateral direction or into the blood (nitric oxide, prostacyclin);

2) factors accumulated in the endothelium and released from during stimulation (von Willebrand factor, P-selectin, tissue plasminogen activator), which can enter the blood not only when the endothelium is stimulated, but also when it is activated and damaged;

3) factors that are not normally synthesized, but whose levels dramatically elevate when the endothelium is activated (endothelin-1, ICAM-1, VCAM-1, E-selectin, PAI-1);

4) factors derived from and accumulated in the endothelium (t-PA) or endothelial membrane proteins (receptors) (thrombomodulin, protein C receptor).

The following biomarkers were evaluated: E-selectin, endothelin-1, matrix metalloproteinase-9 (MMP-9), tissue inhibitor of metalloproteinase-1 (TIMP-1), MMP-9/TIMP-1 ratio, transforming growth factor β-1 (TGF-β1), VWF.

The protein E-selectin is involved in the binding of leukocytes to the endothelial wall due to numerous factors, including when the endothelium is damaged and inflammatory cytokines are expressed [10]. Thus, estimating blood levels of E-selectin is important not only for determining ED, but also for predicting the development of cardiovascular diseases (CVDs). As one of the most active participants of vascular platelet hemostasis [11], von Willebrand factor (VWF) has been shown to play a significant role in the formation of clots in small arteries [12]. Thus, increased plasma levels of VWF can be considered as the main predictor of hypercoagulation in patients with ED.

Since matrix metalloproteinases (MMPs) take a leading role in the development of such processes as morphogenesis, resorption, tissue remodeling, angiogenesis, their increased concentration affects the progression of atherosclerosis, plaque destabilization, and vascular remodeling (due to the degradation of various protein components) [13–15]. Among the family of molecules that reduce MMP activity, TIMP-1 regulates the enzymatic activity of MMP-9. In order to permit the reorganization of the extracellular matrix for preventing hyperactivation, it is necessary to maintain the balance between MMPs and their inhibitors, including TIMPs [16]. Endothelin-1 is one of the main triggers of vasospasm, which targets muscle receptors and provokes their contraction to increase BP and vascular stiffness [17]. The crucial role of endothelin-1 in staging and assessing the nature of the pathological process occurring in the vasculature was also hypothesized [18]. Thus, estimating endothelin-1 levels can play a fundamental role in determining the pathophysiological mechanisms that prevail in the development of AH. TGF-β1 belongs to a huge family of proteins that regulate many processes of proliferation, differentiation, adhesion of various cells, involvement in the processes of reproduction, embryonic growth, etc. Since increased concentration of TGF-β1 has been shown to be most often associated with endothelial damage, determining TGF-β1 levels becomes a useful consideration in the detection of ED.

All these closely interrelated factors form a virtually closed system, in which the interconnected processes are indefinitely looped. In this regard, assessing ED using various biomarkers is of great prognostic significance.

Thus, the efficacy of treatment and prognosis for patients with AH, including those with DM type 2, can be determined not only by BP, but also by the reduction of ED, which particularly affects the prognosis. According to previous studies, means for influencing the renin-angiotensin-aldosterone system (RAAS) are among the most effective treatments for patients with AH. In the present study, in which angiotensin-converting enzyme (ACE) inhibitors are mainly administered, perindopril arginine (A) was used. This is supported by a large evidence base (EUROPE, ADVANCE, HYVET, ASCOT, PROGRESS) [19–21], as well as having significant organ protective properties, which are crucial for patients with AH and DM [22].

Objective

To study the changes in the plasma levels of vascular remodeling markers in patients with AH, including those

with concomitant DM type 2, during the 12-month administration of perindopril A.

Material and Methods

Open, non-randomized, observational study was conducted in Cardiology Department No. 1 of I.M. Sechenov First Moscow State Medical University (the Russian Federation). The study included patients with AH grade 1–2 divided into the groups with comparable size depending on the presence of DM type 2. All patients underwent clinical examinations before the administration of perindopril A and after 12 months of treatment. Before the inclusion, all patients received comparable concomitant treatment (calcium channel blockers, beta-blockers). DM was compensated in all patients to ensure comparable blood glucose levels; 90% of patients were treated with biguanides. At baseline, ACE inhibitors or angiotensin II receptor blockers were discontinued, with perindopril A 10 mg/day being prescribed following the two-week washout period. Follow-up visits were performed to assess the treatment efficacy once every 3 months. Exclusion criteria were as follows: secondary forms of AH; DM type 1; coronary artery disease (CAD); chronic heart failure functional class III–IV; systemic diseases; cancer; clinically significant rhythm and conduction disorders; glomerular filtration rate less than 50 mL/min 1.73 m2; severe liver dysfunction.

Patients with AH were divided into 2 groups depending on the presence of DM type 2: Group 1 included AH patients without DM (n=32, 18 female and 14 male patients); Group 2 comprised AH patients with DM 2 DM (n=30, 19 female and 11 male patients). The groups were comparable by age, sex, duration of AH. Characteristics of the patients are detailed in Table 1.

Enzyme-linked immunosorbent assay was used to determine the levels of biomarkers of ED and vascular remodeling (MMP-9, TIMP-1, E-selectin, endothelin-1, TGF-β1, VWF).

Data were processed using IBM SPSS v.22.0; data analysis used non-parametric criteria. Quantitative variables were expressed using the median and lower and upper quartiles (Me [LQ; UQ]), as well as minimum and maximum values. Statistical significance of the differences between the two samples was determined using the Mann–Whitney test (independent samples) and Wilcoxon test (dependent samples, i.e., before/after comparisons). Differences were statistically significant with $p<0.05$.

Results

The 12-month follow-up examination showed that the target BP levels were achieved in both groups. Changes in the serum marker levels were evaluated in the study groups. Table 2 represents a comparison of biomarker levels in patients with AH before and after treatment.

The estimation of biomarker levels before and after treatment with perindopril A 10 mg/day revealed a statistically significant decrease in the levels of MMP-9 and TIMP-1 ($p<0.001$ and $p=0.005$, respectively) along with normalized TIMP-1 levels. Positive changes were also observed in the levels of endothelin-1. While this was a statistically significant decrease, return to normal was not achieved. No statistically significant differences were found for the other parameters (see Table 2). Thus, the levels of markers of fibrosis and vasoconstriction decreased in patients with AH.

The assessment of changes in biomarker levels in AH patients with DM type 2 identified a statistically significant decrease in the concentration of MMP-9 before and after therapy; however, reference values were not achieved ($p=0.011$). There were no statistically significant differences in the levels of TIMP-1, endothelin-1, E-selectin, and VWF ($p=0.260$; $p=0.940$, $p=0.140$, and $p=0.320$, respectively) during therapy. Although a statistically significant decrease was found in the levels of TGF-β1, all values were within the reference range (Table 3).

Thus, the lack of statistically significant changes in the biomarkers of interest in the group of AH patients with DM is most likely due to more severe vascular damage. However, decreased levels of MMP-9 may be indicative of mitigating fibrosis of the vascular walls.

There was a statistically significant decrease in the levels of MMP-9 in both groups: by 28.6% ($p=0.010$) and 33.2% ($p=0.001$) in Group 1 and Group 2, respectively. It is notable

Table 1. Demographic characteristics of patients included in the study

Parameter	AH + DM type 2 (n=30)	AH (n=32)	p
Age, years	60.5 [56; 64.75]	58.5 [54.75; 65.0]	0.311
Male/female	11/19	14/18	0.570
Duration of AH, years	12 [9.25; 15]	12.0 [9.0; 14.25]	0.799
BMI, kg/m2	35.6 [33.7; 37.8]	28.66 [26.82; 29.83]	< 0.001
Glucose, mmol/L	6.3 [6.0; 7.43]	5.1 [4.8; 5.2]	< 0.001
Creatinine, mg/dL	1.14 [0.9; 1.25]	0.86 [0.8; 0.99]	< 0.001
GFR, mL/min/1.73m^2	62.09 [52.73; 71.65]	76.99 [72.00; 94.01]	< 0.001
SBP, mm Hg	158 [156; 163.5]	156 [153; 160]	0.024
DBP, mm Hg	94 [90; 97.5]	88 [86; 90]	< 0.001

AH – arterial hypertension; DM – diabetes mellitus; BMI – body mass index; GFR – glomerular filtration rate; SBP – systolic blood pressure; DBP – diastolic arterial hypertension.

ISSN 0022-9040. Kardiologiia. 2022;62(1). DOI: 10.18087/cardio.2022.1.n1890

that the reference values were not achieved in any group. Moreover, there were no statistically significant differences in this indicator (p=0.660) between the groups (Figure 1).

Matrix metalloproteinase-9

The statistically significant difference between the groups in the decrease in TIMP-1 levels (p=0.001) should be noted. Although no statistically significant decrease in this biomarker was detected in AH patients with DM type 2 (p=0.260), it decreased by 39.3% (p=0.005) in Group 1 and returned to normal (Figure 2).

The comparison of the stoichiometric ratio of the fibrosis marker and its inhibitor (MMP-9/TIMP-1) showed no statistically significant changes in any group after 12 months of treatment. There were also no statistically significant changes in LVEF in any group (p>0.05).

Evaluation of the trends in the severity of ED revealed a statistically significant decrease in endothelin-1 levels only in AH patients without DM type 2 to 0.38 [0.2; 1.2] ng/mL (p=0.009).

Thus, perindopril A at 10 mg/day had a more pronounced effect on reducing the levels of fibrosis markers in patients without DM. The significant decrease in the vasoconstriction marker in patients without DM confirms the earlier conclusion of a more severe vascular damage in patients with DM.

Discussion

Diseases such as AH and DM involve endothelial dysfunction and vascular remodeling, which mirrors the increased expression of extracellular matrix proteins. An experimental study carried out by Flamant et al. showed that initial AH is associated with the induction of matrix metalloproteinases and collagen degradation [23].

ACE inhibitors have the largest evidence base of all antihypertensive drugs regarding the effect on vascular remodeling. This class of drugs is also effective in patients with hypertensive heart disease, including those with DM. Moreover, clinical trial data show that ACE inhibitors play an important role in the prevention of chronic kidney disease (CKD) progression. According to the Seventh Report of the Joint National Committee (JNC7), the European Society of Hypertension/European Society of Cardiology (2003 ESH-ESC), as well as the Japanese Society of Hypertension, ACE inhibitors are recommended for the treatment of patients with AH and CKD [24]. Perindopril was chosen among ACE inhibitors for this study due to the large evidence base describing its effect on the prognosis in patients with CVDs (EUROPE, ADVANCE, HYVET, ASCOT, PROGRESS). The role of ACE inhibitors in improving endothelial function was also shown in the PERTINENT study [25].

In our study, changes in biomarker levels were demonstrated during a treatment with perindopril 10 mg/day for 12 months. Although no statistically significant differences were found between the study groups in the levels of fibrosis biomarkers MMP-9 and TIMP-1, and the MMP-9/TIMP-1 ratio, the levels of MMP-9 and TIMP-1 were elevated in both groups. Given the elevated levels of serum markers of vascular remodeling, namely MMP-9 TIMP-1, TGF-β1 and endothelin-1, these

Table 2. Changes in biomarker levels in patients with AH before treatment and in 12 months of administering perindopril A 10 mg/day

Parameter	References	Baseline	In 12 months	p
Matrix metalloproteinase-9, ng/mL	< 139.4	218.5 [189.0; 276.0]	146.0 [114.3; 216.3]	< 0.001
Tissue inhibitor of metalloproteinase-1, ng/mL	9–321	431.5 [386.8; 488.5]	262.0 [225.8; 342.3]	0.005
Transforming growth factor β-1, ng/mL	5,222–13,731	3,938.5 [1,808.8; 7,694.0]	2,526.5 [1,726.3; 4,253.8]	0.076
Endothelin-1, ng/mL	< 0.26	1.73 [0.63; 2.30]	0.38 [0.20; 1.19]	0.009
E-selectin, ng/mL	21–186	36.2 [28.5; 50.1]	35.7 [22.9; 41.9]	0.160
von Willebrand factor, IU/mL	0.5–1.5	0.58 [0.50; 0.73]	0.58 [0.47; 0.73]	0.670

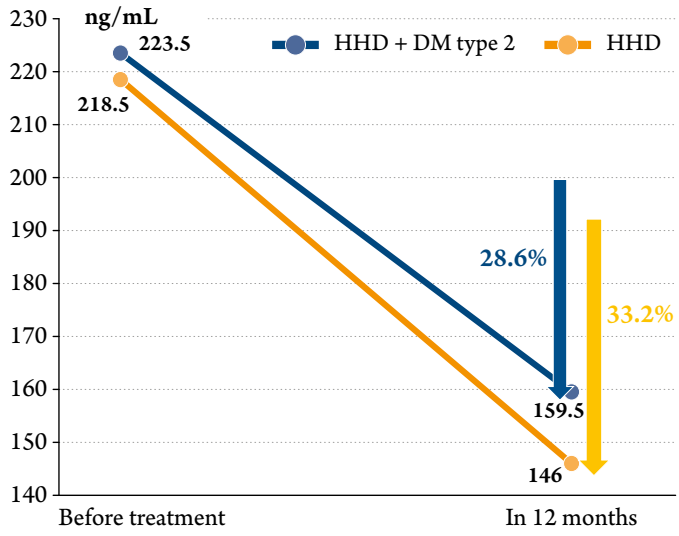
Table 3. Changes in biomarker levels in patients with AH and DM type 2 before treatment and in 12 months of administering perindopril A 10 mg/day

Parameter	References	Baseline	In 12 months	p
Matrix metalloproteinase-9, ng/mL	< 139.4	223.5 [172.5; 254.0]	159.5 [115.3; 228.8]	0.011
Tissue inhibitor of metalloproteinase-1, ng/mL	9–321	459.5 [286.8; 726.5]	419.0 [310.5; 505.8]	0.260
Transforming growth factor β-1, ng/mL	5,222–13,731	116489.0 [4117.8; 37933.8]	2933.5 [1571.8; 11286.5]	0.050
Endothelin-1, ng/mL	< 0.26	0.46 [0.29; 1.30]	0.74 [0.45; 1.13]	0.940
E-selectin, ng/mL	21–186	51.4 [31.9; 65.2]	45.8 [32.2; 61.2]	0.140

changes can mainly be caused by the extracellular matrix restructuring, as well as the progression of fibrosis and ED. Thus, MMP-9 and TIMP-1 play a significant role in the proliferation (degradation and reorganization) of the extracellular matrix components, which underlie the progression of vascular fibrosis [26]. The involvement of metalloproteinases in the mechanisms of vascular wall remodeling has already been studied, demonstrating a significant effect on the vascular wall remodeling through the migration, proliferation, and apoptosis of smooth muscle cells, endothelial, and inflammatory cells, which determine the formation of intima [27]. According to previous studies, RAAS activation in AH also increases the production of metalloproteinases [28]. The observed activation of MMP-9 and TIMP-1 in our patient confirms the involvement of the combination of MMP-9 and TIMP-1 in the processes of vascular remodeling. Our findings are consistent with the Flavia Mariana Valente study, which revealed a significant increase in the levels of MMP-9 in hypertensive crisis [25]. Earlier, an increase in the MMP-9 levels was described during the formation and progression of atherosclerosis, leading to unfavorable outcomes and cardiovascular death [29]. Increased levels of MMP-9 and TIMP-1 can also predict the development of CAD and other vascular diseases.

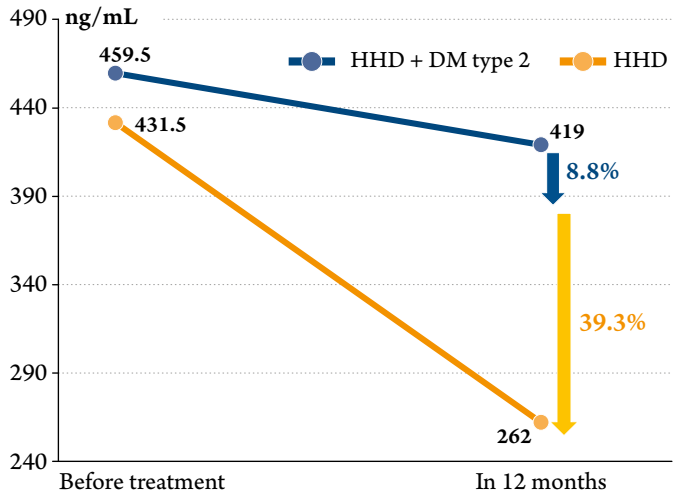
While TGF-β1 remained within the reference values, the intergroup comparison showed that TGF-β1 was significantly higher in AH patients with DM than those without DM. Since TGF-β1, whose production increases in hyperglycemia, is a factor in increased vascular wall stiffness, this identified feature mirrors more pronounced vascular remodeling in this group of patients; among the endothelial function markers (endothelin-1, E-selectin, and VWF), only changes in the levels of endothelin-1 were observed in both groups. We also detected a statistically significant increase in the levels of endothelin-1 in AH patients without DM type 2 as compared to those with DM type 2. Endothelin-1, as a powerful vasoconstrictor, is expected to largely determine the degree of ED and predict the clinical manifestations of various diseases. Endothelin-1 is considered as a marker and predictor of the severity of CVDs, which contributes to the development of vascular atherosclerosis, ischemic brain damage, pulmonary and systemic hypertension [30–32]. Thus, elevated levels of endothelin-1 may be indicative of ED and prevailing processes of vasoconstriction in the study groups. Previous studies also showed that increased serum levels of endothelin-1 are associated with higher systolic and diastolic BP [33]. Several studies have also provided evidence of improved microcirculation in various target organs [28].

Figure 1. MMP-9 levels in AH patients with and without DM type 2 before and after 12 months of treatment



MMP – matrix metalloproteinase-9; AH – arterial hypertension; DM – diabetes mellitus; HHD – hypertensive heart disease.

Figure 2. TIMP-1 levels in AH patients with and without DM type 2 before and after 12 months of treatment



TIMP-1 – tissue inhibitor of metalloproteinase-1; AH – arterial hypertension; DM – diabetes mellitus; HHD – hypertensive heart disease.

Conclusion

Our study showed that long-term treatment with angiotensin-converting enzyme inhibitor perindopril A can slow down the remodeling of the vascular bed, referred to as early vascular aging. This is manifested as decreased levels of biomarkers responsible for fibrosis, proliferation, and vasoconstriction, which reduces vascular stiffness at all levels. The significant role played by decreased levels of biomarkers in the organ protective properties

ISSN 0022-9040. Kardiologiia. 2022;62(1). DOI: 10.18087/cardio.2022.1.n1890

of perindopril A is of direct relevance to the prognosis for patients suffering from such disorders. In order to select the most effective therapy, further research into the role of matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1, endothelin-1, and transforming growth factor β-1 in vascular wall remodeling is clearly required.

No conflict of interest is reported.

The article was received on 01.09.2021

REFERENCES

1. Yasmin, Wallace S, McEniery CM, Dakham Z, Pusalkar P, Maki-Petaja K et al. Matrix Metalloproteinase-9 (MMP-9), MMP-2, and Serum Elastase Activity Are Associated With Systolic Hypertension and Arterial Stiffness. Arteriosclerosis, Thrombosis, and Vascular Biology. 2005;25(2):372–8. DOI: 10.1161/01.ATV.0000151373.33830.41
2. Vatutin N.T., Sklyannaya E.V. Prevalence of arterial hypertension and risk factors in young adults. Archive of internal medicine. 2017;7(1):30–4. [Russian: Ватутин Н.Т., Склянная Е.В. Распространенность артериальной гипертензии и факторов риска у лиц молодого возраста. Архивъ внутренней медицины. 2017;7(1):30-4]. DOI: 10.20514/2226-6704-2017-7-1-30-34
3. Dedov I.I., Shestakova M.V., Mayorov A.Yu., Vikulova O.K., Galstyan G.R., Kuraeva T.L. et al. Standards of specialized diabetes care. Edited by Dedov I.I., Shestakova M.V., Mayorov A.Yu. 8th edition. Diabetes mellitus. 2017;20(1S):1–121. [Russian: Дедов И.И., Шестакова М.В., Майоров А.Ю., Викулова О.К., Галстян Г.Р., Кураева Т.Л. и др. Алгоритмы специализированной медицинской помощи больным сахарным диабетом. Под ред. Дедова И.И., Шестаковой М.В., Майорова А.Ю. 8-й выпуск. Сахарный диабет. 2017;20(1S):1-121]. DOI: 10.14341/DM20171S8
4. Kobalava Zh.D., Konradi A.O., Nedogoda S.V., Shlyakhto E.V., Arutyunov G.P., Baranova E.I. et al. Arterial hypertension in adults. Clinical guidelines 2020. Russian Journal of Cardiology. 2020;25(3):149–218. [Russian: Кобалава Ж.Д., Конради А.О., Недогода С.В., Шляхто Е.В., Арутюнов Г.П., Баранова Е.И. и др. Артериальная гипертензия у взрослых. Клинические рекомендации 2020. Российский кардиологический журнал. 2020;25(3):149-218]. DOI: 10.15829/1560-4071-2020-3-3786
5. Harvey A, Montezano AC, Lopes RA, Rios F, Touyz RM. Vascular Fibrosis in Aging and Hypertension: Molecular Mechanisms and Clinical Implications. Canadian Journal of Cardiology. 2016;32(5):659–68. DOI: 10.1016/j.cjca.2016.02.070
6. Castorena-Gonzalez JA, Staiculescu MC, Foote C, Martinez-Lemus LA. Mechanisms of the Inward Remodeling Process in Resistance Vessels: Is the Actin Cytoskeleton Involved? Microcirculation. 2014;21(3):219–29. DOI: 10.1111/micc.12105
7. Sato Y, Yamamoto E, Sawa T, Toda K, Hara T, Iwasaki T et al. High-sensitivity cardiac troponin T in essential hypertension. Journal of Cardiology. 2011;58(3):226–31. DOI: 10.1016/j.jjcc.2011.07.009
8. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Journal of Hypertension. 2013;31(7):1281–357. DOI: 10.1097/01.hjh.0000431740.32696.cc
9. Oliver JJ, Webb DJ, Newby DE. Stimulated Tissue Plasminogen Activator Release as a Marker of Endothelial Function in Humans. Arteriosclerosis, Thrombosis, and Vascular Biology. 2005;25(12):2470–9. DOI: 10.1161/01.ATV.0000189309.05924.88
10. Burdick MM, Bochner BS, Collins BE, Schnaar RL, Konstantopoulos K. Glycolipids Support E-Selectin-Specific Strong Cell Tethering under Flow. Biochemical and Biophysical Research Communications. 2001;284(1):42–9. DOI: 10.1006/bbrc.2001.4899
11. Hamsten A. The hemostatic system and coronary heart disease. Thrombosis Research. 1993;70(1):1–38. DOI: 10.1016/0049-3848(93)90221-9
12. Over J, Sixma JJ, Bruïne MH, Trieschnigg MC, Vlooswijk RA, Beeser-Visser NH et al. Survival of 125iodine-labeled Factor VIII in normals and patients with classic hemophilia. Observations on the heterogeneity of human Factor VIII. Journal of Clinical Investigation. 1978;62(2):223–34. DOI: 10.1172/JCI109120
13. Ikeda U, Shimada K. Matrix metalloproteinases and coronary artery diseases. Clinical Cardiology. 2003;26(2):55–9. DOI: 10.1002/clc.4960260203
14. Manna P, Jain SK. Obesity, Oxidative Stress, Adipose Tissue Dysfunction, and the Associated Health Risks: Causes and Therapeutic Strategies. Metabolic Syndrome and Related Disorders. 2015;13(10):423–44. DOI: 10.1089/met.2015.0095
15. Blankenberg S, Rupprecht HJ, Poirier O, Bickel C, Smieja M, Hafner G et al. Plasma Concentrations and Genetic Variation of Matrix Metalloproteinase 9 and Prognosis of Patients With Cardiovascular Disease. Circulation. 2003;107(12):1579–85. DOI: 10.1161/01.CIR.0000058700.41738.12
16. Rogova L.N., Shesternina N.V., Zamechnik T.V., Fastova I.A. Matrix metalloproteinases, their role in physiological and pathological processes (review). Bulletin of New Medical Technologies. 2011;18(2):86–9. [Russian: Рогова Л.Н., Шестернина Н.В., Замечник Т.В., Фастова И.А. Матриксные металлопротеиназы, их роль в физиологических и патологических процессах (обзор). Вестник новых медицинских технологий. 2011;18(2):86-9]
17. Opgaard OS, Cantera L, Adner M, Edvinsson L. Endothelin-A and -B receptors in human coronary arteries and veins. Regulatory Peptides. 1996;63(2–3):149–56. DOI: 10.1016/0167-0115(96)00036-5
18. Vasina L.V., Petrishchev N.N., Vlasov T.D. Markers of endothelial dysfunction. Regional blood circulation and microcirculation. 2017;16(1):4–15. [Russian: Васина Л.В., Петрищев Н.Н., Власов Т.Д. Эндотелиальная дисфункция и ее основные маркеры. Регионарное кровообращение и микроциркуляция. 2017;16(1):4–15]. DOI: 10.24884/1682-6655-2017-16-1-4-15
19. Mourad J-J, Waeber B, Zannad F, Laville M, Duru G, Andréjak M. Comparison of different therapeutic strategies in hypertension: a low-dose combination of perindopril/indapamide versus a sequential monotherapy or a stepped-care approach. Journal of Hypertension. 2004;22(12):2379–86. DOI: 10.1097/00004872-200412000-00021
20. Chapman N, Huxley R, Anderson C, Bousser MG, Chalmers J, Colman S et al. Effects of a Perindopril-Based Blood Pressure–Lowering Regimen on the Risk of Recurrent Stroke According to Stroke Subtype and Medical History: The PROGRESS Trial. Stroke. 2004;35(1):116–21. DOI: 10.1161/01.STR.0000106480.76217.6F
21. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):1269–324. DOI: 10.1161/HYP.0000000000000066
22. Toto RD, Rinner S, Ram CVS. ACE inhibitors and target organ protection: An expanded role for these antihypertensive agents? Postgraduate Medicine. 2004;116(2):11–48. DOI: 10.3810/pgm.2004.08.1567
23. Flamant M, Placier S, Dubroca C, Esposito B, Lopes I, Chatziantoniou C et al. Role of Matrix Metalloproteinases in Early Hypertensive Vascular Remodeling. Hypertension. 2007;50(1):212–8. DOI: 10.1161/HYPERTENSIONAHA.107.089631
24. Scientific Committee of the PERTINENT Sub-Study, EUROPA-PERTINENT Investigators. PERTINENT – perindopril-thrombosis,

inflammation, endothelial dysfunction and neurohormonal activation trial: a sub-study of the EUROPA study. Cardiovascular Drugs and Therapy. 2003;17(1):83–91. DOI: 10.1023/a:1024394610648
25. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). The Lancet. 1998;352(9131):837–53. DOI: 10.1016/S0140-6736(98)07019-6
26. Brugts JJ, Boersma E, Chonchol M, Deckers JW, Bertrand M, Remme WJ et al. The Cardioprotective Effects of the Angiotensin-Converting Enzyme Inhibitor Perindopril in Patients With Stable Coronary Artery Disease Are Not Modified by Mild to Moderate Renal Insufficiency: insights from the EUROPA trial. Journal of the American College of Cardiology. 2007;50(22):2148–55. DOI: 10.1016/j.jacc.2007.08.029
27. Moskalenko M.I. The involvement of genes of matrix metalloproteinases in the development of arterial hypertension and its complication (review). Research Result. Medicine and Pharmacy. 2018;4(1):53–69. [Russian: Москаленко М.И. Вовлеченность генов матриксных металлопротеиназ в формирование артериальной гипертензии и ее осложнений (обзор). Научный результат. Медицина и фармация. 2018;4(1):53–69]. DOI: 10.18413/2313-8955-2018-4-1-53-69
28. Falkovskaya A.Yu., Mordovin V.F., Pekarskiy S.E., Ripp T.M., Zyubanova I.V., Sitkova E.S. et al. Matrix metalloproteinases in patients with resistant hypertension and type 2 diabetes mellitus: relation with renal blood flow and kidney function. Arterial Hypertension. 2019;25(1):34–45. [Russian: Фальковская А.Ю., Мордовин В.Ф., Пекарский С.Е., Рипп Т.М., Зюбанова И.В., Ситкова Е.С. и др. Система матриксных металлопротеиназ у больных резистентной артериальной гипертензией, ассоциированной с сахарным диабетом 2-го типа: связь с состоянием почечного кровотока и функцией почек. Артериальная гипертензия. 2019;25(1):34-45]. DOI: 10.18705/1607-419X-2019-25-1-34-45
29. Daiber A, Steven S, Weber A, Shuvaev VV, Muzykantov VR, Laher I et al. Targeting vascular (endothelial) dysfunction: Targeting vascular (endothelial) dysfunction. British Journal of Pharmacology. 2017;174(12):1591–619. DOI: 10.1111/bph.13517
30. Giles LV, Tebbutt SJ, Carlsten C, Koehle MS. The effect of low and high-intensity cycling in diesel exhaust on flow-mediated dilation, circulating NOx, endothelin-1 and blood pressure. PLOS ONE. 2018;13(2):e0192419. DOI: 10.1371/journal.pone.0192419
31. Stepanova Yu.I., Gonchar I.A. Endothelin-dependent effects in cerebrovascular pathology of ischemic genesis. Medical news. 2013;10:12–8. [Russian: Степанова Ю.И., Гончар И.А. Эндотелинзависимые эффекты при цереброваскулярной патологии ишемического генеза. Медицинские новости. 2013;10:12-8]
32. Hlubocká Z, Umnerová V, Heller S, Peleska J, Jindra A, Jáchymová M et al. Circulating intercellular cell adhesion molecule-1, endothelin-1 and von Willebrand factor-markers of endothelial dysfunction in uncomplicated essential hypertension: the effect of treatment with ACE inhibitors. Journal of Human Hypertension. 2002;16(8):557–62. DOI: 10.1038/sj.jhh.1001403
33. Valente FM, de Andrade DO, Cosenso-Martin LN, Cesarino CB, Guimarães SM, Guimarães VB et al. Plasma levels of matrix metalloproteinase-9 are elevated in individuals with hypertensive crisis. BMC Cardiovascular Disorders. 2020;20(1):132. DOI: 10.1186/s12872-020-01412-5