Volume 7, № 21, March 2019
ISSN: 2309-0901 (Print)
ISSN: 2311-1631 (OnLine)
http://www.heart-vdj.com

International Heart and Vascular Disease Journal

Journal of the Cardioprogress Foundation

The association of genotype and alleles 174G/C (rs1800795) frequency of Il6 gene with clinical data in patients with atrial fibrillation, arterial hypertension in combination with extra-cardiac pathology

Can QRS Duration Predict Microvascular Reperfusion after Primary Percutaneous Coronary Intervention?

New European guidelines for the management of arterial hypertension. Comments of Russian experts

International Heart and Vascular Disease Journal
Journal of the Cardioprogress Foundation

The *International Heart and Vascular Disease Journal* is a peer-reviewed open access publication printed quarterly. The journal features original research articles, case reports, clinical reviews, editorials, and letters to the Editor. All published articles are freely accessible from the journal's website.

The publication of articles within the journal is free of charge for authors. Guidelines for authors on submitting manuscripts are available at: www.cardioprogress.ru

Contact details:
Cardioprogress Foundation and Editorial Office:
Room 213, Building 2, Prospect Gostinichny 6, Moscow 127106, Russia
Editorial Office tel.: (+7) 965 236 1600
Official website: http://www.heart-vdj.com

Editorial correspondence should be sent to:
Mehman Mamedov, Deputy Editor,
editor.ihvdj@gmail.com
Articles for publication should be sent to:
Anna Arteyeva, Associate Editor,
submissions.ihvdj@gmail.com

Printed in Russia

The Journal is in the List of the leading scitntific journals and publications of the Supreme Examination Board (VAK)

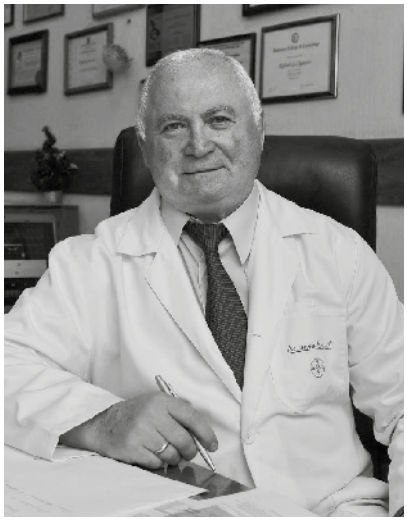
Complete versions of all issues are published: www.elibrary.ru, www.cyberleninka.ru

International Heart and Vascular Disease Journal

Journal of the Cardioprogress Foundation

Volume 7, № 21, March 2019
DOI: 10.15829/2311-1623-6-21

Contents



Editor's Welcome

Dear colleagues!

In the 21st issue of the International Heart and Vascular Disease Journal, there are the leading article, original and review articles, and comments of Russian experts on the new European guidelines for the management of arterial hypertension.

The leading article of this issue was done by the group of Egyptian researchers on the possibility of using QRS duration as a predictor of microvascular reperfusion after primary percutaneous coronary intervention (PCI). 60 patients after ST-segment elevation myocardial infarction took part in clinical trial. Authors concluded that in patients with ST-segment elevation, prolonged QRS duration was associated with a low myocardial blush grade (MBG), a sign of impaired microvascular reperfusion.

Traditional "Original articles" section includes three works. The first article investigates the association of genotype and alleles 174G/C (rs1800795) frequency of Il6 gene with clinical data in patients with atrial fibrillation, arterial hypertension in combination with extra-cardiac pathology. In the second article, the group of Kazakh researchers established a correlation between vascular age, atherogenic coefficient and 5-year risk of cardiovascular complications (CVC) in patients with arterial hypertension. Vascular age can be an independent prognostic factor for arterial hypertension and cardiovascular complications development. The third article studied the prevalence and interactions of attitude to medical care and physical activity in men and women aged 25-64 years of open urban population of Tuymen. Authors assume that the results on the correlation of attitude to medical care and physical activity and the objective-subjective indicator of public health may be used as the scientific basis for organizing complex preventive regional programs.

The review article is dedicated to the analysis of the results of most important clinical trials represented during scientific sessions of American Heart Association held in November 2018. Specialists traditionally are very interested in this section.

The "Expert opinion" section presents opinion of the leading Russian experts on the main states of the new European guidelines for the management of arterial hypertension, including target blood pressure levels, management algorithms for patients with different cardiovascular risk and additional risk factors/ comorbidities.

We invite everybody to collaborate with the journal. We are waiting for your original papers, review articles, discussions, and opinions about problems, treatment and prophylaxis recommendations.

Rafael G. Oganov
Editor-in-Chief
President of the "Cardioprogress" Foundation

International Heart and Vascular Disease Journal • Volume 7, № 21, March 2019

Journal of the Cardioprogress Foundation

LEADING ARTICLE

Can QRS Duration Predict Microvascular Reperfusion after Primary Percutaneous Coronary Intervention?

Mohammad M Al-Daydamony[1], El-Sayed M Farag[1], Ahmed Fathy[1], Ghada Ebraheem[1], Ahmed Shawky[1], Nader T Kandeel[1], Hany Abdelwahab[1], Ahmed Shaker[1], Mohamed Abdel shafy Tabl[2], Iman Samy[3]

[1] Zagazig University, Zagazig, Egypt.
[2] Benha University, Benha, Egypt.
[3] National Heart Institute, Cairo, Egypt.

Autors

Mohammad M Al-Daydamony, M. D., cardiologist, Department of Cardiology, Zagazig University, Zagazig, Egypt.
El-Sayed M. Farag, M. D., Department of Cardiology, Zagazig University, Zagazig, Egypt.
Ahmed Fathy, M. D., Department of Cardiology, Zagazig University, Zagazig, Egypt.
Ghada Ebraheem, M. D., Department of Cardiology, Zagazig University, Zagazig, Egypt.
Ahmed Shawky, M. D., Department of Cardiology, Zagazig University, Zagazig, Egypt.
Nader T Kandeel, M. D., Department of Cardiology, Zagazig University, Zagazig, Egypt.
Hany Abdelwahab, M. D., Department of Cardiology, Zagazig University, Zagazig, Egypt.
Ahmed Shaker, M. D., Department of Cardiology, Zagazig University, Zagazig, Egypt.
Mohamed Abdel shafy Tabl*, M. D., Department of Cardiology, Benha University, Benha, Egypt.
Iman Samy, M. D., master of cardiology, Department of Cardiology, National Heart Institute, Cairo, Egypt.

Background. *In patients with ST-segment elevation myocardial infarction (STEMI), primary percutaneous coronary intervention (PCI) was associated with early and sustained restoration of blood flow compared to fibrinolytic therapy. Impaired myocardial blush grade (MBG), may be present in many after successful PCI. Prolonged QRS was found to be associated with an increased morbidity and mortality after STEMI.*

Objectives*. To find out if prolonged QRS in STEMI patients can predict low MBG after primary PCI.*

* Corresponding author. Tel.: +2001223723050. E-mail: mshafytabl@yahoo.com

Patients and Methods. *Sixty STEMI patients were included in our study. History taking, clinical examination, ECG with measuring of QRS duration, primary PCI, and echocardiography were done to them. QRS duration was measured before and after PCI and the change was calculated.*

Results. *Patients with low MBG (0-1) had significantly higher QRS duration before and after PCI and significantly lower change after PCI (p <0.00001 for each).Independent predictors for MBG were in order of significance: QRS duration before PCI (p <0.00001), QRS duration after PCI (p <0.00001), Troponin level (p <0.00001), symptom to balloon time (p =0.0063), and CK-MB level (p=0.015). QRS duration 89 ms could predict low MBG with sensitivity 82.6%, specificity86.5%, positive predictive value 79.2%, and negative predictive value 88.9%.*

Conclusion. *In STEMI patients undergoing primary PCI, prolonged QRS duration was associated with a low MBG, a sign of impaired microvascular reperfusion. QRS duration before and after PCI were found to be independent predictors for low MBG (0-1).*

Keywords: *primary PCI; Microvascular Reperfusion; Myocardial Blush Grade; STEMI; QRS duration.*

Conflicts of interest: None declared.

Received: 1.02.2019 **Accepted:** 16.02.2019

Introduction

Despite the major advances in its management, ST-segment elevation myocardial infarction (STEMI) is still a leading cause of death and morbidity all over the globe [1, 2].The main goal of therapy in STEMI is to open the occluded artery, restore transluminal coronary flow, restore microvascular flow and sustain the myocardial perfusion [3].Primary percutaneous coronary intervention (PCI) was found to be superior to fibrinolytic therapy in treating STEMI patients. Primary PCI was associated with early and sustained restoration of thrombolysis in myocardial infarction (TIMI) flow 3 compared to fibrinolytic therapy [4]. However, even after successful opening of infarct related artery with primary PCI and restoration of TIMI flow 3, an impaired myocardial reperfusion as shown by poor myocardial blush grade (MBG), may be present in many patients which is associated with poor short and long term outcome [5]. So, it might be useful to search for predictors for poor myocardial perfusion in STEMI patients undergoing primary PCI.

The prolongation of QRS duration, evaluated by a standard 12-lead ECG, is a marker of left ventricular dysfunction and has been associated with a poor prognosis in STEMI patients [6] and was also found to be associated with an increased risk of impaired ventricular systolic function and adverse events [7, 8]. However, the relation between QRS duration and microvascular reperfusion as manifested by impaired MBG after primary PCI in STEMI patients has not been yet studied. Therefore, the aim of our work was to find outif the presence of prolonged QRS in the surface ECG of STEMI patients can predict a poor microvascular reperfusion and a low MBG after primary PCI.

Patients and Methods

This observational study was performed in the Cardiology Department, Zagazig and Benha Universities in co operation with National Heart Institute during the period from January 2016 till May 2017. Sixty STEMI patients undergoing primary PCI were included in our study. The inclusion criteria were: confirmed first acute STEMI, which was defined by the presence of typical chest pain that lasts for at least 20 minutes in addition to ST-segment elevation ⩾ 0.1 mV in at least two contiguous leads [9].All patients were presented within 12 hours of beginning of symptoms. Primary PCI was done to all patients, primary PCI with considered successful when there is less than 20% residual stenosis and TIMI flow 3 of the infarct-related artery defined as normal flow, which fills the distal coronary bed completely [10].

Patients with left bundle branch block, with prior coronary revascularization, prior STEMI, or when primary PCI was not performed, were excluded from our. Our study included 60STEMI patients. Our Institutional Review Board had approved the study protocol.

After we obtained a written informed consent, an in addition to routine history and clinical examination, we did the following to every patient:

Complete standard 12-lead electrocardiography (ECG) was done on arrival to every patient. In the present study, all measurements were obtained from infarct-related artery leads. Admission ECG was uti-

lized for diagnosis of STEMI and for measurement of QRS duration. The QRS duration was measured manually with the help of a caliper and a magnifying lens (to diminish the effect of the ST deviation on the measurement). Measurements were done by two expert cardiologists who were unaware of other clinical and angiographic data. The average value of the measurements obtained by the two investigators was taken into account for statistical analysis in each patient. ECG was repeated 60 minutes after PCI and change in QRS duration was calculated by subtracting post-angioplasty QRS duration from pre-angioplasty QRS duration.

Primary PCI was done to all patients within 12 hours of onset of symptoms by at least two expert interventionists. At least one of the operators met the criteria of individual operator level of the 2007 Clinical Competence Statement on Cardiac Interventional Procedures and its revision [11].Direct stenting, balloon dilatation and stenting, balloon dilatation alone, and/or thrombus aspiration were done as indicated. Glycoprotein (GP) IIb/IIIa inhibitor (eptifibatide) was given as appropriate, according to operator opinion.

TIMI flow was assessed by operators. Only patients with TIMI 3 flow were considered as successful PCI and included in our study [10].

Myocardial blush grade (MBG) was assessed offline by two expert angiographers who were unaware of each other's results and of the patients' other data. MBG was assessed visually following the dye density score: MBG 0 = contrast density or no myocardial blush, MBG 1 = minimal contrast density or myocardial blush, MBG 2 = moderate contrast density or myocardial blush but did not reach that obtained during angiography of a noninfarct-related coronary artery, MBG 3 = normal contrast density or myocardial blush whichequals that obtained during angiography of a noninfarct-related coronary artery [12].

Echocardiographic studies were performed for all patients using the GE VIVID E9 machine with 2.5-MHz transducer within 24 hours of admission. The studies were performed by two operators unaware of each other's measures and of the patients' clinical and angiographic data. Views were taken while the patients were in the left lateral position.Left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) was measured from the apical two-chamber and apical four-chamber views. Ejection fraction (EF) was calculated using the Simpson's method [13]. Wall motion score (WMS) was measured from the apical-4 and apical-2 chamber views using the sixteen segments model and giving a score to each segment according to its motion as following, normal = 1, hypokinetic = 2, akinetic = 3, dyskinetic = 4, and aneurysm = 5, and then WMS was calculated as the sum of scores of the 16 segments. Wall motion score index (WMSI) was calculated by dividing WMSI by 16 [13].

Statistical analysis. All data were analyzed using the SPSS for Windows package program (Version 20.0, Armonk, NY, USA: IBM Corp.). Differences between patients' group and control group were analyzed using x2 test and student's t-test. Correlations between different variables were investigated by Pearson correlation analysis. The logistic regression analysis was evaluated by the Hosmer–Lemeshow goodness-of-fit test.The receiver operating characteristic (ROC) curve was made to analyze for cutoff points of different parameters and their relation to MBG. A p value < 0.05 was regarded as being statistically significant.

Results

Our study included 60 STEMI patients, 49 males and 11 females. Their ages ranged from 34 to 83 years, with a mean age of 55.8±10.62 years. Patients were divided into two groups according to MBG:

Group 1: Included patients with MBG 0 or 1. This group included 23 patients, 19 males and 4 females; their mean age was 55.4±10.46 years.

Group 2: Included patients with MBG 2 or 3. This group included 37 patients, 30 males and 7 females; their mean age was 56.1±10.85 years.

There was no significant difference between the two study groups regarding other clinical, echocardiographic, angiographic, or PCI data. Patients with MBG 0-1 had significantly higher Troponin I level (p <0.00001), higher CK-MB level (p = 0.002), significantly higher QRS duration at first ECG (p <0.00001), significantly higher QRS duration after PCI (p <0.00001), significantly lower change in QRS duration (p <0.00001). Coronary angiography and PCI data showed that patients with MBG 0-1 had significantly lower incidence of left anterior descending artery (LAD) as a culprit for STEMI (p = 0.02) and significantly higher incidence of right coronary artery (RCA) as a culprit for STEMI (p = 0.009) (Table 1).

The independent predictors for myocardial blush grade in the order of significance were QRS duration before PCI (p <0.00001), QRS duration after PCI (p<0.00001), Troponin I level (p <0.00001), symptom to balloon time (p = 0.0063), and CK-MB level (p = 0.015) (Table 2).

Table 1. **Comparison between the two groups.**

	Group I MBG 0-1 (n = 23)	Group II MBG 2-3 (n = 37)	P value
Age (years)	55.4±10.46	56.1±10.85	0.137
Sex Male Female	19 (82.6 %) 4 (17.4%)	30 (81.1 %) 7 (18.9 %)	0.882
Hypertension	14 (60.9 %)	24 (64.9 %)	0.755
Diabetes	5 (21.7 %)	12 (32.4 %)	0.371
Smoking	17 (73.9 %)	28 (75.7 %)	0.878
Dyslipidaemia	7 (30.4 %)	13 (35.1 %)	0.707
Anterior STEMI	12 (52.2 %)	27 (73 %)	0.101
Troponin I level (ng/ml)	1.52±0.45	0.86±0.55	< 0.00001
CK-MB (IU/L)	82.4±29.77	59.1±23.02	0.002
QRS duration: - First (ms)	89.35±9.05	77.08±9.30	< 0.00001
- Second (ms)	85.52±8.51	71.14±8.35	< 0.00001
- Change (%)	3.83±2.72	7.71±3.59	< 0.00001
LVEDV (ml)	103.7±21.8	98.2±19.4	0.326
LVESV (ml)	43.8±13.6	39.7±15.2	0.283
EF (%)	59.4±9.11	60.7±10.21	0.61
Stenting	22 (95.6 %)	35 (94.6 %)	0.855
Baseline stenosis (%)	96.2±3.6	95.5±4.3	0.499
Stent diameter (mm)	2.89±0.626	3.11±0.714	0.215
Stent length (mm)	14.9±5.81	16.2±6.27	0.417
Culprit vessel: - LAD	13 (56.5 %)	31 (83.8 %)	0.02
LCX	2 (8.7 %)	2 (5.4 %)	0.619
RCA	8 (34.8 %)	3 (8.1 %)	0.009
OM	0 (0 %)	1 (2.7 %)	0.427

Data are expressed as mean±SD or number (%).STEMI: ST-segment elevation myocardial infarction. LVEDV= left ventricular end diastolic volume, LVESV= left ventricular end systolic volume, EF = ejection fraction. LAD = left anterior descending artery. LCX = left circumflex artery. RCA = right coronary artery. OM = obtuse marginal artery. TIMI = thrombolysis in myocardial infarction.

Table 2. **Logistic regression analysis for independent predictors of myocardial blush grade.**

Predictor	Odd ratio	95 % CI	P value
QRS duration before PCI	11.89	9.52-14.26	<0.00001
QRS duration after PCI	10.79	8.75 - 12.83	<0.00001
Troponin I level	9.16	7.54 - 10.79	<0.00001
Symptom to balloon time	6.11	4.87-7.35	0.0063
CK-MB level	4.49	3.21-5.78	0.015

CI = confidence interval. PCI = percutaneous coronary intervention. CK = creatine kinase.

The cut-off values for predictors of myocardial blush grade were shown in (Table 3). Regarding QRS duration before PCI, the cut-off point was 89 ms, the area under the curve (AUC) was 0.852, sensitivity was 82.6%, specificity was 86.5 %, positive predictive value (PPV) was 79.2 %, and negative predictive value (NPV) was 88.9 %. Regarding symptom to balloon time, the cut-off point was 4 hours, AUC was 0.798, sensitivity was 67.6%, specificity was 82.6%, PPV was 86.2%, and NPV was 61.3%.Regarding Troponin I level, the cut-off point was 1.2 ng/ml, AUC was 0.716, sensitivity was77.8%, specificity was 73.9 %, PPV was 82.4 %, and NPV was 68.1%.Regarding CK-MB level, the cut-off point was 44 ng/ml, AUC was 0.699, sensitivity was37.8 %, specificity was 95.6%, PPV was 93.3%, and NPV was 48.9%. The receiver operating characteristic (ROC) curves for different parameters are shown in (figure 1).

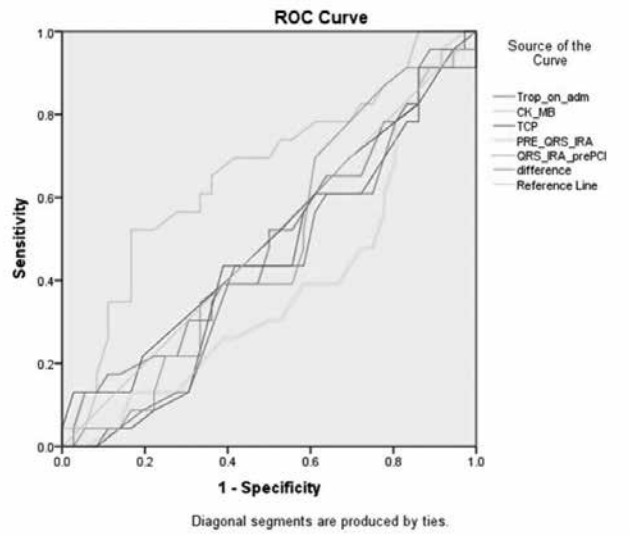


Figure 1. The receiver operating characteristic (ROC) curves for different parameters.

Discussion

In the present work, we tried to explore the relation between the QRS duration and the degree of microvascular reperfusion as assessed by MBG after successful primary PCI in STEMI patients. Our results showed a strong relation between them. Patients with low MBG (0-1) had significantly wider QRS either before or after

Table 3. **Cut-off values for predictors of myocardial blush grade.**

Predictor	Cut-off point	AUC	Sensitivity	Specificity	PPV	NPV
QRS duration before PCI	89 ms	0.852	82.6 %	86.5 %	79.2 %	88.9 %
Symptom to balloon	4 hours	0.798	67.6 %	82.6 %	86.2 %	61.3 %
Troponin	1.2 ng/ml	0.716	77.8 %	73.9 %	82.4 %	68.1 %
CK-MB	44 ng/ml	0.699	37.8 %	95.6 %	93.3 %	48.9 %

AUC = area under the curve. PCI = percutaneous coronary intervention. CK = creatine kinase.

PCI and the change of QRS duration was significantly lower in them. Among independent predictors for low MBG, QRS duration was the most significant. QRS duration before PCI was a good predictor for MBG with good sensitivity, specificity, positive, and negative predictive values.

Acute myocardial infarction is a noteworthy reason for mortality and major morbidities such as heart failure and fatal arrhythmias [2]. Impaired microvascular reperfusion is a critical prognostic determinant in patients experiencing primary PCI [4]. In spite of the fact that primary PCI is capable of restoring blood flow in the infarct-related artery in the vast majority of STEMI patients, however left ventricular dilatation, systolic dysfunction, and heart failure still occur in a significant proportion of patients after successfully performed primary PCI [14]. Many investigators had studied the relation between microvascular reperfusion, MBG, and their effect on LV dilatation and outcome after primary PCI. Henriques and his colleagues have found that MBGwas able to predict mortality in patients after primary angioplasty even in the presence of with TIMI 3 flow. They also found that infarct size was larger and left ventricular EF was lower in patients low MBG (0-1) [15].

In patients with cardiogenic shock, a high MBG (2-3) was found to be a strong indicator of survival after rescue PCI [16]. Myocardial blush grade, symptom to door time, and symptom to balloon time were found to be the only independent and significant predictors for left ventricular dilatation and remodeling in STEMI patients after successful primary PCI [17]. In their study, Şahan and Karamanlıoglu [18] have found a strong association between low MBG and ventricular arrhythmias in STEMI patients after primary PCI. This association was especially manifest in patients with who experienced ventricular fibrillation during their hospital stay. The simple resting 12-lead ECG is an exceedingly important tool not only in diagnosing STEMI patients but also on risk stratifying them. The initial ECG was able to predict 30 days all-cause mortality after STEMI in the GUSTO-I population. The sum of ST-segment deviation, QRS duration, and evidence of prior myocardial infarction were independent predictors of mortality in this study [19]. The presence of fragmented QRS complex at the 48th hour of STEMI was found to be a strong predictor of mortality and major adverse cardiovascular events in patients experiencing primary PCI [20].

In the Hirulog and Early Reperfusion or Occlusion-2 trial study, the initial QRS duration and its changes after 60 minutes was strongly related to 30-days mortality in STEMI patients receiving thrombolytic therapy [21]. Also the VALIANT trial investigators have found that when the QRS duration was prolonged it was associated with larger LVEDV, LVESV, and reduced EF even when it was still within the normal range. Prolonged QRS was also associated with an increased risk for development of heart failure cardiovascular mortality after STEMI [22]. In concordance with our study, Maden and his colleagues have found that the initial QRS duration on admission was related to the development of no-reflow in acute STEMI patients treated with primary PCI [23].

The association between QRS duration, extent of myocardial ischemia, and prognosis is quite complex. From the pathological point of view, myocardial necrosis and scarring with possible injury to Purkinje fibers may result in impaired myocardial conduction [24] which results in prolongation of QRS duration. So, prolonged QRS duration after STEMI may be a sign of prolonged ischemia which in turn may explain its association with the impaired microvascular reperfusion which is presented in our study by low MBG.

Conclusion

In STEMI patients undergoing primary PCI, prolonged QRS duration was associated with a low MBG, a sign of impaired microvascular reperfusion.

QRS duration before and after PCI and the change in QRS duration were found to be independent predictors for low MBG (0-1). Further studies with larger scales of patients may be needed to uncover the association between QRS duration, myocardial reperfusion, and prognosis in STEMI patients undergoing primary PCI.

Study limitations

Actually our study had several limitations. First, we measured the QRS duration manually, that means there was no standardization. Second,we did not follow-up our patients to find the effect of prolonged QRS and impaired MBG on cardiac events. Third, we included a relatively small number of patients.

Conflict of interest: None declared.

References

1. Puymirat E, Simon T, Cayla G, Cottin Y, Elbaz M, Coste P, et al.: Acute Myocardial Infarction changes in Patient Characteristics, Management, and 6-Month Outcomes Over a Period of 20 Years in the FAST-MI Program (French Registry of Acute ST-Elevation

or Non-ST-elevation Myocardial Infarction). Circulation. 2017.117.030798.

2. Acharya T, Salisbury AC, Spertus JA, Kennedy KF, Bhullar A, Reddy HKK, et al.: In-Hospital Outcomes of Percutaneous Coronary Intervention in America's Safety Net: Insights From the NCDR Cath-PCI Registry. JACC Cardiovasc Interv 2017, 10 (15): 1475-1485.
3. Roe MT, Ohman EM, Maas AC, Christenson RH, Mahaffey KW, Granger CB, et al.: Shifting the open-artery hypothesis downstream: the quest for optimal reperfusion. J Am Coll Cardiol 2001, 37 (1): 9-18.
4. Keeley EC, Boura JA and Grines CL.: Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003, 361 (9351): 13-20.
5. Brener SJ, Dizon JM, Mehran R, Guerchicoff A, Lansky AJ, Farkouh M, et al.: Complementary prognostic utility of myocardial blush grade and ST-segment resolution after primary percutaneous coronary intervention: analysis from the HORIZONS-AMI trial. Am Heart J 2013, 166 (4): 676-83.
6. Hathaway WR, Peterson ED, Wagner GS, Granger CB, Zabel KM, Pieper KS, Clark KA, et al.: Prognostic significance of the initial electrocardiogram in patients with acute myocardial infarction. GUSTO-I Investigators. Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries. JAMA 1998, 279 (5): 387-91.
7. Açil T, Türköz R, Açil M, Sezgin AT, Baltali M, Gülcan O, et al.: Value of prolonged QRS duration as a predictor of low cardiac output syndrome in patients with impaired left ventricular systolic function who undergo isolated coronary artery bypass grafting. Am J Cardiol 2006, 98 (10): 1357-62.
8. Abdelnoor M, Nitter-Hauge S, Risum O, Svennevig JL and Amlie JP. Duration of preoperative electrocardiographic QRS complex and the incidence of heart arrest after aorto coronary bypass surgery. Scand Cardiovasc J 2000, 34 (2): 186-91.
9. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al.: American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013, 127 (4): e362-425.
10. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. N Engl J Med 1985, 312 (14): 932-6.
11. Harold JG, Bass TA, Bashore TM, Brindis RG, Brush JE Jr, Burke JA, et al: ACCF/AHA/SCAI 2013 update of the clinical competence statement on coronary artery interventional procedures: a report of the American College of Cardiology Foundation/American Heart Association/American College of Physicians Task Force on Clinical Competence and Training (Writing Committee to Revise the 2007 Clinical Competence Statement on Cardiac Interventional Procedures). J Am Coll Cardiol 2013, 62 (4): 357-96.
12. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B et al : ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2016, 133 (11): 1135-47.
13. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, et al: American Society of Echocardiography's Guidelines and Standards Committee, European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005, 18 (12): 1440-63.
14. Bolognese L, Neskovic AN, Parodi G, Cerisano G, Buonamici P, Santoro GM, et al.: Left ventricular remodeling after primary coronary angioplasty: patterns of left ventricular dilation and long-term prognostic implications. Circulation 2002, 106 (18): 2351-7.
15. Henriques JP, Zijlstra F, van't Hof AW, de Boer MJ, Dambrink JH, Gosselink M, et al.: Angiographic assessment of reperfusion in acute myocardial infarction by myocardial blush grade. Circulation 2003, 107(16): 2115-9.
16. Tarantini G, Ramondo A, Napodano M, Bilato C, Isabella G, Razzolini R, Iliceto S. Myocardial perfusion grade and survival after percutaneous transluminal coronary angioplasty in patients with cardiogenic shock. Am J Cardiol 2004, 93 (9): 1081-5.
17. Farag EM & Al-Daydamony MM : Symptom-to-balloon time and myocardial blush grade are predictors of left ventricular remodelling after successful primary percutaneous coronary intervention. Cardiovasc J Afr 2017, 28 (3): 186-190.
18. Şahan E & Karamanlıoglu M.: Myocardial blush grade can predict the early ventricular arrhythmias after acute coronary syndrome. Indian Heart J 2016, 68: 375.
19. Hathaway WR, Peterson ED, Wagner GS, Granger CB, Zabel KM, Pieper KS, et al. Prognostic significance of the initial electrocardiogram in patients with acute myocardial infarction. GUSTO-I Investigators. Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries. JAMA 1998, 279 (5): 387-91.
20. Ari H, Cetinkaya S, Ari S, Koca V & Bozat T. : The prognostic significance of a fragmented QRS complex after primary percutaneous coronary intervention. Heart Vessels 2012, 27 (1): 20-8.

21. Wong CK, Gao W, Stewart RA, French JK, Aylward PE, White HD. Et al.: Relationship of QRS duration at baseline and changes over 60 min after fibrinolysis to 30-day mortality with different locations of ST elevation myocardial infarction: results from the Hirulog and Early Reperfusion or Occlusion-2 trial. Heart 2009, 95 (4): 276-82.
22. Yerra L, Anavekar N, Skali H, Zelenkofske S, Velazquez E, McMurray J, Pfeffer M, et al.: Association of QRS duration and outcomes after myocardial infarction: the VALIANT trial. Heart Rhythm 2006, 3 (3): 313-6.
23. Maden O, Kaçmaz F, Selçuk MT, Selçuk H, Alyan O, Aksu T, et al: Relation of admission QRS duration with development of angiographic no-reflow in patients with acute ST-segment elevation myocardial infarction treated with primary percutaneous interventions. J Electrocardiol 2008, 41 (1): 72-7.
24. Friedman PL, Fenoglio JJ & Wit AL. Time course for reversal of electrophysiological and ultrastructural abnormalities in subendocardial Purkinje fibers surviving extensive myocardial infarction in dogs. Circ Res 1975, 36 (1): 127-44.

International Heart and Vascular Disease Journal • Volume 7, № 21, March 2019

Journal of the Cardioprogress Foundation

The association of genotype and alleles 174G/C (rs1800795) frequency of Il6 gene with clinical data in patients with atrial fibrillation, arterial hypertension in combination with extra-cardiac pathology

L.D. Khidirova [1], D.A. Yakhtonov [1], V.N. Maximov [2], S.A. Zenin [3]

[1] Novosibirsk State Medical University, Novosibirsk, Russia.
[2] Institute of Cytology and Genetics, Federal Research Center, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russia.
[3] Novosibirsk Regional Cardiological Health Center, Novosibirsk, Russia.

Authors:

Ludmila D. Khidirova*, M.D., Ph.D., associate professor of the Department of Clinical Pharmacology and Evidence-based Cardiology, Novosibirsk State Medical University, Novosibirsk, Russia.
David A. Yakhtonov, M.D., Ph.D., doctor of sciences, professor of the Department of Clinical Pharmacology and Evidence-based Cardiology, Novosibirsk State Medical University, Novosibirsk, Russia.
Vladimir A. Maximov, M.D., Ph.D., doctor of sciences, professor, head of the Laboratory of Molecular Genetic Studies of Internal Diseases, Research Center for Preventive and Internal Medicine, Institute of Cytology and Genetics, Federal Research Center, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russia.
Sergey A. Zenin, M.D., Ph.D., doctor of sciences, head of the Department of Surgical Treatment of Complex Heart Rhythm Disturbances and Electrocardiostimulation, Novosibirsk Regional Cardiological Health Center, Novosibirsk, Russia.

Objective. *To study the genotype and allele frequency of 174G/C (rs1800795) polymorphism of Il6 gene in patients with atrial fibrillation, arterial hypertension in combination with extra-cardiac pathology and to establish its association with clinical data.*

Materials and methods. *161 patients with persistent and paroxysmal AF and second stage AH aged 53.3±7.1 years were included in the study. We estimated clinical, anthropometrical and laboratory parameters, the results of instrumental tests: 24-Hour Holter ECG monitoring, 24-Hour arterial pressure monitoring, transthoracic echo-*

* Corresponding author. Tel.: +7-923-112-92-18. E-mail: h_ludmila73@mail.ru

cardiography. The test of -174G / C (rs1800795) polymorphism of the IL6 gene was performed by polymerase chain reaction followed by restriction fragment length polymorphism analysis.

Results. *We had 7.19 % cases of emergency admission. 4.19 % of them were due to cardiac embolism, 14.37 % — due to CHF decompensation and 15.57 % due to recurrent AF. We proved the association of rs1800795 polymorphism of IL6 gene and DM (p=0.024). The factors connected with AF were: left atrial volume (p = 0.027), end-diastolic volume (p = 0.021) and the presence of C allele of polymorphic marker G (–174) C of IL-6 gene (p = 0.003). When analyzing the frequencies of the genotypes with the rs1800795 polymorphism of the IL6 gene in patients with various comorbidities with recurrent AF, we found that the frequency of CC genotype is higher in patients with recurrent AF in the group with subclinical hypothyroidism. The frequency of heterozygous CG genotype of rs1800795 was higher in patients with cardiac embolism (OR 2.25; 95 % CI 1.01–5.04 p=0.05) compared with patients without cardiac embolism. Patients with CC genotype had higher level of galectin-3 (p<0.022) compared with patients with other genotypes.*

Conclusion. *Screening of exposure genes and studying their polymorphisms become an important research area, since gene polymorphism can influence the progression and development of atrial fibrillation complications.*

Key words: *atrial fibrillation, arterial hypertension, polymorphism, rs1800795 polymorphism of IL6 gene*

Conflicts of interest: nothing to declare.

Received: 01.02.2019 **Accepted:** 16.02.2019

Introduction

Atrial fibrillation (AF) is one of the most common stable arrythmias [1]. The frequency of AF has doubled over the last years. Possible reasons of such increase may include: increasing number of elderly patients, improvement of AF diagnosis at outpatient level, increasing number of acute myocardial infarction survivors (AMI), etc. [2].

It is remarkable that the frequency of AF is increasing and progressing. The term «AF progression» means the development of chronic AF from paroxysmal form [3]. 2.2 million of US citizens had paroxysmal or persistent AF that in 67 % of cases progressed to chronic AF during the 5-year follow-up. 8.2 million people of 512 million European population have AF with 1:4 risk of progression in men and women aged 40 years. It is predicted that the number of people with this arrhythmia will increase from 2.5 million in the early 2000s up to 15 million in 2050 in the United States [4]. Nowadays many clinical studies are devoted to risk factors (RF) of AF, including the main factor — arterial hypertension (AH), which contributes to ventricular hypertrophy and atrial dystrophy. However, the progression of AF needs more attention [5, 6].

As genetics is developing, idiopathic AF becomes less frequent. Familiar AF is autosomal dominant disease due to impaired function of various potassium channels during phase 3. Less frequent, AF may be autosomal recessive or sex linked disease – due to impaired function of sodium channels [7].

Familiar AF may be an independent nosological unit, or may be accompanied by channelopathies, for example short or long QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia. AF may also be associated with structural genetic cardiomyopathies, such as familial dilated cardiomyopathy, hypertrophic cardiomyopathy, idiopathic restrictive cardiomyopathy, arrhythmogenic right ventricular dysplasia, and with unclassified diseases (non-compaction cardiomyopathy, endocardial fibroelastosis) [8].

During large meta-analysis involving over ten GWAS (genome wide association study) of different ethnicity, some phenotypic traits were associated with polymorphisms: high density lipoproteins (HDL), triglycerides, blood pressure (BP) [9]. Some of identified loci are common for all traits, some lie in extragenic spaces, some locate in genes of proteins that were unknown to be involved in biological pathway of this trait. A number of authors showed the association of rs2200733 and rs1800795 polymorphisms with postoperative AF [10]. The IL-6 protein is produced by endothelial cells, vascular smooth muscle cells, and myocytes during ischemia. Its level is associated with AF in patients with

coronary artery disease, after cardiac surgery, cardioversion and catheter ablation [11, 12].

Objective

To study the genotype and allele frequency of 174G/C (rs1800795) polymorphism of IL6 gene in patients with atrial fibrillation, arterial hypertension in combination with extra-cardiac pathology and to establish its association with clinical data.

Materials and methods

161 patients took part in prospective cohort study. The criteria of inclusion were: age of 45–65 years, stage 3 of AH (ESH/ESC, 2018), paroxysmal of persistent AF (RSC, ASSA, ACSR, Moscow, 2017) and one of the following diseases: type 2 diabetes mellitus (DM (EASD/ESC, 2017), subclinical hypothyroidism (SCH), central obesity (CO (AACE/ACE, 2014), chronic obstructive pulmonary disease (COPD (ERS, 2017). We estimated clinical, anthropometrical and laboratory parameters, the results of instrumental tests: ECG, 24-Hour Holter ECG monitoring, 24-Hour arterial pressure monitoring using SCHILLER monitoring system (Schiller, Switzerland), echocardiography (Echo CG) in M and 2D modes using Vivid 7 ultrasound machine (General Electric, USA). The level of galectin-3 was determined with enzyme immunoassay using «Human Galectin-3 ELISA kit; eBioscience» (Bender MedSystems GmbH, Austria), minimum concentration of determination — 0.12 ng/ml. The level of NT-proBNP was determined using the «NTproBNP-ELISA-Best kit». CRP (C-reactive protein) was determined using ELISA test system (Biomerica), USA.

The test of -174G / C (rs1800795) polymorphism of the IL6 gene was performed by polymerase chain reaction followed by restriction fragment length polymorphism analysis.

DNA isolation from blood leukocytes was performed using phenol-chloroform extraction method [Smith K., 1990]. The test of -174G / C (rs1800795) polymorphism of the IL6 gene was performed by polymerase chain reaction followed by restriction fragment length polymorphism analysis (PCR with RFLP). The study design is presented in table 1.

According to the definition of an expert consensus document (HRS / EHRA / ECAS, 2012), the term «progression of AF» means the development of chronic AF from paroxysmal form.

All patients signed an informed consent to participate in research. The study was approved by the local ethical committee of Novosibirsk State Medical University.

Statistical analysis. Statistically significant predictors of complications were determined by multifactor logistic regression analysis. Optimal models of multifactor regression analysis were developed using the direct and inverse step models. In multifactor model we estimated: the stage and FC of CHF (NYHA), Echo CG data, left ventricular mass index (LVMI) and biochemical markers of myocardium remodeling: galectin-3 and NT-proBNP. We also estimated hemodynamic parameters: left atrium diameter (LA), end-diastolic diameter (EDD), heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP); biochemical parameters: C-reactive protein (CRP) as a marker of inflammation, uric acid, glomerular filtration rate (GFR) and fibrinogen. The level of significance (p) was taken as 0.05. The lower threshold of statistical power was 80 %. Statistical analysis of obtained data was done using Rstudio software (version 0.99.879 — © 2009–2016 RStudio, Inc., USA, 250 Northern Ave, Boston, MA 02210 844–448-121, info@rstudio.com).

Results and discussion

Average age of participants was 53.3±7.1 year. During the period of follow-up of 167 patients with AF and AH, 15.57 % had AF progression, 14.37 % — CHF decompensation, 4.19 % — cardiac embolism and 7.19 % were admitted due to emergency (Figure 1).

Table 1. **The study design**

Observational cohort study of patients with AF and AH aged 45–60 years (n=161)				
AF/AH — comparison group n=37	AF/AH/COPD n=30	AF/AH/SCH n=25	AF/AH/DM n=36	AF/AH/CO n=33

Estimation of clinical parameters	ECG, 24-Hour Holter ECG monitoring, 24-Hour arterial pressure monitoring «Schiller»	Echo CG «General Electric, USA»,	NTproBNP Galectin-3 «Human Galectin-3 ELISA kit; eBioscience», «NTproBNP-ELISA-Best kit»	Biochemical spectrum «Vector Best», ELISA using ELISA test system, Biomerica, США	The test of -174G / C (rs1800795) polymorphism. PCR with RFLP. SibEnzyme, Russia.

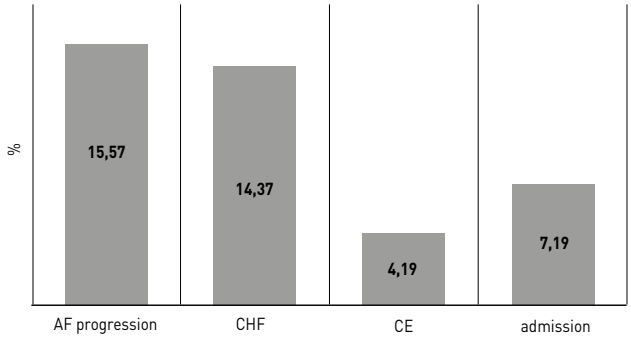


Figure 1. Development and progression of AF complications over the year

When analyzing the frequencies of the genotypes and alleles rs1800795 of the IL6 gene in patients with various comorbidities, we found statistically significant differences in DM group (p=0.047).

The analysis of the frequencies of the genotypes and alleles rs1800795 polymorphism of the IL6 gene in patients with various comorbidities is presented in table 2.

The odds ratio of SS genotype in DM group is significantly lower compared with comparison group (5.6% vs 27.0; p = 0.024). The frequency CC genotype of rs1800795 is different between DM and AH groups (p=0.025), and DM and CO groups (p=0.020). The frequency of allele C did not increase significantly in COPD group. Although, there are data on association between the development of AF in patients with COPD, inflammation and rs1800795. The factors associated with AF were: the volume of the LA (p = 0.027), EDD (p = 0.021) and carriage of allele C of the polymorphic marker G (–174) C of the IL-6 gene (p = 0.003) [13].

When comparing the frequencies of the genotypes and alleles rs1800795 of the IL6 gene in patients with various comorbidities with and without recurrent AF, no statistically significant differences were found. This may be associated with relatively large investigated group. Earlier, a number of authors showed an association of the rs1800795 polymorphism with postoperative AF. The IL-6 protein is produced by endothelial cells, vascular smooth muscle cells, and myocytes during ischemia [15–17].

When analyzing the frequencies of the genotypes with the rs1800795 polymorphism of the IL6 gene in patients with various comorbidities with and without recurrent AF, we found that the frequency of CC genotype is higher in patients with recurrent AF in the group with subclinical hypothyroidism and in comparison group. The frequency of CC genotype was lower in COPD group and it was the same in patients with and without recurrent AF in DM group. The frequency of recurrent AF was lower in SCH group in patients with CG genotype, p=0.030 (Table 3).

Some patients had CE over the year after treatment. When comparing the frequencies of the genotypes with the rs1800795 polymorphism of the IL6 gene in patients with and without CE, the frequency of heterozygous CG genotype of rs1800795 was higher in

Table 2. **The frequencies of the genotypes and alleles rs1800795 polymorphism of the IL6 gene in patients with various comorbidities**

Genotypes	Comparison group		COPD		SCH		DM		CO	
	n	%	n	%	n	%	N	%	n	%
CC	10	27.0	7	23.3	7	28.0	2	5.6	9	27.3
CG	17	46.0	14	46.7	13	52.0	21	58.3	15	45.4
GG	10	27.0	9	30.0	5	20.0	13	36.1	9	27.3
Alleles	**%**		**%**		**%**		**%**		**%**	
C	50.0		46.7		54.0		34.7		50.0	
G	50.0		53.3		46.0		65.3		50.0	

Table 3. **The frequencies of the genotypes with the rs1800795 polymorphism of the IL6 gene in patients with various comorbidities with and without recurrent AF**

	Comparison group				DM			
	Recurrent AF				Recurrent AF			
	No		Yes		No		Yes	
Genotypes	n	%	n	%	n	%	N	%
CC	3	17.6	7	35.0	1	5.9	1	5.3
CG	10	58.8	7	35.0	9	52.9	12	63.2
GG	4	23.5	6	30.0	7	41.2	6	31.6
Genotypes	SCH				COPD			
CC	1	12.5	6	35.3	4	36.4	3	15.8
CG	7	87.5	6	35.3	3	27.3	11	57.9
GG	0	0	5	29.4	4	36.4	5	26.3

patients with CE (OR 2.25; 95% CI 1.01–5.04 p=0.05) (Table 4). The association between stroke and allele G rs1800795 carriage was shown in population [18].

Table 4. **The frequencies of the genotypes with the rs1800795 polymorphism of the IL6 gene in patients with and without CE**

Genotypes	CE			
	No		Yes	
	n	%	N	%
CC	33	24.8	4	12.5
CG	61	45.9	21	65.6
GG	39	29.3	7	21.9
Significance of differences, p	0.117			
	n	%	N	%
CG+GG	100	75.2	28	87.5
CC	33	24.8	4	12.5
Significance of differences, p	0.161			
	n	%	N	%
CC+GG	72	54.1	11	34.4
CG	61	45.9	21	65.6
Significance of differences, p	0.050			
Relative risk	2.25			
95% CI RR	1.01–5.04			

When analyzing the frequencies of the genotypes with the rs1800795 polymorphism of the IL6 gene in patients with various comorbidities, CHF development and admission, no statistically significant differences were found.

When comparing average values of various parameters in patients with different genotypes of rs1800795 polymorphism of IL6 gene using the Kruskal-Wallis test, we found significant differences by the level of HDL, creatinine and galectin-3.

When comparing the values of the studied parameters in patients of the CC genotype with a group of patients with CG and GG genotypes, the significance of differences remains the same (table 5). Patients with CC genotype had higher level of galectin-3 (p<0.022) compared with patients with other genotypes, p=0.022.

Conclusion

When analyzing the frequencies of the genotypes with the rs1800795 polymorphism of the IL6 gene in patients with various comorbidities with recurrent AF, we found that the frequency of CC genotype is higher in patients with recurrent AF in the group with SCH. When comparing the frequencies of CG genotype of rs1800795 of the IL6 gene in patients with and without CE, the frequencies of heterozygous CG genotype was higher in patients with CE. According to logistic regression analysis, the factors associated with AF include: volume of the LA, EDD and carriage of allele C of the polymorphic marker G (–174) C of the IL-6 gene. Patients with CC genotype had higher level of galectin-3 compared with patients with other genotypes.

Conflict of interest: None declared.

References

1. Shlyakhto E.V., Ezhov A.V., Zenin S.A. et al. Clinical portrait of a patient with atrial fibrillation in the Russian Federation. global register data gloria af. Russian Journal of Cardiology. 2017; 22 (9): 21–27. Russian
2. Martsevich S.Y., Navasardyan A.R., Kutishenko N.P. et al. The assessment of compliance to the use of new oral anticoagulants in patients with atrial fibrillation according to the profile register. Rational Pharmacotherapy in Cardiology. 2014; 10 (6): 625–630. Russian
3. Bustamante J.O., Rucnudin A., Sachs F. Stretch-activated channels in heart cells: relevance to cardiac hypertrophy. J. Cardiovasc. Pharmacol. 1991; 1 (17): 110–113.
4. Chowdhury E.K., Owen A., Krum H., Wing L.M., Nelson M., Reid C.M. Second Australian National Blood Pressure Study Management Committee. Systolic blood pressure variability is an important predictor of cardiovascular outcomes in elderly hypertensive patients. J Hypertens. 2014; 32 (3): 525–533.
5. Niculina S.Yu., Sulman V.A., Kuznecova O.O. et al. Clinical and genetic features of atrial fibrillation. Racional'naja farmakoterapija v kardiologii. 2008; 4 (2): 13–8. Russian
6. Lip G.Y.H., Coca A., Kahan T. et al. Hypertension and cardiac arrhythmias: executive summary of a consensus document from the European Heart Rhythm Association (EHRA) and ESC Council on Hypertension, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). Eur Heart J Cardiovasc Pharmacother. 2017; 3: 235–50.
7. Unger R.H., Scherer P.E. Gluttony, sloth and metabolic syndrome: a roadmap to lipotoxisity. ends Endocrinol. Metab. 2010; 21 (6): 345–352.
8. Volchkova E.A., Nikitin A.G., Zotova I.V., Zateyshchikova A.A., Shavrin I.V., Safaryan V.I., Nosikov V.V., Zateyshchikov D.A. Association of atrial fibrillation in patients with chronic obstructive pulmonary disease with interleukin-6 gene polymorphism. Cardiology. 2015; 55 (11): 31–36. Russian
9. Titov B.V., Barsova R.M., Martynov M.Yu., Nikonova A.A., Favorov A.V., Gusev E.I., Favorova O.O. Polymorphic variants of genes encoding interleukin-6 and fibrinogen, the risk of ischemic stroke and fibrinogen levels. 2012; 1 (46): 93–102. Russian
10. Newton-Cheh C., Johnson T., Gateva V. et al. Genome-wide association study identifies eight loci associated with blood pressure. Nat Genet. 2009 Jun; 41 (6): 666–76. doi: 10.1038/ng.361

11. Hong K.W., Go M.J., Jin H.S., et al. Genetic variations in ATP2B1, CSK, ARSG and CSMD1 loci are related to blood pressure and/or hypertension in two Korean cohorts. J Hum Hypertens. 2010; 24 (6): 367–372.
12. Ding K., Kullo I.J. Geographic differences in allele frequencies of susceptibility SNPs for cardiovascular disease. BMC Med Genet. 2011 Apr 20.
13. Jeemon P., Pettigrew K., Sainsbury C., Prabhakaran D., Padmanabhan S. Implications of discoveries from genome-wide association studies in current cardiovascular practice. World J Cardiol. 2011; 3 (7): 230–247.
14. Xi B., Shen Y., Reilly K.H., Wang X., Mi J. Recapitulation of four hypertension susceptibility genes (CSK, CYP17A1, MTHFR, and FGF5) in East Asians. Metabolism. 2013; 62 (2): 196–203.
15. Xi B., Zhao X., Chandak G.R., Shen Y., Cheng H., Hou D., Wang X., Mi J. Influence of obesity on association between genetic variants identified by genome-wide association studies and hypertension risk in Chinese children. Am J Hypertens. 2013; 26 (8): 990–996.
16. AlSaleh A., Maniou Z., Lewis F.J., Hall W.L., Sanders T.A., O'Dell S.D.; MARINA Study Team. Interaction between a CSK gene variant and fish oil intake influences blood pressure in healthy adults. J Nutr. 2014; 144 (3): 267–272.
17. Lahtinen A.M., Noseworthy P.A., Havulinna A.S., Jula A., Karhunen P.J., Kettunen J., Perola M., Kontula K., Newton-Cheh C., Salomaa V. Common genetic variants associated with sudden cardiac death: the Finscdgen study. PLoS One. 2012; 7 (7): 416–475.
18. Gaudino M., Andreotti F., Zamparelli R. et al. The -174G/C interleukin-6 polymorphism influences postoperative interleukin-6 levels and postoperative atrial fibrillation. Is atrial fibrillation an inflammatory complication? Circulation. 2013; 9 (108): 195–199.

International Heart and Vascular Disease Journal • Volume 7, № 21, March 2019

Journal of the Cardioprogress Foundation

Vascular condition assessment in patients with arterial hypertension

N.Zh. Mirzagalieva[1], R.A. Aringazina[2], A.P. Astrakhanov[1], M.A. Otesin[1]

[1] Marat Ospanov West Kazakhstan State Medical University, Aktobe, Kazakhstan
[2] Syrdarya Central Pospital, Kyzylorda, Kazakhstan

Authors

Nurzhamal Zh. Mirzagalieva, M.D., head of Syrdarya Central Hospital of Kyzylorda region, Kyzylorda Region, Syrdarya District, Kazakhstan;
Raisa A. Aringazina, M.D., Ph.D., associate professor of the Department of Internal Medicine No. 1, West Kazakhstan Medical University, Aktobe, Kazakhstan;
Rustemuly A. Astrakhanov*, internal medicine intern, head of the Youth Scientific Society of West Kazakhstan Medical University, Aktobe, Kazakhstan.
Askaruly M. Otesin, internal medicine intern, head of the Youth Scientific Society of West Kazakhstan Medical University, Aktobe, Kazakhstan.

Objective. *To study vascular age, 5-year risk of cardiovascular complications and atherogenic coefficient in men and women with arterial hypertension.*

Materials and methods. *We observed medical history of 105 patients, who were admitted to the department of internal medicine of Syrdarya central hospital. The estimation of vascular age and 5-year risk of cardiovascular complications was performed with the ASCORE risk score model. Atherogenic coefficient was calculated with the formula: (conventional unit) (total cholesterol — high density lipoproteins)/ high density lipoproteins. Statistical data processing was performed using the STATISTICA 10 software and correlation and regression analysis.*

Results *The average age for men was 64.6 ± 9.5 years and 66.9 ± 10.05 years for women. Vascular age, estimated with ASCORE, and biological age were different and tended to increase in both groups (70.2 ± 10.8 and 74.2 ± 9.8, respectively). 2.56 % of men had low risk, 25.64 % had moderate risk, 69.23 % had high risk and 2.56 % — very high 5-year risk of cardiovascular complications estimated with ASCORE. 6.06 % of women had low risk, 30.3 % had moderate risk, 60.6 % had high, and 3.03 % had very high risk of cardiovascular complications. Atherogenic coeffi-*

* Corresponding author. Tel.: 87474935776. E-mail: astrakhanov.akezhan@mail.ru

cient had direct correlation with the 5-yesr risk of cardiovascular complications (r = 7019; p = 0.0000). Vascular age also correlated with the 5-year risk of cardiovascular complications (regression coefficient R^2 = 57.6 %; p= 0.0000).

41.1 % of men had normal atherogenic coefficient, 51.3 % had moderate risk of atherosclerosis, and 3 % had high risk of atherosclerosis. 43.9 % of women had normal atherogenic coefficient, 39.9 % and 16.6 % had moderate and high risks of atherosclerosis, respectively.

Conclusion. *Thus, we established a correlation between vascular age, atherogenic coefficient and 5-year risk of cardiovascular complications in patients with arterial hypertension. Vascular age can be an independent prognostic factor for arterial hypertension and cardiovascular complications development.*

Vascular age can be used as a screening method for examining patients with arterial hypertension, as a biomarker for predicting cardiovascular complications.

Key words: *arterial hypertension, vascular age, ASCORE risk score, vascular risk assessment, atherogenic coefficient.*

Conflicts of interest: nothing to declare.

Received: 26.01.2019 **Accepted:** 20.02.2019.

Introduction

We estimated vascular age and 5-year risk of cardiovascular complications in men and women with arterial hypertension (AH). We also estimated the difference between vascular and biological age. All patients were treated in the department of internal medicine of Syrdarya central hospital of Kyzylorda Region.

AH is one of the most important risk factors for all cardiovascular diseases (CVD), including coronary artery disease (CAD), left ventricular hypertrophy, valvular heart disease, heart rhythm disturbances, including atrial fibrillation, stroke and kidney failure. The difference between high normal blood pressure and arterial hypertension is based on the correlation of blood pressure (BP) with cardiovascular complications (CVC). Arterial hypertension prevalence is about 30–45 % in European population with sharp increase with age. Recommendations for the treatment and prevention of CVD should be based on total cardiovascular risk, which can be estimated using different models. However, age significantly affects total risk, so young people (especially women) are unlikely to achieve high risk, even if they have more than one major risk factor and obvious increase of relative risk. Therefore, models based on age and blood pressure should also include ethnical factor due to large differences between countries [1, 2]. One of the most clear and informative indicators is the atherogenic cholesterol coefficient by A.N. Klimov [4]. Calculation of the coefficient is based on the levels of total cholesterol (TC) and high-density lipoproteins (HDL). The index of atherogenicity has high prognostic value on the risk mortality associated with atherosclerosis (CAD and stroke) [3, 4].

Experts create national programs, improve guidelines and develop new scales to estimate total risk of these diseases [5]. However, nowadays there is no single concept that integrates age, atherosclerotic, hypertensive, metabolic and functional changes in the vascular wall [7]. Cardiovascular mortality is still high and there's need for new pathophysiological models for better understanding of cardiovascular risks based on the new data. An assessment of the functional state and structure of vascular wall — vascular age — can predict the development of cardiovascular pathology and its complications [5]. Vascular age is easy to determine and reflects individual cardiovascular risk [6]. In 2013 experts developed the new algorithm called ASCORE for risk estimation in patients with AH without previous CVD and antihypertensive treatment based on the results of 5-year ASCOT BPLA (n = 15955) trial [9]. They also developed simple scale (ASCORE-S) that allows to disregard laboratory parameters [10, 11]. Various literature sources showed the correlation between atherogenic coefficient and the risk of cardiovascular complications (CVC). Therefore, we decided to use this parameter in our study [13].

Objective

To study vascular age, 5-year risk of CVC and atherogenic coefficient in men and women with arterial hypertension.

Materials and methods

We observed medical history of 105 patients, who were admitted to the department of internal medi-

cine of Syrdarya central hospital. Average age of all patients was 66,06 ± 9,9. 39 men and 66 women. Patients were divided into two groups depending on their gender. The inclusion criterium was the history of 2nd or 3d grade of AH. Patients with NYHA classes III–IV of heart failure, cancer, decompensated diseases of different organ systems, MI and acute cerebrovascular accident (ACA) survivors and patients with chronic cardiovascular and hematological diseases were excluded from the study. Vascular age and the risk of cardiovascular complications were estimated with ASCORE. Atherogenic coefficient was calculated with the formula: (conventional unit) (TC — HDL) [14]. We also took into account demographic parameters, smoking, the level of systolic blood pressure (SBP), TC, HDL, glucose and creatinine [11]. Statistical data processing was performed using the STATISTICA 10 software and correlation and regression analysis.

Results and discussion

The average age for men was 64.6 ± 9.5 years and 66.9 ± 10.05 years for women. Vascular age, estimated with ASCORE, and biological age were different and tended to increase in both groups (70.2 ± 10.8 and 74.2 ± 9.8, respectively)(figure 1). 2.56 % of men had low risk, 25.64 % had moderate risk, 69.23 % had high risk and 2.56 % — very high 5-year risk of cardiovascular complications estimated with ASCORE (figure 2). 6.06 % of women had low risk, 30.3 % had moderate risk, 60.6 % had high, and 3.03 % had very high risk of cardiovascular complications (Figure 3).

We analyzed lipid spectrum of the patients to estimate atherogenic coefficient. TC in men was 4,6 ± 0,9 and HDL — 1,2 ± 0,4, in women — 4,1 ± 1,0 and 1,2 ± 0,6, respectively. Low density lipoproteins (LDL) — 2,2 ± 0,4 in men and 2,3 ± 0,9 in women. Triglycerides — 1,2 ± 0,1 and 1,17 ± 0,6, respectively. Atherogenic coefficient correlated with the risk of cardiovascular complications (r = 7019; p = 0,0000) (figure 4). Vascular age also correlated with the 5-year risk of cardiovascular complications in regression analysis (regression coefficient R^2 = 57.6 %; p = 0.0000).

41.1 % of group 1 (men) had normal atherogenic coefficient, 51.3 % had moderate risk of atherosclerosis, and 3 % had high risk of atherosclerosis (figure 5).

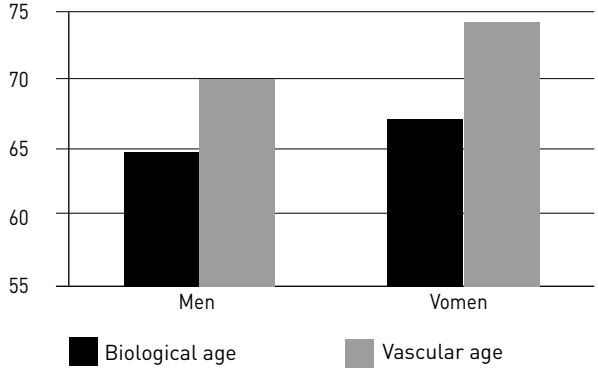


Figure 1. The difference between vascular and biological age

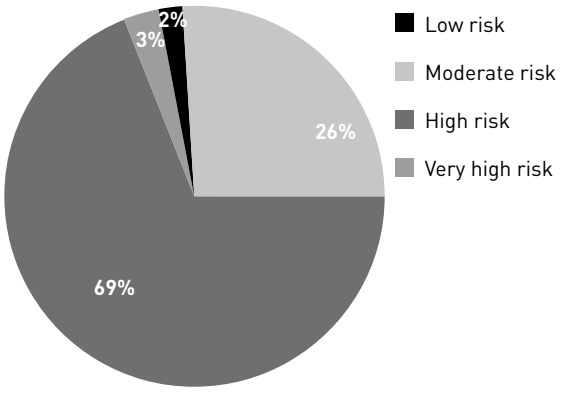


Figure 2. Results of 5-year risk of cardiovascular complications estimation with ASCORE in men (%)

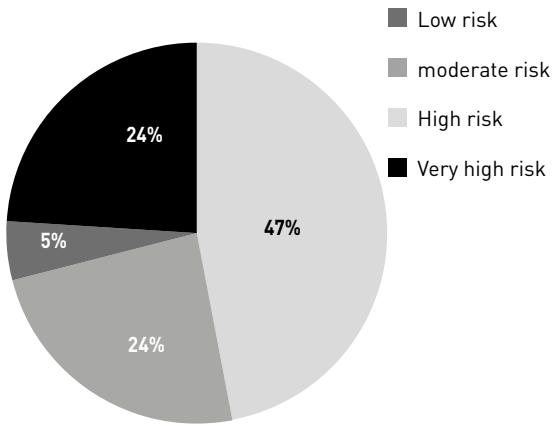


Figure 3. Results of 5-year risk of cardiovascular complications estimation with ASCORE in women (%)

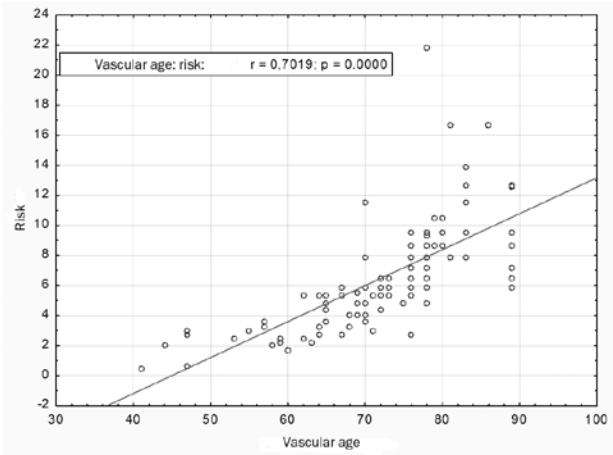


Figure 4. Correlation between vascular age and 5-year risk of cardiovascular complications

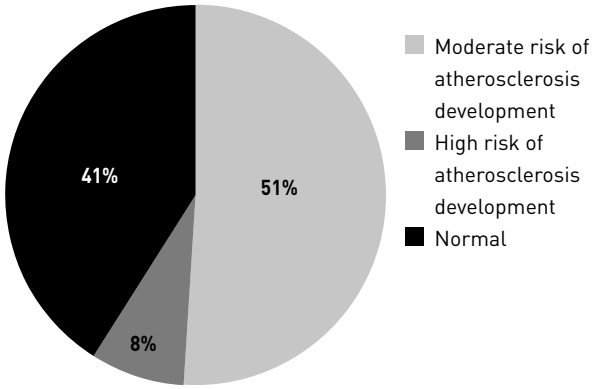


Figure 5. The risk of atherosclerosis development in patients with AH (men,%)

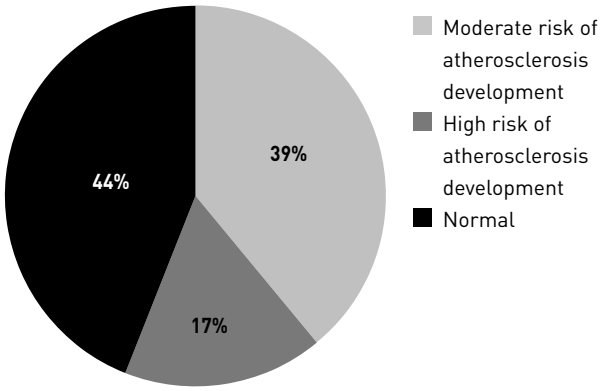


Figure 6. The risk of atherosclerosis development in patients with AH (women,%)

43.9 % of group 2 (women) had normal atherogenic coefficient, 39.9 % and 16.6 % had moderate and high risks of atherosclerosis, respectively (figure 6).

According to Russian authors (Kutmeneva K.A., Abdullaeva E.Kh., Budnikova N.V.) [12] there's an increase of vascular age and 5-year risk of cardiovascular complications in relation to biological age in patients with AH. According to other authors (Gómez-Marcos M.A., Martínez-Salgado C., Martin-Cantera C., Recio-Rodríguez J.I., Castaño-Sánchez Y., Giné-Garriga M., Rodriguez-Sanchez E., García-Ortiz L.) there's an increase of atherogenic index — the risk of atherosclerosis in patients with AH.

Conclusion

Thus, we established a correlation between vascular age, atherogenic coefficient and 5-year risk of CVC in patients AH. Vascular age can be an independent prognostic factor for AH and CVC.

Vascular age can be used as a screening method for examining patients with AH, as a biomarker for predicting CVC.

Conflict of interest: None declared.

References

1. Sverre E. Kjeldsen, Hypertension and cardiovascular risk: General aspects. Pharmacological Research, 2018; 129 (March 2018): 95–99.
2. Parfenov V.A., Ostroumova T.M., Perepelova E.M., Perepelov V.A., Kochetkov A.I., Ostroumova O.D. Brain perfusion, cognitive function, and vascular age in middle-aged patients with essential hypertension. Cardiology. 2018; 58 (5): 23–31. Russian.
3. Protasov K.V., Sinkevich D.A., Fedorishina O.V., Dzizinsky A.A. Vascular age as an integral indicator of heart and vessel remodeling in patients with hypertension. Siberian medical journal (Irkutsk). 2011; 105 (6): 37–40. Russian.
4. Klimov A.N., Nikulicheva N.G. The metabolism of lipids and lipoproteins and its disorders. — SPb.: Peter Kom, 1999. — 512 p. Russian.
5. Drapkina O.M., Fadeeva M.V. Vascular age as a risk factor for cardiovascular diseases. Arterial hypertension. 2014; 4: 224–231. Russian.
6. Karpov Y.A., Sorokin E.V. The Effect of combined antihypertensive therapy on the risk of cardiovascular complications and vascular age: results of a multicenter open study Advant'age. Atmosphere. Cardiology news. 2015; 3: 2–10. Russian.
7. Protasov K.V., Sinkevich D.A., Fedorishina O.V. Vascular age and cardiovascular remodeling in arterial hypertension. Arterial hypertension. 2011; 5: 448–453. Russian.
8. Sinkevich, D.A., Protasov K.V., Dzizinsky A.A. The Concept of «Vascular age» as a new approach to the assessment of cardiovascular risk. Siberian medical journal. 2011; 6: 9–13. Russian.
9. Lopez-Gonzalez A.A., Aguilo A., Frontera M., BennasarVeny M., Campos I., Vicente-Herrero T. et al. Effectiveness of the Heart Age tool for improving modify able cardiovascular risk factors in a Southern European population: a randomized trial. Eur J PrevCardiol. 2015; 22 (3): 389–96).
10. Prieto-Merino D., Dobson J., Gupta A.K., Chang C.L., Sever P.S., Dahlof B. et al. ASCORE: an up-to-date cardiovascular risk score for hypertensive patients reflecting contemporary clinical practice developed using the (ASCOT-BPLA) trial data. J Hum Hypertens. 2013; 27 (8): 492–496).
11. Dahlof B., Sever P.S., Poulter N.R., Wedel H., Beevers D.G., Caulfield M. et al. 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 multicenter randomised controlled trial. Lancet. 2005; 366 (948): 895–906.
12. Kutmanova K.A., Abdullayeva, E.H., Budnikova N. In Vascular age and five-year risk of developing cardiovascular complications: gender differences. Materials III all — Russian educa-

tional and scientific conference of students and young scientists with international participation in the XIII regional festival «Young scientists — the development of the Ivanovo region» 2017: 93–95. Russian.

13. Makoveev E.A. Atherogenic Index as an integral indicator of the destruction of the target organ (the heart) and hypertension. Universum. 2013; 1 (1): 2. Russian.
14. McCance K.L., Huenter S.E. Pathophysiology. The Biologic Basis for Disease in Adults and Children. 5th ed. Elsevier. — 2006. — 1779 p.
15. Gómez-Marcos M.A., Martínez-Salgado C., Martin-Cantera C., Recio-Rodríguez J.I., Castaño-Sánchez Y., Giné-Garriga M., Rodriguez-Sanchez E., García-Ortiz L. Therapeutic implications of selecting the SCORE (European) versus the D'AGOSTINO (American) risk charts for cardiovascular risk assessment in hypertensive patients. BMC Cardiovasc Disord. 2009; 9 (May 11): 17. doi: 10.1186/1471–2261-9–17

International Heart and Vascular Disease Journal • Volume 7, № 21, March 2019

Journal of the Cardioprogress Foundation

Attitude to medical care and physical activity in population: gender aspects, prevalence and interrelations

A.M. Akimov[1,2], M.M. Kaymova[1,2], V.V. Gafarov[2]

[1] Tyumen Cardiology Research Center, Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russia.

[2] Interdepartmental Laboratory of Cardiovascular Diseases Epidemiology of the Russian Academy of Sciences, Novosibirsk-Tomsk-Tyumen, Russia

Authors

Alexander M. Akimov*, M.D., Ph.D., researcher, Laboratory of Epidemiology and Prevention of Cardiovascular Diseases (Tyumen Cardiology Research Center, Tyumen, and National Research Medical Center, Tomsk), Interdepartmental Laboratory for Epidemiology of Cardiovascular Diseases, Research Institute of Therapy and Preventive Medicine, Novosibirsk, Russia

Marina M. Kayumova, M.D., Ph.D., researcher in the Laboratory of Cardiovascular Disease Epidemiology and Prevention, Tyumen Cardiology Research Center; researcher in the Interdepartmental Laboratory of Cardiovascular Diseases Epidemiology, Tomsk, Russia.

Valery V. Gafarov, M.D., Ph.D., doctor of sciences, head of Interdepartmental Laboratory for Epidemiology of Ca rdiovascular Diseases, Research Institute of Therapy and Preventive Medicine, Novosibirsk, Russia.

Objective. *To study the prevalence and interactions of attitude to medical care and physical activity workplace in men and women aged 25–64 years and belonging to the open urban population of Tumen.*

Materials and methods. *The study was based on cardiological screening among a representative sample of population, the response amounted to 77,7%. The sample of 2000 people was taken from the electoral lists of one of the administrative districts of Tumen and divided into four groups of different age and gender (25–30, 35–44, 45–54, 55–64 years), consisted of 250 persons each. Stress at work was determined using the WHO questionnaire «MONICA-psychosocial».*

Results. *The results of this study showed that men of working age had negative attitude to physical activity, which did not depend on their attitude to medical care. At the same time, men with negative attitude to medical care*

* Corresponding author. Tel.: +7 (982) 910-17-78. E-mail: akimovam@infarkta.net

were less active, and men with positive attitude to medical care felt more active compared with other people of the same age. Attitude to medical health did not affect physical activity in women. However, women with negative attitude to medical care, unlike men, felt more active.

Conclusion. *Thus, the results on the correlation of attitude to medical care and physical activity and the objective-subjective indicator of public health obtained in this study may be used as the scientific basis for organizing complex socially oriented preventive programs with the main focus on the needs of risk groups – men of working age.*

Key words: *medical care, physical activity, open population, gender differences.*

Conflicts of interest: nothing to declare.

Received: 15.01.2019 **Accepted:** 16.02.2019.

Introduction

Health of working population is one of the main factors of productivity and economic growth that determines safety and welfare of society.

Many researches have shown, that physical activity in combination with many factors is very important to maintain and improve the quality of life [1–5]. Thus, according to results of University of Michigan's (USA) study on sociodemographic risk factors, chronic diseases, and a history of smoking, people with low muscular strength have 50 % higher chance of early death [6].

At the same time, attitude to medical care is one of the most important objective-subjective indicators of health in population. Many universities conducted studies on medical care and public knowledge in matters of health. Such knowledge is necessary for everyday life of people, so each person can formulate his own opinion and make decisions about his own health [7, 8].

Attitude to medical care is one of the objective-subjective health indicators that is related to population's behavioral characteristics and the risk of non-communicable diseases, including primary cardiovascular diseases. Nowadays population's behavioral including attitude not only to physical activity, but to health and medical care in each case can affect civilization and has its benefits and risks [9, 10].

According to many researches attitude to medical care has gender differences that may be used as the scientific basis for organizing complex socially oriented preventive programs based on the level of medical care in particular area and the possibilities of population in increasing physical activity.

Objective

To study the prevalence and interactions of attitude to medical care and physical activity workplace in men and women aged 25–64 years and belonging to the open urban population of Tumen.

Materials and methods

The study was conducted in the framework of cardiological screening among men and women aged 25–64 years belonging to the open urban working population of Tyumen. A representative population, that involved 2000 participants, was taken from the electoral lists of one of the administrative districts of Tyumen, and included 250 men and women of each age group (25–34, 35–44, 45–54, 55–64 years), the response amounted to 77.7 %.

Questioning of participants was conducted using WHO-MONICA psychosocial questionnaire "Knowledge and attitude towards their health" [11]. Questions of the questionnaire were accompanied by a list of fixed answers, including attitude to physical activity and medical care, from which the respondents could choose the most correct answer, by their opinion.

Statistical analysis was done using SPSS 11.5 Statistics, Statistica 7.0 software and Microsoft Excel spreadsheets, according to the methods of variance statistics. The research data for categorical variables are represented in fractions (percent) for men and women. Pearson's chi-squared test (X^2) was used to determine the statistical significance of the results between different groups.

Results

According to data analysis, 10,5 % of men and 15,2 % of women in open urban population of Tyumen "often" and "very often" had positive experience of medical care (table 1).

We found the following results when comparing men and women aged 25–64 years of open urban population in their attitude to physical activity and medical care.

Table 1. **Did you have positive experience of medical care?**

Question / attitude Abs. %	Never n=272/155 (32%/22%)		Once or twice n=186/151 (21.9%/21.5%)		A few times n=303/290 (35.6%/41.3%)		Often n=80/94 (9.4%/13.4%)		Very often n=9/13 (1.1%/1.8%)	
	abs.	%	abs.	%	abs	%	abs.	%	abs.	%
1. Do you exercise (excluding your work)?										
1.1. I don't need this	52/7	19.2/4.4***	27/4	14.5/2.6***	33/10	10.9/3.4***	10/3	12.5/3.2*	5/2	55.6/15.4*
1.2. I should exercise, but I don't	134/81	49.3/52.3	92/88	49.4/58.3	150/174	49.5/60.1*	32/47	40.0/50.0	1/7	11.1/53.8*
1.3. I tried unsuccessfully	36/35	13.2/22.6*	26/28	14.0/18.5	63/60	20.8/20.7	16/21	20.0/22.3	0/4	0.0/30.8
1.4. I exercise regularly	48/30	17.6/19.4	39/29	21.0/19.2	54/45	17.8/15.5	20/23	25.0/24.5	2/0	22.2/0.0
1.5. According to my doctor, exercising is contraindicated to me	2/2	0.7/1.3	2/2	1.1/1.3	3/1	1.0/0.3	2/0	2.5/0.0	1/0	11.1/0.0
2. Did your physical activity (moving. exercising. etc.) change over the last 12 months?										
2.1. Yes, I became more active	40/22	14.7/14.2	21/23	11.3/15.2	35/36	11.6/12.4	9/8	11.3/8.5	1/0	11.1/0.0
2.2. No	168/100	61.8/64.5	111/99	59.7/65.6	193/185	63.6/63.8	45/64	56.3/68.1	7/11	77.8/84.6
2.3. I became less active	64/33	23.5/21.3	54/29	29.0/19.2*	75/69	24.8/23.8	26/22	32.5/23.4	1/2	11.1/15.4
3. How do you estimate your physical activity compared with people of the same age?										
3.1. I am significantly more active	36/21	13.2/13.5	21/30	11.3/19.9*	34/30	11.2/10.3	7/6	8.8/6.4	2/0	22.2/0.0
3.2. I am a little more active	78/31	28.7/20.0*	53/39	28.5/25.8	81/77	26.7/26.6	23/28	28.8/29.8	3/2	33.3/15.4
3.3. I am the same	124/73	45.6/47.1	72/54	38.7/35.8	132/118	43.6/40.7	33/45	41.3/48.0	3/8	33.3/61.5
3.4. I am a little less active	26/21	9.6/13.6	34/17	18.3/11.3	44/49	14.5/16.9	13/14	16.3/14.9	1/2	11.1/15.4
3.5. I am significantly less active	8/9	2.9/5.8	6/11	3.2/7.2	12/16	4.0/5.5	4/1	5.0/1.1	0/1	0.0/7.7

Comment: Significance of differences between men and women is signed with * in the right corner of the table cell.

Statistically significant gender differences were found in negative answer to question about physical exercise (the answer "I don't need this") regardless to attitude to medical care. Men who didn't understand the necessity of physical exercise were prevalent compared with women regardless to answer to the question "Did you have positive experience of medical care?" (the answer "never" — 19.2% and 4.4%, p <0.001; "ones or twice" — 14.5% and 2.6%, p <0.001; "several times" — 10.9% and 3.4%, p <0.001; "Often" — 12.5% and 3.2%, p <0.05; "very often" — 55.6% and 15.4%, p <0.05, respectively).

Women with positive attitude to medical care (had positive experience) answered "I should exercise, but I don't" to the question about physical activity more frequent compared with men — "a few times" — 49.5% and 60.1%, p<0.05, "very often" — 11.1% — 53.8%, p<0.05, respectively.

Women who never had positive experience of medical care answered "I tried unsuccessfully" to the question "Do you exercise?" more frequent compared with men (13.2% and 22.6%, p<0.05, respectively).

Women who had positive experience of medical care once or twice became less active over the last year compared with men (19.2% and 29.0%, p<0.05, respectively).

Meanwhile, women who had positive experience of medical care ones or twice felt more active compared with other people of the same age (19.9% and 11.3%, p <0.05 respectively). Men who never had positive experience of medical care felt more active compared with other people of the same age (28.7% and 20.0%, p<0.05, respectively).

Discussion

The results of the current study showed that in general smallest part of open urban working population of Tyumen "often" or "very often" had positive experience of medical care. At the same time, when considering gender aspect, we found that men and women had different attitude to medical care that reflects the correlation between physical activity of population and emotional component and showed that healthy lifestyle includes not only behavioral characteristics (for example, attitude to physical activity) but the desire to undergo medical examination (and have positive experience).

The analysis showed that men of working age mostly had negative attitude to exercising regardless to their attitude to medical care. At the same time, men with negative attitude to medical care were more active and men with positive attitude to medical care felt more active compared with people pf the same age. This correlation shows that physical activity in men compared with women in general positively affects attitude to life circumstances, including medical care.

Attitude to medical care didn't affect the desire to exercise in women. But women who never had posi-

tive experience of medical care felt more active compared with men and people of the same age.

The results of current study are comparable with data of previous studies on the open urban population of Tyumen on the physical activity in association with social gradient and on the attitude to health in association with factors of chronic stress in gender aspects [13, 14].

Thus, according to data of these studies, men from groups of managers, specialists and engineers had the highest physical activity, but even these groups were less active than women [13]. At the same time, single men (compared with single women) had more negative attitude to preventive medical examination [12]. Thus, according to data based on selective social groups and the results of current study, we can assume that healthy lifestyle in men's population include behavioral characteristics (physical activity) and objective-subjective indicator of health in population (attitude to preventive medical examination and medical care).

Previous studies also showed that women with secondary and higher education as well as non-working women (most of the population) had the highest desire of physical activity [13]. At the same time, women were more responsible to their health and were more prepared to take urgent measures in case of emergency or chest pain [14]. Thus, according to data obtained in previous and current studies on Tyumen population, healthy lifestyle less correlated with emotional component, including positive and negative experience of preventive medical examinations and medical care, in women.

Conclusion

Thus, the results on the correlation of attitude to medical care and physical activity and the objective-subjective indicator of public health (based on the model of Tyumen city) may be used as the scientific basis for organizing complex socially oriented preventive programs with the main focus on the needs of risk groups — men of working age and on the awareness of the city administration on the attitude to medical care in population.

Conflict of interest: None declared.

References

1. Oganov R.G., Maslennikova G.Ya. Demographic situation and cardiovascular disease in Russia: problem scope and possible solutions. Cardiovascular Therapy and Prevention. 2007; 6 (8): 7–14. Russian
2. Mamedov M.N. Dynamics of risk factors and cardiovascular diseases: analytical review of international and Russian data for 2017. International Heart and Vascular Disease Journal. 2018; 6 (19): 32–37. Russian
3. European recommendations for the prevention of cardiovascular diseases in clinical practice (revision 2016). Journal of Cardiology. 2017; 6 (146): 7–85. doi: 10.15829/1560–4071-2017-6-7-85. Russian
4. Akimov A.M. Physical activity and level of education in an open male population. Siberian Medical Journal (Tomsk). 2013; 3: 81–84. Russian
5. Akimov A.M. Physical activity and level of education in open male population. Omsk scientific bulletin. 2015; 2: 238–240. Russian
6. Duchowny K. Do Nationally Representative Cutpoints for Clinical Muscle Weakness Predict Mortality? Results From 9 Years of Follow-up in the Health and Retirement Study. The Journals of Gerontology: Series A, 169 23 2018.
7. Sorensen K., Van den Broucke S., Fullam J. et al. Health literacy and public health: a systematic review and integration of definitions and models. BMC Public Health. — 2012 72 80. Mode of Access: http://www.ncbi.nlm.nih.gov/ pubmed/22276600 — Date of Access: 15, 2017.
8. Kayumova M.M., Gafarov V.V., Smaznov V.Yu. et al. Self-assessment of health, attitude towards own health and medical care in male population. World of science, culture and education 2011; 6 (31): 161–167. Russian
9. Boytsov S.A. Mechanisms of reduction in coronary heart disease mortality in different countries of the world. Preserving medicine. Preventive medicine. 2013; 16 (5): 9–19. Russian
10. Mulerova T.A., Maksimov S.A., Ogarkov M.Yu. Comprehensive assessment of cardiovascular risk factors of arterial hypertension in indigenous and non-indigenous inhabitants of Mountain Shoria. Sistemnie gipertensii. 2017; 1:17–22. http://dx.doi.org/10.26442/2075–082X_14.1.17–22. Russian
11. Gafarov V.V., Gromova E.A., Gagulin I.V., Gafarova A.V. Effects of stress on risk of arterial hypertension in general male population of 25–64 years old: 14 years of follow up (epidemiological study on the basic of the WHO programm «MONICA — PSYCHOSOCIAL»). Arterial'naya Gipertenziya. 2013; 19 (1): 27–31. Russian
12. Akimov A.M., Akimova A.A., Gakova E.I. et al. The attitude towards one`s own health and family status in the urban population: gender differences. The world of science, culture, education. 2016; 6 (61): 282–285. Russian
13. Akimova E.V., Akimov M.Yu., Gakova E.I. et al. Gender activity and social gradient in an open urban population: Gender differences. Profilakticheskaya meditsina. 2017; 20 (4): 31–36. Russian
14. Akimov A.M., Kayumova M.M., Gafarov V.V., Kuznetsov V.A. Attitude to prevention of heart diseases and stress in the family in the open city population: prevalence, interrelations. The Siberian medical journal. 2018; 33 (4): 148–153. Russian

International Heart and Vascular Disease Journal • Volume 7, № 21, March 2019

Journal of the Cardioprogress Foundation

REVIEW ARTICLE

Congress of American Heart Association 2018: results of clinical trials

S.G. Kanogorsky[1], M.N. Mamedov[2]. R.G. Oganov[2]

[1] Kuban State Medical University. Krasnodar. Russia

[2] National Research Center for Preventive Medicine of the Ministry of Healthcare of the Russian Federation, Moscow, Russia

Authors

Sergey G. Kanorskii*, M.D., Ph.D., doctor of sciences, professor, head of the Department of Therapy № 2, Faculty of Advanced Training and Professional Retraining of Specialists, Kuban State Medical University, Krasnodar, Russia.

Mekhman N. Mamedov, M.D., Ph.D., doctor of sciences, professor, head of the Laboratory of Interdisciplinary Approach for Prevention of Chronic Non-infectious Diseases, National Research Center for Preventive Medicine, Moscow, Russia.

Rafael G. Oganov, M.D., Ph.D., doctor of sciences, professor, academician of the Russian Academy of Sciences, head of the department of comorbid conditions, National Research Center for Preventive Medicine, Moscow, Russia.

This article contains a report of eight most important clinical trials represented during scientific sessions of American Heart Association held in Chicago, US, November 10-12, 2018.

Conflicts of interest: nothing to declare.

Received: 15.01.2019 **Accepted:** 16.02.2019.

Last summit of American Heart Association was held in Chicago (USA), November 10-12, 2018. 12654 specialists from over 100 countries took part in over 800 scientific sessions, where were over 1000 speakers – world leaders in the cardiovascular diseases (CVD) studies.

During the congress they discussed: new American guideline on the management of blood cholesterol [1], physical activity guidelines [2], guideline for the evaluation and management of bradycardia and cardiac conduction delay [3]. The results of new most

* Corresponding author. Tel. 8 918 3558281. E-mail: kanorskysg@mail.ru

important clinical studies that can significantly affect clinical practice are presented in this article.

Cardiovascular Prevention

The **VITAL** study is the first large-scale project on the role of the vitamin D and omega-3 fatty acids supplementation in the primary prevention of cardiovascular disease and cancer in men aged ≥50 years and women ≥55 years.

In 2×2 factorial design 25871 primary healthy US citizens (5106 were African American) were randomized to either vitamin D3 (2000 IU/day) or placebo, and to eicosatetraenoic and docosahexaenoic acids in 1.3 : 1 ratio (1 g per day) or placebo. The primary outcome was any invasive cancer or/ and the summary of major cardiovascular events (myocardial infarction (MI), stroke, CV death). Secondary outcomes included any localization cancer, cancer death, death from MI/ stroke/ percutaneous coronary intervention (PCI)/ coronary artery bypass grafting and/or any component of cardiovascular primary outcome.

During the follow-up of 5.3 years cancer was diagnosed in 1617 participants — 793 of 12927 in vitamin D group and 824 of 12944 in placebo group (relative risk (RR) — 0.96 with 95% coincidence interval (CI) from 0.88 to 1.66; p=0.47). Major cardiovascular event was seen in 805 participants — 396 in vitamin D group and 409 in placebo group (RR 0.97 with 95% CI from 0.85 to 1.12; p=0.69).

The risk of death was not significantly different in the vitamin D group compared with placebo including death from any localization cancer (RR 0.83 with 95% CI from 0.67 to 1.02); breast cancer (1.02 with 95% CI from 0.79 to 1.31); prostate cancer (RR 0.88 with 95% CI from 0.72 to 1.07); colorectal cancer (1.09 with 95% CI from 0.73 to 1.62); the summary of major cardiovascular events and coronary revascularization (RR 0.96 with 95% CI from 0.86 to 1.08); MI (RR 0.96 with 95% CI from 0.78 to 1.19); stroke (0.95 with 95% CI from 0.76 to 1.20); cardiovascular death (1.11 with 95% CI from 0.88 to 1.40) and all-cause mortality (total — 978 cases, RR 0.99 with 95% CI from 0.87 to 1.12). The risk of hypercalcemia and other adverse events wasn't increased during treatment [4]. Therefore, vitamin D did not reduce the incidence of invasive cancer or major cardiovascular events compared with placebo.

During the follow-up of 5.3 years major cardiovascular complications (CVC) were diagnosed in 386 of 12933 in omega-3 fatty acids group and in 419 of 12938 in placebo group (RR 0.92 with 95% CI from 0.80 to 1.06; p=0.24), invasive cancer was diagnosed in 820 and 797 participants, respectively (RR 1.03 with 95% CI from 0.93 to 1.13; p=0.56). Total number of cardiovascular events (RR 0.93 with 95% CI from 0.82 to 1.04); the incidence of any localization stroke (RR 1.04 with 95% CI from 0.83 to 1.31); cardiovascular death (RR 0.96 with 95% CI from 0.76 to 1.21); cancer death (total — 341 cases, RR 0.97 with 95% CI from 0.79 to 1.20); deaths from any other cause (total — 978 cases. RR 1.02 with 95% CI from 0.90 to 1.15) did not differ significantly between groups. But omega-3 polyunsaturated fatty acids decreased the risk of MI (RR 0.72 with 95% CI from 0.59 to 0.90), MI mortality (RR 0.50 with 95% CI from 0.26 to 0.97) and PCI mortality (RR 0.78 with 95% CI from 0.63 to 0.95), especially in patients with low fish consumption and African Americans. The risk of bleeding or other serious adverse effects didn't increase significantly [5]. Generally, additional intake of omega-3 fatty acids did not reduce the risk of cardiovascular events or cancer compared with placebo.

The most reliable result of the VITAL study is that vitamin D and omega-3 fatty acids did not significantly reduce the incidence of primary outcomes - severe CVD or invasive cancer, despite possible interest in individual frequency differences of secondary outcomes.

Patients with hypertriglyceridemia have increased risk of ischemic events. Highly purified ethyl eicosapentaenoic acid ester reduces triglycerides level without increasing the level of low-density lipoproteins (LDL), which lead to the studies on its effect on ischemic complications.

The **REDUCE-IT** [6] trial included 8179 patients with known CVD (for secondary cardiovascular events prevention, 70.7% of all patients), diabetes mellitus or other risk factors (RF) (for primary cardiovascular events prevention), who were already on statin therapy with fasting level of triglycerides of 1.52-5.63 mmol/l and LDL of 1.06-2.59 mmol/l. Patients were randomized to either 2 g of eicosapentaenoic acid twice daily with food (n = 4.089) or placebo (n = 4.090). During the 4.9 years of follow-up the primary outcomes (cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization or unstable angina) were diagnosed in 17.2% of cases in eicosapentaenoic acid group compared with 22.0% in placebo (RR 0.75 with 95% CI from 0.68 to 0.83; p=0.00000001). Secondary outcomes (cardiovascular death, nonfatal MI, nonfatal stroke) - in 11.2% and 14.8% (RR 0.74 with 95% CI from 0.65 to 0.83; p=0.0000006), all-cause mortality

- in 4.3% and 5.2% (RR 0.80 with 95% CI from 0.66 to 0.98; p=0.03) of cases, respectively. The effects of treatment were comparable in secondary and primary prevention cohorts (interaction p=0.46) among men and women (interaction p=0.44) in and outside the US (interaction p=0.38) in patients with and without diabetes mellitus (DM) and those who did not have diabetes initially (interaction p=0.29), as well as in subgroups with exclusion criteria of 2.26 mmol / l (interaction p=0.62) and 1.7 mmol /l (interaction p=0.68) triglyceride level. Prescribed treatment did not affect the course of heart failure. Eicosapentaenoic acid group patients were more commonly admitted compared with placebo due to atrial fibrillation or flutter (3.1% vs. 2.1%; p=0.004) and serious adverse bleeding events (2.7% vs. 2.1%; p=0.06). The frequency of severe adverse events did not differ significantly.

Obtained results cannot be fully explained only by eicosapentaenoic acid effect on lipids and indicate its possible pleiotropic effects (antithrombotic, anti-inflammatory, stabilization of cell membranes and / or atherosclerotic plaques) that shows the new way to reduce the risk of CVC. However, in our country patients need to take 10 capsules per day to reach the dose of 4 g of eicosapentaenoic acid that will lead to an increase in its cost and gastrointestinal disorders.

DECLARE TIMI-58 trial [7] included patients with type 2 diabetes mellitus (DM2) and 6.5%- 12%. level of glycosylated hemoglobin and creatinine clearance ≥ 60 mL/min. Trial included 6974 patients with established CVD (IHD, cerebrovascular pathology, peripheral arteries disease — secondary prevention cohort) and 10186 patients with multiple RF (men ≥55 years and women ≥60 years with at least one additional risk factor: arterial hypertension, dyslipidemia or tobacco use — primary prevention cohort). Patients were randomized to either dapagliflozin 10 mg daily — selective inhibitor of sodium-glucose cotransporter type 2 — or placebo. During treatment dapagliflozin reduced body mass by 1.8 kg and arterial hypertension by 2.7/0.7 mmHg. During the follow-up of 4.2 years primary safety and efficacy outcome — summary of major cardiovascular events (CV death, MI or ischemic stroke) was registered in 8.8% of cases in dapagliflozin and in 9.4% in placebo group (p<0.001 result without superiority of effect — RR 0.93 with 95% CI from 0.84 to 1.03; p=0.17). Secondary efficacy outcome (CV death or heart failure hospitalization) appeared in 4.9% in dapagliflozin and in 5.8% in placebo group (RR 0.83 with 95% CI from 0.73 to 0.95; p=0.005) and indicated lower frequency of heart failure hospitalization (RR 0.73 with 95% CI from 0.61 to 0.88) without significant differences in CV death frequency between groups (RR 0.98 with 95% CI from 0.82 to 1.17). Dapagliflozin was effective in preventing renal events (glomerular filtration rate decrease ≥40% with values <60 ml/min/ per 1.73 m^2, new end-stage renal disease, renal or cardiovascular death) – 4.3% versus 5.6% in placebo group (RR 0.76 with 95% CI from 0.67 to 0.87), but wasn't effective in reducing all-cause mortality — 6.2% versus 6.6%, respectively (RR 0.93 with 95% CI from 0.82 to 1.04). Serious adverse effects that lead to treatment cessation were more common in dapagliflozin group — diabetic ketoacidosis (0.3% vs. 0.1% in placebo group. p = 0.02) and genital infections (0.9% vs. 0.1% in placebo group. p<0.001).

According to data of large-scale randomized studies inhibitors of type 2 sodium-glucose cotransporter reduce the risk of major cardiovascular events due to atherosclerosis only in patients with established CVD. They also reduce the incidence of heart failure and renal events in a wide range of patients during secondary and primary prevention. However, additional data from ongoing studies are needed to conclude on patients with type 2 diabetes and heart failure without additional RF.

Inflammation is associated with atherothrombosis that was confirmed during kanakinumab treatment - monoclonal antibodies that inhibit inflammation by neutralizing interleukin-1ß. Without affecting the lipid spectrum of blood plasma this extremely expensive drug significantly reduced the incidence of major cardiovascular events compared with placebo [8]. The CIRT study [9] investigated the possibility inhibiting inflammation with similar benefit by using low dose of inexpensive methotrexate (15–20 mg once a week).

4786 patients after MI or with coronary artery disease and DM2 or metabolic syndrome were randomized to either methotrexate or placebo. All patients received folic acid 1 mg daily. The median follow-up was 2.3 years. Unlike previous studies among patients with rheumatoid arthritis or other cause systemic inflammation, methotrexate did not reduce interleukin-1ß, interleukin-6 and C-reactive protein levels compared with placebo. The primary outcome (nonfatal MI, nonfatal stroke or cardiovascular death) was diagnosed in 170 patients in methotrexate and in 167 patients in placebo group (3.46/100 person-years vs. 3.4/100 person-years; RR 1.01 with 95% CI from 0.82 to 1.25). The primary outcome plus hospitalization for unstable angina requiring unplanned revascularization was 4.13 vs. 4.31/100 person-years

(RR 0.96 with 95% CI from 0.79 to 1.16). Methotrexate group had tendency to increase risk of cardiovascular death (0.92 vs. 0.80/100 person-years; RR 1.14 with 95% CI from 0.76 to 1.72) and all-cause mortality (1.80 vs. 1.55/ 100 person-years; RR 1.16 with 95% CI from 0.87 to 1.56). Methotrexate increased liver enzymes, reduced leucocytes, hematocrit level and the incidence of basal cell carcinoma compared with placebo (31 vs. 10 cases; p=0.002).

We need to reduce levels of interleukin-1β, interleukin-6 and C-reactive protein to prevent atherothrombosis without affecting lipid levels in patients with stable atherosclerosis. It is interesting to find out the results of LoDoCo study where the effect of colchicine on interleukin-1β level is evaluated.

We still don't have results of prospective randomized studies on the effectiveness of lipid-lowering therapy in elderly patients despite a significant increase of hypercholesterolemia among them. 3796 patients ≥75 years and with low-density lipoprotein cholesterol (LDL-C) levels ≥3.6 mmol/l without HAD took part in **EWTOPIA75** [10] trial and were randomized to either ezetimibe 10 mg daily plus dietary counseling (n = 1.716) or dietary counseling only (n = 1.695). After 5 years of follow-up LDL-C (p<0.001) and triglycerides (p=0.003) levels were significantly lower in ezetimibe group compared with placebo and level of high-density lipoproteins did not differ significantly (p=0.119). The primary cardiovascular outcome (sudden cardiac death, nonfatal or fatal MI, percutaneous coronary intervention or coronary artery bypass grafting, nonfatal or fatal stroke) was registered significantly less frequent in ezetimibe group (RR 0.659 with 95% CI from 0.504 to 0.862; p=0.002). The risk of cerebrovascular events and all-cause mortality did not differ significantly between groups. Adverse effects in ezetimibe and control group appeared in 10.62% vs. 9.62% of cases.

The results of EWTOPIA75 study for the first time prospectively showed the possibility of atherosclerotic cardiovascular events primary prevention with lipid-lowering therapy among patients ≥75 years. The limitations were: open-label study since the control arm did not receive a placebo pill, the participation of only Japanese who may respond to treatment differently due to polymorphism of NPC1L1 gene. Obtained data may serve as basis for new placebo-controlled studies among more ethnically diverse population.

Heart failure

Acute decompensated heart failure is one of the most common causes of admission and diuretics and vasodilators have been its basic treatment for a long time.

In PARADIGM-HF trial sacubitril/valsartan compared with enalapril among patients with heart failure due to reduced ejection fraction ≤40%, reduced cardiovascular death or hospitalization for heart failure [11]. Patients who were recently hospitalized with decompensated heart failure and required intravenous therapy were excluded from PARADIGM-HF, therefore, the efficacy and safety of sacubitril / valsartan in this case is still unknown.

881 patients hospitalized with acute decompensated chronic heart failure or episode of acute chronic heart failure with elevated N-terminal pro–B-type natriuretic peptide (NT-proBNP) ≥1600 pg/ml or B-type natriuretic peptide ≥400 pg/ml took part in **PIONEER-HF** [12] trial.

During hospitalization patients were stabilized (systolic blood pressure ≥100 mm Hg for the preceding 6 hours prior to randomization; no symptomatic hypotension; no increase in intravenous diuretic or vasodilators dose; no intravenous inotropic drugs for 24 hours prior to randomization) and randomized to sacubitril/valsartan (the goal — 97mg/ 103 mg twice a day; n = 440) or enalapril (the goal — 10 mg twice a day; n = 441). Dose titration was based on the BP dynamics during 8 weeks. The primary outcome (time-averaged reduction in NT-proBNP during week 4 and 8 compared with initial level) was 29% lower in sacubitril/valsartan group compared with enalapril (95% CI from 19 to 37; p < 0.0001). Safety outcomes did not differ between groups: rates of worsening renal function (13.6% vs. 14.7%; RR 0.93 with 95% CI from 0.67 to 1.28), hyperkalemia (11.6% vs. 9.3%; RR 1.25 with 95% CI from 0.84 to 1.84), symptomatic hypotension (15.0% vs. 12.7%; RR 1.18 with 95% CI from 0.85 to 1.64) and angioedema (0.2% vs. 1.4%; RR 0.17 with 95% CI from 0.02 to 1.38). Serious composite events (death, HF hospitalization, LV assist device implantation or listing for transplant) were less frequent in sacubitril/valsartan group (RR 0.54 with 95% CI from 0.37 to 0.79; p=0.001), mostly due to lowering the risk of heart failure hospitalization (8.0 vs. 13.8%; p=0.005).

Sacubitril/valsartan reduced NT-proBNP to a greater degree than enalapril among patients admitted with acute decompensated heart failure and reduced ejection fraction without increasing the risk of worsening renal function, hyperkalemia, symp-

tomatic hypotension and angioedema. According to the authors, these findings will allow to start using optimal pharmacotherapy in the hospital instead of initiating angiotensin-converting enzyme inhibitor and prescribe sacubitril / valsartan only at the outpatient stage.

Patients with dilated cardiomyopathy who recovered heart function often ask if it is possible to attempted its withdrawal, for example, during pregnancy. The safety of this action remained unknown.

Patients with dilated cardiomyopathy who recovered their left ventricular ejection fraction from <40% to ⩾50, normal LV end-diastolic volume, N-terminal pro–B-type natriuretic peptide <250 ng/L during treatment took part in opened **TRED-HF** [13] trial. Patients were randomized to either withdrawal of medications (n = 25) or continuation of medications (n = 26). After 6 months patients in the medication continuation arm crossed over to medication discontinuation. The primary endpoint was a relapse of dilated cardiomyopathy within 6 months (reduction in left ventricular ejection fraction of > 10% and to <50%, an increase in left ventricular end-diastolic volume by more than 10% and to higher than the normal range, a two-fold rise in NT-pro-BNP concentration and to more than 400 ng/L or clinical evidence of heart failure at which point treatments were re-established) was diagnosed in 11 (44%) patients only from the withdrawal of medications group (Kaplan-Meier estimate of event rate 45.7% with 95% CI from 28.5 to 67.2; p=0.0001). After 6 months 25 (96%) of 26 patients from continuation group attempted its withdrawal and during the following 6 months, nine patients met the primary endpoint of relapse (Kaplan-Meier estimate of event rate 36.0% with 95% CI from 20.6 to 57.8). No deaths were reported in either group due to careful dynamic monitoring and quick resumption of the therapy if needed.

Many patients with dilated cardiomyopathy who consider themselves recovered have a high probability of a rapid relapse after its withdrawal, which indicate that therapy shouldn't be interrupted.

Empagliflozin — a sodium–glucose cotransporter type 2 selective inhibitor — reduced the risk of major cardiovascular events, all-cause mortality and cardiovascular hospitalization in patients with DM2 and established CVD during **EMPA-REG OUTCOME** trial [14]. Mechanisms of empagliflozin remain unclear, but may include natriuresis, reduction of interstitial edema, heart pre- and afterloads, left ventricular wall stress, improved kidney and cardiovascular function and heart's energetical processes.

Left ventricular mass is a strong and independent predictor of MI, heart failure, cardiovascular and all-cause mortality, and left ventricular hypertrophy regression during treatment correlates with clinical outcomes. The effect of empagliflozin 10 mg per day on left ventricular remodeling was estimated in 97 patients with DM2 (glycated hemoglobin ⩾6.5% and ⩽10%) and stable HAD during **EMPA-HEART Cardiolink-6** [15] trial with cardiac magnetic resonance. Left ventricular mass index reduced in empagliflozin and placebo groups after 6 months -2.6 g/m^2 vs. 0.01 g/m^2 (p = 0.01) and left ventricular myocardial mass — 7.71 g vs. 0.39 g, respectively. This effect was more significant in patients with initially higher left ventricular myocardial mass index (interaction p=0.007). The ejection fraction tended to increase in patients without significant end-systolic (p=0.36) and end-diastolic (p=0.55) left ventricular volumes (+2.21% vs. -0.01% in placebo; p=0.07). Empagliflozin therapy did not affect initially low NT-proBNP and troponin I levels.

Empagliflozin promoted early statistically and clinically significant left ventricular remodeling, which could improve outcomes during EMPA-REG OUTCOME trial and other studies with similar medications. The effects of empagliflozin were observed in patients with normotension, preserved left ventricular ejection fraction, no heart failure and during standard therapy (metformin, statins and angiotensin converting enzyme inhibitors or angiotensin II receptor blockers).

Practical integration of most important clinical studies data presented during scientific sessions of the American Heart Association in 2018 may improve most common CVD treatment and prevention.

More detailed information on the scientific event held in November 2018 in Chicago is presented on the official website: https://professional.heart.org

Conflict of interest: None declared.

References

1. Grundy S.M., Stone N.J., Bailey A.L. et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018; Nov 8. [Epub ahead of print]
2. Piercy K.L., Troiano R.P., Ballard R.M. et al. The Physical Activity Guidelines for Americans. JAMA. 2018; Nov 12. [Epub ahead of print]

3. Kusumoto F.M., Schoenfeld M.H., Barrett C. et al. 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardiaand Cardiac Conduction Delay: A Report of the American College of Cardiology/American HeartAssociation Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm. 2018; Oct 31. [Epub ahead of print]
4. Manson J.E., Cook N.R., Lee I.M. et al. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. N Engl J Med. 2018; Nov 10. [Epub ahead of print]
5. Manson J.E., Cook N.R., Lee I.M. et al. Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. N Engl J Med. 2018; Nov 10. [Epub ahead of print]
6. Bhatt D.L., Steg P.G., Miller M. et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med. 2018; Nov 10. [Epub ahead of print]
7. Wiviott S.D., Raz I., Bonaca M.P. et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2018; Nov 10. [Epub ahead of print]
8. Ridker P.M., Everett B.M., Thuren T. et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017; 377(12):1119-1131.
9. Ridker P.M., Everett B.M., Pradhan A. et al. Low-Dose Methotrexate for the Prevention of Atherosclerotic Events. N Engl J Med. 2018; Nov 10. [Epub ahead of print]
10. Ouchi Y. Ezetimibe in Prevention of Cerebro- and Cardiovascular Events in Middle- to High-Risk, Elderly (75 Years Old or Over) Patients With Elevated LDL-Cholesterol: A Multicenter, Randomized, Controlled, Open-Label Trial. AHA Scientific Sessions, November 10, 2018, Chicago, Illinois. https://professional.heart.org
11. McMurray J.J., Packer M., Desai A.S. et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014; 371(11):993-1004.
12. Velazquez E.J., Morrow D.A., DeVore A.D. et al. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. N Engl J Med. 2018; Nov 11. [Epub ahead of print]
13. Halliday B.P., Wassall R., Lota A.S. et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. Lancet. 2018; Nov 9. [Epub ahead of print]
14. Zinman B., Wanner C., Lachin J.M. et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015; 373(22):2117-2128.
15. Verma S. et al. EMPA-HEART Cardiolink-6 Trial: A Randomized Trial Evaluating the Effect of Empagliflozin on Left Ventricular Structure, Function and Biomarkers in People With Type 2 Diabetes (T2D) and Coronary Heart Disease. AHA Scientific Sessions, November 11, 2018, Chicago, Illinois. https://professional.heart.org

International Heart and Vascular Disease Journal • Volume 7, № 21, March 2019

Journal of the Cardioprogress Foundation

New European guidelines for the management of arterial hypertension. Comments of Russian experts

During the European Congress of Cardiology held in August 2018, new guidelines on arterial hypertension were presented. They included a revision of the cardiovascular risk estimation, algorithms of antihypertensive therapy combinations and management for certain groups of patients. First of all, we expected possible changes in target blood pressure levels followed by the US recommendations. The opinion of the leading Russian experts on the main states of the new European guidelines for the management of arterial hypertension is presented.

Key words: *arterial hypertension, new European guidelines, target blood pressure levels.*

Conflicts of interest: nothing to declare.

Received: 17.01.2019 **Accepted:** 27.01.2019.

The Russian medical community has been waiting for the publication of new European guidelines for the management of arterial hypertension (AH) [1]. It was interesting to see the its differences compared with American Heart Association guidelines, primarily regarding target blood pressure (BP) levels, the list of main antihypertensive drugs, the classification of hypertension. The leading Russian experts gave their comments on main states of new European guidelines that are listed below.

Sergei G. Kanorskii (Krasnodar)

2018 ESC/ESH guidelines for the management of AH kept previous classification — AH starts from office systolic BP (SBP) of 140 mmHg and/or office diastolic BP (DBP) of 90 mmHg [1]. ACC/AHA 2017 guidelines are more progressive and suggest to define AH from 130/80 mmHg [2]. It is necessary to expand the practice of measuring BP while patient is relaxed, as it was illustrated during SPRINT trial, which affected the opinion of American experts. There is no need to delay non-pharmacological and pharmacological treatment and wait until BP reaches 140/90 mmHg when target organs may be damaged and the tolerance for BP of 115–130/70–80 mmHg is lower [3].

Authors of European guidelines suggest to treat most patients with two-drug combination therapy initially to compensate the «late start» of the therapy. But the risk of hypotension in this case is higher, therefore, monotherapy is not prohibited.

It is remarkable that target DBP is 70–80 mmHg, but SBP should not be lower than 120 mmHg, because it may lead to adverse consequences.

New European guidelines pay more attention to individualization of antihypertensive therapy in elderly patients compared with American guidelines. Treatment of elderly patients without taking into account their biological age can be inadequate and poor tolerated.

New European guidelines show that it is important to eliminate excessive (according to available data) BP decrease, therefore, target BP has upper and lower limits. Intense antihypertensive treatment tends to be used among wider groups of patients, including elderly patients. In near future we might be able to reduce the progression of atherosclerosis in population with 1–2 injections of Inclisiran per year, improve tolerance to low BP and inhibit age-related changes in arteries.

European experts proposed several algorithms for AH pharmacotherapy in different clinical situations with priority to fixed combinations of medications that will improve the quality of physician's routine and provide more efficient achievement and maintenance of target BP. Uncontrolled arterial hypertension is usually the result of poor adherence to prescribed therapy. Authors of European guidelines fairly consider this problem as one of the most important and pay special attention to it. It is even more relevant for Russia.

Grigory G. Arabidze, professor (Moscow)

European experts announced BP target levels. The objective of treatment should be to lower BP <140/90 mmHg in all patients and, provided that the treatment is well tolerated, treated BP values should be target to 130/80 mmHg or lower in most patients, although "in some groups the evidence is less compelling".

The recommendations are mainly based on data of meta-analysis of 123 studies with 613,815 participants, published 2 years ago that showed 20 % reduction of major cardiovascular events and 13 % of all-cause mortality when an SBP reached <130 mmHg, and meta-analysis of 50 studies with 190362 participants published in 2016 that showed a 25 % reduction of major cardiovascular events when SBP reached <130 mm Hg, but risk reduction effectiveness decreased with lower blood pressure baseline. Thus, BP reduction below 130/80 mmHg will be more effective in patients with initially higher BP.

Meta-analysis data included elderly patients, but BP decrease below 130/80 mmHg is limited by known comorbidities, adverse effects, including impaired cognitive function.

The increase in patients with initial two-drug combination therapy is reasonable due to more aggressive treatment targets and a possibility to use combinations of drugs in various dosages (also due to economic reasons) that increase therapy adherence.

We found misprinting in the text of guidelines, for example, in section 8.14.1 "... target BP of approximately <130/80 mmHg in patients with coronary artery disease (CAD) appears safe and can be recommended, but achieving a BP <120/80 mm Hg is not recommended", considering the meaning of previous text the BP should be <120/70 mm Hg.

The section devoted to the management of resistant hypertension is based on a good evidence data, but completeness, quality of analysis, structure of algorithms for the management of these patients is lower compared with the AHA guidelines, published in September 2018 [2].

Galina A. Baryshnikova, professor (Moscow)

AH classification did not change on the level of BP — there are still three grades of BP, although the stages of AH have been added to stratification table. For many years in Russia we indicated not only the grade, but the stage of AH in the diagnosis.

We were afraid that beta-blockers would be excluded from the list of basic antihypertensive treatment, but they are still the first-line treatment for concomitant CAD, chronic heart failure (CHF), arrhythmias, aortic aneurysm, and AH in pregnant women, although it is not recommended to start treatment of uncomplicated hypertension with them.

More extensive use of home blood pressure monitoring is recommended, a major advantage of which is the exclusion of white-coat hypertension. It is remarkable that in this case the criteria for AH is BP≥ 135/85 mmHg, not ≥ 140/90 mmHg.

Target BP remains lower than 140/90 mmHg. After reaching this level of BP, it is recommended to continue decrease of SBP below 130 mmHg in case of good tolerance. Concomitant diseases should not limit the physician in decreasing BP below 130 mmHg including concomitant CAD, stroke / increase of intima-media complex thickness (IMT) in history, diabetes mellitus (DM). Only in case of chronic kidney disease (CKD) is it recommended to lower BP below 140 mmHg and leave it in the range from 130 to 140 mm Hg. It is remarkable that there is no requirement to reduce SBP

under 120 mmHg (target BP during SPRINT study, the results of which were used as the basis for new guidelines for the diagnosis and treatment of hypertension in Australia and China), it was also recommended not to reduce SBP under 120 mmHg [3].

DBP was previously recommended to reduce below 90 mm Hg (in case of DM — below 85 mm Hg); new recommendations, regardless of age and concomitant diseases, recommend to maintain DBP in the range of 70–80 mmHg.

We are glad to see maximum simplification of algorithms for the treatment of uncomplicated AH, two-drug combination therapy (ACE inhibitors + calcium antagonists or diuretics) are recommended initially, and three-drug combination therapy at the next stage of treatment (ACE inhibitors + calcium antagonists + diuretics). The next stage is adding spironolactone, alpha-blockers and beta-blockers to therapy. Monotherapy can be used in a limited range of patients with AH: 1 grade of AH and low risk of cardiovascular complications (CVC), which include the absence of risk factors, target organs damage, DM, CKD, and cardiovascular diseases (CVD).

It is recommended to monitor patients' adherence to prescribed therapy, as the main reason for low efficacy of antihypertensive therapy, and to use fixed combinations of antihypertensive drugs, which are widespread in Russia, especially since there is fixed three-drug combination therapy (RAAS blocker + calcium antagonist + diuretic).

It is surprising that imidazoline receptor agonists (moxonidine and rilmenidine) were not mentioned in the new recommendations. These drugs (especially moxonidine) have become widely spread as part of combination therapy for the treatment of AH in patients with insulin resistance, obesity, and the management of hypertensive crisis (sublingual). Moxonidine was mentioned only once (in the list of drugs that should not be used in patients with AH and concomitant CHF).

Olga A. Koshelskaya, professor (Tomsk)

New European guidelines for the management of AH are significantly different compared with last recommendations of American experts, despite the same classes and data level of evidence [1].

Both guidelines recommend to use home blood pressure monitoring and ambulatory blood pressure monitoring to confirm the diagnosis of AH and to control adherence and compliance to therapy, pay attention to the role of nurses and pharmacists in teaching patients, have similar point of view on the treatment of resistant hypertension and on more intensive treatment of AH in elderly with reference to their safety.

However, European experts are conservative in determining AH and intensity of therapy. According to American guidelines, BP of 130–139 / 80–89 mm Hg referees to grade 1 of AH, ESC / ESH guidelines define grade 1 from 140–159 / 90–99 mmHg.

New European recommendations, name not only the upper threshold of target BP, but its target ranges compared with previous European guidelines. There is also a tendency to decrease target BP level in patients under 65 years: from "below 140/90 mm Hg" to "130 / 70–79 mm Hg with good tolerance" with BP lower limit of 120/70 mm Hg. However, since the regulation of systolic and diastolic BP is not independent and can have discordant dynamics during treatment in some patients, it is important to identify priorities in achieving both components of target BP.

In contrast to the ACC/AHA 2017 guidelines, a more cautious approach is recommended for SBP lowering in patients over 65 years, and its target level is determined as the range "from 140 to 130 mmHg", which is reasonable due to common vascular comorbidities in these patients. The recommendations for treatment of patients with CAD and very high risk of CVC, as well as patients with 3–4 stages of CKD are more conservative and include target range of blood pressure of 130–139 / 85–89 mmHg, while American experts recommend target level of BP for these categories of patients <130/80 mm Hg, which is reasonable only for patients with proteinuria [2]. Thus, the available data on the pathogenesis of non-proteinuric CKD, often found in patients with AH and DM, allow us to consider an intense decrease in systolic BP in patients with CKD without high albuminuria / proteinuria as the cause of renal hypoperfusion.

It is remarkable that specific therapy algorithms instead of "choosing among any five classes of antihypertensive drugs" and the use of fixed combinations, including two-drug combination therapy at the initial stage will increase patient's adherence and improve prognosis of the disease.

Yury A. Bunin, professor (Moscow)

ESC guidelines for the management of AH are balanced, clear and, in our opinion, their structure, scientific and practical significance have been between the best ones over the last twenty years. Guidelines safe many previous states (classification of AH, risk factors and associated diseases, approaches to drug

combinations, etc.), and give reasonable BP levels from which we should start treatment of patients of various age (18–65 years — from 140/90 mm Hg and more; 65–79 years — 140/90 mm Hg and more; 80 years and older — 160/90 mm Hg and more). In contrast to ACC/AHA 2017 guidelines, pharmacological treatment of high normal BP (130–135 / 85–89 mmHg), even at very high risk of complications is not effective sufficiently (class IIb) [2].

Target BP levels (DBP regardless of age should be less than 80 mmHg — 70–79 mmHg; SBP in patients under 65 years — 120–129 mmHg; SAD in patients over 65 years — 130–139 mmHg) are based on the data of randomized clinical trials, which showed the improvement of the prognosis (reduction of all-cause mortality, stroke, etc.) at these levels of BP.

The problem of BP level and the development of dementia in different age groups is more difficult: only in patients aged 50 years (not older) SBP ≥ 130 mmHg increases the risk of its occurrence. Therefore, this section requires clarification and, future changes may occur in recommended target BP levels primarily in elderly patients — over 65 years.

The section on the antihypertensive drugs include calcium antagonists, ACE inhibitors, angiotensin II receptor blockers, thiazides and thiazide-like diuretics as the first-line treatment for most patients (patients with uncomplicated AH, CAD, CKD). Beta-blockers can be considered as treatment only if there are specific indications, such as CHF, CAD or in young women planning pregnancy (with dihydropyridines), and sometimes can be reserved for add-on therapy as well as with spironolactone and alpha blockers. Guidelines emphasize that beta-blockers prevent the development of stroke less effective compared with other antihypertensive drugs.

The section on secondary AH contains useful additional information, but, unfortunately, it is unreasonably brief.

Thus, in the opinion of Russian experts, the new European guidelines in most cases have practical evidence-based recommendations that can be used in our country by various physicians for the management of AH. Practical use of new European guidelines will improve the effectiveness of treatment of AH in Russia and eventually reduce cardiovascular mortality.

References

1. 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal. 2018 September 2018; 39 (33): 3021–3104. https://doi.org/10.1093/eurheartj/ehy339
2. 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: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018; 71: e127-e248.
3. Berlowitz D.R., Foy C.G., Kazis L.E., Bolin L.P., Conroy M.B., Fitzpatrick P., Gure T.R., Kimmel P.L., Kirchner K., Morisky D.E., Newman J., Olney C., Oparil S., Pajewski N.M., Powell J., Ramsey T., Simmons D.L., Snyder J., Supiano M.A., Weiner D.E., Whittle J.; SPRINT Research Group. Effect of Intensive Blood-Pressure Treatment on Patient-Reported Outcomes. N Engl J Med. 2017 Aug 24; 377 (8): 733–744.

International Heart and Vascular Disease Journal • Volume 7, № 21, March 2019

Journal of the Cardioprogress Foundation

Author Guidelines

MANUSCRIPT PUBLICATION RULES IN THE INTERNATIONAL HEART AND VASCULAR DISEASE JOURNAL

Disclaimer: Edition of rules come into force since November, 2018. The rules describe the conditions of publication of manuscripts (articles) through the site http://www.heart-vdj.com. The editorial Board is ready to answer questions and help authors by e-mail: submissions.ihvdj@gmail.com.

The *International heart and vascular disease journal* has been published since 2013. It is official journal of the Cardioprogress Foundation. The target audience of this peer-reviewed journal is cardiologists and internal disease specialists. The journal is primarily focused on questions of epidemiology, prevention, and cardiac pharmacotherapy. It also publishes lectures and literature reviews on various problems of modern cardiology, reports on new diagnostic methods, and other information which is important for the practitioners.

The General criteria for the publication of articles in the International heart and vascular disease journal are the relevance, novelty of the material and its value in theoretical and/or applied aspects.

The languages of publications are Russian and English. Journal is peer-reviewed, with multistage editing. Editorial board is presented by the leading cardiologists from different countries and Russia.

International heart and vascular disease journal aims to ensure that its publications fulfill the requirements of international publishing standards, such as the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, by the International Committee of Medical Journal Editors, ICMJE (http://www.icmje.org), and the recommendations by the Committee on Publication Ethics, COPE (http://www.publicationethics.org.uk).

All clinical trials should be performed and described in full accordance with the CONSORT standards (http://www.consort-statement.org), observational research — STROBE (http://www.strobe-statement.org), systematic reviews and meta-analyses — PRISMA (http://www.prisma-statement.org), diagnostic accuracy — STAR (http://www.stard-statement.org).

I. The International heart and vascular disease journal accepts the following manuscripts:

1) *Original papers* present the results of clinical studies. The word limit is 3.000 (including references, tables, and figure legends). The maximal number of references is 15. The structured abstract should contain 5 sections (**Aim, Material and Methods, Results, Conclusion**, and **Key words**), and be no longer than 300 words.

2) *Lectures*, or clinically oriented reviews, are written by experts in broader areas of medicine. Lectures could be focused on epidemiology, pathophysiology, diagnostics, treatment, and prevention. The word limit is 5.000 (including references, tables, and figure legends). The maximal reference number is 80. The unstructured abstract is no longer than 150 words.

3) *Literature reviews* are focused on more specific topics, compared to lectures. The word limit is 4.500 (including references, tables, and figure legends). The maximal reference number is 50. The unstructured abstract is up to 150 words.

4) *Clinical case* is a brief report on a complex diagnostic problem and its solution, or a description of

a rare clinical observation. The word limit is 600 (including references, tables, and figure legends). The maximal number of references is 5. No abstract is required.

5) *Clinical opinion* informs the readers on the topics of cardiovascular medicine and related disciplines. The word limit is 2.500 (including references, tables, and figure legends). The maximal number of references is 15.

The journal accepts for publication original phase 2, 3 and 4 clinical studies. Literature reviews should be based on sources not older than 5 years.

II. Information about the article, which includes the following sections, is combined into a single file «letter (cover)»:

1) the manuscript is not under consideration in another edition; 2) has not been previously published; 3) contains a full disclosure of the conflict of interest; 4) all authors meet the criteria of authorship, it was read and approved; 5) the author (s) are responsible for the power of attorney submitted in the manuscript materials. 6) all contact information of the author responsible for correspondence; 7) information about previous publications of the authors on the same topic or pre-publication.

If the manuscript is a part of the thesis, it is necessary **to specify** the estimated terms of thesis defense.

The «letter of direction (accompanying)» should be made out on one or two sheets. Using the form of the official institution-at the choice of the author's team. In the address: «to The chief editor of the Russian cardiology journal, academician of RAS, Professor Oganov R. G.». The signatures of **all authors** should be placed at the bottom.

«Directional (cover) letter» is scanned. File format. jpeg attached as an additional file of the manuscript.

The absence of a letter or incomplete text of the letter (not containing the above items) is the basis for refusal to accept the manuscript for consideration.

III. Registration on the Website and information about the authors.

1. **Any of the authors can submit an article to the journal.** Usually it is the one who then conducts correspondence with the editorial office and to whose mail notification letters come (when submitting a manuscript through the site, you can choose to send notifications to all authors).

The author registers on the site, entering his full name. In the form to be filled in when submitting an article, all authors and all additional information (places of work, positions, academic titles, institutions, ORCID — all authors) are indicated.

If the author has several places of work, it is written: 1. «The name of the institution...» 2. «Name of institution.»... The name of the institution is written in abbreviated form, for example, Moscow state University, Moscow. Brackets are not put.

How to fill in the article metadata: all data that is entered in the «article metadata» must exactly match the data specified in the text of the article!

1. Authors ' names (you can not write in full, the format of the journal provides for the publication of names and initials. Therefore, in the» Windows», where the name and patronymic of the authors are written in capital letters with a dot (example: A.).

2. Names of institutions (write the official name. At the same time — there is a reduction of Federal, STATE, etc.; the quotation marks are placed; Ministry of health of Russia, a city without the letter G.

3. Positions and titles (using traditional abbreviations: PhD, senior researcher, leading researcher, PhD, C.b.N., MD), head reduces to the head., then write the full name of the laboratory/Department / Department; Director, head, Professor — is not reduced.

4. The order of the authors. Authors ' priority should be entered into the system in accordance with the order of the article. The movements are made by small arrows «top» / «bottom», which are located under the data of each of the authors. The data of the author responsible for the correspondence, put a dot in a circle denoting this information. Other authors point do not put.

5. Summary. Sections of the abstract should exactly match the sections prescribed In the rules for authors. If the sections are not correct, the Editors will ask to correct them. What the authors are currently publishing on the site will then be included in all systems after the final publication. Be careful!

6. Making literary references. Submitted article will not be reviewed until the correction of literary references in accordance with the rules for authors is made. The authors «forget» and somewhere to remove point (such inconsistencies can be corrected in the Revision), but if the design literature is radically different from what is required or present hyperlinks, the Editors will not start with the article to eliminate errors.

7. Keyword. They are written with a small letter, separated by a semicolon. At the end put a point. In

the text of the article the keywords are written separated by commas.

A file is prepared separately in Word, which is then sent as an additional file. The file must contain:

1. Title page of the manuscript. The title of the manuscript is written in capital letters, without hyphenation, in bold. Initials and surnames of authors-Ivanov I. I., Petrov P. p. the full name of organization (s) from which (s) there was a manuscript, the city, the country is Given. Footnotes are in Arabic numerals after the authors ' names and before the names of institutions.

Example of design:

THE PREVALENCE OF RISK FACTORS OF NONCOMMUNICABLE DISEASES IN THE RUSSIAN POPULATION IN 2012–2013. THE RESEARCH RESULTS OF THE ESSE-RF

Muromtseva G. A. [1], Kontsevaya A.V. [1], Konstantinov V. V. [1], Artamonova G. V. [2], Galaganova T. M. [3],...

[1] FGBU State research center of preventive medicine of the Ministry of health of Russia, Moscow;

[2] FGBU Research Institute of complex problems of cardiovascular diseases SB RAMS, Kemerovo;

[3] RD VPO North Ossetian state medical Academy, Vladikavkaz;..., Russia.

2. Information about the authors, where indicated: full name, place of work of all authors, their positions, ORCID; full contact information is required for one (or more) of the author and includes e-mail, available phone number.

All members of the group of authors should meet all four criteria of authorship set forth in the ICMJE recommendations: 1) concept and design development or data analysis and interpretation, and 2) manuscript justification or verification of critical intellectual content, and 3) final approval for publication of the manuscript, and 4) consent to be responsible for all aspects of the work, and assume that issues relating to the thoroughness and diligent execution of any part of the study submitted are duly investigated and resolved. This information should also be contained in the document.

If the submitted material has authors who do not meet the criteria of authorship, but have made some contribution to the work, they should be listed in this document and at the end of the article in the section of Acknowledgements.

3. Information on conflict of interest / funding.

The section contains the disclosure by all authors of possible relations with industrial and financial organizations that may lead to a conflict of interest in connection with the material presented in the manuscript. It is desirable to list the sources of funding for the work. If there is no conflict of interest, it is written: «Conflict of interest is not declared.» Information on the existence of a conflict of interest should also be reflected in the Conflict of interest section at the end of the article.

4. Information about grants. Should be mentioned at the end of the article in the section Acknowledgements and at the end of the section Material and methods — with a full description of the role of the source of funding in the performance of work (design, information collection, analysis, data interpretation, etc.).

5. Information and ethics in the study.

Example of design:

The study was carried out in accordance with the standards of good clinical Practice (Good Clinical Practice) and the principles of the Helsinki Declaration. The study Protocol was approved by the Ethical committees of all participating clinical centers. Prior to being included in the study, written informed consent was obtained from all participants.

This information should also be reflected in the Material and methods section of the article.

All additional information (permits, questionnaires, etc.) can be requested from the authors in addition to the preparation of the work for printing.

6. Information on overlapping publications (if available).

7. Copyright. The use of any material (tables, figures) marked with a copyright icon in the article should be confirmed by a special permission from the author or publisher.

8. Information about the obtained consent in patients for the study.

Obtaining consent from patients for the study should also be reflected in the Material and methods.

9. For all clinical trials: information about the registration and placement of data on the study in any public register of clinical trials. The term «clinical study» refers to any research project that affects people (or groups of subjects) with/or without a comparative control group, studies the interaction between interventions to improve health or the results obtained. The world health organization offers the primary register: International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/network/primary/en/index.html). The clinical study is considered to be reliable in a group of more than 20 patients.

10. The number of words in the article (excluding summaries, sources of literature, figure captions and tables), the number of tables and figures.

The absence of an information file or incomplete text (not containing the above items) is the basis for refusal to accept the manuscript for consideration.

IV. Manusctipt submision check-list

Since the main file of the manuscript is automatically sent to the reviewer for» blind review», it should not contain the names of the authors and institutions. The file contains only the following sections:

1. Article title
2. Summary with key words
3. List of abbreviations
4. Text
5. Acknowledgements (if any)
6. List of references
7. Tables, figures (if they can be embedded in the text of Word format).

The article title is written in capital letters (PREVALENCE of RISK FACTORS...), the end point is not needed. The title should clearly reflect the purpose of the work.

Summary with key words-sections are drawn up each with a separate line, highlighted in bold. The abstract should contain only those sections that are described in the rules for authors. For example, there is no section «Relevance» in the summary. The authors prescribe the relevance of their work in the introductory section of the manuscript.

List of abbreviations — when compiling a list of abbreviations to the article, including text, tables and figures, only those used by the author 3 or more times are included. Usually shrink often used in manuscripts of the terms (e.g., hypertension, CHF FC) and title of clinical trials (SOLVD, TIMI, HOPE).

The first reference to an abbreviation is always accompanied by the full spelling of the abbreviated concept, and the abbreviation is indicated in brackets. For example, blood pressure (BP); heart rate (HR). Capital letters are more often used to denote abbreviations. If abbreviations are used only in tables and figures, and are not used in the text, they should not be included in the list of abbreviations, but should be given a transcript in the note to the table or figure. The summary of the article, as a separate document, is subject to the same rules as the article (abbreviations are made when they are used 3 or more times).

Abbreviations should be generally accepted and understandable to the reader, in accordance with the generally accepted norms in the scientific literature. Undesirable abbreviations that coincide in writing with others that have a different meaning.

Abbreviations in the list of abbreviations are written in alphabetical order, separated by commas, in solid text, using «dash». **Example of design:** BP-blood pressure, HR-heart rate.

Text — the text of the manuscript of the original works should be structured: Introduction, Material and methods, Results, Discussion and Conclusion. The text of reviews and lectures can be unstructured.

Text is printed on A4 sheet, font size — 12 pt, line spacing — 1.5, margins 2 cm on all sides. The system of SI units is used for processing the material, the% sign is put through a space from the number, the value of p is written with a semicolon: $p < 0.0001$; the value of n is written with a small letter (n=20); signs >, <, ±, =, +, — when numerical values are written without a space; the value of «year» or «year» is issued — 2014 or 2002–2014.

The article should be carefully verified by the author (s). The authors are responsible for the correctness of citation, doses and other factual materials.

Introduction — it is necessary to describe the context and prerequisites of the work (what is the essence of the problem and its significance). It sets certain goals or describes the object of the study, or a hypothesis that needs to be tested by comparison or observation. Only those sources that directly indicate the problem are cited.

Statistics — all published materials are reviewed by an expert in statistics and must meet «Uniform requirements for manuscripts submitted to biomedical journals» (Uniform Requirements for Manuscripts Submitted to Biomedical Journals, Ann Intern Med 1997, 126: 36–47). In the preparation of the statistical part of the work it is recommended to use special guidelines, for example, the European journal of cardiology: www.oxfordjournals.org/our_journals/eurheartj/for_authors/stat_guide.html

Statistical methods are described in detail in the Material and methods section.

Acknowledgements — all participants who do not meet the authorship criteria should be listed in the Acknowledgements section, which is located at the end of the article before the Literature section.

Making graphs, diagrams and drawings — tables and figures should provide the reader with visual information, be interesting and educational. They should be placed after the text of the article, as the reviewer and editor look at the manuscript as a whole.

However, to print in the journal (at the stage of creating a layout) graphics, diagrams and drawings are required in electronic form in the formats «MS Excel», «Adobe Illustrator», «Corel Draw», «MS PowerPoint», photos with a resolution of at least 300 dpi.

The names of the graphs and figures, as well as notes to them should be placed under the figure/graph or placed at the end of the article.

These files are referred to as additional files. Figures should not repeat the materials of the tables.

Tables should contain the compressed, necessary data. Each table is placed at the end of the text (after the list of references) with the number, name and explanation (note, abbreviations).

The tables should clearly indicate the dimension of the indicators and the form of data (M±m; M±SD; Me; Mo; percentiles, etc.). All figures, totals and percentages should be carefully verified, and also correspond to the mention in the text. The explanatory notes are given below the table, if necessary. The footnotes must be in the following order: *, †, §, ||, ¶, #, **, †† etc.

Abbreviations should be listed in a footnote below the table in alphabetical order (for tables its list of abbreviations!).

Each first mention of a figure or table in the text is highlighted with a yellow marker. If a reference to a figure or table is included in the sentence, the full spelling of the word «figure 1», «table 1» is used; if the words are enclosed in brackets, the abbreviation is used (Fig. 1), (table. 1).

Providing the main file of the manuscript with the names of the authors or institutions is the basis for refusal to accept the manuscript for consideration.

V. The list of references.

In the form to fill in when submitting the article provides a list of cited literature (section — Literature).

Literary references are listed in the order of citation in the manuscript. The text refers to the serial number of the cited work in square brackets [1] or [1, 2]. Each link in the list is on a new line. All documents referred to in the text should be included in the list of references.

References to works that are not in the list of references and Vice versa, references to unpublished works, as well as to works of many years ago (>10 years) are not allowed. The only exceptions are rare highly informative works. Especially close attention to this item, please pay to those authors who submit «literature Review».

The bibliographic description contains the names of the authors up to three, after which, for domestic publications should indicate «et al.», for foreign — «et al.» When citing articles from journals indicate in the following order the output: the name and initials of the authors, the name of the source, year, volume, number, pages (from and to). When citing articles from the collections indicate the output: name, initials, title, title of the collection, place of publication, year of publication, page (from and to).

If you want to make a quotation of the authors ' names in the text, you must specify the name of the first author with the initials, the year of work. Example design: Smith AA, et al. (2018).

With the purpose of increase of citation in the journal is the transliteration of Russian sources with the use of the official languages in the following order: the authors and the journal title is transliterated in the Latin alphabet, and the name of the article is semantic transliteration (translation into English). The name of the source where the work is published is transliterated in Latin if the source (journal) does not have an official name in English).

All Russian-language sources of literature should be presented in the transliterated version of the model given below.

The author (s) are responsible for the correctness of the data given in the references.

The list of references should correspond to the format recommended by the American National organization For information standards (national Information Standards organization — NISO), adopted by the National Library of Medicine (NLM) for databases (Library's MEDLINE/PubMed database) NLM: http://www.nlm.nih.gov/citingmedicine Oh? The names of periodicals may be abbreviated. Usually this form of writing is accepted by the publisher; it can be found on the website of the publisher, or in the list of abbreviations Index Medicus.

Mandatory all articles DOI specified, all books ISBN. References to dissertations, patents, theses and any collections without output and ISBN are not accepted.

Examples of link design:

Article citation:

Smith A, Jones B, Clements S. Clinical translation of tissue-engineered airway. Lancet. 2008;372:1201–09. doi:10.00000/0000–0000-.

Russian-language sources with transliteration:

Bart BYa, Larina VN, Brodskyi MS, et al. Cardiac remodelling and clinical prognosis in patient

with chronic heart failure and complete left bundle branch block. Russ J Cardiol. 2011;6:4–8. (In Russ.) Барт Б.Я., Ларина В.Н., Бродский М.С., и др. Ремоделирование сердца и прогноз больных с хронической сердечной недостаточностью при наличии полной блокады левой ножки пучка Гиса. Российский кардиологический журнал. 2011;6:4–8. doi:10.15829/1560–4071-2011–6-4–8.

Book:

Shlyakhto EV, Konradi AO, Tsyrlin VA. The autonomic nervous system and hypertension. SPb.: Meditsinskoe izdatel'stvo; 2008. (In Russ.) Шляхто Е.В., Конради А.О., Цырлин В.А. Вегетативная нервная система и артериальная гипертензия. СПб.: Медицинское издательство; 2008. ISBN 0000–0000.

Chapter:

Nichols WW, O'Rourke MF. Aging, high blood pressure and disease in humans. In: Arnold E, ed. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 3rd ed. London/Melbourne/Auckland: Lea and Febiger; 1990. p.398–420. ISBN 0000–0000.

Russian chapter:

Diagnostics and treatment of chronic heart failure. In. National clinical guidelines 4th ed. Moscow: Silicea-Polygraf; 2011. pp.203–93. (In Russ.) Диагностика и лечение хронической сердечной недостаточности. В кн: Национальные клинические рекомендации. 4-е издание. М.: Силицея-Полиграф; 2011.сс.203–96. ISBN 0000–0000.

Webpage:

Panteghini M. Recommendations on use of biochemical markers in acute coronary syndrome: IFCC proposals. eJIFCC 14. http://www.ifcc.org/ejifcc/vol14no2/1402062003014n.htm (28 May 2004)

All sources of literature are checked for correctness through the system of the Russian electronic library. Significant errors in citation or duplication of the source are the reason for the return of the manuscript to the authors for revision.

VI. Preparation of manuscript.

The author prepares the following documents to upload the manuscript to the site:

The main file Is the text of the article (the system renames it after loading, so it does not matter how it is called).

Additional files-Directional (accompanying) letter, Information file with the Title page, information about the authors and disclosure of conflicts of interest, files with pictures.

For more information on placing articles on the website you can read http://cardiovascular.elpub.ru/jour/announcement

VII. Copyright and publishing policy.

This section regulates the relationship between the editorial Office (Publisher) of *International heart and vascular disease journal* (the «editorial Office») and the author or group of authors who submitted their manuscript for publication in the *International heart and vascular disease journal* (the «Author»).

The author, by sending the article to the Editor, agrees that the editorial Board of the journal shall be transferred to the exclusive property rights to use the manuscript (transferred to the Editorial Board of the journal material, including such protected objects of copyright as photos of the author, drawings, diagrams, tables, etc.), including the reproduction in print and on the Internet; distribution; translation into any languages of the peoples of the world; export and import of copies of the journal with the article of the Author for distribution, to bring to the public.

The editorial Board reserves the right to reduce and edit the materials of the manuscript, to carry out scientific editing, to reduce and correct articles, to change the design of graphs, drawings and tables to bring into line with the design of the journal, without changing the meaning of the information provided.

When using the article, the editors have the right to supply it with any illustrated material, advertising and allow third parties to do so.

The editorial Board has the right to assign the rights received from the Author to third parties and has the right to prohibit third parties from any use of materials published in the journal for commercial purposes.

The author guarantees that he has exclusive rights to use the submitted material. In case of violation of this guarantee and the presentation of claims to the editorial Board, the Author independently and at his own expense undertakes to settle all claims. The editorial Board is not responsible to third parties for violation of the Author's guarantees.

The Author retains the right to use the published material, its fragments and parts for personal, including scientific and teaching purposes.

The Author transfers the above rights to the Editors without limitation of their validity period, in the territory of all countries of the world without limitation, including the territory of the Russian Federation.

The rights to the manuscript are considered to be transferred By the author of the editorial Office from

the moment of sending an information letter about the acceptance of the manuscript to the press.

Reprinting of materials published in the journal by other individuals and legal entities is possible only with the written permission of the editorial Board, with the obligatory indication of the journal name, number and year of publication.

The editors are not responsible for the accuracy of the information provided by the Author.

The author, sending the manuscript to the Editor, gives permission to use and process personal data.

The editorial Board reserves the right to reduce and correct the articles, to change the design of graphs, figures and tables to comply with the standard of the journal, without changing the meaning of the information provided. In case of untimely response of the author (s) to the request of the editorial Board, the editorial Board may at its discretion make changes to the article or refuse to publish.

Sending to the editor of works that have already been sent to other publications or printed in them is absolutely not allowed. The editors are not responsible for the accuracy of the information provided by the authors. Articles sent in violation of the rules of registration are not accepted by the editorial Board for consideration.

VIII. The procedure for rewiewing manuscripts

1. The manuscript should be sent in electronic form to the Editor through the website — http://www.heart-vdj.com. The manuscript should be drawn up in accordance with these requirements for scientific articles submitted for publication in the journal.

2. The author is sent a notification letter of receipt of the manuscript with the number (ID), which will be used in subsequent correspondence. The author can track the stages of work on his manuscript through the site. Since the process of bringing the manuscript to the necessary standards takes enough expert time, the payment for the initial review of the article was introduced, which the author (s) are required to carry out after the article is posted on the site.

3. The manuscript must pass the primary selection: the Editorial Board has the right to refuse publication or send comments to the article, which must be corrected by the Author before reviewing.

— checking the completeness of the manuscript: if you do not comply with the requirements of the Rules for the authors to complete the manuscript or its design, the Editors have the right to refuse to publish or in writing to require to send the missing materials or to correct the version already downloaded to the site.

— Manuscripts are checked in the «Antiplagiat» system. The originality of the manuscript should be at least 75 %. We expect manuscripts submitted for publication to be written in an original style that involves new thinking without the use of previously published text. Manuscript with originality below 75 % shall not be admissible.

4. All manuscripts submitted to the journal are sent to one of the permanent reviewers or an independent expert according to the profile of the research.

5. The review process is anonymous both for the Author and for the reviewers. The manuscript is sent to the reviewer without the names of the authors and the name of the institution.

6. The editorial Board informs the Author of the results of the review by e-mail.

7. If the reviewer makes a conclusion about the possibility of publication of the article and does not make significant corrections, the article is given to the expert on statistics and after a positive report is accepted for further work.

8. If the reviewer makes a conclusion about the possibility of publication of the article and gives instructions on the need for its correction, the Editorial Board sends the review to the Author with a proposal to take into account the recommendations of the reviewer in the preparation of a new version of the article or to refute them. In this case, the Author needs to make changes to the last version of the article file, which is located on the site (download file from the site, make changes and place the corrected article again, after removing the primary (uncorrected) version). The revised article is re-sent for review, and the conclusion is given that all the recommendations of the reviewer were taken into account. After receiving a positive response of the reviewer, the article is given to the expert on statistics and after a positive report is accepted for further work.

9. If the reviewer makes a conclusion about the impossibility of publication of the article. The author of the reviewed work is given the opportunity to read the text of the review, if he does not agree with the conclusions of the reviewer. In case of disagreement with the opinion of the reviewer, the Author has the right to provide a reasoned response to the Editor. The article can be sent for re-review or for approval to the editorial Board. The editorial Board or its authorized editor shall send its response to the Author.

10. All manuscripts that have been reviewed and evaluated by an expert in statistics are submitted to the editorial Board, which decides on the publication.

After the decision on the admission of article for publication, the Editorial office inserts the publication of the article in terms of publications. Information about the annual (thematic) plan of publications is placed on the website of the journal.

11. The decision to publish a manuscript is made solely on the basis of its significance, originality, clarity of presentation and compliance of the research topic with the direction of the journal. Reports on studies in which negative results are obtained or the provisions of previously published articles are challenged are considered on General grounds.

12. Original reviews are kept in the Editorial office for 5 years from the date of publication.

13. In case of a decision to refuse to publish an article, its archive copy remains in the electronic system of the editorial Board, but access to it by editors or reviewers is closed.

IX. The manner of publication of manuscripts

1. According to the requirements of the Higher attestation Commission, the journal provides priority for post-graduate and doctoral works, the period of their publication depends on the expected date of protection, which the authors must specify in the primary documents attached to the manuscript.

2. Each issue of the journal is formed by a separate Executive editor appointed by the editor-in-Chief and/or editorial Board. It is the responsibility of the editor-in-charge to select high-quality articles for publication, and he can be guided by both thematic principles and a separate scientific direction.

3. All selected articles are submitted to the scientific editor and proofreader. After creating the layout of the article and editing it, the article will be available to the Author through the site. At this stage, it will be possible to send comments on the text of the article. The author is obliged to send his / her consent to the publication or his / her comments within the established time specified in the cover letter.

4. The editorial office does not send the author's copy by mail or PDF of the article by e-mail, access to the published numbers is open.

Subscription to the printed version is carried out by half a year (through subscription agencies).

X. After the publication in the journal

1. Information on publication is distributed in the following scientific citation databases: Russian science citation index, CYBERLENINKA and others. The article is assigned a DOI index and the full text is publicly available on the journal's website.

2. Information about the publication of the issue is distributed by mailing of The Cardioprogress Foundation and in social networks.

3. We expect the authors of the articles to actively make efforts to bring the results of their research to the public, namely: to have a personal page on the Internet (personal page), to monitor and update your profile ORCID and RecsearcherID, to involve colleagues in their work through social networks.

XI. Revocation or correction of articles

The full text of the journal's policy on Revocation and correction of articles is available in the information section on the website. The editors follow COPE Recommendations issued by the Committee on publishing ethics (COPE) — http://www.publicationethics.org.uk. in cases:

Editors of journals should consider the opinion of the publication, if:

they have clear evidence of the unreliability of the information published, either as a result of conscious actions (for example, falsification of data), or due to good faith errors (for example, errors in calculations or experiments); the findings have been previously published in another publication and there is no proper reference, authorization and justification for re-publication (i.e. duplicate publication).); it is plagiarism; describes unethical research.

Editors of journals should consider the concerns, if:

they received information about the authors ' inappropriate actions, but there is no clear evidence of such behavior; there are arguments that the results of the work are unreliable, and the institution in which the authors work is not going to find out the truth; they believe that the investigation into the alleged violations committed by the authors in connection with the publication has either not been or will not be fair, impartial and convincing; the authors ' violations are being investigated, but the results are not expected soon enough.

Journal editors should consider making amendments if:

a small part of the rest of the high-quality publication is unreliable (especially because of conscientious errors); the list of authors / sponsors contains errors (i.e., it does not contain someone who is worthy to be an author, or a person who does not meet the authorship criteria).

In most cases, a review is not appropriate if:

authorship needs to be changed, but there is no reason to doubt the validity of the findings.

XII. Position E-log backup (if journal is no longer published)

The purpose of backup is to prevent loss of information in case of hardware, software, critical and crisis situations, etc.

Information of the following main categories is subject to backup: — personal information of authors (personal directories on file servers); — pdf of published articles; — information about literary links to the article in the DOI system.

All this information is publicly available in The system of the Russian citation index on the website of the Electronic library www.elibrary.ru

XIII. Journal subscription

Information on subscriptions is available on the journal website in the section «Subscription»:

XIV. Journal subscription

The name of the journal in English is International heart and vascular disease journal.

Official sites where information about the journal is placed:

http://www.heart-vdj.com

On the reception of the articles, making decisions about publication, reviews — mmamedov@mail.ru

On organizational issues (working with the site, subscription) — editor.ihvdj@gmail.com

Editorial office:

Room 213, Building 2, Prospect Gostinichny 6, Moscow 127106, Russia

e-mail: editor.ihvdj@gmail.com

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. The manuscripts are accepted if has not been published or submitted for publication elsewhere.

2. The file of the submitted article is in the format of a Microsoft Word document. It does not contain the names of the authors and institutions.

Files with a letter of transmittal and General information have been prepared for upload to the site.

3.The cited literature is presented in full, framed by the Rules for the authors and does not contain duplicates. All references are indicated in the text of the article.

4. Text should be typed with an interval of one line spacing, font Times New Roman, 12 pt; to highlight the accents it is recommended to use italics rather than underlining (except Internet links). All images, graphics and tables are placed within the text according to the meaning of the particular part of text (and not at the end of the document).

5. Text should follow the stylistic and bibliography requirements as stated in Regulations located in the Part «About Us.»

6. Please, remove the authors' names from the title of the article and other parts of the document to ensure the anonymity of reviewing.

Copyright Notice

Authors who publish with this journal agree to the following terms:

1. Authors retain copyright and grant the journal right of first publication with the work simultaneously licensed under a Creative Commons Attribution License that allows others to share the work with an acknowledgement of the work's authorship and initial publication in this journal.

2. Authors are able to enter into separate, additional contractual arrangements for the non-exclusive distribution of the journal's published version of the work (e.g., post it to an institutional repository or publish it in a book), with an acknowledgement of its initial publication in this journal.

3. Authors are permitted and encouraged to post their work online (e.g., in institutional repositories or on their website) prior to and during the submission process, as it can lead to productive exchanges, as well as earlier and greater citation of published work (See The Effect of Open Access).

Privacy Statement

Specified when registering the names and addresses will be used solely for technical purposes of a contact with the Author or reviewers (editors) when preparing the article for publication. Private data will not be shared with other individuals and organizations.

ISSN: 2309-0901 (Print)

ISSN: 2311-1631 (Online)

FOUNDATION FOR THE ADVANCEMENT OF CARDIOLOGY

"CARDIOPROGRESS"

knowledge, observation, action

Official website: www.cardioprogress.ru

Tel: 007 965 236 1600

Email: inf.cardio@gmail.com

Moscow, Russia