ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

# РОССИЙСКИЙ КАРДИОЛОГИЧЕСКИЙ ЖУРНАЛ.
# ОБРАЗОВАНИЕ
## Russian Journal of Cardiology. EDUCATION

НАУЧНО-ПРАКТИЧЕСКИЙ РЕЦЕНЗИРУЕМЫЙ МЕДИЦИНСКИЙ ЖУРНАЛ

РОССИЙСКОЕ КАРДИОЛОГИЧЕСКОЕ ОБЩЕСТВО

## IN ISSUE:



S4 | 2020

РОССИЙСКОЕ КАРДИОЛОГИЧЕСКОЕ ОБЩЕСТВО

**Russian Society of Cardiology**

**Scientific peer-reviewed medical journal**

Mass media registration certificate № 017388 dated 06.04.1998

**Periodicity** — 12 issues per year
**Circulation** — 7 000 copies

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

**The Journal is included in Scopus, EBSCO, DOAJ**

**Russian Citation Index:**
**SCIENCE INDEX (2018) 3,054**
**Impact-factor (2018) 1,082**

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

**Instructions for authors:** *https://russjcardiol.elpub.ru/jour/about/submissions#authorGuidelines*

**Submit a manuscript:** *www.russjcardiol.elpub.ru*

**Subscription:** *www.roscardio.ru/ru/subscription.html*

**Open Access**



**Printed:** OneBook, Sam Poligraphist, Ltd. 129090, Moscow, Protopopovsky per., 6. www.onebook.ru



Font's license №180397 от 21.03.2018

# RUSSIAN JOURNAL OF CARDIOLOGY EDUCATION

**№ 25 (S4) 2020**

*founded in 1996*



**Editorial office:**
119049, Moscow,
ul. Shabolovka, 23-254
e-mail: cardiojournal@yandex.ru
Tel. +7 (985) 768 43 18

**Publisher:**
Silicea-Poligraf
e-mail: cardio.nauka@yandex.ru

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-S4

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

# CONTENTS

## ORIGINAL ARTICLES



## CLINICAL CASE



## LITERATURE REVIEWS



MANUSCRIPT PUBLICATION RULES (2019)
http://russjcardiol.elpub.ru/jour/about/submissions#authorGuidelines

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-4149

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

# Efficiency of remote blood pressure monitoring in outpatients with hypertension: a pilot project in a city ambulatory care clinic

Sharapova Yu. A.[1], Starodubtseva I. A.[1], Villevalde S. V.[2]

**Aim.** In a pilot project, to evaluate the effectiveness of remote blood pressure (BP) monitoring in outpatients followed up for hypertension (HTN).

**Material and methods.** A total of 1,121 patients (707 women and 414 men) with hypertension were included in the pilot project (mean age, 52,0±12,0 years; BP, 151,4±9,1/96,9±10,3 mm Hg). Patients independently measured BP and entered the values into self-management paper diaries (n=886), in digital form to their personal account (n=200), or transmitted data from BP monitor using installed mobile application (n=35). Each of the three groups was assessed at baseline and after 6 months. We assessed achievement of BP targets, medication adherence using the Morisky Green scale, the prevalence of patients with fixed-dose antihypertensive therapy, and the ambulance call rate.

**Results.** Prior to the study, 15,2% (n=171) of hypertensive patients regularly monitored their BP. After 6 months, the mean systolic BP decreased from 151,4±9,1 to 135,5±10,1 mm Hg (p<0,01), diastolic BP — from 96,9±10,3 to 85,8±6,3 mm Hg (p<0,01). The proportion of patients adhering to treatment (Morisky Green score of 4) increased from 17,9 to 55,4%, the frequency of prescribing dual antihypertensive therapy — from 25,8 to 43,3%, triple therapy — from 11,5 to 22,9%, fixed-dose combinations — from 25,4 to 51,6%. At the same time, the proportion of patients who achieved the target BP values increased from 14,5 to 43,1%, while the ambulance call rate decreased from 19,3 to 16,9%.

**Conclusion.** The use of remote BP monitoring methods, including BP monitors with automated data transmission, increases the prescription rate of combined antihypertensive therapy and proportion of patients who achieved the target BP, as well as decreases the ambulance call rate.

**Keywords:** hypertension, remote monitoring, blood pressure, follow-up monitoring.

**Relationships and Activities:** none.

[1]N. N. Burdenko Voronezh State Medical University, Voronezh; [2]Almazov National Medical Research Center, St. Petersburg, Russia.

Sharapova Yu. A.* ORCID: 0000-0002-4269-2143, Starodubtseva I. A. ORCID: 0000-0002-4665-2966, Villevalde S. V. ORCID 0000-0001-7652-2962.

*Corresponding author: shajulia2007@yandex.ru

**Received:** 16.10.2020
**Revision Received:** 12.11.2020
**Accepted:** 15.12.2020



**For citation:** Sharapova Yu. A., Starodubtseva I. A., Villevalde S. V. Efficiency of remote blood pressure monitoring in outpatients with hypertension: a pilot project in a city ambulatory care clinic. *Russian Journal of Cardiology*. 2020;25(S4):4149. (In Russ.) doi:10.15829/1560-4071-2020-4149

Hypertension (HTN) is the main contributor (~42%) to cardiovascular disease pattern, being simultaneously not only one of the main risk factors for complications, but also significantly decreasing life expectancy due to premature disability [1]. Decrease in systolic blood pressure (SBP) by 10 mm Hg is associated with a significant reduction in risk of coronary artery disease by 20%, stroke by 17%, heart failure and all-cause death by 27% and 13%, respectively [2]. According to a meta-analysis by Thomopoulos C, et al. differences in SBP levels 12 mm Hg and diastolic blood pressure (DBP) 5 mm Hg are associated with significant reductions in all unfavorable outcomes, including mortality. Blood pressure (BP) decrease, regardless of antihypertensive drugs (AHD) taken, is associated with a decrease in the risk of stroke and most cardiovascular events [3].

Effectiveness of hypertension treatment depends not only on the correct and timely diagnosis and choice of the optimal treatment strategy, but also on patient medical adherence [4]. BP values obtained from blood pressure self-monitoring (BPSM) can be a valuable addition to office ones in the diagnosis of HTN and monitoring the treatment effectiveness. BP data recorded in by BPSM correlates more strongly with target organ damage and the prognosis of the disease than office blood pressure, and its predictive value is comparable to the data obtained with 24-hour monitoring, after adjusting for sex and age [5]. BPSM has been proven to increase patient medcial adherence [6]. According to the 2020 Russian Society of Cardiology guidelines, telemonitoring of systemic hemodynamic parameters with data transmission to a medical institution is recommended for patients with HTN (level of evidence, B; class of recommendations, I) [7]. In a pilot project based on ambulatory care clinic, the aim was to assess the effectiveness of remote blood pressure monitoring in achieving target values and increasing medical adherence of patients, as well as to assess ambulance call rate and changes in prescribing fixed-dose combinations.

## Material and methods

For remote BP monitoring, including using automatic monitors with the function of data transmission, on the basis of Voronezh City Clinical Polyclinic № 1, 1,121 patients with HTN were included. The study was approved by the ethics committee of the N. N. Burdenko Voronezh State Medical University. There were following inclusion criteria: patients with hypertension over 18 years of age, signed informed consent, dispensary observation due to HTN, regular intake of antihypertensives, absence of severe comorbities (diabetes with a glycated hemoglobin level >9%, Child-Pugh score class B and C liver cirrhosis, chronic kidney disease with a glomerular filtration rate <30 ml/min/1,73 $m^2$, severe asthma, active cancer, mental illness). All patients signed informed consent. The clinical characteristics of patients are presented in Table 1.

The patients were divided into 3 groups: patients who transmitted data from BP monitor using installed mobile application (group 1, n=35); those who independently measured BP and entered the values into personal account (group 2, n=200); those who kept a self-management paper diaries (group 3, n=886) (Figure 1).

All patients were trained in the BPSM. It was recommended to independently measure blood pressure twice a day. Home SBP <135 mm Hg and DBP <85 mm Hg were considered as target.

Patients of group 1 received BP monitors A&D UA-911BT (Japan) with data transfer via Bluetooth. Each monitor had an internal number to identify the patient in the healthcare information system (HIS). Group 2 patients entered their blood pressure values into their personal records 2 times a day before they reached their target values, and once they reached their target values, they entered them once a day. The data entered by the patient in the self-monitoring diary or transmitted from a smartphone were transferred to the HIS server of the medical organization and reflected in the patient's personal electronic medical record. The attending physician and emergency room physician saw the results of the blood pressure measurement in the Tonometry module from the automated workstation. The HIS automatically calculated the average value of SBP and heart rate for a certain time interval. When SBP >150 mmHg was measured, a physician received an alert message, which ensured prompt decision-making on treatment adjustments by making an appointment with the attending physician. In the event of an increase in systolic blood pressure >170 mmHg, a telephone call was made in advance to decide whether or not an emergency treatment was required.

Group 3 patients were given a self-monitoring diary when they filled in their informed consent. Patients were advised to contact the attending physician by telephone if their blood pressure rose above the tolerance level (individual for each patient). The nurse made structured telephone contact at least once a week until the patients reached their target BP values, clarified their BP values and, if necessary, set a date and time for a visit to the doctor. The achievement of BP control was assessed using BPSM data, including at interim visits to the doctor's office.

Treatment adherence was assessed using the Moriski-Green scale at face-to-face visits [8]. The Moriski-Green scale consists of four items relating to the patient's attitude towards taking medication, completed by the patient. Alternatively, the physician can read out the questions and mark the answers. In the original scale, each item is scored on a "yes" or "no" basis, with a "yes" score of 0 and a "no" score of 1. Patients with a score of 4 are considered committed to treatment, <4 are not committed to treatment.

**Table 1**

**Clinical and demographic characteristics of patients in the remote BP monitoring group**

| Parameter | Baseline |
|---|---|
| Total number of hypertensive patients (n) | 1121 |
| Men, n (%) | 414 (37,1) |
| Age, years, M±σ | 52±12,0 |
| Body mass index >25 kg/m$^2$, n (%) | 774 (69,1) |
| Smoking >20 cigarettes per day, n (%) | 260 (23,2) |
| Capillary blood glucose >6,1 mmol/L, n (%) | 41 (3,7) |
| Triglycerides >1,7 mmol/L, n (%) | 341 (30,4) |
| Total cholesterol >4,9 mmol/L, n (%) | 334 (29,8) |
| GFR <60 ml/min/1,73 m$^2$, n (%) | 18 (1,6) |
| CAD, n (%) | 114 (10,2) |
| Diabetes, n (%) | 47 (4,2) |

**Abbreviations:** CAD — coronary artery disease, GFR — glomerular filtration rate.

After 6 months of follow-up, the following measures were analyzed: the achievement of target SBP values (<135 mm Hg), adjustments in therapy and the number of drugs in the patient needed to achieve the target BP values, as well as adherence to treatment, changes in the number of emergency medical calls due to BP increase.

Results were analyzed using Statistica 10 package (Dell Software Company, USA). Descriptive statistics with calculation of mean values (M), standard deviation, and standard error (m) were used. The normality of distribution was analyzed using the graphical histogram, the Kolmogorov-Smirnov and Lilliefors tests, as well as determining asymmetry, kurtosis and their standard errors. Univariate and multivariate analysis of variance were used as methods of statistical analysis to identify differences between the mean values. The threshold level of statistical significance was 0,05.

## Results

Thirteen (1,1%) patients (8 males and 5 females), 11 of whom were of working age, dropped out of the study within 6 months. Five patients dropped out for technical reasons (difficulty in entering data) during the first month and 5 patients dropped out due to employment after reaching the target BP values. Four patients were lost in contact (did not answer the phone).

According to the survey, only 15,2% (n=171) of patients had self-monitored blood pressure before the study. The initial target BP values (<140/<90 mmHg)

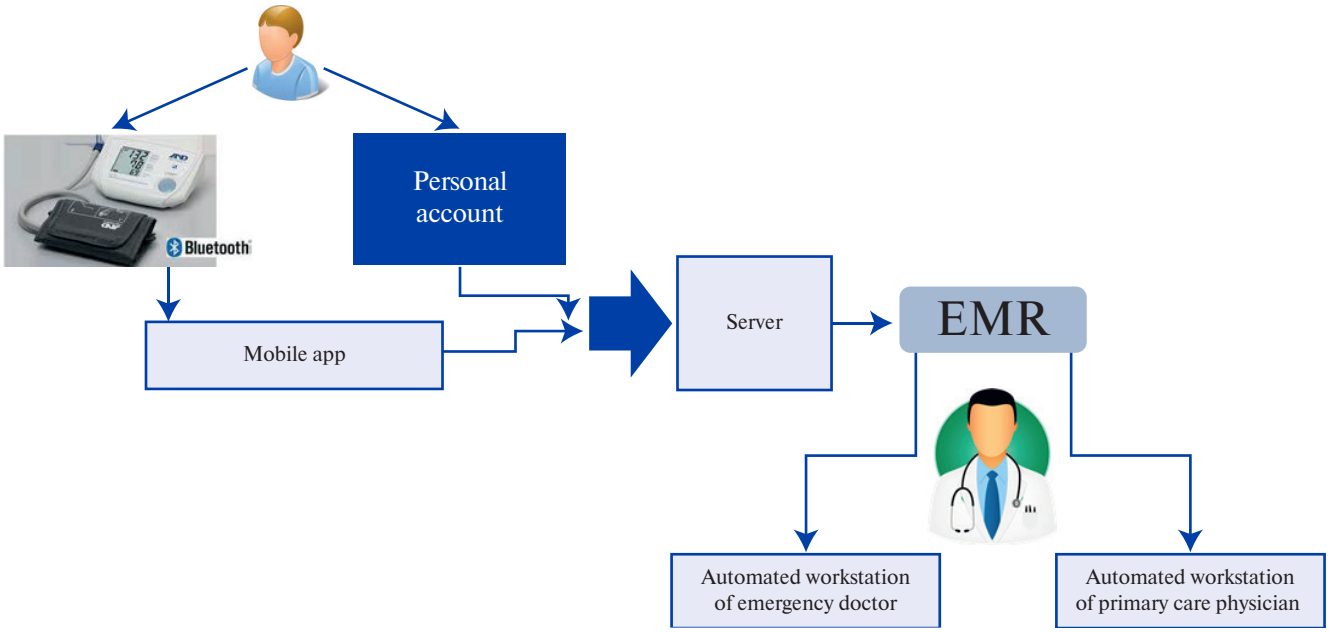


**Figure 1.** Model of remote BP data transmission.
**Abbreviation:** EMR — electronic medical record.

were recorded in 14,5% (n=162) of the patients according to their outpatient medical records. During the 6 months of the study a significant decrease of BP was observed in the group of patients with remote BP monitoring in general, and the proportion of patients who reached the target values of BP increased by 3 times, which occurred against the background of the 1,7-fold increase in the frequency of dual AHT, 2-fold increase in triple therapy and 2,5-fold increase in fixed-dose combinations (Table 2). Angiotensin-converting enzyme inhibitors were the most frequently prescribed AHD. At the same time, there was an increase in the prescription of calcium channel blockers by 13%, angiotensin II receptor antagonists by 12%, and diuretics by 11% (Figure 2). After 6 months, the Moriski-Green score increased from 2,15 to 3,18, and the proportion of patients committed to AHT was 3,1 times (Table 2). In general, remote BP monitoring promoted a more aggressive approach to prescribing combined AHT, but even with this strategy, only 43,1% of patients reached their target BP values.

The use of automatic BP monitors with remote data transmission in group 1 was associated with a 5,4-fold (up to 77,1%) increase in the proportion of patients achieving target BP values, a 2,4-fold (up to 60,0%) increase in the proportion receiving AHT in fixed-dose combinations and a 4,9-fold (up to 82,9%) increase in medical adherence (Table 3).

During the follow-up period, 11 patients (all of whom filled out paper-based self-monitoring diaries) had cardiovascular complications: 8 patients were diagnosed with non-fatal ischaemic stroke and 3 with non-fatal myocardial infarction. Of the 8 patients who had ischaemic stroke, 5 patients had irregular BP measurements and were taking combined AHT. Six patients had comorbid complications (diabetes, chronic kidney disease). Of the 11 patients, 7 continued to fill out self-monitoring diaries after the events and were seen by specialists, while 3 patients had pronounced cognitive impairment after the ischemic stroke.

During the 6 months of the study compared to the same period before the project, the number of emergency calls for due to BP increase decreased by 14,8% (Table 2).

Thus, the use of remote BP monitoring, including remote BP monitors, was associated with improved follow-up of patients with HTN over 6 months.

**Table 2**

**Dynamics of the parameters of the effectiveness of 6-month remote BP monitoring in the general group (n=1121)**

| Parameter | Baseline | After 6 months |
|---|---|---|
| SBP, mm Hg | 151,4±9,1 | 135,5±10,1** |
| DBP, mm Hg | 96,9±10,3 | 85,8±6,3** |
| Achievement of target BP values, n (%) | 162 (14,5) | 484 (43,1)* |
| Medical adherence, n (%) | 201 (17,9) | 621 (55,4)* |
| The proportion of patients who are assigned: | | |
| — dual AHT, n (%) | 290 (25,8) | 486 (43,3)* |
| — triple AHT, n (%) | 129 (11,5) | 257 (22,9)* |
| — more than three antihypertensives, n (%) | 27 (2,4) | 67 (5,9)* |
| — fixed-dose combinations | 285 (25,4) | 579 (51,6) |
| The number of patients who were visited by the emergency medical team with the reason “increased blood pressure”, n (%) | 216 (19,3) | 189 (16,9)* |

**Note:** * — p<0,05, ** — p<0,01, the significance of differences between the baseline and achieved values.

**Abbreviations:** AHT — antihypertensive therapy, BP — blood pressure, DBP — diastolic blood pressure, SBP — systolic blood pressure.

## Discussion

The remote patient follow-up model is the most relevant and acceptable, aiming to analyze large numbers of patients at one time, using automatic or semi-automatic mechanisms to summarize information. Remote patient follow-up can theoretically help to reduce the number of visits associated with disease exacerbation as well as adverse life-threatening consequences [9]. Based on an economic analysis of remote BP monitoring in the Russian Federation, the project should be considered as not only efficient but also fast-paying, fully implementable by regional forces [10].

A meta-analysis of the efficacy of remote BP monitoring in patients with HTN summarized the results of 46 randomized controlled trials, which together included 13875 patients. The meta-analysis showed that, compared with conventional treatment, remote monitoring reduced clinical SBP and DBP by 3,99 mm Hg (p<0,001) and 1,99 mm Hg (p<0,001), respectively. The use of telemonitoring promoted BP normalization (relative risk, 1,16; p<0,001) [11]. However, a systematic review by Milevski M, et al. highlights a number of shortcomings in the use of remote BP monitoring. The authors note the small size of the evidence base for BP monitoring in patients with HTN. The results obtained using smartphone apps are also questioned. Errors made in the measurement of BP by patients, as well as

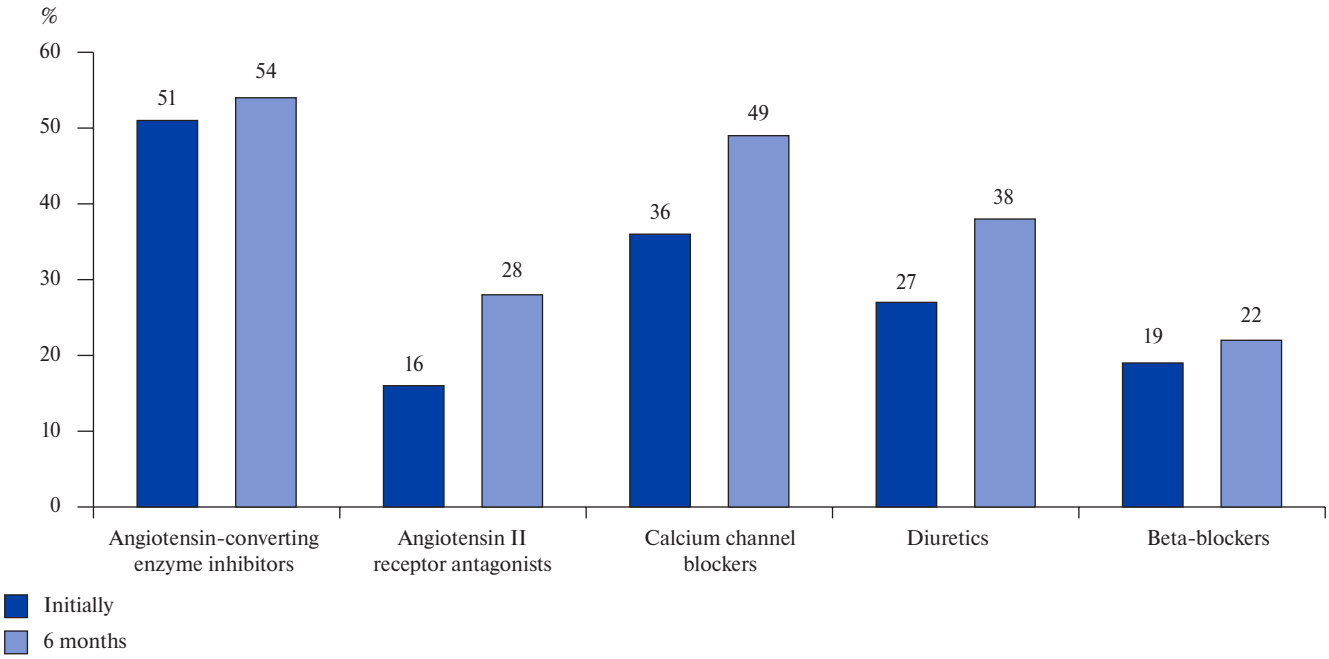


**Figure 2.** Dynamics of the appointment of antihypertensives' groups.

**Table 3**

**Dynamics of the parameters of the effectiveness of 6-month remote BP monitoring in various groups**

| Parameter | Group 1 (n=35) | | Group 2 (n=200) | | Group 3 (n=886) | |
|---|---|---|---|---|---|---|
| | Baseline | After 6 months | Baseline | After 6 months | Baseline | After 6 months |
| Systolic blood pressure, mm Hg | 152±5,2 | 131,2±8,9 | 151,3±7,1 | 132,4±9,2 | 151,8±6,3 | 136,8±10,2 |
| Diastolic blood pressure, mm Hg | 95,8±10,1 | 83,1±5,9 | 96,2±8,8 | 84,2±6,1 | 96,5±7,6 | 86,7±5,9 |
| Achievement of target BP values, n (%) | 5 (14,2) | 27 (77,1) | 29 (14,5) | 92 (46,0)* | 128 (14,4) | 365 (41,1)* |
| Medical adherence, n (%) | 6 (17,1) | 29 (82,9)* | 36 (18) | 118 (59,0)* | 159 (17,9) | 474 (53,4)* |
| Proportion of patients received fixed-dose combinations, n (%) | 8 (25,0) | 21 (60,0)* | 50 (25,0)* | 101 (52,0)* | 227 (25,6) | 459 (51,8)* |
| The number of patients who calls for ambulance due to BP increase, n (%) | 7 (20,0) | 4 (11,4) | 38 (19,0) | 32 (16,0) | 171 (19,3) | 153 (17,3)* |

**Note:** * — p<0,01, the significance of differences between the baseline and achieved values.
**Abbreviation:** BP — blood pressure.

reduced adherence due to the lack of staff attention to the results obtained, according to the authors, play against the use of telemedicine in BP monitoring [12].

The Saratov Research Institute of Cardiology developed remote BP monitoring technology based on mobile phone text messages in 2012, where the effectiveness of remote BP monitoring technology in HTN patients was evaluated on the basis of clinical guideline compliance indicators. The evaluation of remote BP monitoring in HTN patients made it possible to determine the improvement of the performance of the most significant therapeutic measures after its implementation [13]. Thus, all HTN patients (n=97) began to regularly report BP measurement results to their attending physician, and physicians, in turn, were more likely to prescribe combined AHT (increase from 70% to 82%, p<0,05) for uncontrolled BP, which was accompanied by a significant increase in the frequency of reaching the target BP. At the end of 12-month follow-up, mean SBP and DBP was 130,5±10,4 and 81,8±7,3 mm Hg (p<0,05). According to American research, bi-directional automated text messaging is an

effective way to collect patient BP data. Text-message reminders alone are an effective way of encouraging patients to record BP measurements [14-16].

Significant reductions in SBP and DBP by an average of 15 mm Hg and 11 mm Hg ($p<0,05$) at six-month follow-up in this study demonstrates the effects of remote control and associated changes in AHT tactics — an increase in the proportion of patients prescribed dual AHT by 1,7 times, triple therapy by 2 times, and fixed-dose combinations by 2,5 times. In a study at the Saratov Research Institute of Cardiology, the proportion of patients using combined AHT increased by 17,1% after one year of follow-up, while the proportion of patients receiving combination therapy at baseline differed significantly (39,2% and 70%), which may have affected the achieved SBP and DBP values [13].

The results of this study indicate that the use of remote BP monitoring for 6 months is associated with a 3,1-fold increase in adherence to AHT. In addition, there was a 12,5% reduction in the ambulance call rate (Table 2).

The main problematic issues encountered in this pilot project are patients' lack of adherence to lifestyle recommendations and insufficient adherence to treatment precisely after target BP levels have been achieved, especially among working patients. A special role in the functioning of the project is played by information technology (data exchange, telemedicine), training of medical staff and patients [17].

The issues of treatment adherence and patient motivation for lifestyle changes in the use of remote BP monitoring require further research.

A limitation of the study is its non-randomized, non-comparative design.

## Conclusion

The use of remote BP monitoring methods, including BP monitors with automated data transmission, increases the prescription rate of combined antihypertensive therapy (dual AHT from 25,8 to 43,3%, triple therapy — from 11,5 to 22,9%, and fixed-dose combinations — from 25,4 to 51,6%) and proportion of patients who achieved the target BP (from 14,5 to 43,1%), as well as decreases the ambulance call rate from 19,3 to 16,9%.

Further 12-month implementation of the project will assess the cost-effectiveness of remote BP monitoring, including by reducing the ambulance call rate.

**Relationships and Activities:** none.

## References


1. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020:396:1135-59. doi:10.1016/S0140-6736(20)30752-2.
2. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2015:418-25. doi:10.17116/dokkardio2015418-25.
3. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: Effects of various classes of antihypertensive drugs — overview and meta-analyses J Hypertension. 2015;33(2):195-211. doi:10.1097/HJH.0000000000000447.
4. Machilskaya OV. Factors determining adherence to treatment of patients with arterial hypertension (literature review). Cardiology and cardiovascular surgery. 2016.3:355-65. (In Russ.) doi:10.17116/kardio20169355-65.
5. Bliziotis IA, Destounis A, Stergiou GS. Home versus ambulatory and office blood pressure in predicting target organ damage in hypertension: a systematic review and meta-analysis. J Hypertens. 2012;30:1289-99. doi:10.1097/HJH.0b013e3283531eaf.
6. Tucker KL, Sheppard JP, Stevens R, et al. Self-monitoring of blood pressure in hypertension: a systematic review and individual patient data meta-analysis. PLoS Med. 2017;14:e1002389. doi:10.1371/journal.pmed.1002389.
7. Kobalava ZD, Konradi AO, Nedogoda SV, et al. Arterial hypertension in adults. Clinical guidelines 2020. Russian Journal of Cardiology. 2020;25(3):3786. (In Russ.) doi:10.15829/1560-4071-2020-3-3786.
8. Morisky DE, Green LW, Levine DM. Concurrent and presictive validity of a self-reported measure of medication adherence. Med Care. 1986;24(1):67-74.
9. Oleinikov VE, Chizhova OV, Dzhazovskaya IN, et al. Economic justification for the use of an automatic system for remote monitoring of blood pressure. Healthcare Of The Russian Federation. 2019;63(1):14-21. (In Russ.)
10. Kontsevaya AV, Komkov DS, Boitsov SA. The modeling as a technique of evaluation of expediency of remote monitoring of arterial tension at the regional level. Healthcare Of The Russian Federation. 2017;61(1):10-16. (In Russ.) doi:10.18821/0044-197X-2017-61-1-10-16.
11. Duan Y, Xie Z, Dong F, et al. Effectiveness of home blood pressure telemonitoring: a systematic review and meta-analysis of randomized controlled studies. Journal of Human Hypertension. 2017;31:427-37. doi:10.1038/jhh.2016.99.
12. Mileski M, Kruse CS, Catalani J, Haderer T. Adopting Telemedicine for the Self-Management of Hypertension: Systematic Review. JMIR Med Inform. 2017;5(4):e41. doi:10.2196/medinform.6603.
13. Posnenkova OM, Korotin AS, Kiselev AR, Gridnev VI. Evaluation of the effectiveness of technology for remote monitoring of blood pressure in patients with arterial hypertension based on indicators of clinical recommendations. Cardio-IT. 2015;2(2):e0203. (In Russ.)
14. Anthony CA, Polgreen LA, Chounramany J, et al. Outpatient blood pressure monitoring using bi-directional text messaging. J Am Soc Hypertens. 2015;9(5):375-81. doi:10.1016/j.jash.2015.01.008.
15. Gandapur Y, Kianoush S, Kelli HM, et al. The role of mHealth for improving medication adherence in patients with cardiovascular disease: a systematic review. Eur Heart J Qual Care Clin Outcomes. 2016;2(4):237-44. doi:10.1093/ehjqcco/qcw018.
16. McInnes DK, Petrakis BA, Gifford AL, et al. Retaining homeless veterans in outpatient care: a pilot study of mobile phone text message appointment reminders. Am J Public Health. 2014;104 Suppl 4(Suppl 4):S588-94. doi:10.2105/AJPH.2014.302061.
17. Shlyakhto EV, Zvartau NE, Villevalde SV, et al. Cardiovascular risk management system: prerequisites for developing, organization principles, target groups. Russian Journal of Cardiology. 2019;(11):69-82. (In Russdoi:10.15829/1560-4071-2019-11-69-82.

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-4157

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

# Short-term outcomes of Ozaki procedure: a multicenter study

Chernov I. I.[1], Enginoev S. T.[1,2], Komarov R. N.[3], Bazylev V. V.[4], Tarasov D. G.[1], Kadyraliev K. B.[5], Tungusov D. S.[4], Arutyunyan A. V.[3], Chragyan A. V.[6], Batrakov P. A.[4], Ismailbaev A. M.[3], Tlisov B. M.[3], Weymann A.[7], Pompeu M. B. O. Sá[8], Zhigalov K.[7]

**Aim.** To analyze the short-term outcomes of Ozaki procedure.

**Material and methods.** This retro-prospective multicenter study included 724 patients with aortic valve (AV) disease, who underwent AV neo-cuspitization (AVNeo) from 2015 to 2019. The register included 395 (54,5%) men and 329 (45,5%) women. The median age of patients was 63 (57-67) years (minimum age, 10 years; maximum age, 83 years). A total of 496 (68,6%) patients had aortic stenosis, 44 (6%) — aortic regurgitation, 184 (25,4%) — aortic stenosis and regurgitation. Infective endocarditis as a cause of AV disease was diagnosed in 23 (3,2%) patients. NYHA class III-IV heart failure was in 348 (48%) patients. Atrial fibrillation was registered before surgery in 141 (19,5%) patients.

**Results.** In total, 314 (43,4%) patients underwent a single intervention (AVNeo), while the remaining 410 (56,6%) patients underwent combined operations. Access to the heart was performed through a median sternotomy in 687 (95%) patients, and in 37 (5%) patients through a ministernotomy. The median cardiopulmonary bypass time was 130 (110-130) min, while the myocardial ischemic time — 104 (86-122) min. In-hospital mortality was 1,6%. The maximum and mean pressure gradient after surgery were 10,9 (7,4-14,8) mm Hg and 5,3 (3,5-7,3) mm Hg, respectively. The AV effective orifice area (EOA) and indexed EOA after surgery were 3 (2,5-3,9) $cm^2$ and 1,6 (1,3-2) $cm^2/m^2$, respectively. Thirteen (1,8%) patients received a pacemaker. Acute renal failure was recorded in 4 (0,5%) patients, stroke — in 3 (0,4%), and sternal infection — in 10 (1,4%).

**Conclusion.** The Ozaki procedure is feasible and reproducible, has good short-term outcomes with excellent hemodynamic parameters. Further research is needed to assess long-term results.

**Keywords:** Ozaki procedure, aortic valve neo-cuspitization, aortic valve.

**Relationships and Activities:** none.

[1]Federal Center for Cardiovascular Surgery, Astrakhan, Russia; [2]Astrakhan State Medical University, Astrakhan, Russia; [3]I. M. Sechenov First Moscow State Medical University, Moscow, Russia; [4]Federal Center for Cardiovascular Surgery, Penza, Russia; [5]S. G. Sukhanov Federal Center for Cardiovascular Surgery, Perm, Russia; [6]JSC "Medicine", Moscow, Russia; [7]Department of Thoracic and Cardiovascular Surgery, West German Heart and Vascular Center Essen, University Hospital of Essen, University Duisburg-Essen, Essen, Germany; [8]Division of Cardiovascular Surgery of Pronto Socorro Cardiológico de Pernambuco — PROCAPE, University of Pernambuco, Recife, Brazil.

Chernov I. I. ORCID: 0000-0002-9924-5125, Enginoev S. T.* ORCID: 0000-0002-8376-3104, Komarov R. N. ORCID: 0000-0002-3904-6415, Bazylev V. V. ORCID: 0000-0001-6089-9722, Tarasov D. G. ORCID: 0000-0002-0866-3939, Kadyraliev K. B. ORCID: 0000-0002-4007-7665, Tungusov D. S. ORCID: 0000-0001-9272-7423, Arutyunyan A. V. ORCID: 0000-0002-1730-9050, Chragyan A. V. ORCID: 0000-0002-7651-4476, Batrakov P. A. ORCID: 0000-0002-7270-4977, Ismailbaev A. M. ORCID: 0000-0001-8545-3276, Tlisov B. M. ORCID: 0000-0003-4094-8771, Weymann A. ORCID: 0000-0003-2966-6159, Pompeu M. B. O. Sá ORCID: 0000-0001-5356-2996, Zhigalov K. ORCID: 0000-0002-6440-3736.

*Corresponding author:
Soslan.Enginoev@gmail.com

**Received:** 23.10.2020
**Revision Received:** 23.11.2020
**Accepted:** 29.11.2020



**For citation:** Chernov I. I., Enginoev S. T., Komarov R. N., Bazylev V. V., Tarasov D. G., Kadyraliev K. B., Tungusov D. S., Arutyunyan A. V., Chragyan A. V., Batrakov P. A., Ismailbaev A. M., Tlisov B. M., Weymann A., Pompeu M. B. O. Sá, Zhigalov K. Short-term outcomes of Ozaki procedure: a multicenter study. *Russian Journal of Cardiology*. 2020;25(S4):4157. (In Russ.) doi:10.15829/1560-4071-2020-4157

Aortic valve (AV) replacement is the gold standard in the treatment of AV disease. There are cases that lead to a prosthesis-patient mismatch after AV replacement with both mechanical and biological prostheses, especially in patients with a small aortic annulus (AA) [1]. In 2011, Ozaki Sh, et al. [2] reported on their method of AV neo-cuspitization (AVNeo), ie, AV replacement with glutaraldehyde-treated autologous pericardium (Figure 1), using special templates (Figure 2). Considering that this technique is new and not many centers perform this operation, in 2019 we created the Russian AVNeo register to assess short- and long-term outcomess. Our first short-term results were published with 170 patients after AVNeo [3]; a little later, the results of surgical treatment of patients with small AA with good short-outcomes were reported [4]. In this study, we want to analyze the short-term outcomes of the register, to find out if AVNeo is an acceptable and reproducible technique.

## Material and methods

**Study design.** We performed the retro-prospective multicenter study of patients with AV disease selected for the Ozaki procedure. The study was approved by the local ethics committee of each participating institution.

**Echocardiographic data.** All patients underwent AV echocardiography before and after surgery. The maximum and mean AV gradient, the effective orifice area (EOA) (Figure 3), aortic regurgitation (AR) degree, including structural, Doppler, quantitative and qualitative parameters recommended by the American Society of Echocardiography [4], was assessed. For the classification of prosthesis-patient mismatch, guidelines for visualization of artificial heart valves were used [5].

**End points.** The primary endpoints were in-hospital mortality and hemodynamic echocardiographic after AVNeo. Secondary endpoints were postoperative complications: arrhythmias requiring permanent pacing; stroke; infectious complications; acute renal failure (requiring hemodialysis).

A total of 724 patients were included in the registry, who were operated on from 2015 to 2019 (Figure 4). Among the patients, as shown in Table 1, there were 395 (54,5%) men and 329 (45,5%) women. The median age of the patients was 63 (57-67) years. The minimum age was 10 years and the maximum age was 83 years (Figure 5). Most of the patients were over 60 years old.

The most common causes of AV dysfunction were aortic stenosis — 496 (68,6%) patients, AR — 44 (6%), aortic stenosis and AR — 184 (25,4%) patients. Infective endocarditis as a cause of AV disease was diagnosed in 23 (3.2%) patients. Manifested class III-IV heart failure occurred in 348 (48%) patients. Every fifth patient has a history of atrial fibrillation. The number of valves was estimated in 664 patients, and bicuspid AV was diagnosed in 106 (16%) patients. Preoperative echocardiography revealed the median AA of 21 (20-24) mm, systolic pulmonary artery pressure (SPAP) of 32 (25-40) mm Hg, SPAP >25 mm Hg in 521 (72%) patients, left ventricular ejection fraction of 60 (53-67)%. Patient baseline characteristics and risk factors are presented in Table 1.

**Statistical analysis.** Statistical processing was performed using the IBM SPSS Statistics 26 software package (Chicago, IL, USA). All quantitative variables were analyzed for the distribution type using the Kolmogorov-Smirnov test. Central tendencies and scattering of quantitative traits, having a normal distribution, were described as the mean and standard deviation (M±SD). In the case of a non-normal distribution, this was presented as median (interquartile range of the 25th and 75th percentiles) and Me (Q1-Q3). In most samples, a nonparametric distribution was revealed.

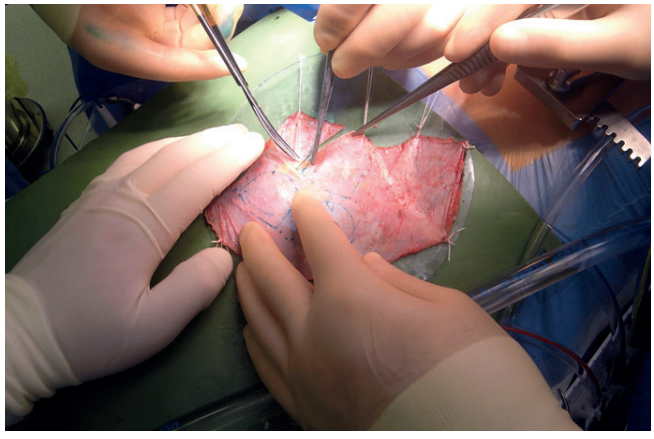

**Figure 1.** One of the Ozaki procedure stages: excision of the glutaraldehyde-treated pericardium for the AV replacement.


**Figure 2.** Template and sizers for Ozaki procedure (www.avneo.net).

**Table 1**

**Initial characteristics of the patients and risk factors**

| Demographic | AVNeo-724 |
|---|---|
| Age, years (Me (Q1-Q3)) | 63 (57-67) |
| Men/women, % | 54,5/45,5 |
| BMI, kg/m$^2$ (Me (Q1-Q3)) | 29,1 (25,5-32,9) |
| BSA, m$^2$ (M±SD) | 1,9±0,2 |
| NYHA class of HF (Me (Q1-Q3)) | 2 (2-3) |
| NYHA class III-IV HF, n (%) | 348 (48) |
| Comorbidity, n (%) | |
| Coronary artery disease | 353 (48,7) |
| Prior myocardial infarction | 75 (12,9) out of 583 available |
| Diabetes | 137 (19) |
| Chronic renal failure | 5 (0,7) |
| COPD | 36 (5) |
| Peripheral artery disease | 43 (6) |
| AF | 141 (19,5) |
| Prior open-heart surgery | 23 (3,2) |
| Percutaneous coronary interventions | 35 (5,4) из 643 |
| Pacemaker or ICD | 5 (0,9) из 582 |
| Indications for surgery, n (%) | |
| Severe AS | 496 (68,6) |
| Severe AR | 44 (6) |
| AS and AR | 184 (25,4) |
| IE | 23 (3,2) |
| Echocardiographic data | |
| LVEF, % (Me (Q1-Q3)) | 60 (53-67) |
| PASP, mm Hg (Me (Q1-Q3)) | 32 (25-40) |
| PASP >25 mm Hg, n (%) | 521 (71) |
| AA diameter (Me (Q1-Q3)) | 21 (20-24) |
| Aortic valve morphology, n (%) | |
| Bicuspid | 106 (16) из 664 |

**Abbreviations:** ICD — implantable cardioverter defibrillator, AR — aortic regurgitation, AS — aortic stenosis, CAD — coronary artery disease, BMI — body mass index, IE — infective endocarditis, BSA — body surface area, PASP — pulmonary artery systolic pressure, LVEF — left ventricular ejection fraction, AF — atrial fibrillation, COPD — chronic obstructive pulmonary disease, CRF — chronic renal failure, HF — heart failure, NYHA — New York Heart Association.

## Results

**Peri- and postoperative data.** In total, 314 (43,4%) patients underwent an isolated AVNeo, and the remaining 410 (56,6%) patients underwent combined interventions. Access to the heart was performed through a median sternotomy in 687 (95%) patients,

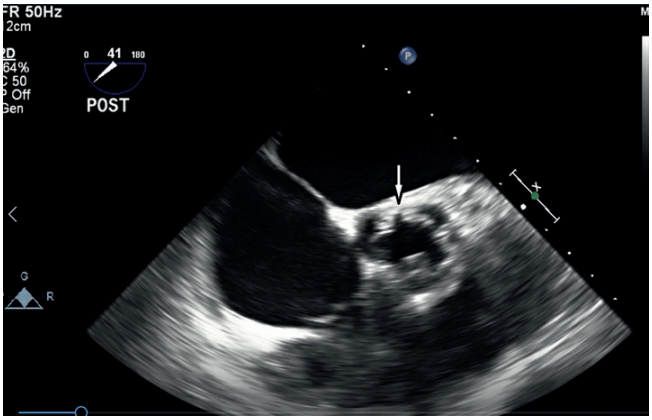


**Figure 3.** Aortic valve effective orifice area after Ozaki procedure.

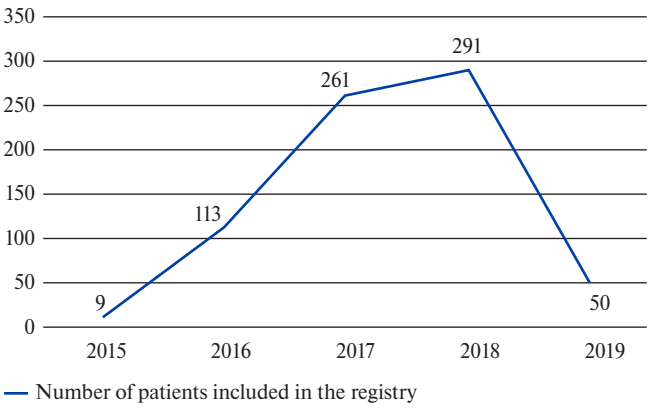


**Figure 4.** Number of patients included in the registry.

and in 37 (5%) patients through a mininotomy. The median extracorporeal circulation time was 130 (110-130) min, and the time of myocardial ischemia was 104 (86-122) min (Table 2). Inhospital mortality rate was 1,6% (Table 3). Thirteen (1,8%) patients received a pacemaker. Acute renal failure was diagnosed in 4 (0,5%) patients, stroke — in 3 (0,4%), sternal infection — in 10 (1,4%) (Table 3).

**Postoperative echocardiography.** The maximum and mean AV pressure gradients after surgery were 10,9 (7,4-14,8) mm Hg and 5,3 (3,5-7,3) mm Hg, respectively. AV EOA and EOA index after surgery were 3 (2,5-3,9) cm$^2$ and 1,6 (1,3-2) cm$^2$/m$^2$, respectively. One (0,1%) patient had a moderate patient-prosthesis mismatch and one (0,1%) had a pronounced one. After the AVNeo, 11 patients (1,5%) had moderate AR and 1 (0,1%) had severe AR. A patient with severe AR underwent AV replacement before discharge from the hospital (Table 4).

## Discussion

Autologous pericardium has been regularly used since the early cardiac surgery. In 1963, Bjoerk VO

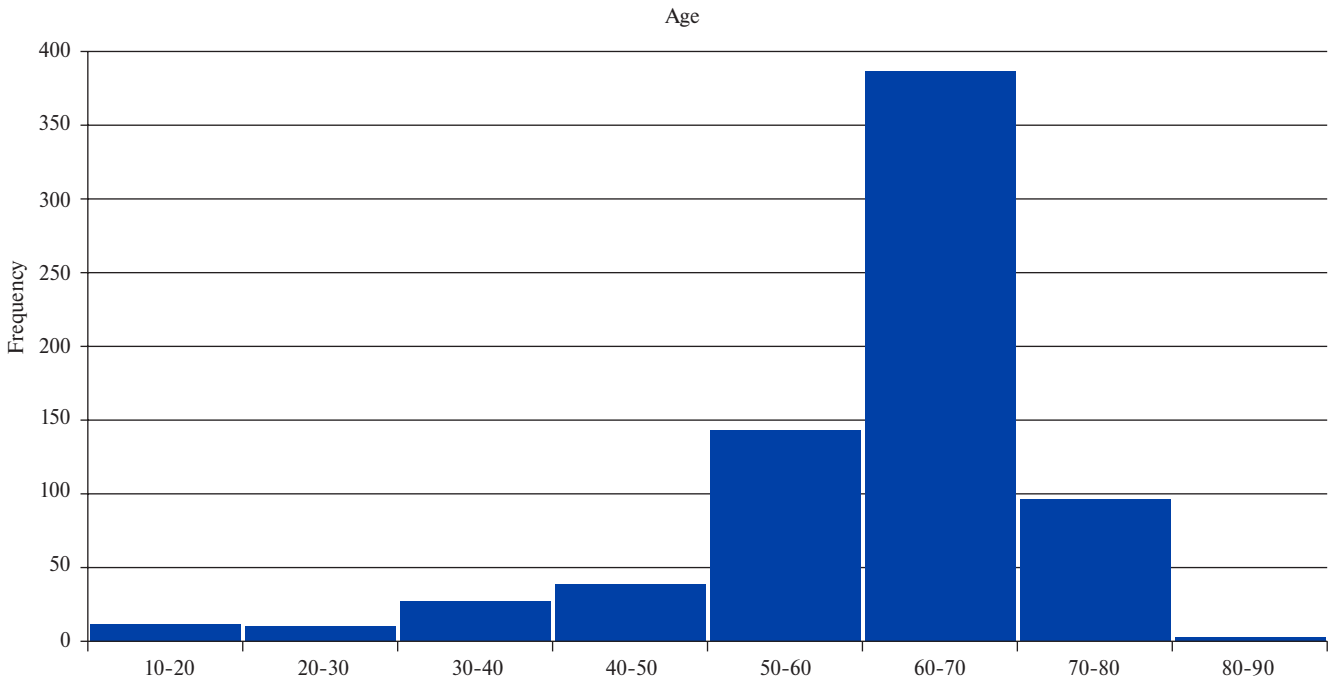


**Figure 5.** Age of patients included in the registry.

and Hultquist G [6] performed AV replacement by creating valves from the autologous pericardium. In 2011, Ozaki Sh, et al. [2] reported on their method of AV neo-cuspitization (AVNeo) with glutaraldehyde-treated autologous pericardium, using special templates treated. There is also a website (www.avneo.net), which contains useful information related to AVNeo. AVNeo can be considered an attractive option due to its low cost, universal indications without any restrictions related to the AA size and need for anticoagulation, as well as potentially excellent hemodynamic parameters after surgery. The most important results of our study were low mortality rate (1,6%) (Table 3). According to Fallon JM, et al. [8], after AV replacement with various prostheses, the frequency of moderate and pronounced patient-prosthesis mismatch occurs in 54% and 11% of cases, respectively. The same authors [7] have shown that any "patient-prosthesis" mismatch significantly reduces long-term survival and increases the rehospitalization rate for both heart failure and reoperations. According to our data, only in 0,1% of cases there was a moderate and pronounced patient-prosthesis mismatch (Table 4). The multicenter study [4] from our registry has been published: AVNeo (Ozaki procedure) in patients with AA ⩽21 mm. The mean AA diameter was 19,8±1,1 mm. The maximum and mean pressure gradients after surgery were 11,8±5,9 mm Hg and 7,3±3,5 mm Hg, respectively. EOA and EOA index averaged 2,5±0,4 $cm^2$ and 1,3±0,3 $cm^2/m^2$ after surgery, respectively. According to our registry, the AA diameter before surgery was measured in 458 patients, of which 256 (56%) patients had AA ⩽21 mm. Rosseikin EV, et al. [8] compared mininotomy and complete median sternotomy during Ozaki procedure. The duration of the operation and cardiopulmonary bypass was longer in the mininotomy group, but the groups

**Table 2**

**Intraoperative parameters**

| Parameters | AVNeo |
|---|---|
| Operation duration, min (Me (Q1-Q3)) | 279 (243-327) |
| Cardiopulmonary bypass time, min (Me (Q1-Q3)) | 130 (110-130) |
| Myocardial ischemic time, min (Me (Q1-Q3)) | 104 (86-122) |
| Median sternotomy, n (%) | 687 (95) |
| Mininotomy, n (%) | 37 (5) |
| Isolated intervention on AV, n (%) | 314 (43,4) |
| Combined interventions, n (%) | 410 (56,6) |
| CABG | 207 (28,6) |
| Ascending aorta replacement | 184 (25,4) |
| Carotid endaterectomy | 12(1,6) |
| Mitral valve surgery | 70 (9,6) |
| Tricuspid valve surgery | 29 (4) |

**Abbreviations:** AV — aortic valve, CABG — coronary artery bypass grafting.

**Table 3**

**Postoperative results**

| Parameters | AVNeo-724 |
|---|---|
| In-hospital mortality, n (%) | 12 (1,6) |
| Pericardiocentesis, n (%) | 8 (1,1) |
| Permanent pacemaker implantation, n (%) | 13 (1,8) |
| Stroke, n (%) | 3 (0,4) |
| AV IE, n (%) | 0 (0) |
| Superficial and deep wound infection, n (%) | 10 (1,4) |
| ARF, n (%) | 4 (0,5) |
| Mechanical ventilation time, h (Me (Q1-Q3)) | 12 (9-15) |
| Hospital stay, days (Me (Q1-Q3)) | 13 (10-16) |

**Abbreviations:** AV — aortic valve, IE — infective endocarditis, ARF — acute renal failure.

**Table 4**

**Postoperative echocardiographic parameters**

| Parameters | AVNeo-724 |
|---|---|
| Peak AV gradient, mm Hg (Me (Q1-Q3)) | 10,9 (7,4-14,8) |
| Mean AV gradient, mm Hg (Me (Q1-Q3)) | 5,3 (3,5-7,3) |
| Grade II-III AR, n (%) | 12 (1,6) |
| AV EOA, $cm^2$ (Me (Q1-Q3)) | 3 (2,5-3,9) |
| AV EOA index, $cm^2/m^2$ (Me (Q1-Q3)) | 1,6 (1,3-2) |
| Moderate patient-prosthesis mismatch, n (%) | 1 (0,1) |
| Pronounced patient-prosthesis mismatch, n (%) | 1 (0,1) |
| LVEF after surgery, % (Me (Q1-Q3)) | 60 (52-68) |

**Abbreviations:** AV — aortic valve, AR — aortic regurgitation, EOA — effective orifice area, LVEF — left ventricular ejection fraction.

did not differ in myocardial ischemic time. There were also no significant differences in other endpoints. In our study, mininotomy was performed in 5% of cases. Several studies [9, 10] have reported excellent results with Ozaki procedure in children. Currently, our registry includes 12 (1,6%) patients under 18 years of age. Shigeyuki Ozaki [11] over 12 years from April 2007 to March 2019 operated >1100 patients. The mean age of the patients was 67,7±14,9 years. In general, the long-term survival rate within 12 years was 84,6%. Freedom from reoperation rate was 95,8%.

**Study limitations.** The main limitation of this study was the lack of medium- and long-term outcomes. We plan to monitor patients to obtain long-term results.

## Conclusion

The Ozaki procedure is feasible and reproducible, has good short-term outcomes with excellent hemodynamic parameters. Further research is needed to assess long-term results.

**Relationships and Activities:** none.

## References


1. Sá MPBO, de Carvalho MMB, Sobral Filho DC, et al. Surgical aortic valve replacement and patient-prosthesis mismatch: a meta-analysis of 108 182 patients. Eur J Cardio-Thoracic Surg. 2019;56:44-54. doi:10.1093/ejcts/ezy466.
2. Ozaki S, Kawase I, Yamashita H, et al. Aortic valve reconstruction using self-developed aortic valve plasty system in aortic valve disease. Interact Cardiovasc Thorac Surg. 2011;12:550-3. doi:10.1510/icvts.2010.253682.
3. Arutyunyan V, Chernov I, Komarov R, et al. Immediate outcomes of aortic valve neocuspidization with glutaraldehyde-treated autologous pericardium: A multicenter study. Brazilian J Cardiovasc Surg. 2020;35(3):241-248. doi:10.21470/1678-9741-2020-0019.
4. Sá MPBO, Chernov I, Marchenko A, et al. Aortic Valve Neocuspidization (Ozaki Procedure) in Patients with Small Aortic Annulus (⩽21 mm): A Multicenter Study. Struct Hear. 2020:1-7. doi:10.1080/24748706.2020.1792595.
5. Lancellotti P, Pibarot P, Chambers J, et al. Recommendations for the imaging assessment of prosthetic heart valves: a report from the European Association of Cardiovascular Imaging endorsed by the Chinese Society of Echocardiography, the Inter-American Society of Echocardiography, and the Brazilian. Eur Hear J — Cardiovasc Imaging. 2016;17:589-90. doi:10.1093/ehjci/jew025.
6. Bjoerk Vo, Hultquist G. Teflon and pericardial aortic valve prostheses. J Thorac Cardiovasc Surg. 1964;47:693-701.
7. Fallon JM, DeSimone JP, Brennan JM, et al. The Incidence and Consequence of Prosthesis-Patient Mismatch After Surgical Aortic Valve Replacement. Ann Thorac Surg. 2018;106:14-22. doi:10.1016/j.athoracsur.2018.01.090.
8. Rosseikin EV, Kobzev EE, Bazylev VV. Minimally invasive Ozaki technique. Angiol Sosud Khir. 2019;25(3):142-55. (In Russ.) doi:10.33529/ANGI02019319.
9. Wiggins LM, Mimic B, Issitt R, et al. The utility of aortic valve leaflet reconstruction techniques in children and young adults. J Thorac Cardiovasc Surg. 2020;159:2369-78. doi:10.1016/j.jtcvs.2019.09.176.
10. Baird CW, Sefton B, Chávez M, et al. Congenital Aortic and Truncal Valve Reconstruction Utilizing the Ozaki Technique: Short term Clinical Results. J Thorac Cardiovasc Surg. 2020. doi:10.1016/j.jtcvs.2020.01.087.
11. Ozaki S. Ozaki Procedure: 1,100 patients with up to 12 years of follow-up. Turkish J Thorac Cardiovasc Surg. 2019;27(4):454. doi:10.5606/tgkdc.dergisi.2019.01904.

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-4231

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

# SIRENA score for in-hospital mortality risk assessment in patients with acute pulmonary embolism

Ehrlich A. D.[1,2], Barbarash O. L.[3], Burns S. A.[3], Schmidt E. A.[3], Duplyakov D. V.[4,5]

**Aim.** To create a new prognostic scale for in-hospital mortality risk assessment in patients with pulmonary embolism (PE).

**Material and methods.** The study was carried out on the basis of Russian register of acute pulmonary embolism SIRENA.

**Results.** Based on the Russian register of acute pulmonary embolism SIRENA (n=609; women — 50,7%; mean age — 63,0±14,5 years), independent predictors of in-hospital death were determined: left ventricular ejection fraction <40%, immobilization in the last 12 months, creatinine clearance <50 ml/min, syncope as a PE symptom, cyanosis at admission. Each of these factors with a value of 1 became a component of the novel SIRENA score. At the score of 0, 1, 2, 3 and more, in-hospital mortality was 3,1%, 7,0%, 16,7% and 40,0%, respectively. Mortality with a SIRENA score <2 (low risk) was 5,0%, and with a score ≥2 (high risk) — 24,3% (relative risk (RR), 4,87; 95% confidence interval (CI), 2,97-7,98; p<0,001). Predictive sensitivity and specificity for in-hospital mortality were 62,7% and 78,5%, respectively. The area under the ROC curve was 0,76 (95% CI, 0,69-0,83), which did not differ significantly from sPESI score — 0,73 (95% CI, 0,66-0,80). With a high risk for sPESI and SIRENA, the mortality was 27,1%, which was significantly higher compared to patients with a high risk only for sPESI — 13,9% (RR, 1,94; 95% CI, 1,36-2,82; p<0,001), but did not differ significantly compared with patients at high risk according to SIRENA score — 24,3% (RR, 1,11; 95% CI, 0,75-1,65; p=0,78).

**Conclusion.** Based on the Russian register of acute pulmonary embolism, the SIRENA score was developed, which has a high accuracy (sensitivity, 62,7%; specificity, 78,5%) in predicting in-hospital mortality.

**Keywords:** pulmonary embolism, register, SIRENA score, outcomes, risk stratification.

**Relationships and Activities:** none.

[1]Pirogov Russian National Research Medical University, Moscow; [2]Bauman City Clinical Hospital № 29, Moscow; [3]Research Institute for Complex Issues of Cardiovascular Diseases, Kemerovo; [4]Samara State Medical University, Samara; [5]V. P. Polyakov Samara Regional Clinical Cardiology Dispensary, Samara, Russia.

Ehrlich A. D.* ORCID: 0000-00003-0607-2673, Barbarash O. L. ORCID: 0000-0002-4642-3610, Burns S. A. ORCID: 0000-0003-1002-1895, Schmidt E. A. ORCID: 0000-0003-3215-2140, Duplyakov D. V. ORCID: 0000-0002-6453-2976.

*Corresponding author:
alexeyerlikh@gmail.com

**Received:** 23.11.2020
**Revision Received:** 06.12.2020
**Accepted:** 15.12.2020



**For citation:** Ehrlich A. D., Barbarash O. L., Burns S. A., Schmidt E. A., Duplyakov D. V. SIRENA score for in-hospital mortality risk assessment in patients with acute pulmonary embolism. *Russian Journal of Cardiology*. 2020;25(S4):4231. (In Russ.) doi:10.15829/1560-4071-2020-4231

Modern treatment of pulmonary embolism (PE) according to the European Society of Cardiology guidelines [1] involves risk stratification. The currently used risk stratification is based on clinical manifestations of the disease, echocardiographic data, assessment of myocardial necrosis markers, and also on the assessing combined risk using the pulmonary embolism severity index (PESI) or its simplified version (sPESI) [2]. At the same time, the practical use of the PESI or sPESI scores shows that some important factors, undoubtedly associated with the prognosis, remain outside this index, which can reduce the accuracy of risk stratification.

The aim was to create a new prognostic scale for in-hospital mortality risk assessment in patients with PE.

## Material and methods

The study was based on the Russian register of acute pulmonary embolism SIRENA. The peculiarities of register organization, inclusion and exclusion criteria, as well as the main results are described in detail in previous publications [3]. Inclusion in the register was carried out sequentially for 12 months from April 2018 to April 2019 in 20 hospitals in 15 cities of Russia. The creation of a predictive scale was not the primary aim of the register and the analysis was performed retrospectively.

**Statistical analysis.** Independent predictors of in-hospital mortality became components of the novel prognostic score. The identification of these factors was carried out by univariate and multivariate regression analysis. Since the register protocol did not provide assessing the full PESI score, the predictive value of the new score was compared with the sPESI score. Comparison of prognostic scores was carried out by assessing the areas under the ROC curves.

## Results

**Characteristics of patients.** The register included 609 patients (women — 50,7%, mean age — 63,0±14,5 years, minimum-maximum — 19-94 years). In the past, PE was in 56 (9,2%) patients, deep vein thrombosis — in 118 (19,4%) patients. During the 12 months preceding hospitalization, 95 patients (15,6%) underwent surgery, 77 (12,6%) had a long period of immobilization, 25 (4,1%) had limb fractures, 18 (3,0%) had myocardial infarction, 19 (3,1%) took oral contraceptives.

One hundred four patients (17,1%) had a history of cancer, of whom 36 (34,6%) had distant metastases, and 34 (32,7%) patients received treatment for an active cancer at the time of PE.

One hundred forty-two patients (23,3%) had a history of heart failure, 116 (19,0%) — atrial fibrillation, 400 (65,7%) — hypertension, 90 (15,2%) — diabetes, 55 (9,0%) — chronic kidney disease, 54 (8,9%) — chronic obstructive pulmonary disease.

When included in the register, the proportion of patients with systolic blood pressure (BP) <100 mm Hg was 11,8%, the proportion of patients with tachypnea (respiratory rate >30 bpm) — 2,8%, the proportion of patients with tachycardia (heart rate >110 bpm) — 17,7%, the proportion of patients with reduced oxygen saturation ($SpO_2$ <90%) — 20,2%.

Cyanosis with PE signs was detected in 176 (30,2%) patients. Lower limb asymmetry and edema was observed in 217 (35,6%) and 223 (36,6%) patients, respectively.

Shortness of breath was the most common manifestation of PE. Five hundred forty (90,4%) patients complained about it. One hundred seventy-eight patients (29,8%) had chest pain as the main symptom, and 179 (30,0%) had syncope.

The sPESI score was assessed in 586 (96,2%) patients, while a low risk of death (sPESI score of 0) was found in 205 (33,7%) patients.

Thrombolytic therapy during hospitalization was carried out in 152 patients with PE (25,0%). Five hundred sixty patients (92,0%) received anticoagulant therapy in the hospital, while parenteral anticoagulants were used in 474 (77,8%) patients and oral anticoagulants — 457 (75,0%) patients.

During the hospitalization (media, 11 days; 1-3 quartiles, 7-15 days), 60 patients died. Mortality rate was 9,9%.

**Creation of a predictive score.** Univariate regression identified 52 factors associated with death during hospitalization, which were studied using multivariate regression. The results of this analysis identified independent predictors of in-hospital death (Table 1).

Subsequently, to create a prognostic score, it was decided to consider each of the independent predictors of death as one of the components of a novel score. It was decided to compare the accuracy of two possible models: the more complex (when each score component was assigned a value approximately equal to its odds ratio) and the simplified (when each score component was assigned a value of 1). Areas under the ROC curve values for a complex and simplified model did not differ significantly (Figure 1). Therefore, for practice it was advisable to use a simplified model (SIRENA score — Table 2).

**Predictive value of the SIRENA score.** The relationship between various values of the SIRENA score and in-hospital mortality rate is shown in Figure 2, It can be seen that increased SIRENA score is associated with increased in-hospital mortality rate.

**Table 1**

**Independent predictors of in-hospital mortality in patients included in the SIRENA register**

| Factors | OR | 95% CI | P |
|---|---|---|---|
| Left ventricular ejection fraction <40% | 5,734 | 1,627-20,205 | 0,007 |
| Immobilization in the previous 12 months | 4,999 | 1,523-16,406 | 0,008 |
| Creatinine clearance <50 ml/min | 4,833 | 1,793-13,026 | 0,002 |
| Syncope as a pulmonary embolism symptom | 2,833 | 1,043-7,697 | 0,041 |
| Cyanosis on admission | 2,330 | 1,106-4,911 | 0,026 |

**Note:** creatinine clearance calculated using the Cockcroft-Gault equation.
**Abbreviations:** CI — confidence interval, OR — odds ratio, PE — pulmonary embolism.

Due to the small number of patients with SIRENA score of 4 and 5, in Figure 2, data on patients with score ⩾3 are combined. At the same time, the difference between patients with 0 points and those with 1 point was insignificant (relative risk (RR), 2,24; 95% confidence interval (CI), 0,93-5,39), while between patients with 1 and 2 points and between patients with 2 and ⩾3 points, the differences were significant (RR, 2,39; 95% CI, 1,24-4,59 and RR, 2,40; 95% CI, 1,38-4,16, respectively).

The ROC-curve value for the SIRENA score in relation to in-hospital mortality was 0,76 (95% CI, 0,69-0,83). The predictive sensitivity and specificity for high risk on the SIRENA score were 62,7% and 78,5%, respectively.

According to the ROC-curve, a cut-off point was found for dividing the SIRENA score into the low risk (0-1 points) and high risk (⩾2 points) categories for death during hospitalization. An almost five-fold significant difference in in-hospital mortality rate between high and low risk values on the SIRENA score was shown (RR, 4,87; 95% CI, 2,97-7,98; P<0,001 (Figure 3).

**Comparison of the predictive value of SIRENA and sPESI scores.** In the study group, among 205 patients with low risk on the sPESI score (0), 7 people died during hospitalization (3,4%), and among 380 patients with high risk (⩾1), 53 people died (13,9%) (RR, 4,09; 95% CI, 1,89-8,82; p<0,001). The proportion of patients whose risks on the SIRENA and sPESI scores coincided (i.e., were either high or low on both scores) was 55,1%. The area under the ROC-curve for the sPESI score for in-hospital death was 0,73 (95% CI, 0,66-0,80). The difference with the similar parameter of the SIRENA score was insignificant (Figure 4).

In patients with high risk on both scores (sPESI+SIRENA), the mortality rate during hospitalization was 27,1%, which was significantly higher compared with patients at high risk only for sPESI —

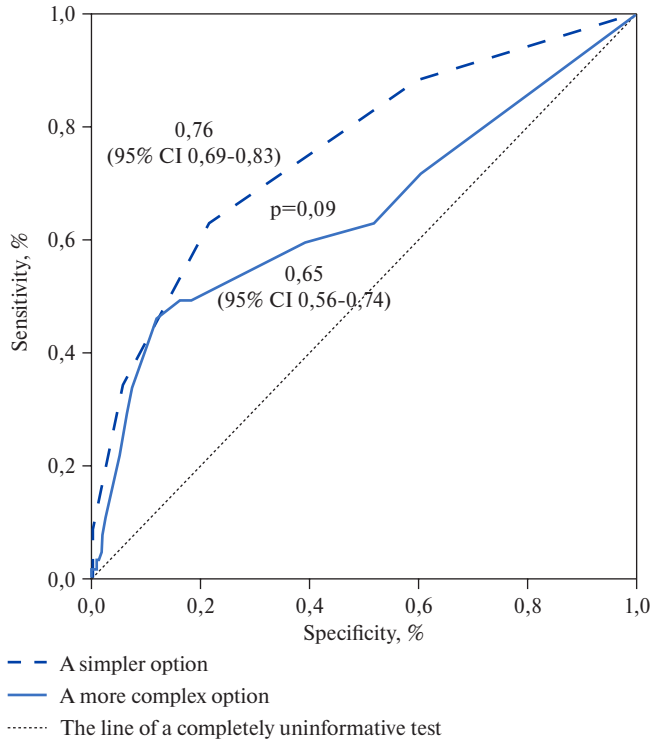


**Figure 1.** Areas under the ROC curves for the simplified and complex versions of the SIRENA score.
**Abbreviation:** CI — confidence interval.

**Table 2**

**SIRENA* score**

| Factors | Points |
|---|---|
| Left ventricular ejection fraction <40% | 1 |
| Immobilization in the previous 12 months | 1 |
| Creatinine clearance <50 ml/min | 1 |
| Syncope as a pulmonary embolism symptom | 1 |
| Cyanosis on admission | 1 |

**Note:** * — total score is summed up.
**Abbreviation:** PE — pulmonary embolism.

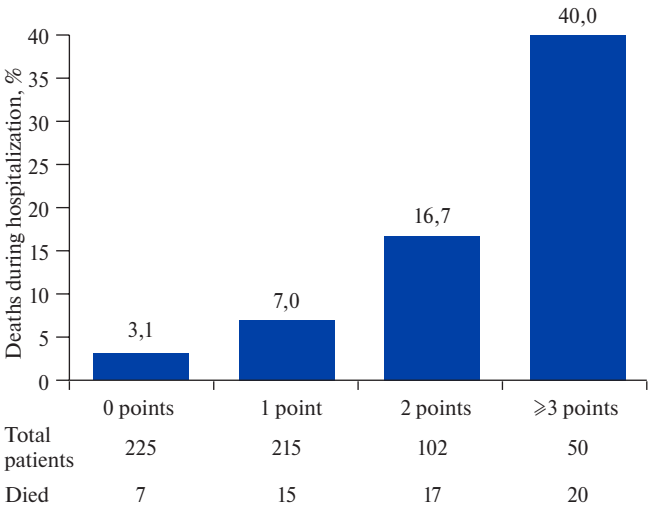


**Figure 2.** Relationship between different values of the SIRENA score and in-hospital mortality rate.

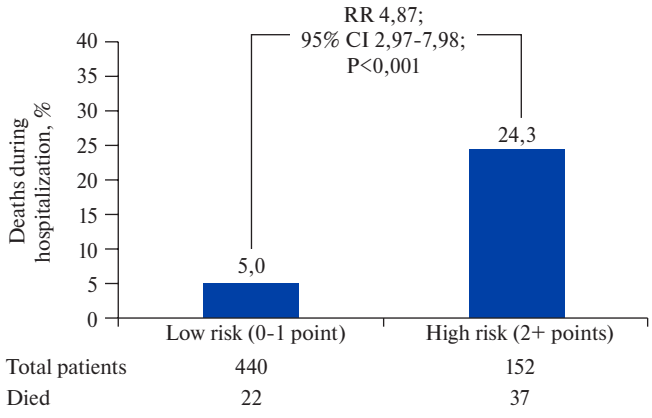


**Figure 3.** In-hospital mortality rate, depending on the high or low risk on the SIRENA score.
**Abbreviations:** CI — confidence interval, RR — relative risk.

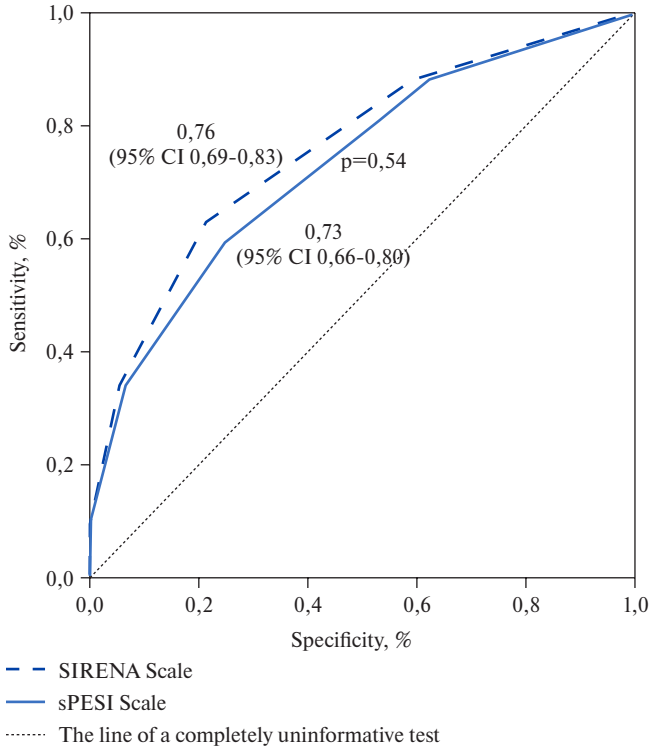


**Figure 4.** Areas under the ROC curves for in-hospital mortality for the SIRENA and sPESI scores.
**Abbreviation:** CI — confidence interval.

13,9% (RR, 1,94; 95% CI, 1,36-2,82; p<0,001), but did not differ significantly in comparison with patients with high risk on the SIRENA score — 24,3% (RR, 1,11; 95% CI, 0,75-1, 65; p=0,78) (Figure 5).

## Discussion

In the presented study, an attempt was made to create a new prognostic score to determine the risk of in-hospital mortality rate due to PE. The problem of predicting short-term outcomes in pulmonary embolism is quite relevant, since understanding the degree of risk is not only empirical knowledge, but also an important link in determining the management of patients.

Currently, the generally accepted prognostic model is the PESI and sPESI scores, which are the most accurate in comparison with other prognostic scores [2, 4-6]. At the same time, it is quite obvious that the sPESI score is not ideal and universal, since all possible factors of an unfavorable prognosis cannot be included in it (as in any other score). Therefore, the search for new opportunities to improve prognosis in patients with PE is of great clinical importance.

The data obtained in the SIRENA register is an important source of information on the management of patients with PE in Russian hospitals. But the prognostic score based on these results may become applicable not only in Russia, but also in other countries, since the main characteristics of the patients included in the SIRENA register were quite typical.

The novel prognostic score was created in the traditional way, by identifying independent predictors of deaths during hospitalization. It is interesting to note that most of the identified factors, on the one hand, can quite traditionally be associated with a poor prognosis in patients with cardiovascular diseases (reduced left ventricular ejection fraction, syncope, cyanosis, renal dysfunction). On the other hand, it should be noted that they do not directly coincide with risk factors in sPESI score (age, history of cancer or cardiopulmonary disease, low blood pressure, low blood oxygen level, tachycardia). The coincidences between some components of the

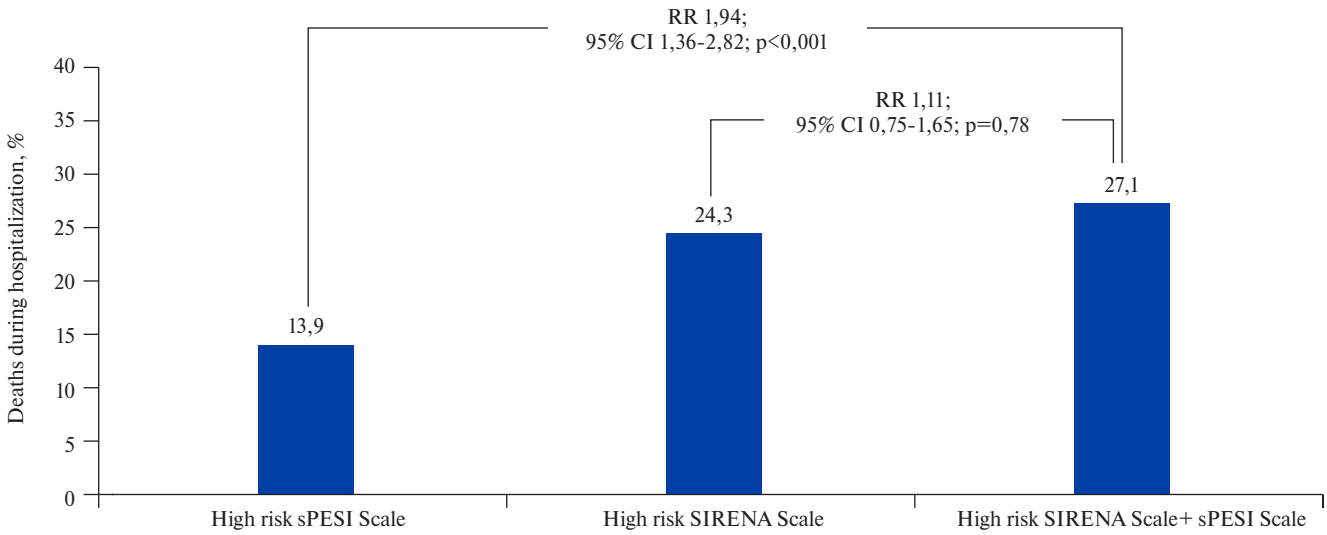


**Figure 5.** In-hospital mortality rate in patients at high risk according to the sPESI, SIRENA score and their combination.
**Abbreviations:** CI — confidence interval, RR — relative risk.

SIRENA and sPESI scores are only indirect (reduced blood oxygen level and cyanosis; cardiopulmonary disease and low left ventricular ejection fraction). This is probably why, in the studied group, the coincidence of death risk indicators between the scores was found only in 55% of patients, and the combination of high risk on both scores was associated with a significantly higher risk of death compared to patients who had a high risk on only one score.

An important prognostic component of the SIRENA score is syncope as a PE symptom. This is a well-known factor of poor prognosis, indirectly reflecting both the volume of the pulmonary artery lesion and right ventricular volume overload [7], as well as early in-hospital death [8]. In addition, syncope is an important diagnostic marker for PE. At the same time, such an obvious risk factor as low blood pressure was not selected in the SIRENA score. At first glance, this may seem like a disadvantage of the SIRENA score, but in fact it is advantage. After all, low blood pressure in PE is almost always an independent, separate factor of very high risk, and the presence of low blood pressure often does not require any other risk assessment. The fact that the blood pressure value is not taken into account in the SIRENA score gives it the potential to be more in demand in clinical practice.

In general, the combination of independent risk factors made up the SIRENA score even without using the numerical odds ratio values. Each of the score components has the same quantity, which is undoubtedly convenient for practical use. A specially conducted comparative analysis showed no advantages of a more complex score version.

The analysis of the predictive value of SIRENA score showed high sensitivity and specificity in predicting in-hospital mortality: 62,7% and 78,5%, respectively. At the same time, the area under the ROC-curve for the SIRENA score was quite high and practically coincided with this parameter in the sPESI score. Comparison of the SIRENA and sPESI scores showed that adding the SIRENA score to sPESI significantly increases the effectiveness of predicting a fatal outcome, while, on the contrary, adding the sPESI to the SIRENA score not increase its predictive accuracy. This may indicate a slightly greater practical value of the SIRENA score.

**Study limitations.** The creation of a predictive score was not the primary aim of the SIRENA register.

The assumption of a high predictive value of the novel score and its comparison with the sPESI should be validated with independent samples, preferably with a large number of patients.

Direct comparison of the SIRENA and sPESI scores may be limited, since the sPESI score was studied for 30-day outcomes, while the SIRENA score was studied for in-hospital events so far.

For further use of the SIRENA score, it is necessary to understand its predictive value for more distant outcomes (not just in-hospital outcomes), and in addition, determine the place of the score in decision-making on patient treatment.

## Conclusion

Based on the Russian register of acute pulmonary embolism, the SIRENA score was developed, which has a high accuracy (sensitivity, 62,7%; specificity, 78,5%) in predicting in-hospital mortality.

The novel SIRENA score includes the following components: 1) left ventricular ejection fraction <40%; 2) immobilization in the previous 12 months; 3) creatinine clearance <50 ml/min; 4) syncope as a PE symptom; 5) cyanosis upon admission. The new SIRENA score is not inferior in predictive accuracy to the sPESI score recommended by the European Society of Cardiology guidelines, and the addition of the SIRENA score to the sPESI increases the predictive accuracy.

**Relationships and Activities:** none.

## References

1. Konstantinides SV, Meyer G, Becattini C, et al. ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41(4):543-603. doi:10.1093/eurheartj/ehz405.
2. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med. 2005;172(8):1041. doi:10.1164/rccm.200506-862OC.
3. Erlikh AD, Atakanova AN, Neeshpapa AG, et al. Russian register of acute pulmonary embolism SIRENA: characteristics of patients and in-hospital treatment. Russian Journal of Cardiology. 2020;25(10):3849. (In Russ.) doi:10.15829/1560-4071-2020-3849.
4. Jiménez D, Aujesky D, Moores L, et al. RIETE Investigators. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010;170(15):1383-9. doi:10.1001/archinternmed.2010.199.
5. Jara-Palomares L, Alfonso M, Maestre A, et al. RIETE investigators. Comparison of seven prognostic tools to identify low-risk pulmonary embolism in patients aged <50 years. Scientific Reports 2019;9(1):20064. doi:10.1038/s41598-019-55213-8.
6. Zhou XY, Ben SQ, Chen HL, Ni SS. The prognostic value of pulmonary embolism severity index in acute pulmonary embolism: a meta-analysis. Respir Res. 2012;13(1):111. doi:10.1186/1465-9921-13-111.
7. Altınsoy B, Erboy F, Tanrıverdi H, et al. Syncope as a presentation of acute pulmonary embolism. Ther Clin Risk Manag. 2016;12:1023-8. doi:10.2147/TCRM.S105722.
8. Barco S, Ende-Verhaar YM, Becattini C, et al. Differential impact of syncope on the prognosis of patients with acute pulmonary embolism: a systematic review and meta-analysis. Eur Heart J. 2018;39(47):4186-95. doi:10.1093/eurheartj/ehy631.

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-4219

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

# Change of concentration of biochemical markers of dysfunction of endothelium at intake of inhibitors of tyrosinekinase of I and II generations at patients with a chronic myeloid leukemia as risk factor of development of cardiovascular complications

Naumova K. V.[1], Davydkin I. L.[1], Lomaia E. G.[2], Stepanova T. Yu.[1], Kuzmina T. P.[1], Zammoyeva D. B.[2]

**Aim.** Identification of interrelation of endothelial dysfunction at patients with chronic myeloid leukemia (CML), the accepting inhibitors tyrosine of kinases (TKI) I and the II generations (TKI1 and TKI2 respectively), and development of arterial hypertension.

**Material and methods.** Examination of 137 patients with CML in the chronic phase (CP) is conducted, the median of age — 47 years. 24 of them were with for the first time the verified diagnosis of CML and earlier did not accept TKI, they have made group of control. Other patients accepted TKI: 39 patients — imatinib 400 mg/day, 36 — dasatinib 100 mg/day, 38 — nilotinib 800 mg/day) more than 6 months. In biochemical analysis of blood indicators of lipidic range were defined. Level detection of ET-1 and VEGF was made by means of enzyme immunoassay. To all patients measurement of the heart rate (HR) and the arterial blood pressure (ABP) on both hands at an interval of 2 minutes from previous was once taken.

**Results.** In group of patients from CML accepting nilotinib authentically significant increase in levels of systolic and diastolic ABP ($p<0,001$) in comparison with group of control, with group of the patients accepting imatinib and dasatinib is noted. The most serious changes of lipidic range are noted at the patients accepting nilotinib. In all groups statistically significant increase in level of C-reactive protein, fibrinogen, homocysteine, endothelin-1 and VEGF in comparison with group of control is revealed. The most expressed changes are found in group of the patients accepting nilotinib, values of parameters of C-reactive protein, fibrinogen, homocysteine, endothelin-1 and VEGF are changed authentically ($p<0,001$) and statistically significantly differ in comparison with group for the first time of the revealed patients with CML and groups of reception of imatinib and dazatinib.

**Conclusion.** As a result of the conducted research endothelium variation of a function at patients from CML accepting TKI1 and TKI2 is revealed. The above-stated indicators can be used as additional diagnostic criteria for assessment of risk of development of arterial hypertension in patients with CML at reception of TKI.

**Keywords:** chronic myeloid leukemia, cardiotoxicity, endothelial dysfunction.

**Relationships and Activities:** none.

[1]Samara State Medical University, Samara; [2]Almazov National medical research center of the Ministry of Health of the Russian Federation, St. Petersburg, Russia.

Naumova K. V.* — MD, assistant, Chair of Hospital Therapy with a Course in Outpatient Treatment and Transfusion Medicine, ORCID: 0000-0003-3170-1881, Davydkin I. L. — MD, PhD, Professor, Head of Chair of Hospital Therapy with a Course in Outpatient Treatment and Transfusion Medicine, Director of Research and Development Institute of Hematology, Transfusion and Intensive Care, ORCID: 0000-0003-0645-7645, Lomaia E. G. — MD, PhD, Associate Professor, Leading Researcher of the Scientific and Research Laboratory of Oncohematology, ORCID: 0000-0003-3290-7961, Stepanova T. Yu. — MD, PhD, Associate Professor, Chair of Hospital Therapy with a Course in Outpatient Treatment and Transfusion Medicine, ORCID: 0000-0002-3477-1140, Kuzmina T. P. — postgraduate, assistant, Chair of Hospital Therapy with a Course in Outpatient Treatment and Transfusion Medicine, ORCID: 0000-0002-5378-5687, Zammoyeva D. B. — MD, hematologist at Oncology and Hematology Department, ORCID: 0000-0002-0284-8895.

*Corresponding author: senechka.naumova@rambler.ru

**Received:** 03.12.2020
**Revision Received:** 08.12.2020
**Accepted:** 15.12.2020

**For citation:** Naumova K. V., Davydkin I. L., Lomaia E. G., Stepanova T. Yu., Kuzmina T. P., Zammoyeva D. B. Change of concentration of biochemical markers of dysfunction of endothelium at intake of inhibitors of tyrosinekinase of I and II generations at patients with a chronic myeloid leukemia as risk factor of development of cardiovascular complications. *Russian Journal of Cardiology*. 2020;25(S4):4219. (In Russ.) doi:10.15829/1560-4071-2020-4219

Within the last decades there was progress in treatment of oncological pathology, the amount of drugs for anticarcinogenic therapy which are aimed at the alarm ways connected with cellular proliferation has increased (for example, inhibitors of tyrosinekinase (TKI)). Thanks to modern chemotherapy, the considerable results concerning duration and quality of life of patients [1] are achieved. However, modern anticarcinogenic therapy leads to serious side effects, in particular from cardiovascular system — to cardiotoxicity, which can be shown by development of arterial hypertension, disturbances of rhythm, heart failure, changes on ECG, dysfunction of left ventricle [2-5].

The chronic myeloid leukemia (CML) represents the myeloproliferative new growth caused by activation of oncogene of BCR-ABL1 [6]. Frequency of CML increases with age and by estimates in the Russian Federation is 0,7 cases on 100 people [7]. TKI are basis of treatment of CML [8]. In the first line and the subsequent therapy use imatinib, nilotinib and dasatinib; bosutinib is shown for patients with resistance or intolerance to the previous therapy of TKI. Ponatinib is used at patients with mutation of T315I or at other mutations for which there is no other therapy of TKI [9]. Significant progress in development of TKI has led to increase in life expectancy and to improvement of quality of life of patients [1]. However, an important place is given to the development of adverse events (AEs) and comorbidity during therapy.

Safety of therapy is important for sick CML at constant uses of TKI that it is connected with requirement of continuous treatment [10]. In spite of the fact that the majority of AEs initially arise at early stage of treatment, emergence of some adverse events including clinically significant cardiovascular and metabolic, it is possible months or even years later has begun therapies [11]. The median of age, sick CML in the Russian Federation makes 49 years therefore these patients can have associated diseases and risk factors which increase probability of the mediated toxicity TKI during prolonged treatment [12].

Dysfunction of endothelium to which leads oxidizing stress and inflammation is the pathophysiological cornerstone of development of the majority of cardiovascular diseases: the permeability of vascular wall for lipoproteins changes, there is activation of molecules of adhesion of leukocytes and moving of leukocytes to arterial wall [13]. Reduction of products and/or availability of nitrogen oxide (NO) and also imbalance between the vasodilators and vasoconstrictors developed by endothelium is characteristic of development of endothelial dysfunction [14]. On model of endothelium of rats, it is shown that increase in NO, endothelin-1 (ET-1) and other inflammatory markers can be induced by hyperhomocysteinemia [15]. Homocysteine is minor product of numerous biological processes in human body and, being raised, can be connected with heavy atherosclerosis and thrombotic occlusion [16]. ET-1 is the most powerful vasoconstrictor identified today, making extremely strong reduction of number of blood vessels of mammals of *in vitro*, including arteries and veins of the person [17]. The vascular endothelial growth factor (VEGF) has pro-angiogenic activity and also increases permeability of vessels and is necessary in human body for forming and maintenance of endothelial permeability [18].

However, the problem of diagnostics of endothelial dysfunction as predictor of arterial hypertension at oncohematological patients remains poorly studied that is of special interest for scientists.

Purpose of the study. To reveal interrelation of endothelial dysfunction at patients with CML, the accepting TKI I and the II generations, and development of arterial hypertension.

## Material and methods

Examination of 137 patients with CML in chronic phase aged from 30 till 50 years on the basis of hematology unit of clinic of Samara State

Medical University, the Institute of Experimental Medicine and Biotechnologies Samara State Medical University, Almazov National medical research center of the Ministry of Health of the Russian Federation. The diagnosis of CML (ICD X C92.1 code) has been established according to the recommendations of the European Society LeukemiaNet (2013) on the basis of results of clinical laboratory researches and detection of Ph-chromosome and/or gene of BCR-ABL [19]. On the basis of the above-stated criteria also the disease phase has been established.

Inclusion Criteria:

1. Patients with Ph-positive chronic myeloid leukemia in chronic phase prior to treatment or the accepting inhibitors of tyrosinekinase of I (TKI1) imatinib and the II (TKI2) generations (dasatinib, nilotinib).
2. Existence of the informed consent of the patient to participation in research.
3. Patients aged 30 to 50 years.

Exclusion Criteria:

1. Acute disorder of cerebral circulation within 6 months before inspection.
2. The postponed myocardial infarction.
3. Existence of diabetes mellitus of I, II types.
4. Existence of chronic disease of kidneys of the I-V stage
5. Existence of coronary heart disease with its clinical manifestations (the II-IV functional class).
6. Existence of idiopathic hypertension of the III degree prior to therapy of TKI.
7. Existence of other oncological diseases.
8. Inflammatory diseases in aggravation stage.

The number of men has made — 64 (47%), women — 73 (53%). The median of age of patients has made 47 years (30-50). All patients have been divided into four groups. 39 patients accepting imatinib in dose of 400 mg/day have entered into the first group; in the second — 36 patients accepting dasatinib in dose of 100 mg/day; in the third — 38 patients accepting nilotinib in dose of 800 mg/day; in the fourth (group of control) — the patients with for the first time the revealed diagnosis of CML who have not begun to accept TKI. The median of reception of TKI has made 25±5,84 months.

At all patients the anamnesis of course of disease, its duration, duration of reception of TKI in detail became clear. For calculation of the index of body weight (BMI) growth and weight was measured. To all patients routine researches were carried out: the bulk analysis of blood (BAB) on Sysmex KX-21N hemanalyzer (Roche Diagnostics, Switzerland), the biochemical analysis of blood including research of lipidic range, markers of system inflammation — the C-reactive Protein (CRP), fibrinogen, markers of endothelial dysfunction — homocysteine, endothelin-1 (ET-1), angiogenesis marker — vascular endothelial growth factor (VEGF). Level detection of ET-1 and VEGF was made by means of enzyme immunoassay. For definition of ET-1 set (BIOMEDICA GRUPPE) for quantitative definition of human big endothelin (1-38) in blood serum, measurement range has been used: 0,02-3 pmol/L. The VEGF level was determined by set (eBioscience) for quantitative definition of human soluble receptor of 1 vascular endothelial growth factor (sVEGFR1) in serum samples by method of enzyme immunoassay.

To all patients measured the heart rate (HR). Measurement of the arterial blood pressure (ABP) was taken once by means of the auscultatory sphygmomanometer on both hands, repeated measurement of the ABP was taken in 2 minutes from previous.

The data obtained during the research processed, using the standard Microsoft Excel program and package of the certified SPSS 13.0 and Stat Soft Statistica 6.1 programs, the following mathematical-statistical methods have been applied: Kolmogorov-Smirnov's criterion for assessment of normality of distribution of values, standard descriptive statistics (average, standard error of average, median, minimum, maximum), non-parametric Mann-Whitney U-test for comparison of quantitative indices, rank correlation coefficient of Spearman's for interrelation research between quantitative characters. Distinctions considered statistically significant at $p<0,05$ [20].

The research has been executed according to standards of appropriate clinical practice (Good Clinical Practice) and the principles of the Helsinki declaration. The study protocol was approved by the ethical committee of Samara State Medical University.

## Results

The specified groups of patients have been inspected. It is most characteristic of the patients accepting nilotinib 800 mg/day there was periodic increase in arterial blood pressure (mainly in the morning). In detail clinical and demographic characteristics of sick CML are provided in table 1. In the relation of the gender and age characteristic it should be noted bigger number of women in each group, than men without statistically significant distinctions on age. Among patients in the groups receiving TKI statistically significant distinctions on BMI, duration of disease and reception of therapy of TKI were not observed (Table 1).

At the patients accepting imatinib 400 mg us statistically significant differences in the values of $P_{sys}$ and $P_{dias}$, the values of the lipid profile from the control group.

**Table 1**

**Clinical and demographic parameters of patients with CML**

| Indicators | 1st group (CML + Ima 400 mg, n=39) | 2nd group (CML + Dasa 100 mg, n=36) | 3rd group (CML + Nilo 800 mg, n=38) | Control group (n=24) |
|---|---|---|---|---|
| Sex (men/women), n (%) | 18 (46) 21 | 17 (47) 19 | 18 (47) 20 | 11 (46) 13 |
| Age, Me | 47 [30; 50] | 47 [30; 50] | 48 [30; 50] | 46 [30; 50] |
| BMI, Me±SD | 25,46±3,17 | 26,81±4,63 | 26,34±4,08 | 24,72±4,91 |
| Duration of disease, Me±SD, month. | 42±4,36 | 44±4,73 | 47±6,28 | - |
| Duration of therapy, Me±SD, month. | 26±3,82 | 23±4,61 | 24±4,39 | - |
| HR, per min | 75,23±6,29 | 72,84±4,77 | 74,65±5,48 | 73,53±4,16 |
| $P_{sys}$, mm Hg | 127,67±6,25 | 132,61±6,79*/^ | 143,05±4,78**/^^/## | 124,78±5,81 |
| $P_{dias}$, mm Hg | 86,56±4,54 | 85,39±4,58 | 91,84±5,46**/^^/## | 83,23±5,15 |
| TC, mmol/l | 4,89±0,14 | 4,91±0,18* | 6,27±0,22**/^^/## | 4,81±0,17 |
| LDL, mmol/l | 3,07±0,27 | 3,12±0,18 | 4,33±0,28**^^^/## | 3,06±0,13 |
| VLDL, mmol/l | 0,61±0,14 | 0,72±0,08*/^ | 0,92±0,17**/^^/## | 0,61±0,13 |
| HDL, mmol/l | 1,21±0,15 | 1,20±0,11 | 1,16±0,12**/^^/## | 1,19±0,07 |
| TGs, mmol/l | 1,36±0,12 | 1,38±0,11* | 1,85±0,07**/^^/## | 1,33±0,08 |
| AC | 3,03±0,23 | 3,11±0,17* | 3,94±0,27**/^^/## | 2,99±0,14 |

**Notes:** */**/*** — significance of difference with the control group ^/^^/^^^ — sign imost differences compared to group 1, #/##/### — significance of differences compared with group 2. * — p<0,05, ** — p<0,001.

**Abbreviations:** CML — chronic myeloid leukemia, Ima 400 mg — imatinib at a daily dose of 400 mg, Dasa 100 mg — dasatinib at a daily dose of 100 mg, Nilo 800 mg — nilotinib at a daily dose of 800 mg, BMI — body mass index, HR — heart rate, $P_{sys}$ — systolic arterial pressure, $P_{dias}$ — diastolic blood pressure, LDL — low density lipoproteins, VLDL — very low density lipoproteins, HDL — high density lipoproteins, TGs — triglycerides, AC — atherogenic coefficient.

**Table 2**

**Comparative data of indicators of markers of damage of endothelium at patients with CML**

| Indicators | 1st group (CML + Ima 400 mg, n=39) | 2nd group (CML + Dasa 100 mg, n=36) | 3rd group (CML + Nilo 800 mg, n=38) | Control group (n=24) |
|---|---|---|---|---|
| CRP, mg/ml | 2,12±0,26** | 3,06±0,26**/^^ | 5,41±0,32**/^^/## | 1,46±0,25 |
| Fibrinogen, g/l | 3,48±0,22* | 4,02±0,17**/^^ | 4,07±0,16**/^^/## | 3,17±0,16 |
| Homocysteine, μmol/l | 9,53±0,31 | 10,80±0,39 | 10,93±0,28**/^^ | 9,32±0,26 |
| Endothelin-1, pmol/ml | 0,16±0,04* | 0,32±0,02**/^^ | 0,89±0,05**/^^/## | 0,04±0,02 |
| VEGF, pg/ml | 54,78±7,54** | 109,86±12,97**/^^ | 165,36±11,44**/^^/## | 35,53±6,59 |

**Notes:** */**/*** — significance of the difference with the control group, ^/^^/^^^ — significance of the difference in comparison with group 1, #/##/### — significance of the difference in comparison with group 2. * — p<0,05, ** — p<0,001.

**Abbreviations:** CML — chronic myeloid leukemia, Ima 400 mg — imatinib at a daily dose of 400 mg, Dasa 100 mg — dasatinib at a daily dose of 100 mg, Nilo 800 mg — nilotinib at a daily dose of 800 mg, CRP — C-reactive protein, VEGF — vascular endothelial growth factor.

In the group of patients with CML receiving dasatinib at a dose of 100 mg/day a statistically significant increase in systolic blood pressure values was found ($P_{sys}$ 132,41±5,19 mm Hg, p<0,05) compared with the control group and the group of patients taking imatinib 400 mg/day.

Significant changes in the lipid profile were also detected: an increase in the level of VLDL (0,72±0,08 mmol/l, p<0,05) compared with the control group and the first group, an increase in the level of TGs (1,38±0,11 mmol/l, p<0,05) compared with the control group and AC (3,11±0,17, p<0,05) compared with the control group.

In the group of patients with CML taking nilotinib at a dose of 800 mg/day. There was a statistically significant increasing in systolic and diastolic blood pressure levels ($P_{sys}$ 143,21±4,78 and $P_{dias}$ 91,84±5,46 mm Hg, p<0,001) compared with the control group

**Table 3**

**Correlation interrelations between markers of lipidic range and markers of damage of endothelium**

| Indicators | Drug | Homocysteine, μmol/l | Endothelin-1, pmol/ml | VEGF, pg/ml |
|---|---|---|---|---|
| TC | Ima400 | 0,92*** | 0,54*** | 0,96*** |
| | Daza100 | 0,83*** | 0,49** | 0,84*** |
| | Nilo800 | 0,61*** | 0,67*** | 0,22 |
| LDL | Ima400 | 0,67*** | 0,45** | 0,62*** |
| | Daza100 | 0,31* | 0,38* | 0,35** |
| | Nilo800 | 0,43** | 0,39* | 0,81*** |
| VLDL | Ima400 | 0,80*** | 0,36* | 0,77*** |
| | Daza100 | 0,82*** | 0,28 | 0,81*** |
| | Nilo800 | 0,88*** | 0,94*** | 0,28 |
| HDL | Ima400 | 0,88*** | 0,63*** | 0,92*** |
| | Daza100 | 0,84*** | 0,51*** | 0,89*** |
| | Nilo800 | 0,87*** | 0,94*** | 0,36** |
| TGs | Ima400 | 0,94*** | 0,58*** | 0,98*** |
| | Daza100 | 0,93*** | 0,59*** | 0,98*** |
| | Nilo800 | 0,97*** | 0,93*** | 0,43** |
| AC | Ima400 | 0,92*** | 0,57*** | 0,95*** |
| | Daza100 | 0,92*** | 0,58*** | 0,98*** |
| | Nilo800 | -0,02 | 0,92*** | -0,14 |

**Notes:** * — p<0,05, ** — p<0,01, *** — p<0,001.

**Abbreviations:** Ima 400 mg — imatinib at a daily dose of 400 mg, Dasa 100 mg — dasatinib at a daily dose of 100 mg, Nilo 800 mg — nilotinib at a daily dose of 800 mg, VEGF — vascular endothelial growth factor, TC — total cholesterol, LDL — low density lipoproteins, VLDL — very low-density lipoproteins, HDL — high density lipoproteins, TGs — triglycerides, AC — atherogenic coefficient.

**Table 4**

**Correlational interrelation between markers of endothelial damage and values of $P_{sys}$ and $P_{dias}$**

| Indicators | Drug | Homocysteine, μmol/l | Endothelin-1, pmol/ml | VEGF, pg/ml |
|---|---|---|---|---|
| $P_{sys}$ | Ima400 | 0,96*** | 0,57*** | 0,98*** |
| $P_{dias}$ | | 0,82*** | 0,44** | 0,85*** |
| $P_{sys}$ | Daza100 | 0,75*** | 0,62*** | 0,77*** |
| $P_{dias}$ | | 0,93*** | 0,66*** | 0,96*** |
| $P_{sys}$ | Nilo800 | 0,76*** | 0,84*** | 0,31* |
| $P_{dias}$ | | 0,90*** | 0,83*** | 0,42** |

**Abbreviations:** Ima 400 mg — imatinib at a daily dose of 400 mg, Dasa 100 mg — dasatinib at a daily dose of 100 mg, Nilo 800 mg — nilotinib at a daily dose of 800 mg, VEGF — vascular endothelial growth factor, $P_{sys}$ — systolic blood pressure, $P_{dias}$ — diastolic blood pressure.

**Notes:** * — p<0,05, ** — p<0,01, *** — p<0,001.

with a group of patients taking imatinib 400 mg/day and dasatinib 100 mg/day. The most serious changes in laboratory parameters were also noted in the group of patients taking nilotinib 800 mg/day. In the group of patients with CML receiving nilotinib at a dose of 800 mg/day, a statistically significant increase in total cholesterol (6,27±0,22 mmol/l, p<0,001), LDL (4,33±0,28 mmol/l, p<0,001), VLDL (0,92±0,17 mmol/l, p<0,001), TGs (1,85±0,07 mmol/l, p<0,001), AC (3,9±0,27, p<0,001), a statistically significant decrease in HDL (1,16±0,12 mmol/l, p<0,001) in comparison with control groups, patients taking imatinib 400 mg/day, patients taking dasatinib 100 mg/day.

Data on studying of markers of damage of endothelium are in detail provided in table 2.

It should be noted that a statistically significant increase in CRP, fibrinogen, homocysteine, ET-1

and VEGF levels was found in all groups of patients with CML treated with ITK compared with the control group. The most explicied changes were found in group 3 patients, the parameters of CRP, fibrinogen, homocysteine, ET-1 and VEGF changed significantly ($p<0,001$) and statistically significantly different compared with the control group, 1 and 2 groups. Changes in the content of biochemical markers reflect endothelial dysfunction. Particularly noteworthy is the increase in CRP and ET-1 and VEGF, which reflects the unity of the inflammation process.

Correlation analysis was carried out with the purpose to reveal interrelations of indicators of lipidic range and markers of damage of endothelium at the patients accepting ITK. Close interrelations have been revealed in 1, 2 and 3 groups between indicators of lipidic range and markers of damage, among them have been chosen homocysteine, Etendotelin-1 and VEGF (Table 3).

Besides, we carried out a correlation analysis of markers of damage to the endothelium and levels of $P_{sys}$ and $P_{dias}$, during which the close interrelation of indicators was revealed (Table 4).

Patients 3 groups accepting nilotinib 800 mg/day had the clinical features characterizing them as group of persons with high arterial blood pressure. In 24±4,39 months of reception of nilotinib, patients had the arterial hypertension of 1 degree revealed at 38,42% of persons. The highest rates of lipidic profile in interrelation with markers of damage of endothelium can demonstrate development of system inflammatory process.

Thus, in all groups statistically significant correlations of indicators of lipidic range and markers of damage of endothelium have been revealed, at the same time especially significant interrelations were defined at patients from CML accepting nilotinib 800 mg a day. In the last group of patients the share of patients with arterial hypertension, markers of endothelial dysfunction and disturbances of lipidic exchange in comparison as with other groups of patients was authentically higher.

## Discussion

It is known that cardiotoxicity is one of the most dangerous AEs resulting from therapy of oncological diseases and can influence life expectancy. Minimizing of risk of the cardiovascular complications caused by different types of therapy is vital for patients. Therefore patients need to place emphasis on early detection and assessment of risks of cardiovascular diseases at purpose of drugs TKI with CML [21] .

The studying of lipid profile disorders in combination with changes in the content of markers of damage to the vascular endothelium in patients with CML and hypertension is undoubted interesting.

Cardiovascular AEs apparently related to the peculiarities of the action of TKI. There is an opinion that the inhibition of various TKI targets contributes to their different toxicity profiles [9]. All TKI inhibit a number of kinases, but in different values. Compared with most other TKI, dasatinib has a higher inhibitory effect against the Src family kinases, the Bruton tyrosine protein kinase and the alpha receptor for growth factor platelet receptor (PDGFRα); nilotinib is a derivative of imatinib and also inhibits PDGFR and c-Kit; Bosutinib has a higher inhibitory effect against Src-family kinases; Ponatnib has a higher inhibitory effect against PDGFRα, c-Kit and VEGFR-2 [22-26].

The spectrum of potential cardiovascular and metabolic toxicity associated with TKI therapy varies from chronic pathology to potentially life threatening and includes heart failure, prolonged QT interval, arterial hypertension, thrombosis, peripheral arterial occlusive disease, hyperlipidemia, hyperglycemia [11]. So, in patients taking nilotinib 800 mg/day the highest levels of $P_{sys}$ and $P_{dias}$ among all groups are noted, which, probably like other adverse events, is associated with the spectrum of nilotinib inhibited kinases. The analysis of the lipid profile in patients with newly diagnosed CML and patients receiving TKI of I and II generations showed significant changes, especially in patients taking nilotinib 800 mg/day. These patients showed a statistically significant increase in total cholesterol, LDL, VLDL, TGs, a statistically significant decrease in HDL cholesterol, and, as a result, a significant increase in atherogenicity was found. Patients taking dasatinib 100 mg/day are shown less significant but statistically significant changes — an increase in total cholesterol, VLDL, TGs and AC. Such disorders of the lipid profile are consistent with literature data [11].

Arterial hypertension serves as an activator of oxidative stress, which is accompanied by tissue damage and initiates endothelial dysfunction. Endothelial dysfunction initiates further developments leading to changes in the content of vasoactive substances, inflammatory reactions and vascular remodeling, which, in turn, leads to the pathology of target organs [27]. Currently, one of the most studied vasoactive mediators is ET-1 and VEGF, the prognostic significance of which is confirmed in blood diseases [28]. A rat's endothelial model showed that hyperhomocysteinemia can increase the levels of ET-1 and other inflammatory markers [15].

Analysis of the data obtained during the study of endothelial function revealed the following patterns: a significant change in fibrinogen and CRP levels depending on the applied TKI, also significantly changed ET-1 and VEGF, the homocysteine level was significantly different in patients taking 800 mg/day nilotinib in comparison with newly diagnosed patients with CML and patients taking imatinib 400 mg/day. However, the level of fibrinogen was within the reference values (2-4 g/l) and was slightly increased in the dasatinib group of 100 mg/day. and nilotinib 800 mg/day. The obtained data are confirmed in a study of patients with CML and in a number of other works [29]. An increase in CRP levels ($p<0,02$) in patients with CML using hydroxurea, interferon-α and imatinib therapy is confirmed in the study of Humlova Z, et al. in 2010 [30]. According to Fossard G, et al. (2016) comparing the level of homocysteine in patients using imatinib and nilotinib, it was 13,9 μmol/l and 12,20 μmol/l, respectively, the author did not note interconnections between the level of homocysteine and the type of cardiovascular event. However, after conducting a ROC analysis, the authors determined a homocysteine threshold of 13,95 μmol/l, which can select patients with a high risk of morbidity [31].

Data on changes in the concentration of ET-1 in the serum of CML patients in the literature have not been found. In a research by Chand R, et al. (2016) it was noted that the highest serum VEGF levels were observed in CML (1011,5±789,09 pg/ml), which indicates the maximum angiogenic potential in this disease. Another important sign was a significant decrease in the level of VEGF in the serum after treatment of CML (294,84±401,17 pg/ml, $p=0,037$). This is shown the importance of angiogenesis in the pathogenesis of hematological malignant neoplasms [32].

Identified in the course of the study, the interrelation between lipid profile indicators and endothelium damage markers reflects the unity of the inflammation process resulting from the use of a number of TKI preparations.

Before starting treatment of TKI, each patient needs to evaluate cardiovascular and metabolic risk factors, which, together with an understanding of the toxicity profiles of each TKI, will help determine the most appropriate drug. Regular monitoring and early recognition of AE during treatment will help reduce endothelio-toxicity [11], and modification of an aggressive risk factor with the onset of prophylactic treatment can prevent undesirable cardiovascular events. Appropriate treatment choices along with the prevention and treatment of TKI-related toxicity can help prevent premature cessation of therapy and optimize long-term results in patients with CML.

The team of authors acknowledges that the study had a number of limitations, given the small sample size, a multi-dimensional analysis was not carried out. However, we found it possible to present the obtained data, since from our point of view, it is necessary to trace the association of hypertension in changes in endothelial function in patients with CML when using TKI and the development of cardiovascular complications in the patients observed. Further monitoring of patients with CML receiving TKI will allow developing tools for predicting cardiovascular events that are available for actual clinical practice in patients with CML before prescribing or during the treatment of TKI.

## Conclusion

As a result of the conducted research endothelium variation of a function at patients from CML accepting TKI1 and TKI2 is revealed. The above-stated indicators can be used as additional diagnostic criteria for assessment of risk of development of arterial hypertension in patients with CML at reception of TKI. It will promote early identification of complications from cardiovascular system that, in turn will allow to improve the forecast of course of disease and quality of life of patients.

**Relationships and Activities.** The authors declare no conflict of interest.

## References


1. McGowan JV, Chung R, Maulik A, et al. Anthracycline chemotherapy and cardiotoxicity. Cardiovasc Drugs Ther. 2017;31:63-75. doi:10.1007/s10557-016-6711-0.
2. Moslehi JJ. Cardiovascular toxic effects of targeted cancer therapies. N Engl J Med. 2016;375:1457-67. doi:10.1056/NEJMra1100265.
3. Domercant J, Polin N, Jahangir E. Cardio-oncology: a focused review of anthracycline-, human epidermal growth factor receptor 2 inhibitor-, and radiation-induced cardiotoxicity and management. Ochsner J. 2016;16:250-6.
4. Abdel-Qadir H, Ethier JL, Lee DS, et al. Cardiovascular toxicity of angiogenesis inhibitors in treatment of malignancy: a systematic review and meta-analysis. Cancer Treat Rev. 2017;53:120-7. doi:10.1016/j.ctrv.2016.12.002.
5. Jain D, Russell RR, Schwartz RG, et al. Cardiac complications of cancer therapy: pathophysiology, identification, prevention, treatment, and future directions. Curr Cardiol Rep. 2017;19:36. doi:10.1007/s11886-017-0846-x.
6. Druker BJ. Translation of the Philadelphia chromosome into therapy for CML. Blood. 2008;112:4808-17. doi:10.1182/blood-2008-07-077958.
7. Turkina AG, Novitskaya NV, Golenkov AK, et al. register of patients with chronic myeloid leukemia in the russian federation: from an observational study to an assessment of the effectiveness of therapy in clinical practice. Clinical oncohematology. 2017;10(3):390-401. (In Russ.) doi:10.21320/2500-2139-2017-10-3-390-401.
8. Pallera A, Altman JK, Berman E, et al. NCCN Guidelines Insights: Chronic Myeloid Leukemia, Version 1. 2017. J Natl Compr Canc Netw. 2016;14(12):1505-12.
9. Rosti G, Castagnetti F, Gugliotta G, Baccarani M. Tyrosine kinase inhibitors in chronic myeloid leukaemia: which, when, for whom? Nat Rev Clin Oncol. 2017;14(3):141-54. doi:10.1038/nrclinonc.2016.139.
10. Huang X, Cortes J, Kantarjian H. Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. Cancer. 2012;118(12):3123-7. doi:10.1002/cncr.26679.
11. Steegmann JL, Baccarani M, Breccia M, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. Leukemia. 2016;30(8):1648-71. doi:10.1038/leu.2016.104.
12. National Cancer Institute, Surveillance epidemiology and end results. SEER stat fact sheets: chronic myeloid leukemia. Available from: http://seer.cancer.gov/statfacts/html/cmyl.html. Accessed 12, 2020.
13. Ross R. Atherosclerosis: an inflammatory disease. Am Heart J. 1999;138(5 Pt 2):419-20. doi:10.1016/s0002-8703(99)70266-8.
14. Lai WKC, Kan MY. Homocysteine-induced endothelial dysfunction. Ann Nutr Metab. 2015;67(1):1-12. doi:10.1159/000437098.
15. Yang RX, Huang SY, Yan FF, et al. Danshensu protects vascular endothelia in a rat model of hyperhomocysteinemia. Acta Pharmacol Sin. 2010;31(10):1395-400. doi:10.1038/aps.2010.167.
16. Brattstrom L, Wicken DE. Homocysteine and cardiovascular disease: cause or effect? Am J Clin Nutr. 2000;72(2):315-23.
17. Inoue A, Yanagisawa M, Takuwa Y, et al. The human preproendothelin-1 gene. Complete nucleotide sequence and regulation of expression. J Biol Chem. 1989;264(25):14954-9.
18. Kamba T, Tam BY, Hashizume H, et al. VEGF-dependent plasicity of fenestrated capillaries in the normal adult microvasculature. Am J Physiol Heart Circ Physiol. 2006;290(2):H560-76. doi:10.1152/ajpheart.00133.2005.
19. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122(6):872-84. doi:10.1182/blood-2013-05-501569.
20. Rebrova OY. Statistical analysis of medical data. Application software package STATISTICA. M.: Media Sphere, 2002. p. 305. (In Russ.) ISBN 5-89084-013-4.
21. Dong J, Chen H. Cardiotoxicity of Anticancer Therapeutics. Front Cardiovasc Med. 2018;5:9. doi:10.3389/fcvm.2018.00009.
22. ICLUSIG® (ponatinib). Full prescribing information. ARIAD Pharmaceuticals, Inc., Cambridge, MA, USA; 2016.
23. BOSULIF® (bosutinib). Full prescribing information. Pfizer Labs, New York, NY; 2016.
24. TASIGNA® (nilotinib). Full prescribing information. Novartis Pharmaceuticals Corporation, East Hanover, NJ; 2016.
25. Sprycel® (dasatinib). Full prescribing information. Bristol-Myers Squibb, Princeton, NJ; 2016.
26. GLEEVEC® (imatinib). Full prescribing information. Novartis Pharmaceuticals Corporation, East Hanover, NJ; 2016.
27. Dzau VJ, Antman EM, Black HR, et al. The cardiovascular disease continuum validated: clinical evidence of improved patient outcomes. Part I: pathophysiology and clinical trial evidence risk factors through stable coronary artery disease. Circulation. 2006;114(25):2850-70. doi:10.1161/circulationaha.106.655688.
28. Davydkin IL, Kurtov IV, Khairetdinov RK, et al. Blood diseases in ambulatory practice: Manual, 2nd ed. and ext. Moscow: GEOTAR Media, 2014. p. 184 (In Russ.) ISBN: 978-5-9704-2725-5.
29. Jain A, Gupta N, Singh T, Agarwal S. A Study of Haemostatic Parameters in Patients of Chronic Myeloid Leukaemia. J Clin Diagn Res. 2016;10(7):OC19-23. doi:10.7860/JCDR/2016/19185.8135.
30. Humlová Z, Klamová H, Janatková I, et al. Changes of Immunological Profiles in Patients with Chronic Myeloid Leukemia in the Course of Treatment. Clin Dev Immunol. 2010;2010:137320. doi:10.1155/2010/137320.
31. Fossard G, Blond E, Balsat M, et al. Hyperhomocysteinemia and high doses of nilotinib favor cardiovascular events in chronic phase Chronic Myelogenous Leukemia patients. Haematologica. 2016;101(3):e86-90. doi:10.3324/haematol.2015.135103.
32. Chand R, Chandra H, Chandra S, Verma SK. Role of Microvessel Density and Vascular Endothelial Growth Factor in Angiogenesis of Hematological Malignancies. Bone Marrow Res. 2016;2016:5043483. doi:10.1155/2016/5043483.

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-4170

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

# Coronavirus disease 2019 in a patient with CADASIL syndrome: a case report

Zaslavskaya E. L.[1], Zaslavsky L. G.[1], Baranova E. I.[1,2], Alekseeva A. M.[1], Markov N. V.[1], Zagidullin N. Sh.[3]

We present a case report of a patient with a previously identified cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), who was admitted due to coronavirus disease 2019 (COVID-19), confirmed by polymerase chain reaction and computed tomography. Examination and treatment of these patients presents certain difficulties due to the large number of thromboembolic complications caused by a combination of congenital and infectious angiopathies. CADASIL syndrome and COVID-19 were manifested by the progression of neurological symptoms and increasing cognitive impairment. During therapy, there was a positive change with a gradual regression of these disorders.

**Keywords:** CADASIL, SARS-CoV-2, COVID-19, stroke, coronavirus disease, anticoagulants.

**Relationships and Activities:** none.

[1]First Pavlov State Medical University, St. Petersburg; [2]Almazov National Medical Research Center, St. Petersburg; [3]Bashkir State Medical University, Ufa, Russia.

Zaslavskaya E. L.* ORCID: 0000-0002-1209-7765, Zaslavsky L. G. ORCID: 0000-0001-9912-1512, Baranova E. I. ORCID: 0000-0002-8788-0076, Alekseeva A. M. ORCID: 0000-0002-3610-2055, Markov N. V. ORCID: 0000-0002-6992-0169, Zagidullin N. Sh. ORCID: 0000-0003-2386-6707.

*Corresponding author:
Dr.kzaslavskaya@gmail.com

**Received:** 30.10.2020
**Revision Received:** 18.11.2020
**Accepted:** 29.11.2020



**For citation:** Zaslavskaya E. L., Zaslavsky L. G., Baranova E. I., Alekseeva A. M., Markov N. V., Zagidullin N. Sh. Coronavirus disease 2019 in a patient with CADASIL syndrome: a case report. *Russian Journal of Cardiology*. 2020;25(S4):4170. (In Russ.) doi:10.15829/1560-4071-2020-4170

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare genetic disorder with autosomal dominant inheritance caused by a mutation in *NOTCH-3* gene, located on the 19p13 chromosome. This disease is characterized by a low prevalence: there are 2-5 cases per 100 thousand people worldwide; however, its incidence in different populations may differ [1].

Clinically, CADASIL syndrome is most often manifested by recurrent ischemic episodes leading to dementia, gait abnormalities, urinary incontinence, pseudobulbar palsy, migraine (with and without aura), and epileptic seizures. Migraine with aura is an early characteristic feature of CADASIL, occurring in 20-50% of patients with an average age of 30 years. Transient ischemic attacks and lacunar strokes in CADASIL occur in 60-85% of patients aged 50-60 years. Cognitive impairment is often an early manifestation of CADASIL syndrome. Epileptic seizures develop in 5-10% of patients [2].

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses a serious threat to humanity and is associated with a wide range of clinical respiratory syndromes ranging from mild upper respiratory tract symptoms to life-threatening progressive viral pneumonia [3]. Patients with severe COVID-19 are characterized by respiratory failure and progressive hypoxemia, which often require respiratory support. Chest computed tomography (CT) in patients with COVID-19 reveals numerous ground glass opacities, predominantly round, of varying length with or without consolidation, which meet Berlin criteria for acute respiratory distress syndrome [4]. The hallmarks of COVID-19 include vascular disease caused by endothelial dysfunction and other factors. COVID-19 is also characterized by coagulopathy, which manifested by skin abnormalities, indicating thrombotic microangiopathy, as well as diffuse alveolar damage due to fibrin thrombi formation; laboratory changes in these patients are characterized by increased levels of D-dimer and ferritin [5].

Much of our knowledge regarding strokes associated with SARS-Cov-2 or those aggravated by a viral infection is based on data from a series of single-center cases, and there are no clear algorithms for treating these patients. Efforts are under way to improve diagnosis, risk factors and treatment approaches in patients with COVID-19-related strokes.

We present a case report of a patient with CADASIL syndrome and moderate COVID-19 — a combination of congenital and infectious angiopathies.

## Case report

Female patient aged 56 years was admitted to the infectious diseases' hospital with a previously identified CADASIL syndrome, confirmed COVID-19, and bilateral viral multisegmented pneumonia. Upon admission, the patient complained about severe weakness and low-grade fever.

**Medical history.** It is known that since 2010 memory loss and gait abnormalities have appeared. Since 2010, sensory aphasia, motor apraxia, impaired right-left orientation, finger agnosia, pseudobulbar palsy, bilateral pyramidal insufficiency, mild bilateral cerebellar ataxia have been diagnosed. In 2015, at the Research Centre for Medical Genetics in Moscow, she was examined for mutations in the *NOTCH3* gene (CADASIL Syndrome). The heterozygous mutation c.548G> T (p.Cys183Phe) was revealed, which confirmed a CADASIL. Subsequent admissions to the neurological clinic showed progression of neurological symptoms, increasing cognitive impairment (Montreal Cognitive Assessment score of 21, Mini-Mental State Exam score of 17, Frontal Assessment Battery of 6). Severe cognitive impairments were diagnosed in 2020 (frontal-subcortical dementia). Duplex ultrasound of the brachiocephalic arteries revealed no atherosclerotic plaques and no intima-media thickening (Figure 1). In 2019, electroencephalography revealed abnormalities within the disorganized type. There was no epileptiform activity.

Using polymerase chain reaction, *Herpes* and *Borrelia* were not revealed in cerebrospinal fluid (CSF) and blood. Any rheumatic disease and antiphospholipid syndrome were not revealed. Oligoclonal IgG bands in serum and CSF was not revealed, while free light chains, kappa and lambda in serum and CSF were not elevated. Myelin basic protein and anti-aquaporin antibodies were in normal range. Analysis for HIV, HBsAg, HCVAb, RW in CSF and blood were negative.

With regular courses of neurometabolic therapy, irregular intake of NMDA receptor antagonists and acetylcholinesterase inhibitors, no significant positive dynamics was observed. Since 2019, the patient has been receiving continuous therapy: perindopril (5 mg) + indapamide (1,25 mg); atorvastatin (10 mg); metformin (850 mg); akatinol memantine (10 mg); levetiracetam (500 mg).

**Development of COVID-19.** Seven-eight days before hospitalization, the patient developed weakness, decreased appetite, cognitive impairment, and low-grade fever. At admission to the infectious diseases' hospital, moderately grave condition was noted. Temperature of 38,0° C. Pulse: 97 bpm, rhythmic, satisfactory filling, symmetrical. Blood pressure: 115/70 mm Hg. Respiration: spontaneous, efficient,

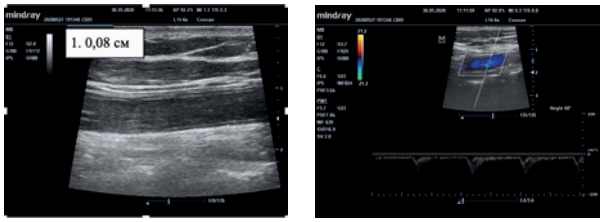


**Figure 1.** Carotid ultrasound.
**Note:** common carotid artery, internal carotid artery, and external carotid artery are patent throughout; diameters are sufficient; velocity parameters are within normal limits (in the common carotid artery, the blood flow rate was 80,0 cm/sec, external carotid artery — 48,0 cm/sec; internal carotid artery — 42,0 cm/sec). The intima-media thickness was 0,08 cm.

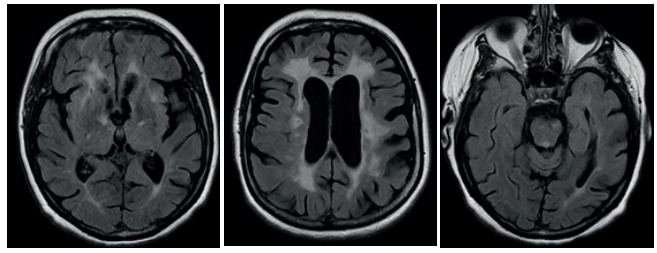

**Figure 2.** Brain MRI.
**Note:** MRI picture of multiple focal discirculatory abnormalities in the brain; numerous post-ischemic lacunar cysts, periventricular areas of leukoaraiosis; expansion of CSF spaces.

**Table 1**

**Changes in haematological parameters**

| Parameters | Reference value | Day 8 | Day 12 | Day 17 | Day 19 |
|---|---|---|---|---|---|
| RBC, $10^{12}$/L | (3,7-4,7) | 5,0 | 4,3 | 4,8 | 4,9 |
| Platelets, $10^9$/L | (150-400) | 191 | 190 | 348 | 327 |
| WBC, $10^9$/L | (4,00-8,80) | 8,34 | 5,94 | 11,25 | 7,13 |
| Neutrophils,% | (46,0-72,0) | 82,7 | | 58,1 | 56,7 |
| Lymphocytes,% | (18,0-40,0) | 11,2 | | 33,4 | 32,7 |
| Creatinine, mmol/L | (0,053-0,097) | 0,081 | 0,059 | | 0,78 |
| CKD-EPI GFR, ml/min/1,73 $m^2$ | (>90,0) | 68,8 | 96,7 | | 79 |
| Ferritin, µg/L | (11,0-307,0) | 296,0 | 317,0 | | 304,0 |
| Troponin I (high-sensitivity), ng/ml | <0,005 | 0,003 | 0,001 | | 0,001 |
| D-dimer, µg/L (FEU) | (<500) | 541 | 485 | | 467 |
| Fibrinogen, g/L | (1,80-3,50) | 6,69 | 5,70 | | 5,42 |
| Procalcitonin, µg/L | (<0,0000) | 0,1113 | 0,0966 | | 0,0700 |

**Abbreviations:** GFR — glomerular filtration rate, RBC — red blood cells, WBC — white blood cells.

**Table 2**

**Arterial blood gas changes**

| Parameters | Reference value | Day 8 | Day 10 | Day 18 |
|---|---|---|---|---|
| pH | (7,350-7,450) | 7,600 | 7,520 | 7,500 |
| $pCO_2$, mm Hg | (35,0-45,0) | 31,0 | 37,0 | 31,0 |
| $pO_2$, mm Hg | (80,0-100,0) | 53,0 | 72,0 | 57,0 |
| $HCO_3$act, mmol/L | (21,0-28,0) | 30,4 | 30,2 | 24,2 |
| BE (ecf), mmol/L | | 8,8 | 7,3 | 1,0 |
| $O_2$ SAT, % | | 92,0 | 96,0 | 92,0 |
| $tCO_2$, mmol/L | | 31,4 | 31,3 | 25,2 |
| Hematocrit, % | (34,0-52,0) | 43,0 | 45,0 | 39,0 |
| Potassium, mmol/L | (3,50-4,50) | 2,70 | 4,40 | 3,50 |
| Sodium, mmol/L | (135,0-148,0) | 131,0 | 144,0 | 132,0 |
| Ionized calcium, mmol/L | (1,12-1,32) | 1,01 | 1,10 | 1,12 |
| Lactate, mmol/L | | 1,30 | 1,8 | 2,00 |
| Biomaterial | | Without $O_2$ therapy | With $O_2$ therapy | Without $O_2$ therapy |

**Table 3**

**Changes of serum CRP concentration**

| Parameter | Reference value | Day 8 | Day 9 | Day 10 | Day 13 | Day 20 |
|---|---|---|---|---|---|---|
| C-reactive protein, mg/L | (0,01-5,00) | 58,24 | 86,16 | 171,47 | 48,02 | 4,77 |

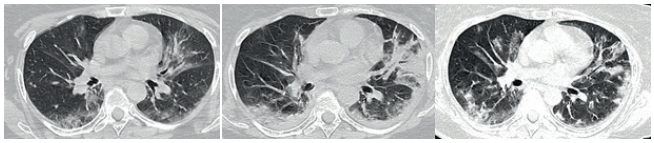

**Figure 3.** Changes of chest CT on the 8th, 14th and 21st days of a viral infection.

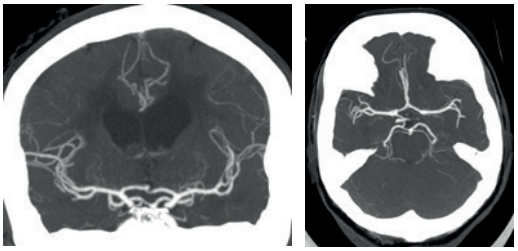

**Figure 4.** Head and neck CT angiography.
**Note:** carotid artery diameter was not altered; no contrasting defects; no pathological tortuosity. The vertebral arteries typically depart, enter the C6 transverse foramen, passable, not narrowed, the left one is dominant. Intracranial segments of the internal carotid arteries, basilar and cerebral arteries are passable, not narrowed. The anterior communicating and right posterior communicating arteries are well developed. The left posterior communicating artery is not developed. There is a diffuse expansion of brain ventricles and decrease in periventricular white matter density.

rhythmic. Respiratory rate of 21 breaths per minute and $SpO_2$ 92% were recorded. Patient communication was significantly limited due to dementia. It was impossible to assess the patient's sense of smell, eye movements, visual fields, and sensitivity. Pupils D=S. Slow photoreaction was noted. Convergence was not appreciated. End-position nystagmus with extreme abduction of the eyeballs was revealed. Corneal reflexes were preserved. Trigeminal neuralgia was not detected. Swallowing was not disturbed. Reduced pharyngeal reflexes and dysarthria were determined. Symptoms of oral automatism were caused. The palmar grasp reflex on the right was revealed. Upper limb muscle tone was increased in a pyramidal pattern. Diffuse muscle wasting. Muscle strength cannot be reliably assessed due to cognitive deficit. Brisk biceps and knee reflexes, D>S; triceps, carporadial, Achilles reflexes, D=S. Abdominal reflexes were preserved. Bilateral Babinski reflex was presented. Pain response was preserved on both sides. Coordination tests could not be assessed. Meningeal signs were not revealed. Thus, the following syndromes were identified: cognitive impairment (frontal-subcortical dementia), pseudobulbar, sensorimotor aphasia, bilateral pyramidal insufficiency, pelvic organ dysfunction of central origin, indicating a multifocal vascular process.

According to magnetic resonance imaging (MRI), a picture of multiple focal discirculatory abnormalities in the brain; numerous post-ischemic lacunar cysts, periventricular areas of leukoaraiosis. Expansion of CSF spaces (Figure 2).

According to chest computed tomography (CT) at admission, grade 2 bilateral viral pneumonia was revealed. The English National Early Warning Score (NEWS) of 6 was detected. Decompensated alkalosis (Ph, 7,600) was noted, as well as a decrease in oxygen partial pressure to 53,0 mm Hg (Table 1). Grade 1 respiratory failure was diagnosed. The blood tests showed a high level of C-reactive protein (CRP), a slight increase in fibrinogen and D-dimer levels. White blood cell count and procalcitonin level were within the normal range (Tables 2, 3).

On the 11th day of illness, the maximum level of CRP (171,47 mg/L) was noted. Chest CT scan revealed glass opacities with multiple foci consolidation (both in the peripheral and central peribronchial areas) and pronounced reticular changes (with predominant localization in the dorsal and dorsal-basal parts). The extent of the lung tissue damage was 65-70%. The high probability of COVID-19 was detected. CT scan meet the criterial for grade 2-3 pneumonia. When compared with previous image, there was a negative trend.

According to the current temporary guidelines for the prevention, diagnosis and treatment of COVID-19, therapy with hydroxychloroquine in combination with azithromycin (hydroxychloroquine 400 mg twice a day, then 200 mg 2 twice a day within 6 days + azithromycin 500 mg 1 time per day for 7 days) is indicated. Taking into account the severe neurological deficit, persistence of fever and the need for oxygen support, an increase in CRP levels and negative dynamics in chest CT, it was decided to abandon this treatment regimen in favor of glucocorticoid drugs. After 10 days of dexamethasone therapy (12 mg per day for 10 days, 8 mg per day for 11 days, 4 mg per day for 12 days, followed by withdrawal of glucocorticoids), the fever was stopped, the CRP level normalized, and the neurological status improved as a slight regression of cognitive impairments — the

comprehension of addressed speech improved. An improvement was also noted in fixing the hammer in the horizontal direction. With the abolition of oxygen support, the increase in lactate level was not observed, which indicated the absence of significant tissue hypoxia (Table 2). According to chest CT image, in the peripheral and central parts of both lungs, lobular merging and multilobular areas of glass opacities with indistinct contours were preserved. Similar nodular compaction in the right upper lobe was identified. Transformation of some interstitial infiltrates into perilobular reticular compactions, parapleural and peribronchovascular areas of consolidation with cord-like contours was determined predominantly in the dorsal-basal areas of both lungs. The extent of lung changes decreased in comparison with previous CT image (Figure 3).

Taking into account the high risk of intravascular thrombosis, the patient received therapy with low molecular weight heparins (enoxaparin sodium) at a therapeutic dose of 1 mg/kg from the first day of hospitalization (bleeding risk was determined using the HAS-BLED score). The effectiveness of anticoagulant therapy was assessed by CT cerebral and chest angiography at the peak of CRP concentration. According to head and neck CT angiography, data suggestive of stenosis/thrombosis were not obtained (Figure 4). No CT signs of thromboembolism of the major and intermediate pulmonary artery branches were obtained.

## Discussion

COVID-19 is a novel disease caused by the SARS-CoV-2 virus, characterized by fever, cough, myalgia and eventually shortness of breath. Despite the characteristic manifestation of COVID-19, atypical symptoms such as gastrointestinal distress and neurological symptoms, including headache, altered mental status, anosmia and seizures, are common. Often, severe patients with COVID-19 develop cardiovascular complications, such as myocardial infarction, stroke, but the relationship between infection and these complications is complex and poorly understood. Herpes viruses, such as the varicella-zoster virus, have been shown to invade the vessel wall, causing cerebral vasculopathy. In comparison, *Cytomegalovirus*, *Chlamydia pneumonie*, and other pathogenic organisms are closely associated with atherogenesis and plaque instability. In addition, recent bacterial or viral infections are known to temporarily exacerbate pre-existing vascular risk factors for stroke [6]. Various COVID-19 reviews have suggested that infection create an inflammatory environment that predisposes to stroke by activating prothrombotic pathways that affect plaque stability, causing endothelial dysfunction, intimal thickening, leading to arterial wall remodelling. In COVID-19 patients, strokes are usually associated with the activation of the renin-angiotensin system, procoagulation, and massive release of inflammatory cytokines (cytokine release syndrome) [7].

Strokes in CADASIL patients tend to damage subcortical structures. Brainstem involvement is much less common [8]. Interestingly, studies on animals have shown that coronaviruses may have tropism to the brainstem. At the same time, previously conducted studies with a group of coronaviruses in preclinical models showed that when coronaviruses penetrate into the brain, the mortality rate in animals increases, which is presumably due to dysfunction of cardiovascular centre in the brainstem [9]. Our patient had risk factors for vascular disease: obesity, hypertension and CADASIL.

The patient's hypertension was controlled within the optimal range, and the CADASIL-related brain abnormalities according to MRI remained stable over the years, as did the neurological symptoms. It is possible that SARS-Cov-2 infection could have contributed to the deterioration of CADASIL course — aggravation of neurological symptoms and cognitive functions. It should be noted that with timely treatment, the patient had a reduced risk of spontaneous thrombosis — D-dimer levels were within normal limits, while the blood concentration of C-reactive protein during glucocorticoid therapy quickly normalized. Treatment with low-molecular-weight heparins in therapeutic dosages was also carried out. Neurological and cognitive impairments were temporary and most likely associated with viral intoxication.

Thus, in patients with a combination of congenital and infectious angiopathies and COVID-19, neuroimaging is necessary to rule out new foci of cerebrovascular disturbance. It is recommended that early initiation of direct anticoagulant therapy may be beneficial in reducing the thromboembolism risk in these patients. In the presence of respiratory failure and depending on the severity of patients with CADASIL and COVID-19, oxygen therapy is recommended to reduce hypoxia, which also affects the progression of neurological symptoms. Such patients are indicated for invasive and non-invasive mechanical ventilation, continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) therapy or high-flow nasal cannula oxygen in patients of moderate severity. The appointment of a specific antiviral treatment is controversial. The appointment of therapy should be carried out in accordance with the COVID-19 guidelines of the Ministry of Health of Russia [10].

**Relationships and Activities:** none.

## References


1. Scheid R, Preul C, Lincke T, et al. Correlation of cognitive status, MRI- and SPECT-imaging in CADASIL patients. Eur J Neurol. 2006;13:363-70. doi:10.1111/j.1468-1331.2006.01245.x.
2. Di Donato I, Bianchi S, De Stefano N, et al. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) as a model of small vessel disease: update on clinical, diagnostic, and management aspects. BMC medicine. 2017;15(1):1-12. doi:10.1186/s12916-017-0778-8.
3. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727-33. doi:10.1056/NEJMoa2001017.
4. Raptis CA, Hammer MM, Short RG, et al. Chest CT and coronavirus disease (COVID-19): a critical review of the literature to date. American Journal of Roentgenology. 2020;215(4):839-42. doi:10.2214/AJR.20.23202.
5. Liu PP, Blet A, Smyth D, Li H. The science underlying COVID-19: implications for the cardiovascular system. Circulation. 2020;142:68-78. doi:10.1161/CIRCULATIONAHA.120.047549.
6. Miller EC, Elkind MS. Infection and stroke: an update on recent progress. Current neurology and neuroscience reports. 2016;16(1):2. doi:10.1007/s11910-015-0602-9.
7. Klok FA, Kruip MJ, Van Der Meer NJ, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thrombosis research. 2020;191:148-50. doi:10.1016/j.thromres.2020.04.041.
8. Chabriat H, Mrissa R, Levy C, et al. Brain stem MRI signal abnormalities in CADASIL. Stroke. 1999;30(2):457-9. doi:10.1161/01.STR.30.2.457.
9. Li YC, Bai WZ, Hashikawa T, et al. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. Journal of medical virology. 2020;92(6):552-5. doi:10.1002/jmv.25728.
10. Temporary guidelines “Prevention, diagnosis and treatment of new coronavirus infection (COVID-19)” Version 8.1 (01.10.2020). (In Russ.) https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/052/219/original/Временные_MP_COVID-19_%28v.8.1%29.pdf?1601561462.

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-4202

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

# Novel biological markers for the diagnosis and prediction of mortality risk in patients with pulmonary embolism

Podlipaeva A. A.[1,2], Mullova I. S.[1,2], Pavlova T. V.[1,2], Ushakova E. V.[2], Duplyakov D. V.[1,2]

Pulmonary embolism (PE) ranks third in the structure of death causes among all cardiovascular diseases after myocardial infarction and stroke. That is why the timely and earliest possible diagnosis of venous thromboembolism is of particular importance, which will help improve both short-term and long-term patient prognosis.

Given the low specificity of current laboratory parameters, such as D-dimer, NT-proBNP, cardiac troponin I, there is an urgent need to search for new biomarkers that can improve the quality of detection and stratification of VTE, including PE. A diagnostic and prognostic test for PE must be accurate, safe, easily accessible and inexpensive, as well as reproducible and non-invasive.

This review presents the currently available literature data on the latest laboratory parameters that characterize right ventricular dysfunction due to PE and provide an evidence base for stratification of the death risk in this category of patients.

**Keywords:** pulmonary embolism, deep vein thrombosis, markers, outcomes, prognosis.

**Relationships and Activities:** none.

[1]Samara State Medical University, Samara; [2]V. P. Polyakov Samara Regional Clinical Cardiology Dispensary, Samara, Russia.

Podlipaeva A. A. ORCID: 0000-0002-2417-6532, Mullova I. S.* ORCID: 0000-0002-9321-6251, Pavlova T. V. ORCID: 0000-0003-3301-1577, Ushakova E. V. ORCID: 0000-0003-2295-676X, Duplyakov D. V. ORCID: 0000-0002-6453-2976.

*Corresponding author:
irinamullova@gmail.com

**Received:** 19.11.2020
**Revision Received:** 03.12.2020
**Accepted:** 15.12.2020



**For citation:** Podlipaeva A. A., Mullova I. S., Pavlova T. V., Ushakova E. V., Duplyakov D. V. Novel biological markers for the diagnosis and prediction of mortality risk in patients with pulmonary embolism. *Russian Journal of Cardiology*. 2020;25(S4):4202. (In Russ.) doi:10.15829/1560-4071-2020-4202

One of the forms of venous thromboembolism (VTE) — pulmonary embolism (PE) — ranks third in the structure of causes of death among all cardiovascular diseases, being behind the myocardial infarction and stroke. From 39 to 115 cases of PE per 100 thousand people are registered in the world, annually [1]. That is why the timely and the earliest possible diagnosis of VTE is having a special importance, which will help to improve both short-term and long-term prognosis of patients.

Diagnosis of PE at the first contact with medical personnel may be difficult due to the presence of non-specific signs and symptoms, such as cough, shortness of breath, tachypnea, hemoptysis, chest pain, which can be observed in a number of other diseases [2]. In addition to the assessment of right ventricular (RV) function by transthoracic echocardiography (EchoCG) and computed tomographic angiography (CT angiography), have been also used the following biological markers — D-dimer, N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin I [3].

For example, the D-dimer is used in clinical practice to diagnose acute forms of VTE and predict the risk of their recurrences. The D-dimer is the product of the splitting of a fibrin clot by plasmin. At the same time, it has a high sensitivity — a negative result allows to confidently rule out PE in patients with a low and medium probability of it, with an accuracy of up to 97%. However, the D-dimer has a low specificity in the diagnosis of PE, resulting from its increase in many physiological and pathological conditions (pregnancy, cancer, inflammatory processes, and others) [4].

NT-proBNP is a peptide hormone that is produced by cardiomyocytes of the heart ventricles. When the RV is overloaded with pressure, the myocardium is overstretched and damaged, which leads to the release of this hormone and troponin I. The level of natriuretic peptides and troponin I in blood plasma shows the severity of RV dysfunction in acute PE [5, 6].

Heart troponin I, like NT-proBNP, is an important predictor of inhospital or 30-day mortality [7]. In a meta-analysis by Bajaj A, et al., elevated troponin I levels were significantly associated with an increased risk of short-term mortality (odds ratio (OR), 4,80; confidence interval (CI), 95%, 3,25-7,08), PE-related mortality (OR, 3,80; CI 95%, 2,74-5,27), and serious adverse events (OR, 3,65; CI, 95% 2,41-5,53) [8].

Considering the insufficient specificity of the above-mentioned laboratory parameters, there is an urgent need to search for new biomarkers that can improve the quality of detection and stratification of VTE, including PE. The diagnostic and prognostic test for the verification of PE should be accurate, safe, easily accessible and not expensive, as well as reproducible and non-invasive [9, 10]. However, at present, none of the diagnostic tests used meets all these criteria, so it is reasonable to further search for appropriate markers. Our review presents the currently available literature data on the latest laboratory indicators that characterize the dysfunction of the RV, which develops because of PE, and have an evidence base for the stratification of death risk in this category of patients.

*Heart-type cytoplasmic fatty acid-binding protein (H-FABP)*

H-FABP is a cytoplasmic protein with a mass of 15 kDa that is highly expressed in cells with active lipid metabolism. It facilitates the intracellular transport of long-chain fatty acids and mainly located in the myocardium (~0,5 mg/g), small amounts of it are presented in the brain and skeletal muscles. H-FABP enters the bloodstream 2 hours after myocardial injury, reaches concentration in 6-8 hours, and returns to normal within 24-36 hours after previous myocardial ischemia. According to a study by Kaczynskaya A, et al., cytoplasmic protein exceeded cardiac troponin I, NT-proBNP and myoglobin in prognosis of 30-day mortality associated with PE. In this study, the levels of myoglobin, cardiac troponin I, NT-proBNP, and H-FABP were evaluated in 77 patients with a confirmed PE (mean age, 65,3±16 years). Hazard ratio analysis showed that plasma concentrations of H-FABP, myoglobin, cardiac troponin I, and NT-proBNP correlated with 30-day mortality. According to the presented multivariate analysis, the predictive ability of H-FABP measured at admission was even higher than for myoglobin, cardiac troponin I, and NT-proBNP [11].

Similar data were obtained in the study of Bajaj A, et al., who published the result of a meta-analysis of 15 large-scale studies that revealed a direct correlation between increased H-FABP levels and the risk of 30-day complications, such as the need for thrombolytic therapy, endotracheal intubation, catecholamine support for hypotension, recurrence of PE and mortality. The sensitivity and specificity of H-FABP were 71% and 74% for predicting 30-day complications, and 90% and 70% for predicting 30-day mortality, respectively [12].

Another meta-analysis by Dellas C, et al. presents a conclusion based on the examination of 1680 patients with PE, for whom the levels of this protein were defined. The authors concluded that H-FABP ⩾6 ng/ml was associated with an unfavorable short-term outcome (OR, 17,7; 95% CI, 6,0-51,9) and all-cause mortality (OR, 32,9; 95% CI, 8,8-123,2) [13]. As a result, cytoplasmic protein is mentioned as a biological marker of myocardial damage in

the recommendations of the European Society of Cardiology (ESC) for the diagnosis and conduction of patients with PE in the 2014 and 2019 versions [3, 14]. Thus, H-FABP is an early marker of myocardial damage and, therefore, with the help of H-FABP, additional prognostic information about acute PE can be obtained.

*Growth differentiation factor-15 (GDF-15)*

Growth differentiation factor-15, also known as macrophage inhibitory cytokine 1, is a protein from the superfamily of transforming growth factor-beta that is synthesized in the myocardium after ischemic and reperfusion injury, as well as during pressure overload of the RV. Circulating levels of GDF-15 have prognostic significance for the patients with acute coronary syndrome and heart failure [15]. Lankeit M, et al. presented the results of a investigation that evaluated the significance of GDF-15 in predicting the outcomes of PE. The Cox regression model established a nearly 3-time increase in the risk of death for the patients with elevated levels of GDF-15. Using a multivariate logistic regression, laboratory parameters (troponin T and NT-proBNP), and EchoCG data, GDF-15 appeared as an independent predictor of 30-day complications (p=0,033). It also showed higher levels of sensitivity and specificity (Figure 1, 2) — the area under the curve (AUC) for GDF-15 was 0,84 (95% CI, 0,76-0,90) compared to 0,72 (95% CI, 0,63-0,80) for cardiac troponin T and 0,65 (95% CI, 0,56-0,73) for NT-proBNP. Thus, the GDF-15 in combination with troponin I, NT-proBNP and EchoCG with the signs of RV dysfunction can increase the reliability of the prognosis assessment. Basing on the results of this study, baseline levels of GDF-15 were identified as independent predictors of long-term mortality (p<0,001). Basing on the above-mentioned factors, the authors conclude that GDF-15 can be considered as a new promising biomarker for stratifying the death risk due to PE [16]. However, to include GDF-15 in the list of examinations of patients with PE, further research is required.

*Copeptin*

Copeptin is the C-terminal part of provasopressin and is a glycosylated polypeptide that consists of 39 amino acids and contains a leucine-saturated main segment. The significance of copeptin has been studied for acute conditions such as pneumonia, sepsis, heart failure, lower respiratory tract infections, gastrointestinal diseases, and ischemic stroke [17]. Nickel NP, et al. found out that copeptin levels were elevated in patients with pulmonary hypertension (PH) [18]. Serum copeptin levels were evaluated in a retrospective cohort of 92 untreated PH patients and in a second prospective cohort of

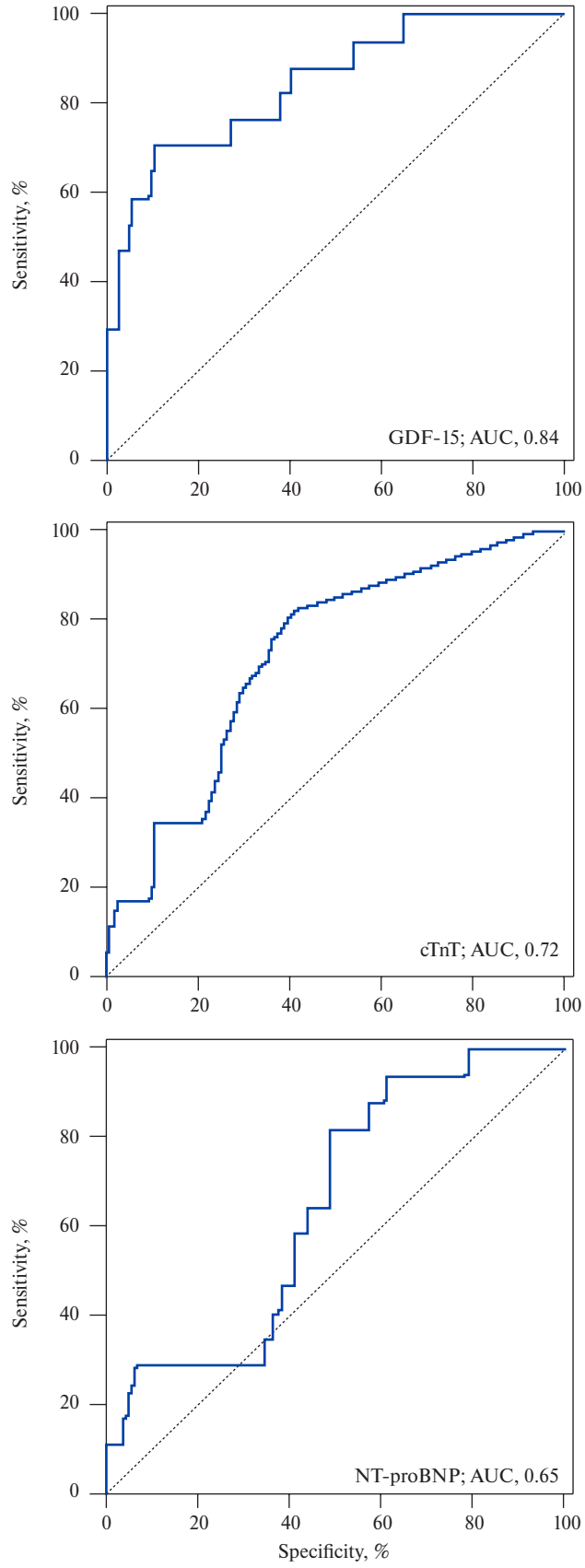


**Figure 1.** Prognostic sensitivity and specificity of growth differentiation factor (GDF-15), cardiac troponin T (cTnT), and N-terminal pro-brain natriuretic peptide (NT-proBNP).

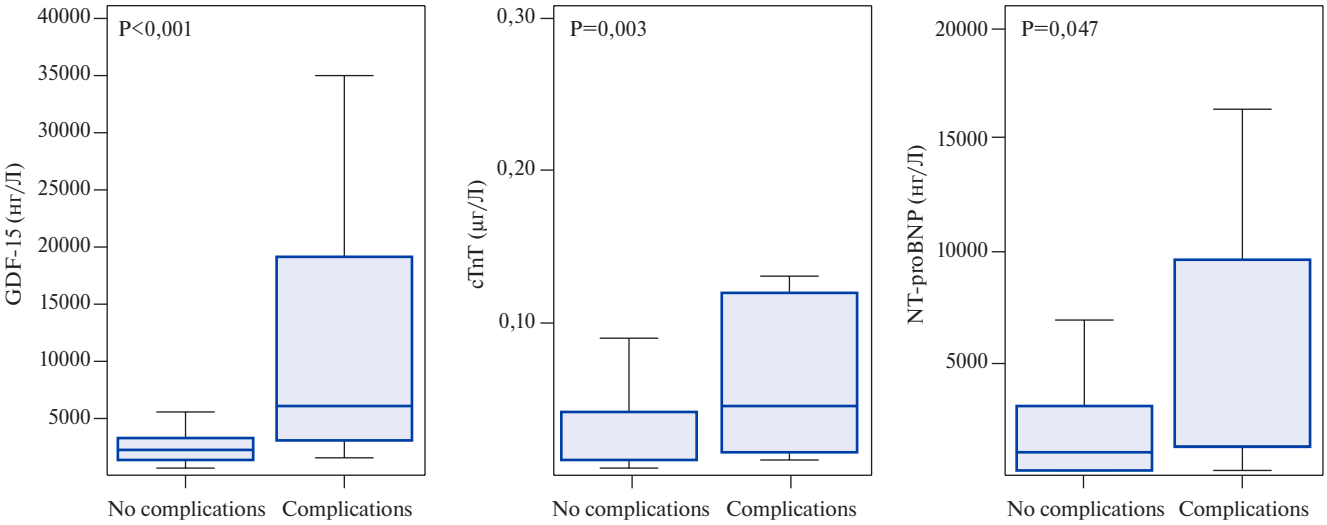


**Figure 2.** Baseline biomarker levels in patients with severe complications in contrast to patients with an uncomplicated 30-day outcome. GDF-15, cTnT, and NT-proBNP levels are expressed as box (25th percentile, median and 75th percentile) and whisker (10 and 90 percentiles).

15 PH patients treated immediately after diagnosis. A comparison of the results showed that the levels of circulating copeptin were increased for untreated patients with PH compared to patients in the control group who received therapy (20,1 pmol/L vs 5,1 pmol/L; p=0,001). Copeptin levels did not correlate with hemodynamic parameters, but decreased after the start of PH therapy (p=0,001). Elevated copeptin levels were associated with the decline of survival level (p<0,001) and proved to be an independent predictor of mortality (OR, 1,4; 95% CI, 1,1-2,0; p=0,02). The result of the study suggests that this polypeptide may be a fairly significant prognostic marker in the stratification of the death risk for patients with acute PE.

In a small study conducted by Kalkan AK, et al. (n=90), patients were divided into 2 groups, depending on the result of CT angiography: with PE (+) (n=47) and without PE (-) (n=43). Copeptin levels were higher in the PE (+) group compared to the PE (-) group: 7,76±4,4 vs 3,81±1,34 ng/dl; p<0,001, respectively. Copeptin levels were significantly correlated with NT-proBNP (r=0,434, p<0,001), D-dimer (r=0,315, p=0,003), and troponin I (r=0,30, p=0,004). An inverse correlation was also found with arterial blood oxygen saturation (r=-0,533, p<0,001) [19]. Thus, the data obtained so far shows that copeptin can be considered as a promising biomarker that will be used as an addition to D-dimer, troponin I, and NT-proBNP in order to improve the accuracy of PE diagnosis [20].

*Indicators of complete blood count*

A complete blood count is one of the most common primary diagnostic procedures. This is a publicly available, widely used, and low-cost study. However, a number of parameters of complete blood count, as a rule, are not considered by clinicians in the aspect of diagnosing and predicting the risk of VTE.

*Red blood cell distribution width (RDW)*

Red blood cell distribution width is part of a complete blood count analysis, which reflects the range of changes in the volume of red blood cells. The main biomolecular mechanism of RDW-PE association is not fully understood, but it is assumed that elevated RDW levels correlate with acute inflammatory markers and blood viscosity indicators. It is believed that such indicators as RDW and the number of red blood cells are important factors contributing to the formation of such prothrombotic conditions as PE and deep vein thrombosis (DVT) [21].

In 2019, a systematic review was published by Hammons L, et al., combining 12 retrospective cohort studies that demonstrated that high levels of RDW are associated with an increased risk of acute PE, severity, and increased mortality in patients with PE. However, the comparison of current studies is limited due to the lack of common approaches to determining the upper limit of RDW (each study uses a different reference value of RDW), the formation of a sample, a wide range of exclusion criteria and the inclusion of various methods used for the diagnosis of PE. Despite the above limitations, the authors of a systematic review showed that RDW as a marker of PE has the right to exist [22]. However, considering the presented data, the significance of RDW in this area requires further study.

*Mean Platelet Volume (MPV)*

MPV reflects the mean platelet volume. There is evidence that MPV is an important variable, since larger platelets have a higher thrombotic potential [23]. MPV is not used as an independent marker in the diagnosis of PE. However, the determination of this indicator may be useful for the initial assessment of PE risk. Elevated MPV has been recognized as an independent risk factor for various clinical conditions associated with hypercoagulation. Gulcan M, et al. (2012) showed that MPV was significantly increased in patients with DVT compared to the control group (8,6±0,8 vs 7,7±0,9 fl, respectively; p<0,001) [24]. Given that PE is a complication of DVT in 50% of cases, MPV may also be directly related to PE [25].

Talay F, et al. published a retrospective study that included patients with suspected PE. As a result of the subsequent sample, 150 patients with confirmed PE and 165 patients without PE were examined [26]. MPV was significantly higher for patients with PE in the conditions of intensive care unit than in the control group (9,42±1,22 fl vs 8,04±0,89 fl, p<0,0001). The area under the curve for patients with a clinically suspected PE, according to the ROC analysis, was 0,634 (95% CI, 0,596-0,702, p=0,023) (Figure 3). The result of this study demonstrated a moderate relationship between the MPV value and PE, if the first was determined at the time of admission of the patient.

In a prospective cohort study of Ghaffari S, et al., the various parameters of complete blood count were also studied, including the MPV. According to the ROC analysis, the sensitivity and specificity of MPV with a cut-off point of 9,85 fl in predicting inhospital mortality was 81% and 50%, respectively. This parameter had lower efficacy for long-term mortality (AUC, 0,54; 95% CI, 0,47-0,61) compared to 30-day mortality. Thus, this marker has demonstrated its significance in determining inhospital all-cause deaths [27]. Perhaps in the future, MPV can prove itself to be a simple and early marker for predicting the death risk for patients with PE, which will become part of the standard protocol for the conducting of patients with VTE.

*Platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR)*

The pathophysiological response of white blood cells to a stress is usually an activation of the sympathetic nervous system and the release of cortisol, as well as an increase in the number of neutrophils, which is associated with a decrease in the number of lymphocytes. This leads to the migration of neutrophils to the affected area. PLR and NLR, as surrogate markers of inflammation, can be used to study the relationship between thrombosis and inflammation during VTE. One of the advantages of PLR and NLR is that they combine information about primary hemostasis and inflammation.

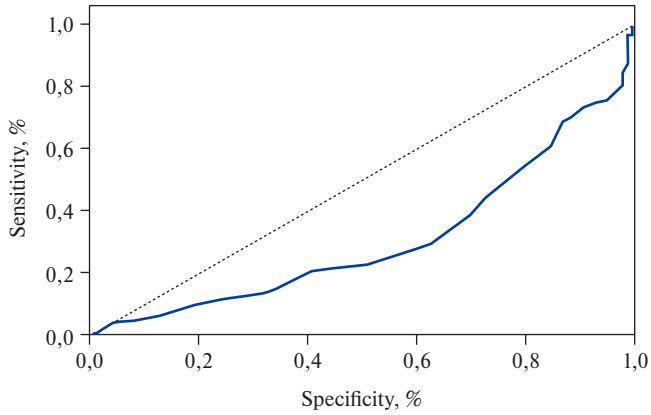


**Figure 3.** ROC analysis of the role of MPV in patients with a clinically suspected PE.

The case-control study by Artoni A, et al., which included 486 patients with VTE, demonstrated that patients with high PLR or NLR did not have an increased risk of VTE complications (OR, 0,89; 95% CI, 0,46-1,76; OR, 0,69; 95% CI, 0,34-1,39, respectively) or cerebral venous thrombosis (OR, 1,65, 95% CI, 0,68-4,00; OR, 0,39. 95% CI, 0,09-1,72, respectively). The authors concluded that there is no association between PLR and NLR values above the acceptable norm and an increased risk of venous thrombosis [28]. However, the data presented are not sufficient for the widespread use of PLR and NLR as markers in the diagnosis of PE, so further larger studies in this area are needed.

*Surfactant protein A (SP-A) and D (SP-D)*

Surfactant is a lipoprotein complex that consists of several phospholipids, neutral lipids (90%), and specific proteins. Protein components, half of which consist of two groups of surfactant-associated proteins: hydrophobic — B (0,7%), C (0,4%), and hydrophilic — A (5,3%) and D (0,6%), make up approximately 10% of the lung surfactant [29]. Among these proteins, SP-A is the most common lung surfactant protein [30, 31]. SP-A is also necessary for the structure of tubular myelin. In a study made by Liu CP, et al. the SP-A level for 32 rats was 1,00±0,00 (control group), 0,44±0,18 (after 24 h), 0,44±0,33 (after 1 week) and 0,52±0,32 (after 2 weeks), respectively (p<0,05), which is conditioned by the developing hypoxia with PE [32]. Thus, the level of SP-A protein significantly decreased in acute PE.

Reduced SP-A expression in the lungs during embolism may be caused by a limited number of type II cells and/or reduced SP-A expression of the

remaining intact cells. At the moment, however, it is difficult to draw conclusions about the significance of SP-A in the diagnosis and prediction of PE risk in humans.

In addition to SP-A, other proteins have been studied, in particular SP-D. Kati C, et al. presented a small study in which 3 groups of patients were identified: patients with diagnosed non-massive PE, submassive PE, and a control group that included healthy people. SP-D levels were determined by immunofluorescence analysis. There were no significant differences in the parameters of this protein between the control group and the group with non-massive PE, but its level was increased in patients with submassive PE [33]. Given the small number of patients (n=60), further studies with a large number of cases, including patients with massive PE, are required.

Thus, qualitative and quantitative changes in the lung surfactant, in particular its protein fractions, are potential markers of lung damage and can be prognostic indicators in patients with PE. In the future, it advisable to pay attention to the presented biomarkers and conduct additional research in this area.

*Lipocalin-type prostaglandin D synthase (L-PGDS)*

L-PGDS can be considered as a protein with a dual function: first, it acts as an enzyme in the production of prostaglandin D2, and, secondly, as an extracellular transporter, due to its lipophilic nature. This marker was first isolated in human cerebrospinal fluid in 1961. MicroRNA of L-PGDS has been found in myocardial cells, in atrial and ventricular endocardial cells, in coronary arteries, in smooth muscle cells, and even in arteriosclerotic plaques. During the last years, the role of L-PGDS has been more frequently studied in the evaluation of kidney function as an alternative to creatinine, as well as as a possible biomarker of cardiovascular diseases.

The prospective study, presented by Mutlu H, et al., involved 90 patients who were admitted to the emergency department with PE, confirmed by CT angiography, as well as 40 healthy volunteers without any diseases. L-PGDS levels were measured in venous blood. For all patients, the risk of death within 30 days was calculated according to the PESI index. As a result, there were significant differences between the levels of L-PGDS in patients with PE and the control group (p=0,024), and the 1-month mortality rate for patients diagnosed with PE was 20% (n=18). The limit value for L-PGDS obtained using the ROC curve analysis for 1-month mortality was 815,26 ng/ml (sensitivity, 83,33%; specificity, 79,17%; AUC, 0,851; OR, 95% CI, 0,760-0,917; p<0,001). Based on this threshold, the logistic regression analysis showed that an increase in L-PGDS simultaneously with an increase in the PESI class (r=0,512, p<0,001) is an independent indicator of death during the first month. The obtained result allows us to consider L-PGDS for predicting the risk of mortality for patients with PE [34].

*Circulating and tissue microRNA*

MicroRNAs are endogenously expressed RNA molecules with a length of 18-22 nucleotides that suppress gene expression at the post-transcriptional level by binding to the three prime untranslated region of the target mRNA. MicroRNAs are involved in almost all biological processes — in cell proliferation, apoptosis, and cell differentiation. It is known that microRNAs play a role in the cardiovascular pathophysiology, including hemostatic disorders [35]. There is evidence that microRNAs are secreted from cells into human biological fluids in both passive and active ways. Such microRNAs are called circulating microRNAs. The change in the expression profile of certain circulating microRNAs reflects the physiological and pathological conditions of cells in which microRNAs are modified and secreted into human biological fluids, such as blood, urine, cerebrospinal fluid, saliva, etc. Circulating microRNAs can be found in various forms — enclosed in exosomes or bound to Ago2 proteins. Due to these forms of transport, the circulating microRNAs are stable and protected from degradation by ribonucleases. Therefore, circulating microRNAs are considered as new potential biomarkers, interesting in many diseases, including VTE.

Xiang Q, et al. analyzed 12 studies in the field of VTE diagnostics that studied microRNAs and presented the following conclusions. The most frequently studied microRNA was miR-134, and the combined results of 12 studies on the predictive ability of this microRNA with a 95% CI showed a sensitivity of 0,82 (0,69-0,91) and a specificity of 0,83 (0,68-0,92). The average AUC value for the ROC curves was 0,89 (0,86-0,92). For other microRNAs, AUC values >0,8, were considered as potential diagnostic indicators. These microRNAs included miR-1233, miR-145, miR-483-3p, miR-582, miR-532, and miR-195 [36]. Thus, this systematic review allows to pay attention to the presented microRNAs in the field of predicting the development of PE in a particular patient.

A study made by Kessler T, et al., which included a small number of patients (n=30), demonstrated that the profile of circulating microRNA-1233 allows to distinguish PE from ST-segment elevation myocardial infarction. MicroRNA-1233 differentiated patients with PE from patients with myocardial infarction and healthy people with

sensitivity of 90 and 90% and specificity of 100 and 92% (AUC, 0,95, p<0,001 and AUC 0,91, p<0,001, respectively) [37]. In the study of Lui T, et al., which also included a small number of patients (n=90), microRNA-221 was determined, the appearance of which correlated with the level of NT-proBNP, troponin I, and D-dimer [38]. Therefore, some microRNAs are possible diagnostic and prognostic markers in patients with PE. However, further research in this area is required to determine the specific microRNAs for PE.

*Apolipoproteins CI, CII, CII, and E*

Apolipoproteins are the protein components of lipoprotein molecules which characterize the blood lipid spectrum. An increase in their concentration is associated with an increased risk of arterial thrombosis [39]. In addition, apolipoproteins can potentially be important in assessing the risk and prognosis of VTE, since an increase in the number of apolipoproteins affects hemostasis and leads to hypercoagulation.

In the study of Orsi FA, et al., a total of 127 patients with VTE and 299 patients without a history of VTE were included. The selection of patients was carried out randomly. The level of apolipoproteins was determined for all patients. The results showed that increased levels of all measured apolipoproteins were associated with higher levels of vitamin K-dependent blood coagulation factors (FII, FVII, FIX, FX, FXI), natural anticoagulants (protein C, protein S, antithrombin), and clot lysis time. In addition, an increase in coagulation factor VIII and von Willebrand factor levels correlated with an increase in apoC-III and apoE levels. Age-and sex-adjusted OR of apolipoproteins E, C-III, CII, and CI to the risk of venous thrombosis were 1,21 (95% CI, 0,98-1,49), 1,19 (95% CI, 0,99-1,44), 1,24 (95% CI, 0,95-1,61) and 1,06 (95% CI, 0,87-1,30) [40]. The authors conclude that the levels of apolipoproteins C-I, C-II, C-III, and E are associated with a variety of blood apoC-III coagulation factors and physiological anticoagulants. At the same time, in the work performed by Van Schouwenburg IM, et al., the lipid profile parameters were not associated with VTE risk [41]. Therefore, this issue remains controversial at the moment, and further research is required to clarify it.

Thus, according to current clinical guidelines, some biological markers (D-dimer, cardiac troponin I, NT-proBNP) are important tools for diagnosing and predicting the risk of death for patients with PE. However, their use has a number of limitations and disadvantages, as a result of which, various biological molecules are currently being studied for the diagnosis of PE. Some of them GDF-15, microRNA, MPV, L-PGDS, SP-A, and SP-D — showed good predictive abilities. At the same time, many of the biomarkers listed in this review are not used in normal clinical practice due to insufficient evidence base. Nevertheless, the results presented on this topic provide the foundation for larger studies and the search for new diagnostic markers.

**Relationships and Activities:** none.

## References


1. Wendelboe AM, Raskob GE. Global burden of thrombosis: epidemiologic aspects. Circ Res. 2016;118:1340-7. doi:10.1161/CIRCRESAHA.115.306841.
2. Duplyakov DV, Pavlova TV, Mullova IS, et al. Differences in the clinical picture and management of patients with confirmed and unconfirmed pulmonary embolism. Russian Journal of Cardiology. 2015;3(119):18-24. (In Russ.) doi:10.15829/1560-4071-2015-03-18-24
3. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). European Heart Journal. 2020;41(4):543-603. doi:10.1093/eurheartj/ehz405.
4. Lippi G, Bonfanti L, Saccenti C, Cervellin G. Causes of elevated D-dimer in patients admitted to a large urban emergency department. Eur. J. Intern. Med. 2014;25(1):45-8. doi:10.1016/j.ejim.2013.07.012.
5. Kucher N, Goldhaber SZ. Cardiac biomarkers for risk stratification of patients with acute pulmonary embolism. Circulation. 2003;108:2191-4. doi:10.1161/01.CIR.0000100687.99687.CE.
6. Pieralli F, Olivotto I, Vanni S, et al. Usefulness of bedside testing for brain natriuretic peptide to identify right ventricular dysfunction and outcome in normotensive patients with acute pulmonary embolism. Am J Cardiol. 2006 May 1;97(9):1386-90. doi:10.1016/j.amjcard.2005.11.075.
7. Cavallazzi R, Nair A, Vasu T, Marik PE. Natriuretic Peptides in Acute Pulmonary Embolism: A Systematic Review. Intensive Care Med. 2008;34(12):2147-56. doi:10.1007/s00134-008-1214-5.
8. Bajaj A, Saleeb M, Rathor P, et al. Prognostic Value of Troponins in Acute Nonmassive Pulmonary Embolism: A Meta-Analysis. Heart Lung Jul-Aug 2015;44(4):327-34. doi:10.1016/j.hrtlng.2015.03.007.
9. Poste G. Bring on the biomarkers. Nature. 2011;469(7329):156. doi:10.1038/469156a.
10. Pradhan NM, Mullin C, Poor HD. Biomarkers and Right Ventricular Dysfunction. Crit Care Clin. 2020;36(1):141-53. doi:10.1016/j.ccc.2019.08.011.
11. Kaczynskaya A, Pelsers MM, Bochowicz A, et al. Plasma heart-type fatty acid binding protein is superior to troponin and myoglobin for rapid risk stratification in acute pulmonary embolism. ClinChimActa. 2006;371(1-2):117-23. doi:10.1016/j.cca.2006.02.032.
12. Bajaj A, Rathor P, Sehgal V, et al. Risk Stratification in Acute Pulmonary Embolism With Heart-Type Fatty Acid-Binding Protein: A Meta-Analysis. J Crit Care. 2015;30(5):1151. doi:10.1016/j.jcrc.2015.05.026.
13. Dellas C, Lobo JL, Rivas A, et al. Risk stratification of acute pulmonary embolism based on clinical parameters, H-FABP and multidetector CT. Int J Cardiol. 2018;265:223-8. doi:10.1016/j.ijcard.2018.04.066.
14. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism Endorsed by the European Respiratory Society (ERS). Russ J Cardiol. 2015;8(124):67-110. doi:10.15829/1560-4071-2015-08-67-110.

15. Wollert KC, Kempf T, Peter T, et al. Prognostic value of growth-differentiation factor-15 in patients with non-ST-elevation acute coronary syndrome. Circulation. 2007;115:962-71. doi:10.1161/CIRCULATIONAHA.106.650846.
16. Lankeit M, Kempf T, Dellas C, et al. Growth differentiation factor-15 for prognostic assessment of patients with acute pulmonary embolism. Am J RespirCrit Care Med. 2008;177(9):1018-25. doi:10.1164/rccm.200712-1786OC.
17. Katan M, Christ-Crain M. The stress hormone copeptin: a new prognostic biomarker in acute illness. Swiss Med Wkly. 2010;140:13101. doi:10.4414/smw.2010.13101.
18. Nickel NP, Lichtinghagen R, Golpon H, et al. Circulating levels of copeptin predict outcome in patients with pulmonary arterial hypertension. Respir Res. 2013;14:130. doi:10.1186/1465-9921-14-130.
19. Kalkan AK, Ozturk D, Erturk M, et al. The diagnostic value of serum copeptin levels in an acute pulmonary embolism. Cardiology J. 2016;23:42-50. doi:10.5603/CJ.a2015.0077.
20. Deveci F, Öner Ö, Telo S, et al. Prognostic value of copeptin in patients with acute pulmonary thromboembolism. ClinRespir J. 2019;13:630-6. doi:10.1111/crj.13071.
21. Akgedik R, Karamanli H, Kurt AB, Günaydın ZY. Usefulness of admission red blood cell distribution width as a predictor of severity of acute pulmonary embolism. Clin Respir J. 2018;12(2):786-94. doi:10.1111/crj.12595.
22. Hammons L, Filopei J, Steiger D, et al. A narrative review of red blood cell distribution width as a marker for pulmonary embolism. J Thromb Thrombolysis. 2019;48;638-47. doi.10.1007/s11239-019-01906-w.
23. Bath PM, Butterworth RJ. Platelet size: measurement, physiology and vascular disease. J Cardiovasc Thorac Res. 2020;12(1):56-62. doi:10.34172/jcvtr.2020.09.
24. Gulcan M, Varol E, Etli M, et al. Mean platelet volume is increased in patients with deep vein thrombosis. Clin Appl Thromb Hemost. 2012;18(4):42730. doi:10.1177/1076029611427437.
25. Varol E, Icli A, Uysal BA, Ozaydin M. Platelet indices in patients with acute pulmonary embolism. Scand J Clin Lab Invest. 2011;71(2):163-7. doi:10.3109/00365513.2010.547596.
26. Talay F, Ocak T, Alcelik A, et al. A New Diagnostic Marker For Acute Pulmonary Embolism In Emergency Department: Mean Platelet Volume. Afr Health Sci. 2014;14(1):94-9. doi:10.4314/ahs.v14i1.15.
27. Ghaffari S, Parvizian N, Pourafkari L, et al. Prognostic value of platelet indices in patients with acute pulmonary thromboembolism. Blood Coagul Fibrinolysis. 1996;7(2):157-61. doi:10.34172/jcvtr.2020.09.
28. Artoni A, Abbattista M, Bucciarelli P, et al. Platelet to Lymphocyte Ratio and Neutrophil to Lymphocyte Ratio as Risk Factors for Venous Thrombosis. Clin Appl Thromb Hemost. 2018;24(5):808-14. doi:10.1177/1076029617733039.
29. Calkovska A, Mokra D, Calkovsky V. Lung surfactant alterations in pulmonary thromboembolism. Eur J Med Res. 2009;14 Suppl 4(Suppl 4):38-41. doi:10.1186/2047-783x-14-s4-38.
30. Rosenberg OA. Pulmonary surfactant and its use in lung diseases. General resuscitation. 2007;1:66-77. (In Russ.)
31. Pastva AM, Wright JR, Williams KL. Immunomodulatory roles of surfactant proteins A and D: implications in lung disease. Proc Am Thorac Soc. 2007 Jul;4(3):252-7. doi:10.1513/pats.200701-018AW.
32. Liu CP, Zhang YJ, Lu WX, et al. The change of pulmonary surfactant associated protein A in acute pulmonary embolism. ZhonghuaJie He He Hu Xi ZaZhi. 2005;28(9):600-3.
33. Kati C, Alacam H, Duran L, et al. The effectiveness of the serum surfactant protein D (Sp-D) level to indicate lung injury in pulmonary embolism. Clin Lab. 2014;60(9):1457-64. doi:10.7754/Clin.Lab.2013.131009.
34. Mutlu H, Kokulu K, Sert ET, Çağlar A. Lipocalin-type prostaglandin D synthase levels are associated with the severity of pulmonary embolism. Heart Vessels. 2020. doi:10.1007/s00380-020-01568-2.
35. Sun Y, Zhang X, Gao H, et al. Expression of microRNA-514a-5p and its biological function in experimental pulmonary thromboembolism. Am J Transl Res. 2019;11(9):5514-30.
36. Xiang Q, Zhang HX, Wang Z, et al. The predictive value of circulating microRNAs for venous thromboembolism diagnosis: A systematic review and diagnostic meta-analysis. Thromb Res. 2019;181:127-34. doi:10.1016/j.thromres.2019.07.024.
37. Kessler T, Erdmann J, Vilne B, et al. Serum microRNA-1233 Is a Specific Biomarker for Diagnosing Acute Pulmonary Embolism. J Transl Med. 2016;14(1):120. doi:10.1186/s12967-016-0886-9.
38. Liu T, Kang J, Liu F. Plasma Levels of microRNA-221 (miR-221) Are Increased in Patients With Acute Pulmonary Embolism. Med SciMonit. 2018;24:8621-26. doi:10.12659/MSM.910893.
39. Griffin JH, Fernandez JA, Deguchi H. Plasma lipoproteins, hemostasis and thrombosis. Thromb Haemost. 2001;86(1):386-94. doi:10.1055/s-0037-1616236.
40. Orsi FA, Lijfering WM, Van der Laarse A, et al. Association of apolipoproteins C-I, C-II, C-III and E with coagulation markers and venous thromboembolism risk. Clin Epidemiol. 2019;11:625-33.
41. Van Schouwenburg IM, Mahmoodi BK, Gansevoort RT, et al. Lipid levels do not influence the risk of venous thromboembolism. Results of a population-based cohort study. Thromb Haemost. 2012;108(5):923-9. doi:10.1160/TH12-06-0426.

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-4181

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

# Hypertension in pregnancy: controversial issues of national and international guidelines

Chulkov V. S.[1], Martynov A. I.[2], Kokorin V. A.[3]

Hypertensive disorders of pregnancy, including pre-existing and gestational hypertension, preeclampsia and eclampsia, complicate up to 10% of pregnancies and represent a significant cause of maternal and perinatal morbidity and mortality. Despite some differences in guidelines, there is consensus that severe hypertension and mild hypertension with organ dysfunction should be managed. However, achieving target values below 160/110 mm Hg remain controversial. The review presents current data on definition, classification, therapy goals and principles used in hypertensive disorders during pregnancy and in the postpartum period in accordance with national and international guidelines.

**Keywords:** hypertension, pregnancy, preeclampsia, treatment.

**Relationships and Activities:** none.

**Acknowledgements.** The study of the efficacy of blood pressure correction device AVR-051 in hypertensive women in the postpartum period is carried out with the support of the Russian Scientific Medical Society of Internal Medicine and OOO Inferum (Yekaterinburg, Russia).

[1]South Ural State Medical University, Chelyabinsk; [2]Moscow State University of Medicine and Dentistry, Moscow; [3]Pirogov Russian National Research Medical University, Moscow, Russia.

Chulkov V. S.* ORCID: 0000-0002-0952-6856, Martynov A. I. ORCID: 0000-0002-9112-8426, Kokorin V. A. ORCID: 0000-0001-8614-6542.

*Corresponding author:
vschulkov@rambler.ru

**Received:** 08.11.2020
**Revision Received:** 25.11.2020
**Accepted:** 29.11.2020



**For citation:** Chulkov V. S., Martynov A. I., Kokorin V. A. Hypertension in pregnancy: controversial issues of national and international guidelines. *Russian Journal of Cardiology*. 2020;25(S4):4181. (In Russ.) doi:10.15829/1560-4071-2020-4181

**Definition and classification**

Hypertension (HTN) definition among pregnant women has not always been standardized. The criterion for HTN in pregnant women is systolic blood pressure (BP) (SBP) ⩾140 mm Hg and/or diastolic BP (DBP) ⩾90 mm Hg, according to the 2000 National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy guidelines [1]. It is required to confirm the blood pressure increase by at least two measurements [2].

Nowadays there are several HTN forms in pregnant women, including chronic HTN, gestational HTN, and preeclampsia (PE), as well as PE, caused by chronic HTN [3-13].

Chronic HTN is the HTN, diagnosed before pregnancy or within the first 20 weeks of its development. HTN criterion is the blood pressure increase ⩾140/90 mm Hg before pregnancy or during its first 20 weeks, which does not disappear after delivery and tends to persist for >42 days after childbirth.

Gestational HTN is defined as an isolated SBP increase ⩾140 mm Hg and/or DBP increase >90 mm Hg, when being measured at least 2 times per 4 hours, developing after the 20$^{th}$ week of pregnancy among women, having normal blood pressure before pregnancy without proteinuria.

PE is a multisystem disorder, complicating pregnancy, childbirth and postpartum period, characterized by increase of SBP ⩾140 mm Hg or DBP ⩾90 mm Hg after the 20$^{th}$ week of pregnancy, when measured at least 2 times per 4 hours among women, who had normal blood pressure before pregnancy, combined with one or several of the following parameters:

— proteinuria (⩾30 mg/mol protein/creatinine ratio; ⩾300 mg/day; or a test strip value ⩾2+);

— kidney damage (creatinine level ⩾90 μmol/l);

— liver damage (elevated transaminase levels, for example, alanine aminotransferase or aspartate aminotransferase >40 IU/l), perhaps with abdominal right upper quadrant or epigastric pain (above stomach);

— neurological complications (for example, altered mental status, blindness, stroke, clonus, severe headaches and persistent scotoma);

— hematological complications (thrombocytopenia — platelet count <150000/μl, disseminated intravascular coagulation, hemolysis);

— uteroplacental dysfunction (for example, intrauterine growth restriction, impaired blood flow in the umbilical artery by Doppler ultrasound, or stillbirth).

PE, caused by chronic HTN, is diagnosed in pregnant women with HTN in the event of PE symptoms emergence.

The experts from the Russian Society of Cardiology (RSC) and the European Society of Cardiology (ESC) suggest to consider hypertension, persisting for 6 weeks (42 days) after delivery, which corresponds to the postpartum period, to be chronic HTN [5, 13], despite the fact that lots of researchers support the position, claiming that hypertension during pregnancy can be classified as chronic, if it persists for >12 weeks after childbirth [14, 15]. In addition, it is worth mentioning that ESC guidelines include "antenatally unclassifiable hypertension", as that which arises before 20 weeks, but has not yet been evaluated after 42 days postpartum for final classification [5]. Several recommendations mention "white-coat hypertension", "masked hypertension", HELLP-syndrome (hemolysis, increased liver enzymes, low platelet count), eclampsia [4, 6-12]. Society of Obstetricians and Gynaecologists of Canada (SOGC) guidelines (2014) mention chronic and gestational HTN with the presence/absence of concomitant diseases [6].

Hypertension degree assessment plays an important role in addition to its form determination. Blood pressure increase classification in pregnant women can be used to characterize the hypertension degree in any form.

There are moderate (not severe) and severe hypertension [14]:

— moderate hypertension is diagnosed in the event of increased SBP, equal to 140-159 mm Hg and/or DBP, equal to 90-109 mm Hg;

— severe hypertension corresponds to SBP ⩾160 mm Hg and/or DBP ⩾110 mm Hg.

Some recommendations describe 3 blood pressure increase degrees, including mild (140-149/90-99 mm Hg), moderate (150-159/100-109 mm Hg) and severe (⩾160/110 mm Hg) [10].

Revealing two hypertension degrees (moderate and severe) during pregnancy has a fundamental importance for the prognosis, management, treatment and obstetrics [11, 12]. Besides this is a commonly known fact, that severe hypertension during pregnancy is related to high stroke [2, 10] and hypertensive encephalopathy risk even at lower blood pressure levels, compared to the general population [15].

It is worth noting that the American College of Obstetricians and Gynecologists (ACOG) recognized that revealing hypertension in pregnant women contradict the modified diagnostic criteria of the American College of Cardiology (ACC) and the American Heart Association (AHA), which identified stage 1 hypertension at a BP level of 130-139/80-89 mm Hg and stage 2 hypertension at BP level of 140/90 mm Hg [16], which requires the diagnostic criteria revision [3, 12]. The remaining

societies, which published their guidelines after 2017, did not change the diagnostic criteria, despite ACC/AHA guidelines.

**Target BP**

The target BP levels are values below 160/110 mm Hg, according to the international guidelines [3-10]. The cross-sectional study of over 81 million hospitalizations confirmed that hypertensive disorders in pregnancy increase the stroke risk by 5,2 times [17]. In addition, the Control of Hypertension In Pregnancy Study (CHIPS) confirmed that severe hypertension is related to higher rates of maternal mortality, pregnancy loss, premature birth, low birth weight, neonatal care 48 hours later and a several other adverse obstetric outcomes, compared with those in the event of mild hypertension, regardless of PE presence [18].

The issue of aggressive treatment of moderate HTN remains controversial in various guidelines [3, 5, 6, 8, 10, 19]. The differences are caused by the lack of data, which clearly confirm obvious benefits and risks, when reaching different blood pressure levels. Recent Cochrane systematic review of antihypertensive drugs in the mild to moderate hypertension treatment in pregnancy analyzed 31 studies with 3485 women. This research compared different drugs with placebo or treatment absence. In addition, Cochrane systematic review includes 29 studies with 2774 women, comparing antihypertensive drugs. The current review confirmed that antihypertensive drugs halved the women number having severe hypertension risk. However, the effect on reducing the incidence of obstetric complications and adverse pregnancy outcomes hasn't been proved. The data obtained are explained by both different terminology approaches, as well as small samples and heterogeneity of participants [20].

The CHIPS multicenter open-label randomized controlled international trial included data of approximately 1000 women with chronic and gestational HTN (DBP of 90-105 mm Hg or 85-105 mm Hg when taking antihypertensive drugs), divided into 2 groups with less-tight control (target DBP <100 mm Hg) and with tight control (target DBP <85 mm Hg). The composite primary (pregnancy loss or high-level neonatal care for more than 48 hours during the first 28 postnatal days) and secondary outcomes (serious maternal complications occurring up to 6 weeks post partum or until hospital discharge) were the same in both groups. However, it was revealed that severe hypertension more often developed in the less-tight control group than in the tight one [21]. The experts are still discussing the current research results, although two sub-analyses confirm that severe hypertension prevention has benefits for both mother and child [18, 22].

Today even larger multicenter randomized controlled Chronic Hypertension and Pregnancy (CHAP) trial is being conducted in the United States, including pregnant women with chronic HTN, either prescribed or not prescribed with monotherapy at a BP level of 140-159/90-104 mm Hg. In addition, the results are assessed when target BP is <140/90 mm Hg or <160/105 mm Hg in antihypertensive therapy group patients. Primary results include poor perinatal outcomes within up to 2 weeks of postpartum (fetal and neonatal death, severe PE, placental abruption and premature birth <35$^{th}$ week of gestation) and low birth weight (birth weight <10$^{th}$ percentile). About 4700 patients are going to participate in the current research, which is almost 5 times more than in the CHIPS study [23].

Given the fact that about 75% of CHIPS research participants suffered from chronic HTN, CHAP results are expected to either confirm or disprove its results, although the current researches designs are different. If CHAP research results ultimately confirm more tight BP control benefits, it will be required to make further analysis of the blood pressure control safety and benefits during pregnancy at the lower BP targets defined in the 2017 AHA/ACC guidelines on BP control.

**Severe HTN treatment**

Such drugs as hydralazine, calcium channel blockers, methyldopa, urapidil, prazosin, isosorbide and even magnesium sulfate in order to lower blood pressure were used in pregnant women in accordance with various guidelines [24]. Recently, intravenous labetalol, hydralazine, calcium channel blockers (for example, short-acting nifedipine) and methyldopa (not being the most frequently used in most countries) have been used more frequently.

There were two meta-analyses on hydralazine effectiveness studies, including 35 (n=3573) and 21 studies (n=893) showed that pregnant women, taking calcium channel blockers, compared with hydralazine, were less likely to increase blood pressure [24, 25]. Besides hydralazine intake is related to adverse outcomes increase from both women (such as hypotension, caesarean section, placental abruption, oliguria) and fetus (effect on heart rate (HR) and lower Apgar scores within 1 minute, compared with other antihypertensive drugs [25]).

There was significant reduction in maternal side effects in the event of nifedipine intake (relative risk (RR), 0,57; 95% confidence interval (CI), 0,35-0,94), when comparing oral nifedipine with intravenous labetalol, according to seven studies meta-analysis with the 363 women. But it is worth noting that there were no significant differences in blood pressure control, maternal morbidity

or mortality incidence, or the effect on perinatal indicators [26].

Sublingual nifedipine and intravenous nitroglycerin were compared in a triple-blind, placebo-controlled study in a small population (n=34) with severe PE, caused by treatment with magnesium sulfate. The current study showed a more pronounced and rapid antihypertensive response, having less variability in the nitroglycerin group and no significant changes in fetal heart rate, despite vasodilator therapy, with a comparable incidence of side effects among fetus and mother in both groups [27].

Thus, all three agents (nifedipine, labetalol, hydralazine) are still included in the international guidelines [3-7, 9, 10]. Methyldopa or sustained-release nifedipine should be used for oral therapy, in accordance with Russian clinical guidelines (2020). It is not recommended to take the diuretics, since PE decreases the circulating blood volume. It is recommended to use intravenous magnesium sulfate in order to prevent eclampsia and treat seizures [13].

Severe organ dysfunction-free hypertension during pregnancy is deemed a hypertensive urgency. Blood pressure must be reduced to less than 160/110 mm Hg with an initial decrease of 25% in the first hours of treatment and a more gradual decrease in subsequent hours. More intense blood pressure decrease may put contribute to the fetus risk due to insufficient perfusion. In contrast, severe hypertension, related to the organ dysfunction in the pulmonary edema or acute kidney injury form is deemed a hypertensive emergency and BP should be reduced much faster.

It is required to pay a special attention to sharp blood pressure drop prevention, which able to cause complications in mother or fetus due to fall below the critical thresholds. Elevated blood pressure should be reduced to SBP 130-140 mm Hg/DBP 80-90 mm Hg at a rate of 10-20 mm Hg every 10-20 minutes.

ESC and RSC recommend to use nitroglycerin as an intravenous infusion in the event of preeclampsia complicated with pulmonary edema [13, 28]. Blood pressure should be reduced by about 30 mm Hg within 3-5 minutes, then it should be reduced until reaching the target blood pressure <140/90 mm Hg [29]. Its appliance duration should not exceed 4 hours due to the negative effect on the fetus and the cerebral edema risk in mother.

It is recommended to immediately prescribe magnesium sulfate to prevent seizures for patients with PE, suffering from organ dysfunction (for example, severe hypertension and proteinuria or hypertension and neurological complications) or eclampsia [3, 12]. This recommendation was based on randomized, placebo-controlled Magpie Trial with more then 10000 women received magnesium sulfate or placebo with BP >140/90 mm Hg and proteinuria of at least 30 mg/dL. Magnesium sulfate intake resulted in PE risk reduction by 58% as well as maternal mortality reduction, compared with placebo [30]. The current data were confirmed by another research, which shown that eclampsia incidence in women with severe PE was lower with magnesium sulfate intake, compared with patients, taking the calcium channel blocker nimodipine [31].

Magnesium sulfate intake data for eclampsia prevention in women with PE without organ dysfunction are more contradictory and show a large number of patients (~100), requiring treatment to prevent one eclampsia case [3, 8].

**Moderate (non-severe) HTN treatment**

It is recommended to first take methyldopa, labetalol and nifedipine in cases of moderate (non-severe) hypertension [3-10]. There are differences in guidelines due to lack of data on a particular drug benefits to prevent adverse outcomes of the mother and fetus [3-7, 9-13].

It is recommended to take methyldopa as the first line agent for blood pressure control in accordance with American, Canadian, European, Australian/New Zealand and Russian guidelines [3-5, 9-13, 32, 33]. This drug has been studied since the 1960s and has long-term safety data among children, whose mothers took it during pregnancy [34]. The prospective cohort study, evaluating pregnancy outcomes in the first exposure trimester, showed that its intake was not accompanied by teratogenic effects, but there was a higher spontaneous miscarriages and preterm birth rate [33]. It is worth noting that methyldopa is inferior to calcium channel blockers and beta-blockers in the severe hypertension prevention (RR, 0,70; 95% CI, 0,56-0,88, 11 studies, 638 women) and may be associated with a higher caesarean section rate (adjusted RR, 0,84; 95% CI, 0,84-0,95, 13 studies, 1330 women), according to Cochrane review on the antihypertensive drugs intake for mild and moderate hypertension [20]. However, CHIPS subanalysis showed that those women, who regularly took methyldopa, had better primary and secondary outcomes, including neonatal weight, lower rates of severe hypertension, PE and preterm birth, compared to those, who took labetalol [35]. In addition, methyldopa intake was related to fewer adverse outcomes in children, including respiratory distress syndrome, seizures and sepsis, compared with oral labetalol, according to retrospective cohort study [36]. Thus, methyldopa remains the drug to decide whether to take or not, until getting more convincing evidence that it is better than other antihypertensive agents.

Oral labetalol is deemed the first-line drug for moderate hypertension during pregnancy in accor-

dance with international guidelines [3-7, 9], while being actually the only first-line drug, recommended by British guidelines [10]. Approximately 75% of women responded positively to oral labetalol monotherapy in a prospective observational research [37]. Earlier randomized studies, comparing it with methyldopa, failed to find out its safety or efficacy benefits [38, 39], while another study showed a borderline labetalol superiority in the prevention of proteinuria, severe hypertension and hospitalizations during pregnancy. Besides it is worth noting that labetalol was independently associated with fewer cumulative maternal and perinatal adverse events [40]. In addition, the study comparing outpatient BP values in pregnant women, regularly taking oral labetalol or sustained-release nifedipine showed that the labetalol group had a more frequent DBP decrease below 80 mm Hg, which may be related to worse uteroplacental perfusion [41]. As for β-blockers (BB), they are deemed first-line drugs in Canada (acebutolol, metoprolol, pindolol, propranolol) [4]. Australian/New Zealand guidelines include oxprenolol as the first line mild treatment within pregnancy [10]. However, there are some controversies regarding teratogenicity and BB effect on the body weight of newborns. Atenolol is known to cause intrauterine growth retardation [41], and many communities do not recommend its use [3, 10-12]. Cochrane review (2013) on oral BB for the mild and moderate hypertension in pregnant women (12 studies, 1346 women), compared to treatment absence or placebo showed an increased low birth weight risk (RR, 1,36; 95% CI, 1,02-1,82) [42]. However, a recent retrospective cohort study showed that there was no association between BB intake and fetal cardiac abnormalities given the appropriate maternal age, body mass index and comorbidities [43]. In addition, an international cohort study, which included >15000 women, who regularly took BB in the first trimester of pregnancy, did not reveal a significant increase in a risk of congenital malformations (RR, 1,07; 95% CI, 0,89-1,30) [44]. In contrast to the current data, another cohort study, which included >10000 women, who took BB in late pregnancy period, showed higher neonatal bradycardia and hypoglycemia risk (RR >1) among patients of BB group (labetalol, metoprolol and atenolol), except for neonatal bradycardia in those, who took metoprolol (RR, 0,59; 95% CI, 0,32-1,09) [45].

Calcium channel blockers, in particular long-acting nifedipine, are first-line drugs in most guidelines [3-7, 9, 10]. It is worth noting that prospective cohort study has demonstrated a minimal teratogenicity profile with calcium channel blockers in the first trimester [46]. Besides it was found out that they were superior over methyldopa in terms of blood pressure control and safer than labetalol in terms of target blood pressure achievement [20]. One of randomized controlled clinical trials compared oral nifedipine versus labetalol in pregnant women with chronic HTN. Finally, it was revealed that there was a more pronounced decrease in central aortic pressure (by 7,4 mm Hg) with a comparable decrease in peripheral blood pressure in both arms, as well as a slight increase in intensive care unit hospitalization and side effects in newborns among the participants, regularly taking nifedipine [47].

It is worth noting that data on amlodipine (another dihydropyridine calcium channel blocker) are very limited. It was concluded that amlodipine does not provide a teratogenic effect in the first trimester of pregnancy [48], while a small pilot study, comparing amlodipine with furosemide for chronic HTN treatment, did not reveal any differences between them on maternal or perinatal outcomes [49].

**Postpartum HTN**

Blood pressure normalizes during the first days after delivery (29-57%, during the first three days; 50-85%, during the first week) among most women and the normalization time depends on a particular health status [50]. There is a danger of increased blood pressure, which requires careful blood pressure monitoring during the first 5-7 day after childbirth, due to physiological circulating blood volume increase. According to the study with 151 women, 5,7% of them suffer from PE or eclampsia after childbirth [50]. Another study showed that 55% of cases were *de novo* of total number of patients (n=22), who joined the emergency department with PE within 4 weeks after delivery [51]. Postpartum hypertension, in addition to hypertensive disorders during pregnancy, may be caused by iatrogenic causes, including intake of non-steroidal anti-inflammatory drugs, hypervolemia (after regional anesthesia), pain (with inadequate analgesia) and anxiety [52, 53].

All antihypertensive drugs, taken by a nursing mother, are excreted in breast milk, but most of them are present there in very low concentrations, except for propranolol and nifedipine, which concentration in milk is similar to the concentration in maternal plasma [5, 28].

It is recommended to go through antihypertensive therapy in order to reach the target SBP and DBP values below 160 mm Hg and 110 mm Hg, respectively, with the possible use of urapidil and sodium nitroprusside for severe postpartum hypertension treatment [10, 54, 55]. It is recommended to start therapy with the preferred use rapid-acting drugs (nifedipine, nitroglycerin, sodium nitroprusside intravenously) in

**Table 1**

**General characteristics of parturient women in both groups**

| | Group 1 (n=8) | Group 2 (n=8) |
|---|---|---|
| Age, years | 32,3±4,2 | 33,1±3,6 |
| Primigravida, n | 2 | 0 |
| Miscarriage, n | 2 | 5 |
| Prior PE, n. | 2 | 0 |
| Anemia, n | 3 | 1 |
| Obesity, n | 1 | 1 |
| Chronic HTN, n | 3 | 3 |
| Gestational HTN, n | 4 | 4 |
| PE, n | 1 | 1 |
| Term birth, n | 7 | 8 |
| Preterm birth, n | 1 | 0 |
| Operative delivery, n | 1 | 1 |
| Methyldopa, n | 7 | 4 |
| Methyldopa in combination with nifedipine, n | 1 | 4 |
| Blood pressure achievement <140/90 mm Hg, day | 3,5±1,5 | 12,6±1,6 |
| Complete antihypertensives' withdrawal | 3 | 0 |

**Abbreviations:** HTN — hypertension, PE — preeclampsia.

**Table 2**

**Blood pressure and heart rate values in postpartum women in the compared groups**

| Parameter | Group 1 | | | | Group 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | Day 1 | Day 7 | Day 14 | Effect | Day 1 | Day 7 | Day 14 | Effect |
| SBP | 141,5±8,2 | 129,3±4,4 | 122,3±4,8 | -19,2 | 143,6±7,6 | 141,2±5,8 | 133,3±5,4 | -13,3 |
| DBP | 90,9±3,0 | 80,5±3,1 | 79,5±2,3 | -10,4 | 93±3,5 | 87,5±4,8 | 86,0±4,3 | -7 |
| HR | 84,3±6,2 | 80,1±6,1 | 78,8±3,8 | -5,5 | 86,3±3,5 | 80,0±5,7 | 79,3±6,5 | -6,3 |

**Abbreviations:** DBP — diastolic blood pressure, SBP — systolic blood pressure, HR — heart rate.

severe hypertension or vascular crises (>150-160/100-110 mm Hg for >15 minutes or an isolated increase in DBP >120 mm Hg with target organ damage) [3, 56]. Any classes of antihypertensive drugs can be used for the postpartum hypertension treatment, according to the Russian clinical guidelines on hypertension in adults. However, methyldopa should be avoided due to postpartum depression risk. It is worth noting that the current issue in our country is complicated by the fact that almost all drugs have contraindications, which makes it difficult to prescribe drug correction within lactation. In the current aspect, non-drug hypertension treatment methods in this category of patients are of clinical interest.

Blood pressure correction device AVR-051 (OOO Inferum, Yekaterinburg, Russian Federation, the registration certificate № RZN 2016/3776 dated March 31, 2016) non-invasively effects the distal dermatome areas, located on the left forearm, by a low frequency pulsed electrical current within 5 minutes twice per day [57].

Our aim was to assess non-invasive percutaneous electrical stimulation effect on blood pressure and its safety in postpartum women.

Working hypothesis was as follows: AVR-051 use in addition to standard antihypertensive therapy improves blood pressure control within 14 days after delivery.

Inclusion criteria:

1) age from 18 to 44 years old,
2) hypertension (increased blood pressure 140/90 mm Hg according to at least two measurements with at least 4 hours interval),
3) signed consent.

Exclusion criteria:

1) associated clinical conditions (including strokes, myocardial infarction, etc.),

2) acute fevers,

3) severe vital organs dysfunctions,

4) damage to skin sites affected by the device.

Research algorithm

1. 1-3 days after delivery:

— selecting patients, obtaining informed consent, briefing, obtaining AVR-051 devices and blood pressure self-monitoring diaries.

2. Within 14 days after delivery:

— AVR-051 device appliance 2 times per day (morning and evening), blood pressure self-monitoring diaries with a schedule, phone monitoring. The maximum procedures course duration was 14 days.

**Clinical trial results and their evaluation**

The exposure group consisted of 8 women with various hypertension forms who were subject to non-invasive percutaneous electrical stimulation with AVR-051 device in addition to antihypertensives' intake.

The comparison group consisted of 8 women of the same age and comorbidities with hypertension who took antihypertensive drugs, but were not subjected to AVR-051 device use (Table 1).

In the first group, 7 cases of pregnancy resulted in timely delivery with the healthy children birth and just 1 patient (with PE) required emergency caesarean section at a period of $36^{th}$-$37^{th}$ weeks, which resulted in normal child birth. In the second group, 7 pregnancies were timely completed and just one patient required emergency caesarean section at the $38^{th}$ week due to PE and normally positioned placental abruption. The mothers continued monotherapy with methyldopa (dopegyt) at a dose of 500 to 1000 mg or combined with prolonged nifedipine at a dose of 30 to 60 mg once a day.

The blood pressure and heart rate dynamics among mothers in the comparison groups is shown in Table 2.

There were following conclusions as the result of AVR-051 use for 2 weeks in women in labour with moderate hypertension:

1) target blood pressure levels achievement <140/90 mm Hg was observed by $3^{th}$-$5^{th}$ days of the postpartum period, in contrast to the comparison group, where the current indicators was ensured just by $10^{th}$-$14^{th}$ days due to the standard approach;

2) antihypertensives' dose minimization, mainly methyldopa (250-500 mg) among 5 out of 8 women in labour and with subsequent complete refusal to take the drug after 14 days of follow-up by 3 women. It turned to be impossible to reduce the dose, which were often prescribed in the combination form, in comparison group;

3) positive SBP and DBP dynamics after 1 week in the experimental group and no significant changes in comparison group;

4) device safety among postpartum women due to the absence of side effects in all cases.

Further research in order to assess the current method effectiveness of BP control in postpartum women is required.

## Conclusion

The International Society for the Study of Hypertension in Pregnancy (ISSHP) has been actively studying various approaches to the hypertension issue among pregnant women since 1998 [58]. It is worth noting that there are still discrepancies in the blood pressure measuring rules, the proteinuria criteria and even the terminology used to classify hypertensive disorders during pregnancy [3-13]. So, this confirms the need for further research in order to reach a consensus on approaches to various hypertension forms diagnosis and treatment in pregnant women. Generally, there is a consensus on the approaches to the management of pregnant women with severe and moderate hypertension with organ dysfunction, despite the differences of various international communities. However, target BP levels in pregnant women remain a matter of debate. It is required to develop targeted personalized strategies for the management of pregnant women with various hypertension forms, in addition to studies with direct comparisons of different antihypertensive drugs.

**Acknowledgements.** The study of the efficacy of blood pressure correction device AVR-051 in hypertensive women in the postpartum period is carried out with the support of the Russian Scientific Medical Society of Internal Medicine and OOO Inferum (Yekaterinburg, Russia).

**Relationships and Activities:** none.

## References


1. Report of the National High Blood Pressure Education Program Working Group on high blood pressure in pregnancy. Am J Obstet Gynecol. 2000;183:S1-S22. doi:10.1016/S0002-9378(00)40820-3.
2. ACOG practice bulletin No. 203: chronic hypertension in pregnancy. Obstet Gynecol. 2019;133:e26-e50. doi:10.1097/AOG.0000000000003020.
3. ACOG practice bulletin No. 202: gestational hypertension and preeclampsia. Obstet Gynecol. 2019;133:e1-e25. doi:10.1097/AOG.0000000000003018.
4. Butalia S, Audibert F, Cote AM, et al. Hypertension Canada's 2018 guidelines for the management of hypertension in pregnancy. Can J Cardiol. 2018;34(5):526-31. doi:10.1016/j.cjca.2018.02.021.
5. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J. 2018;39:3165-241. doi:10.1093/eurheartj/ehy340.
6. Magee LA, Pels A, Helewa M, et al. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive summary. J Obstet Gynaecol Can. 2014;36:416-41. doi:10.1016/s1701-2163(15)30588-0.
7. Tranquilli AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. Pregnancy Hypertens. 2014;4(2):97-104. doi:10.1016/j.preghy.2014.02.001.
8. Brown MA, Magee LA, Kenny LC, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens. 2018;13:291-310. doi:10.1016/j.preghy.2018.05.004.
9. Lowe SA, Bowyer L, Lust K, et al. The SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. Aust N Z J Obstet Gynaecol. 2015;55:e1-29. doi:10.1111/ajo.12399.
10. Webster K, Fishburn S, Maresh M, et al. Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance BMJ. 2019;366:l5119. doi:10.1136/bmj.l5119.
11. Diagnosis and treatment of cardiovascular diseases in pregnancy. 2018. National Recommendations. Russian Journal of Cardiology. 2018;(3):91-134. (In Russ.) doi:10.15829/1560-4071-2018-3-91-134.
12. Hypertensive disorders during pregnancy, during childbirth and the puerperium. Preeclampsia. Eclampsia. Clinical recommendations (protocol). Moscow. 2016:72. (In Russ.)
13. Kobalava ZD, Konradi AO, Nedogoda SV, et al. Arterial hypertension in adults. Clinical guidelines 2020. Russian Journal of Cardiology. 2020;25(3):3786. (In Russ.) doi:10.15829/1560-4071-2020-3-3786.
14. Bernstein PS, Martin JN, Barton JR, et al. Consensus bundle on severe hypertension during pregnancy and the postpartum period. J Obstet Gynecol Neonatal Nurs. 2017;46:776-87. doi:10.1016/j.jogn.2017.05.003.
15. Varon J, Marik PE. The diagnosis and management of hypertensive crises. Chest. 2000;118:214-27. doi:10.1378/chest.118.1.214.
16. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Circulation 2018;138:e426-e483. doi:10.1161/CIR.0000000000000597.
17. Leffert LR, Clancy CR, Bateman BT, et al. Hypertensive disorders and pregnancy-related stroke: frequency, trends, risk factors, and outcomes. Obstet Gynecol. 2015;125(1):124-31. doi:10.1097/AOG.0000000000000590.
18. Magee LA, von Dadelszen P, Singer J, et al. The CHIPS randomized controlled trial (control of hypertension in pregnancy study): is severe hypertension just an elevated blood pressure. Hypertension. 2016;68(5):1153-9. doi:10.1161/HYPERTENSIONAHA.116.07862.
19. Chulkov VS, Vereina NK, Sinitsyn SP, et al. Evaluation of an interrelation of target blood pressure achievement and complications and outcomes of pregnancy in arterial hypertension Cardiovascular Therapy and Prevention. 2014;13(6):23-7. (In Russ.) doi:10.15829/1728-8800-2014-6-23-27.
20. Abalos E, Duley L, Steyn DW, et al. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev. 2018;10:CD002252. doi:10.1002/14651858.CD002252.pub4.
21. Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. N Engl J Med. 2015;372:407-17. doi:10.1056/NEJMoa1404595.
22. Pels A, Mol BWJ, Singer J, et al. Influence of gestational age at initiation of antihypertensive therapy: secondary analysis of CHIPS trial data (control of hypertension in pregnancy study). Hypertension. 2018;71(6):1170-7. doi:10.1161/HYPERTENSIONAHA.117.10689.
23. Chronic Hypertension and Pregnancy (CHAP) Project (CHAP). Ongoing clinical trial. https://clinicaltrials.gov/ct2/show/NCT02299414.
24. Duley L, Meher S, Jones L. Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database Syst Rev. 2013;7:CD001449. doi:10.1002/14651858.CD001449.pub3.
25. Magee LA, Cham C, Waterman EJ, et al. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. BMJ. 2003;327(7421):955-60. doi:10.1136/bmj.327.7421.955.
26. Shekhar S, Gupta N, Kirubakaran R, et al. Oral nifedipine versus intravenous labetalol for severe hypertension during pregnancy: a systematic review and meta-analysis. BJOG. 2016;123(1):40-7. doi:10.1111/1471-0528.13463.
27. Manzur-Verastegui S, Mandeville PB, Gordillo-Moscoso A, et al. Efficacy of nitroglycerine infusion versus sublingual nifedipine in severe pre-eclampsia: a randomized, triple-blind, controlled trial. Clin Exp Pharmacol Physiol. 2008;35(5-6):580-5. doi:10.1111/j.1440-1681.2007.04838.x.
28. Williams B, Mancia G, Spiering W, et al. 2018 practice guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC task force for the management of arterial hypertension. J Hypertens. 2018;36:2284-309. doi:10.1097/HJH.0000000000001961.
29. Dennis AT, Solnordal CB. Acute pulmonary oedema in pregnant women. Anaesthesia. 2012;67(6):646-59. doi:10.1111/j.1365-2044.2012.07055.x.
30. Altman D, Carroli G, Duley L, et al. Do women with preeclampsia, and their babies, benefit from magnesium sulphate? The Magpie trial: a randomised placebo-controlled trial. Lancet. 2002;359(9321):1877-90. doi:10.1016/s0140-6736(02)08778-0.31.
31. Belfort MA, Anthony J, Saade GR, et al. A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. N Engl J Med. 2003;348:304-11. doi:10.1056/NEJMoa021180.
32. Hoeltzenbein M, Beck E, Fietz AK, et al. Pregnancy outcome after first trimester use of methyldopa: a prospective cohort study. Hypertension. 2017;70(1):201-8. doi:10.1161/HYPERTENSIONAHA.117.09110.
33. Chulkov VS, Sinitsyn SP, Vereina NK, et al. Features of the structure, anamnesis and results of pregnancy in arterial hypertension. Human ecology. 2009;10:49-54. (In Russ.)
34. Cockburn J, Moar VA, Ounsted M, et al. Final report of study on hypertension during pregnancy: the effects of specific treatment on the growth and development of the children. Lancet. 1982;1(8273):647-9. doi:10.1016/S0140-6736(82)92202-4.
35. Magee LA, von Dadelszen P, Singer J, et al. Do labetalol and methyldopa have different effects on pregnancy outcome? Analysis of data from the control of hypertension in pregnancy study (CHIPS) trial. BJOG. 2016;123(7):1143-51. doi:10.1111/1471-0528.13569.
36. Xie RH, Guo Y, Krewski D, et al. Association between labetalol use for hypertension in pregnancy and adverse infant outcomes. Eur J Obstet Gynecol Reprod Biol. 2014;175:124-8. doi:10.1016/j.ejogrb.2014.01.019.
37. Stott D, Bolten M, Salman M, et al. A prediction model for the response to oral labetalol for the treatment of antenatal hypertension. J Hum Hypertens. 2017;31(2):126-31. doi:10.1038/jhh.2016.50.

38. Plouin PF, Breart G, Maillard F, et al. Comparison of antihypertensive efficacy and perinatal safety of labetalol and methyldopa in the treatment of hypertension in pregnancy: a randomized controlled trial. Br J Obstet Gynaecol. 1988;95(9):868-76. doi:10.1111/j.1471-0528.1988.tb06571.x.
39. Sibai BM, Mabie WC, Shamsa F, et al. A comparison of no medication versus methyldopa or labetalol in chronic hypertension during pregnancy. Am J Obstet Gynecol. 1990;162:960-6; discussion 966-7. doi:10.1016/0002-9378(90)91297-p.
40. Molvi SN, Mir S, Rana VS, et al. Role of antihypertensive therapy in mild to moderate pregnancy-induced hypertension: a prospective randomized study comparing labetalol with alpha methyldopa. Arch Gynecol Obstet. 2012;285(6):1553-62. doi:10.1007/s00404-011-2205-2.
41. Shawkat E, Mistry H, Chmiel C, et al. The effect of labetalol and nifedipine MR on blood pressure in women with chronic hypertension in pregnancy. Pregnancy Hypertens. 2018;11:92-8. doi:10.1016/j.preghy.2017.12.007.
42. Butters L, Kennedy S, Rubin PC. Atenolol in essential hypertension during pregnancy. BMJ. 1990;301:587-9. doi:10.1136/bmj.301.6752.587.
43. Xie RH, Guo Y, Krewski D, et al. β-blockers increase the risk of being born small for gestational age or of being institutionalized during infancy. BJOG. 2014;121(9):1090-6. doi:10.1111/1471-0528.12678.
44. Bateman BT, Heide-Jorgensen U, Einarsdottir K, et al. β-blocker use in pregnancy and the risk for congenital malformations: an international cohort study. Ann Intern Med. 2018;169(10):665-73. doi:10.7326/M18-0338.
45. Bateman BT, Patorno E, Desai RJ, et al. Late pregnancy beta blocker exposure and risks of neonatal hypoglycemia and bradycardia. Pediatrics. 2016;138(3):e20160731. doi:10.1542/peds.2016-0731.
46. Magee LA, Schick B, Donnenfeld AE, et al. The safety of calcium channel blockers in human pregnancy: a prospective, multicenter cohort study. Am J Obstet Gynecol. 1996;174(3):823-8. doi:10.1016/s0002-9378(96)70307-1.
47. Webster LM, Myers JE, Nelson-Piercy C, et al. Labetalol versus nifedipine as antihypertensive treatment for chronic hypertension in pregnancy: a randomized controlled trial. Hypertension. 2017;70(5):915-22. doi:10.1161/HYPERTENSIONAHA.117.09972.
48. Ahn HK, Nava-Ocampo AA, Han JY, et al. Exposure to amlodipine in the first trimester of pregnancy and during breastfeeding. Hypertens Pregnancy. 2007;26(2):179-87. doi:10.1080/10641950701204554.
49. Vigil-De Gracia P, Dominguez L, Solis A. Management of chronic hypertension during pregnancy with furosemide, amlodipine or aspirin: a pilot clinical trial. J Matern Fetal Neonatal Med. 2014;27:1291-4. doi:10.3109/14767058.2013.852180.
50. Bramham K, Nelson-Piercy C, Brown MJ, et al. Postpartum management of hypertension. BMJ. 2013;346:f894. doi:10.1136/bmj.f894.
51. Matthys LA, Coppage KH, Lambers DS, et al. Delayed postpartum preeclampsia: an experience of 151 cases. Am J Obstet Gynecol. 2004;190(5):1464-6. doi:10.1016/j.ajog.2004.02.037.
52. Yancey LM, Withers E, Bakes K, et al. Postpartum preeclampsia: emergency department presentation and management. J Emerg Med. 2011;40(4):380-4. doi:10.1016/j.jemermed.2008.02.056.
53. Ghuman N, Rheiner J, Tendler BE, et al. Hypertension in the postpartum woman: clinical update for the hypertension specialist. J Clin Hypertens. 2009;11(12):726-33. doi:10.1111/j.1751-7176.2009.00186.x.
54. World Health Organization. WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia. Geneva. 2011:38.
55. Amro FH, Moussa HN, Ashimi OA, et al. Treatment options for hypertension in pregnancy and puerperium. Expert Opin Drug Saf. 2016;15(12):1635-42. doi:10.1080/14740338.2016.1237500.
56. Moroz LA, Simpson LL, Rochelson B. Management of severe hypertension in pregnancy. Semin Perinatol. 2016;40(2):112-8. doi:10.1053/j.semperi.2015.11.017.
57. Malakhov VV, Fedorov AA, Gulyaev VYu, et al. The use of percutaneous electrostimulator "ABP-051" for the correction of blood pressure in clinical practice: methodical recommendation. Ekaterinburg: UGMU, 2018. 26 p. (In Russ)
58. Brown MA, Lindheimer MD, de Swiet M, et al. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy. 2001;20(1):IX-XIV. doi:10.1081/PRG-100104165.

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-4140

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

# Increased natriuretic peptides not associated with heart failure

Chaulin A. M.[1,2], Duplyakov D. V.[1,2]

Natriuretic peptides (NPs) are key diagnostic and prognostic biomarkers for patients with heart failure (HF). The main mechanism for increasing serum NP levels, which is characteristic of heart failure, is secretion in response to myocardial wall distention. At the same time, according to Russian and foreign literature, an increase in NPs is reported in a number of many other conditions that are not associated with HF. The study of these causes and mechanisms is necessary to improve the differential diagnosis of HF.

This article discusses the mechanisms of increasing NPs and their diagnostic value in heart failure, as well as a number of other conditions, such as acute coronary syndrome and coronary artery disease, atrial fibrillation, exercise, kidney failure, taking cardiotoxic drugs (chemotherapy) and sacubitril/valsartan. The article also provides data on identifying NPs in non-invasively obtained biological fluids (urine and oral fluid).

**Keywords:** natriuretic peptides, heart failure, exercise, renal failure, atrial fibrillation, sacubitril/valsartan, false positive causes of elevation.

**Relationships and Activities:** none.

[1]Samara Regional Clinical Cardiology Dispensary, Samara; [2]Samara State Medical University, Samara, Russia.

Chaulin A. M.* ORCID: 0000-0002-2712-0227, Duplyakov D. V. ORCID: 0000-0002-6453-2976.

*Corresponding author: alekseymichailovich22976@gmail.com

**Received:** 11.10.2020
**Revision Received:** 24.10.2020
**Accepted:** 20.11.2020



**For citation:** Chaulin A. M., Duplyakov D. V. Increased natriuretic peptides not associated with heart failure. *Russian Journal of Cardiology*. 2020;25(S4):4140. (In Russ.) doi:10.15829/1560-4071-2020-4140

## BIntroduction. Biochemistry and physiology of natriuretic peptides

Laboratory diagnostics of cardiovascular diseases (CVD) is an integral component of a treatment and prevention strategy aimed at early diagnosis, improving the duration and quality of li fe of patients. The search for new laboratory CVD biomarkers and clarification of diagnostic potential of old ones still remain one of the priority research areas [1]. The current key CVD biomarkers used in routine clinical practice include cardiac troponin isoforms and natriuretic peptides (NP). For the first time, NPs and their properties became known in 1981 with the studies by de Bold AJ, et al. The peptide discovered by them in the atrial myocardium had endocrine properties — a natriuretic effect, as a result of which it was named atrial NP (ANP) or A-type NP. Another historical name for this peptide was auriculin because it was found in the atrial appendage. These studies initiated a close study of the hormonal role of the heart. Subsequently, in 1989, in the ventricular cardiomyocytes, brain NP (BNP) or B-type NP was found. It got its name due to the fact that its structure corresponded to the peptide found earlier in the pig brain. And, finally, the third C-type NP (CNP) was identified in 1991 also in pig brain [2]. Thanks to molecular genetic studies, it became clear that NPs are a family of genetically different, but structurally related peptides. They have a similar structural conformation. ANP and BNP are predominantly expressed and secreted by cardiomyocytes (mainly atrial), and therefore are of interest as biomarkers in patients with CVD. At the same time, C-type NP is mainly produced in the central nervous system, endothelium, bone tissue and reproductive system, and its value in cardiology has not yet been established [2, 3]. According to modern concepts, NPs have hormonal/endocrine (vasodilation, natriuresis, suppression of aldosterone and endothelin) and autocrine/paracrine (antihypertrophic, antifibrotic and proangiogenic) effects [3].

NPs are synthesized as preprohormones on the ribosomes of the endoplasmic reticulum, after which they undergo a number of post-translational changes and are converted into mature peptide molecules (hormones). The main clinically significant features of NPs are presented in Table 1.

The primary stimulus for ANP release from cardiomyocytes is atrial wall stretching [4]. Its blood plasma level in healthy people is approximately 20 pg/ml, while in patients with heart failure (HF) it is 10-100 times higher [5, 6]. The elimination half-life is very short (approximately 2 minutes) and its clearance mainly occurs in the lungs, liver and kidneys, with extraction ratios of 24%, 30% and 35%, respectively [7, 8].

BNP, unlike ANP, is stored in a minimum amount in secretory granules of ventricular cardiomyocytes and is secreted immediately in large portions after stimulation. Its plasma level in healthy people is approximately 3,5 pg/ml and can increase more than 100-fold in patients with HF [8, 9]. BNP has a precursor, the pro-BNP, which is cleaved into active BNP and inactive N-terminal pro-brain natriuretic peptide (NT-proBNP). The half-life of BNP is approximately 20 minutes, and NT-proBNP is approximately 120 minutes, which increases its diagnostic value [2]. The clearance of BNP depends mainly on neutral endopeptidase, while the NT-proBNP clearance depends on renal filtration [3, 5].

It has been shown that in patients with HF, the BNP level correlates with the severity of HF [2, 3, 9]. Using NP to confirm the HF and determine the prognosis or severity of the disease is regulated by the current international guidelines [8, 9].

One of the interesting directions of modern research is the study of cardiomarkers' levels in other biological fluids, primarily in urine and oral fluid [1]. In this regard, the study of NP in the oral fluid may be of particular interest for the non-invasive diagnosis of HF. It was shown that the mean level of BNP in the oral fluid of patients with HF is significantly higher than that of healthy patients. Determination of salivary BNP can be a useful method for the diagnosis and follow-up of patients with HF [10].

## Some factors affecting the NP levels

Large-scale multinational Breathing Not Properly study revealed that sex and age factors can have a significant influence on the NP levels [11]. In addition to biological factors, it depends on concomitant diseases such as obesity, coronary artery disease (CAD), acute coronary syndrome, atrial fibrillation (AF), renal failure, physical activity, cardiotoxic effects in the cancer therapy, taking sacubitril/valsartan, as well as false positive interference factors. Moreover, some conditions can either increase or vice versa decrease the NP concentration, which can lead to over- or under-diagnosis of HF. Below we will sequentially consider their impact on the level of NP and also discuss the main mechanisms underlying its increase.

It has been shown that body mass index (BMI) influences the choice of threshold values in the diagnosis of acute HF. Thus, Daniels L, et al. found that in the presence of obesity for the HF diagnosis, it is desirable to reduce the reference values of NP, and with a thin physique, on the contrary, to increase. In this study, the relationship between NP and BMI was revealed. Thus, the mean BNP levels in thin,

**Table 1**

**Characteristics of various NPs**

| Characteristics | ANP | BNP | NT-proBNP |
|---|---|---|---|
| Number of amino acid residues | 28 | 32 | 76 |
| Main location | In atria | In atria and ventricles | In atria and ventricles |
| Reserve in cardiomyocytes | Large (in intracellular granules) | Minimal | Minimal |
| Basal cardiac secretion | ++ | + | + |
| Gene transcription response to myocardial stretching | Slow | Rapid | Rapid |
| Biological activity | Yes | Yes | No |
| Half life | Short (2 min) | Medium (20 min) | Long (60-120 min) |
| Elimination methods | Renal filtration, blood cleavage by proteases | Renal filtration, blood cleavage by proteases | Renal filtration, blood cleavage by proteases |
| Clinical range | 0-2000 pg/ml | 0-5000 pg/ml | 0-35000 pg/ml |

**Abbreviations:** BNP — brain natriuretic peptide, ANP — atrial natriuretic peptide, NT-proBNP — N-terminal pro-brain natriuretic peptide.

overweight and obese patients with acute HF were 643, 462, and 247 pg/ml, respectively. And in patients without HF of a similar physique, the mean values were 52, 35, and 25 pg/ml, respectively. In general, to maintain the sensitivity of BNP in patients with severe obesity, a lower reference value should be used (⩾54 pg/ml), and for thin patients, a higher one (⩾170 pg/ml), which increases the specificity for the diagnosis of HF [12]. McCord J, et al., sudying the effect of BMI on NP levels, confirmed the dependence of the BNP level on the patient's weight. At the same time, when adjusting data on sex, age, severity of HF and kidney injury, BMI accounting did not bring additional diagnostic value [13].

A number of studies report that serum NP concentration in women is significantly higher than in men, however, the specific mechanisms underlying these features are still unknown [14-17]. In women, NP levels may be influenced by menstrual status, menopausal status, or use of hormone therapy [18, 19]. The most likely causes of sex differences in NP levels are thought to be the effects of sex hormones. It was reported that estrogens have a stimulating effect on NP formation, while androgens, on the contrary, inhibit it [14, 17, 20].

In the large study by Lam C, et al. with 4,056 patients, the serum concentration of NT-proBNP in men was significantly lower than in women in similar age groups, regardless of menopausal status and hormone therapy use. In addition, in women who received hormonal contraceptives, NT-proBNP was higher than in women who did not take them [16]. However, women taking hormonal contraceptives had the lowest levels of free testosterone and the highest concentrations of sex steroid binding globulin (SSBG). In both men and women, NT-proBNP increase was associated with a decrease in free testosterone and an increase in SSBG. These data are consistent with the hypothesis that androgens suppress NT-proBNP and suggest that differences in free testosterone may largely explain sex and hormonal differences in circulating NP levels [14]. In other words, there is a direct relationship between the NP levels and SSBG, and there is an inverse relationship between the NP levels and testosterone.

## NPs in acute and chronic types of coronary artery disease

Myocardial ischemia leads to left ventricular (LV) systolic and diastolic dysfunction, which leads to an increase in NP concentration. In addition, when cardiomyocytes die, NPs will also be released into the blood. Thus, it should be expected that the greater the ischemia degree, the greater the NP increase. It is logical to expect that NP will be a valuable prognostic biomarker in both the short and long term in patients with acute coronary syndrome.

Patients with ST-segment elevation myocardial infarction (STEMI) who have serum BNP levels >80 pg/ml on admission have a 7,2-fold increase in 30-day mortality [21]. The ASSENT-2 and ASSENT-PLUS studies reported that the level of NT-proBNP at admission was an independent marker of one-year mortality in STEMI patients receiving thrombolytic therapy [22]. The same was observed in STEMI patients who underwent primary percutaneous coronary intervention [23-25]. In patients with non-STEMI m, the NL levels also have a high predictive value in predicting in-hospital and six-month mortality [26-28].

In chronic coronary artery disease, even the development of insignificant myocardial ischemia led to blood NP increase, while the predictive value of NT-proBNP was superior to that of BNP in predicting the risk of adverse events [29].

## NPs and AF

It is well known that AF can cause dyspnea in the absence of HF and also lead to an increase in serum NPs. The PRIDE (ProBNP Investigation of Dyspnea in the Emergency Department) study included 599 patients who admitted to the emergency department with complaints of shortness of breath. To confirm/rule out the AF, all patients underwent electrocardiography. NT-proBNP levels were determined. AF was detected in 13% of patients at the time of admission, while their mean NT-proBNP level was significantly higher than in patients without AF (2934 pg/ml vs 294 pg/ml, p<0,0001). In patients without acute HF and with AF, the mean NT-proBNP level was significantly higher than in patients without AF (932 vs 121 pg/ml, p=0,02) [30].

In AF patients, it is recommended to use higher cut-off levels of BNP and NT-proBNP for the diagnosis of HF. The BACH (Biomarkers in ACute Heart Failure) study, which included 1445 patients with acute dyspnea, showed that the diagnostic value of BNP and NT-proBNP in acute HF decreased in the presence of AF [31]. The BNP threshold of 100 pg/ml had a specificity of 40% and 79% for the diagnosis of acute HF, respectively, in patients with and without AF. In patients with AF, a threshold of 200 pg/ml led to a significant improvement in the specificity of HF diagnosis compared to the conventional level of 100 pg/ml, with little sensitivity loss [31].

An inverse relationship was also noted between the NP levels and AF, namely, higher concentrations of NP are a risk factor for AF [32]. This may be due to a decrease in the effective refractory period in atrial cardiomyocytes [33].

The onset of AF in the early postoperative period is a poor prognostic factor. According to a meta-analysis with 5 studies, the level of NP can predict the risk of postoperative AF [32, 33].

## NPs and renal failure

NPs are low-molecular-weight peptides, which they can pass through the glomerular filter and blood-saliva barrier into the urine and oral fluid, respectively [1, 10]. Ng L, et al. found that in patients with LV systolic dysfunction, urinary NT-proBNP levels were higher than in controls [34]. Glomerular filtration disorders, characteristic of chronic renal failure (CRF), are accompanied by an increase in serum NPs. However, Franz M, et al. found that in patients with impaired renal function, the NP excretion is increased. The progression of renal failure leads to a significant increase in the circulating NPs [35].

It has been shown that the BNP threshold for HF diagnosis can change if the glomerular filtration rate (GFR) is <60 ml/min/1,73 $m^2$. The BNP level in patients with GFR <60 ml/min/1,73 $m^2$ was 2-4 times higher than in patients with GFR ⩾60 ml/min/1,73 $m^2$ [36, 37]. These findings are consistent with the the multinational Breathing Not Properly study of 1586 patients with acute dyspnea and a GFR <60 ml/min/1,73 $m^2$. It turned out that the optimal threshold values for BNP varied from 70,7 to 225,0 pg/ml for GFR ⩾90 and <30 ml/min/1,73 $m^2$, respectively [38]. Thus, the NP level significantly increases with a GFR decrease, which has a significant impact on the diagnostic value in HF. It is likely that in patients with combination of HF and CRF, higher reference values should be used compared to patients without CRF. The most likely mechanism responsible for the increase in serum levels of NP in CRF is impaired NP elimination with urine.

## NPs and exercise

Prolonged and intense physical activity can adversely affect the state of cardiomyocytes, as evidenced by a significant increase in cardiomarkers such as heart-type fatty acid-binding protein, copeptin, troponin I or T, NPs, and some others [39-42]. Scharhag J, et al. found a NT-proBNP increase in 81 of 105 athletes after prolonged endurance exercise. The degree of NT-proBNP increase depended on the duration and severity of physical activity. The greatest increase in the NT-proBNP was observed in runners who 100-km running (mean value, 200 ng/l; 25/75 percentile, 115/770 ng/l). NT-proBNP was not associated with exercise-induced increases in troponin, but it was positively correlated with exercise time [39]. Considering that after a marathon run, the normalization of NT-proBNP occurs within 72 hours, it is assumed that this is based on a transient cardiomyocyte metabolism impairment [40].

Another hypothetical mechanism is the formation and release of membrane vesicles, in which the cytoplasmic proteins can also escape from the cardiomyocyte. A similar mechanism was first described by Schwartz P, conducting experiments on *in vitro* isolated cultured cardiomyocytes [43].

## Medications affecting the NP levels

Myocardial injury by cardiotoxic drugs, in particular, chemotherapeutic agents used in the treatment of cancer, is accompanied by serum NP increase. NP concentration closely correlates with LV ejection fraction and LV global longitudinal strain after chemotherapy [44].

**Table 2**

**Causes and mechanisms for NP increase**

| Cause of NP increase | Impact and mechanism of increasing NPs |
|---|---|
| Heart failure | Stretching of atrial and ventricular myocardium |
| Biological factors:<br>— Sex<br>— Age<br>— BMI | Female patients have higher levels of NPs, presumably due to the stimulating effect of female sex hormones and the inhibitory effect of male sex hormones on NP synthesis<br>Older patients have higher NP levels<br>Patients with a lower BMI have higher NP levels |
| CAD and ACS | Cardiomyocyte damage and release of cytosolic proteins, including NPs |
| AF | Myocardial ischemia due to imbalance between the oxygen delivery and required volume for adequate myocardial function |
| Renal failure | Decrease in GFR leads to decreased elimination of NPs in urine and an increase in the blood serum |
| Physical exercise | Increased myocardial load, transient ischemia, membrane vesicles |
| Cardiotoxic (chemotherapy drugs) | Cardiomyocyte damage and release of cytoplasmic enzymes and proteins, including NPs |
| Sacubitril/valsartan | Sacubitril/valsartan inhibits the neprilisin, which leads to NP accumulation |
| False positive causes of increase | — Heterophilic antibodies<br>— Rheumatoid factor<br>— Preanalytical errors (hemolysis, lipemia, blood clots) |

**Abbreviations:** CAD — coronary heart disease, BMI — body mass index, NPs — natriuretic peptides, ACS — acute coronary syndrome, GFR — glomerular filtration rate, AF — atrial fibrillation.

One of the factors contributing to a change in cardiomarker concentration is its metabolic characteristics, in particular, the half-life. Elimination of many cardiomarkers, including NPs, is carried out by blood filtration in the kidneys. The degradation of protein molecules is mediated by enzymes inside and outside the cell. To date, it is known that NPs circulating in the blood are cleaved by neprilysin, which belongs to the class of zinc-dependent metalloproteases. When neprilysin is blocked, the BNP molecules are not cleaved and circulate in the blood (accumulate) longer, and their concentration increases [45, 46]. Sacubitril in combination with the angiotensin receptor antagonist valsartan inhibits neprilysin, thereby increasing the blood concentration of BNP. In addition to the diagnostic value, this also has a therapeutic effect, since NPs have a beneficial effect on the myocardium of HF patients [45]. At the same time, the neprilysin does not degrade NT-proBNP, therefore, inhibition of neprilisin with sacubitril/valsartan does not affect the NT-proBNP concentration in any way. Therefore, in patients taking sacubtril/valsartan, it is recommended to determine NT-proBNP for diagnostics [45, 46].

## Reasons for a false positive increase in NPs

A false positive increase in NPs may be due to the heterophile antibodies [47-49]. The interference mechanism is associated with the effect of heterophile antibodies on the immune reaction between the diagnostic anti-NP antibody and the corresponding antigen. However, the number of cases described in the literature on false positive NPs due to heterophile antibodies is significantly lower than the number of cases described in terms of the effect of heterophile antibodies on cardiac troponins. Solter P, et al. revealed the effect of canine heterophile antibodies on enzyme immunoassay in the BNP determination [47]. Collin-Chavagnac D, et al. described a clinical case of a false-positive increase in NPs caused by monoclonal antibodies of the IgM class in a 75-year-old patient with Waldenstrom macroglobulinemia [48]. In this disease, tumor proliferation of B-lymphocytes and hypersecretion of monoclonal IgM are noted, which cause interference in immunochemical laboratory tests. Rheumatoid factor can be another reason for a false-positive increase in NPs [49]. Additional factors affecting the results of laboratory determination of NPs may be preanalytical errors leading to hemolysis, lipemia and blood clots [1, 50, 51]. Such elements adversely affect the optical density of the analyzed solution, which is then used to calculate the concentration of NPs.

The main reasons and mechanisms for increasing the NPs considered above are presented in Table 2.

## Conclusion

NPs are valuable biomarkers widely used for the diagnosis and prognosis of a number of CVDs. An

increased NPs in HF occurs due to cardiac wall stretching, which stimulates the NP secretion by cardiomyocytes. In addition to HF, there are a number of reasons for the increase in NPs, which may be based on many other mechanisms not associated with myocardial stretching. According to some reports, in addition to blood serum, NPs are present in the oral fluid and urine. Further study is of both practical and research interest.

**Relationships and Activities:** none.

## References


1. Chaulin AM, Karslyan LS, Grigoriyeva EV, et al. Clinical and Diagnostic Value of Cardiac Markers in Human Biological Fluids. Kardiologiia. 2019;59(11):66-75. (in Russ.) doi:10.18087/cardio.2019.11.n414.
2. Nishikimi T, Kuwahara K, Nakao K. Current biochemistry, molecular biology, and clinical relevance of natriuretic peptides. J Cardiol. 2011;57(2):131-40. doi:10.1016/j.jjcc.2011.01.002.
3. Vinnakota S, Chen HH. The Importance of Natriuretic Peptides in Cardiometabolic Diseases. J Endocr Soc. 2020;4(6):bvaa052. doi:10.1210/jendso/bvaa052.
4. Nakao K, Sugawara A, Morii N, et al. The pharmacokinetics of alpha-human atrial natriuretic polypeptide in healthy subjects. Eur J Clin Pharmacol. 1986;31(1):101-3. doi:10.1007/BF00870995.
5. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. Eur J Heart Fail. 2004;6(3):257-60. doi:10.1016/j.ejheart.2003.12.015.
6. Abassi Z, Karram T, Ellaham S, et al. Implications of the natriuretic peptide system in the pathogenesis of heart failure: diagnostic and therapeutic importance. Pharmacol Ther. 2004;102(3):223-41. doi:10.1016/j.pharmthera.2004.04.004.
7. Daniels LB, Maisel AS. Natriuretic peptides. J Am Coll Cardiol. 2007;50(25):2357-68. doi:10.1016/j.jacc.2007.09.021.
8. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200. doi:10.1093/eurheartj/ehw128.
9. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136(6):e137-e161. doi:10.1161/CIR.0000000000000509.
10. Joharimoghadam A, Tajdini M, Bozorgi A. Salivary B-type natriuretic peptide: a new method for heart failure diagnosis and follow-up. Kardiol Pol. 2017;75(1):71-7. doi:10.5603/KP.a2016.0097.
11. Maisel AS, Clopton P, Krishnaswamy P, et al. Impact of age, race, and sex on the ability of B-type natriuretic peptide to aid in the emergency diagnosis of heart failure: results from the Breathing Not Properly (BNP) multinational study. Am Heart J. 2004;147(6):1078-84. doi:10.1016/j.ahj.2004.01.013.
12. Daniels LB, Clopton P, Bhalla V, et al. How obesity affects the cut-points for B-type natriuretic peptide in the diagnosis of acute heart failure. Results from the Breathing Not Properly Multinational Study. Am Heart J. 2006;151(5):999-1005. doi:10.1016/j.ahj.2005.10.011.
13. McCord J, Mundy BJ, Hudson MP, et al. Relationship between obesity and B-type natriuretic peptide levels. Arch Intern Med. 2004;164(20):2247-52. doi:10.1001/archinte.164.20.2247.
14. Wang TJ, Larson MG, Levy D, et al. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. Am J Cardiol. 2002;90(3):254-8. doi:10.1016/s0002-9149(02)02464-5.
15. Redfield MM, Rodeheffer RJ, Jacobsen SJ, et al. Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol. 2002;40(5):976-82. doi:10.1016/s0735-1097(02)02059-4.
16. Lam CS, Cheng S, Choong K, et al. Influence of sex and hormone status on circulating natriuretic peptides. J Am Coll Cardiol. 2011;58(6):618-26. doi:10.1016/j.jacc.2011.03.042.
17. Clerico A, Fontana M, Vittorini S, Emdin M. The search for a pathophysiological link between gender, cardiac endocrine function, body mass regulation and cardiac mortality: proposal for a working hypothesis. Clin Chim Acta. 2009;405(1-2):1-7. doi:10.1016/j.cca.2009.03.050.
18. Chang AY, Abdullah SM, Jain T, et al. Associations among androgens, estrogens, and natriuretic peptides in young women: observations from the Dallas Heart Study. J Am Coll Cardiol. 2007;49(1):109-16. doi:10.1016/j.jacc.2006.10.040.
19. Kawano H, Nagayoshi Y, Soejima H, et al. B-type natriuretic peptide after hormone therapy in postmenopausal women with chest pain and normal coronary angiogram. Menopause. 2008;15(2):352-6. doi:10.1097/gme.0b013e31806548f6.
20. Saenger AK, Dalenberg DA, Bryant SC, et al. Pediatric brain natriuretic peptide concentrations vary with age and sex and appear to be modulated by testosterone. Clin Chem. 2009;55(10):1869-75. doi:10.1373/clinchem.2009.123778.
21. Mega JL, Morrow DA, De Lemos JA, et al. B-type natriuretic peptide at presentation and prognosis in patients with ST-segment elevation myocardial infarction: an ENTIRE-TIMI-23 substudy. J Am Coll Cardiol. 2004;44(2):335-9. doi:10.1016/j.jacc.2004.04.033.
22. Björklund E, Jernberg T, Johanson P, et al. Admission N-terminal pro-brain natriuretic peptide and its interaction with admission troponin T and ST segment resolution for early risk stratification in ST elevation myocardial infarction. Heart. 2006;92(6):735-40. doi:10.1136/hrt.2005.072975.
23. Siva Sankara C, Rajasekhar D, Vanajakshamma V, et al. Prognostic significance of NT-proBNP, 3D LA volume and LV dyssynchrony in patients with acute STEMI undergoing primary percutaneous intervention. Indian Heart J. 2015;67(4):318-27. doi:10.1016/j.ihj.2015.04.023.
24. Tolppanen H, Rivas-Lasarte M, Lassus J, et al. Combined measurement of soluble ST2 and Aminoterminal pro-B-Type natriuretic peptide provides early risk assessment of severity in cardiogenic shock complicating acute coronary syndrome. Crit Care Med. 2017;45:e666-e73. doi:10.1097/CCM.0000000000002336.
25. Wang YP, Wang JH, Wang XL, et al. Roles of ST2, IL-33 and BNP in predicting major adverse cardiovascular events in acute myocardial infarction after percutaneous coronary intervention. J Cell Mol Med. 2017;21(11):2677-84. doi:10.1111/jcmm.13183.
26. Vogiatzis I, Dapcevic I, Datsios A, et al. A Comparison of Prognostic Value of the Levels of ProBNP and Troponin T in Patients with Acute Coronary Syndrome (ACS). Med Arch. 2016;70(4):269-73. doi:10.5455/medarh.2016.70.269-273.
27. Schellings DA, Adiyaman A, Dambrink JE, et al. Predictive value of NT-proBNP for 30-day mortality in patients with non-ST-elevation acute coronary syndromes: a comparison with the GRACE and TIMI risk scores. Vasc Health Risk Manag. 2016;12:471-6. doi:10.2147/VHRM.S117204.
28. Savonitto S, Morici N, Nozza A, et al. Predictors of mortality in hospital survivors with type 2 diabetes mellitus and acute coronary syndromes. Diab Vasc Dis Res. 2018;15(1):14-23. doi:10.1177/1479164117735493.
29. Mishra RK, Beatty AL, Jaganath R, et al. B-type natriuretic peptides for the prediction of cardiovascular events in patients with stable coronary heart disease: the Heart and Soul Study. J Am Heart Assoc. 2014;3(4):e000907. doi:10.1161/JAHA.114.000907.

30. Morello A, Lloyd-Jones DM, Chae CU, et al. Association of atrial fibrillation and amino-terminal pro-brain natriuretic peptide concentrations in dyspneic subjects with and without acute heart failure: results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study. Am Heart J. 2007;153(1):90-7. doi:10.1016/j.ahj.2006.10.005.
31. Richards M, Di Somma S, Mueller C, et al. Atrial fibrillation impairs the diagnostic performance of cardiac natriuretic peptides in dyspneic patients: results from the BACH Study (Biomarkers in ACute Heart Failure). JACC Heart Fail. 2013;1(3):192-9. doi:10.1016/j.jchf.2013.02.004.
32. Mandalenakis Z, Eriksson H, Welin L, et al. Atrial natriuretic peptide as a predictor of atrial fibrillation in a male population study. The Study of Men Born in 1913 and 1923. Int J Cardiol. 2014;171(1):44-8. doi:10.1016/j.ijcard.2013.11.042.
33. Simmers D, Potgieter D, Ryan L, et al. The use of preoperative B-type natriuretic peptide as a predictor of atrial fibrillation after thoracic surgery: systematic review and meta-analysis. J Cardiothorac Vasc Anesth. 2015;29(2):389-95. doi:10.1053/j.jvca.2014.05.015.
34. Ng LL, Loke IW, Davies JE, et al. Community screening for left ventricular systolic dysfunction using plasma and urinary natriuretic peptides. J Am Coll Cardiol. 2005;45(7):1043-50. doi:10.1016/j.jacc.2004.12.058.
35. Franz M, Woloszczuk W, Hörl WH. Plasma concentration and urinary excretion of N-terminal proatrial natriuretic peptides in patients with kidney diseases. Kidney Int. 2001;59(5):1928-34. doi:10.1046/j.1523-1755.2001.0590051928.x.
36. Tsutamoto T, Wada A, Sakai H, et al. Relationship between renal function and plasma brain natriuretic peptide in patients with heart failure. J Am Coll Cardiol. 2006;47(3):582-6. doi:10.1016/j.jacc.2005.10.038.
37. Forfia PR, Watkins SP, Rame JE, et al. Relationship between B-type natriuretic peptides and pulmonary capillary wedge pressure in the intensive care unit. J Am Coll Cardiol. 2005;45(10):1667-71. doi:10.1016/j.jacc.2005.01.046.
38. McCullough PA, Duc P, Omland T, et al. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. Am J Kidney Dis. 2003;41(3):571-79. doi:10.1053/ajkd.2003.50118.
39. Scharhag J, Herrmann M, Urhausen A, et al. Independent elevations of N-terminal pro-brain natriuretic peptide and cardiac troponins in endurance athletes after prolonged strenuous exercise. Am Heart J. 2005;150(6):1128-34. doi:10.1016/j.ahj.2005.01.051.
40. Scherr J, Braun S, Schuster T, et al. 72-h kinetics of high-sensitive troponin T and inflammatory markers after marathon. Med Sci Sports Exerc. 2011;43(10):1819-27. doi:10.1249/MSS.0b013e31821b12eb.
41. Perrone MA, Macrini M, Maregnani A, et al. The effects of a 50 km ultramarathon race on high sensitivity cardiac troponin I and NT-proBNP in highly trained athletes [published online ahead of print, 2020 Jul 10]. Minerva Cardioangiol. 2020;10.23736/S0026-4725.20.05281-0. doi:10.23736/S0026-4725.20.05281-0.
42. Martínez-Navarro I, Sánchez-Gómez JM, Collado-Boira EJ, et al. Cardiac Damage Biomarkers and Heart Rate Variability Following a 118-Km Mountain Race: Relationship with Performance and Recovery. J Sports Sci Med. 2019;18(4):615-22.
43. Schwartz P, Piper HM, Spahr R, Spieckermann PG. Ultrastructure of cultured adult myocardial cells during anoxia and reoxygenation. Am J Pathol. 1984;115(3):349-61.
44. Hinrichs L, Mrotzek SM, Mincu RI, et al. Troponins and Natriuretic Peptides in Cardio-Oncology Patients-Data From the ECoR Registry. Front Pharmacol. 2020;11:740. doi:10.3389/fphar.2020.00740.
45. King JB, Bress AP, Reese AD, Munger MA. Neprilysin Inhibition in Heart Failure with Reduced Ejection Fraction: A Clinical Review. Pharmacotherapy. 2015;35(9):823-37. doi:10.1002/phar.1629.
46. Jhund PS, McMurray JJ. The neprilysin pathway in heart failure: a review and guide on the use of sacubitril/valsartan. Heart. 2016;102(17):1342-7. doi:10.1136/heartjnl-2014-306775.
47. Solter PF, Oyama MA, Sisson DD. Canine heterophilic antibodies as a source of false-positive B-type natriuretic peptide sandwich ELISA results. Vet Clin Pathol. 2008;37(1):86-95. doi:10.1111/j.1939-165X.2008.00002.x.
48. Collin-Chavagnac D, Manchon M, Traulle C, Bernon H. False-positive BNP results in a 78-year-old man caused by monoclonal IgM-kappa: a case report. Clin Chim Acta. 2007;384(1-2):179. doi:10.1016/j.cca.2007.05.020.
49. Xu L, Li H, Yang S, et al. Interference in the indirect antiglobulin test and direct antiglobulin test from rheumatoid factor [published online ahead of print, 2019 Dec 19]. J Int Med Res. 2019;300060519892386. doi:10.1177/0300060519892386.
50. Saenger AK, Jaffe AS, Body R, et al. Cardiac troponin and natriuretic peptide analytical interferences from hemolysis and biotin: educational aids from the IFCC Committee on Cardiac Biomarkers (IFCC C-CB). Clin Chem Lab Med. 2019;57(5):633-40. doi:10.1515/cclm-2018-0905.
51. Daves M, Salvagno GL, Cemin R, et al. Influence of hemolysis on routine laboratory cardiac marker testing. Clin Lab. 2012;58(3-4):333-6.

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-4236

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

# Association of medical staffing and outcomes in cardiovascular diseases

Villevalde S. V., Zvartau N. E., Yakovlev A. N., Solovyeva A. E., Neplyueva G. A., Zaitsev V. V., Avdonina N. G., Fedorenko A. A., Endubaeva G. V., Erastov A. M., Karlina V. A., Panarina S. A., Soloviev A. E., Pavlyuk E. I., Dubinina M. V., Medvedeva E. A., Shlyakhto E. V.

Raised life expectancy of patients with cardiovascular diseases (CVD), due to continuous progress in drug treatment options and widespread use of innovate technologies, increase the burden of CVD on healthcare system. The development of human resources by highly qualified specialists is of fundamental importance. For the rational use of human resources to achieve the targets of federal project on the prevention of cardiovascular diseases, it is necessary not only to analyze the actual situation with medical staffing, but also the potential effects of staff shortages and imbalances on mortality. The review presents evidence of associations between staffing and quality of care and CVD outcomes.

**Keywords:** staffing, cardiologist, specialist, mortality.

**Relationships and Activities:** none.

Almazov National Medical Research Center, St. Petersburg, Russia.

Villevalde S. V. ORCID: 0000-0001-7652-2962, Zvartau N. E.* ORCID: 0000-0001-6533-5950, Yakovlev A. N. ORCID: 0000-0001-5656-3978, Solovyeva A. E. ORCID: 0000-0002-0013-0660, Neplyueva G. A. ORCID: 0000-0001-8811-2450, Zaitsev V. V. ORCID: 0000-0003-1905-2575, Avdonina N. G. ORCID: 0000-0001-9871-3452, Fedorenko A. A. ORCID: 0000-0002-9836-7841, Endubaeva G. V. ORCID: 0000-0001-8514-6436, Erastov A. M. ORCID: 0000-0003-3218-3502, Karlina V. A. ORCID: 0000-0001-9912-7789, Panarina S. A. ORCID: 0000-0003-3450-9916, Soloviev A. E. ORCID: 0000-0003-2378-9940, Pavlyuk E. I. ORCID: 0000-0002-0108-5996, Dubinina M. V. ORCID: 0000-0001-7980-4279, Medvedeva E. A. ORCID: 0000-0002-5130-5192, Shlyakhto E. V. ORCID: 0000-0003-2929-0980.

*Corresponding author:
zvartau_ne@almazovcentre.ru

**Received:** 01.12.2020
**Revision Received:** 10.12.2020
**Accepted:** 15.12.2020



**For citation:** Villevalde S. V., Zvartau N. E., Yakovlev A. N., Solovyeva A. E., Neplyueva G. A., Zaitsev V. V., Avdonina N. G., Fedorenko A. A., Endubaeva G. V., Erastov A. M., Karlina V. A., Panarina S. A., Soloviev A. E., Pavlyuk E. I., Dubinina M. V., Medvedeva E. A., Shlyakhto E. V. Association of medical staffing and outcomes in cardiovascular diseases. *Russian Journal of Cardiology*. 2020;25(S4):4236. (In Russ.) doi:10.15829/1560-4071-2020-4236

**Prevalence of cardiovascular diseases (CVD) and the need for a highly skilled workforce**

Recent decades have seen an increase in life expectancy at birth from 67,2 years in 2000 to 73,5 years in 2019 [1]. This is due to significant advances in the diagnosis and treatment of many diseases, including CVDs. With effective drug therapy and close integration of health care with high technology, CVDs are less fatal but more prevalent. Coronary artery disease (CAD) and stroke have for decades shown the highest disability-adjusted life years (DALYs) and potential contribution to the loss of 'healthy' life years in the age groups 50-74 years and over 75 years [2]. CVDs continue to top the list of causes of hospitalization and mortality in the population. In the Russian Federation (RF), high premature mortality from CVDs, which accounts for ~50% of all deaths, is one of the most acute public health problems [3].

The current burden of CVDs on health systems around the world and their projected growth are driving the need to develop human resource capacity and competencies — as factors key to health promotion, accessibility and quality of care (Figure 1) [4]. The cardiac workforce should be understood as a team of professionals working together to implement the principle of continuity of care. However, at the center of the decision-making system are cardiologists, who interact with patients at all stages of the CVD continuum and at all stages of care. The widespread use of innovative CVD treatment methods and information and communication technologies sets high requirements for the education, professional competencies and skills of the modern cardiologist.

In order to improve the medical infrastructure and increase the availability and quality of health care and, consequently, to increase life expectancy to 78 years by 2030, the Russian Government approved the national project, the aim of which is reduction of CVD mortality to 450 cases per 100000 people by 2024 [5]. Its achievement largely depends on the availability of qualified specialists in the industry. The shortage or uneven territorial distribution of specialists involved in the provision of health care to patients with CVDs can be critical in the implementation of national objectives. Earlier studies indicate the prognostic value of hospitalization and treatment of CVDs in specialized departments [6, 7], which may be associated with their better equipment, the possibility of more intensive monitoring, timely recognition and treatment of life-threatening complications, more frequent prescription of drugs with proven effects on the quality of life of patients. The present review summarizes the available data on the associations of cardiology staffing indicators and quality of care parameters and outcomes in cardiovascular diseases.

**Availability of inpatient cardiologists and in-hospital outcomes for CVDs**

In acute or decompensated chronic CVDs, the availability of highly qualified specialists may be a key factor, in addition to the timeliness and profile of hospitalization. A shortage of inpatient cardiologists can potentially lead to delays in life-saving therapy, as well as missed opportunities to improve long-term outcomes — stabilization and correction of significant risk factors, optimal drug therapy and management plans, and patient education.

To assess the potential relationship between inpatient staffing and hospital outcomes, various indicators have been used — the availability and number of cardiologists, the specialist workload in relation to volumes of care per year or the number of contractual patients (Table 1).

One of the leading causes of hospital admission in CVD patients is decompensated heart failure (HF). According to European studies, 32-44% of HF patients are hospitalized during the year, most of them over 65 years of age [8, 9]. The frequency of rehospitalizations for HF is associated with mortality and inversely correlated with the number of acute care beds in the region [10]. In the analysis of the administrative database of Japan, among patients hospitalized with decompensated HF in hospitals without cardiologists, hospital mortality was significantly higher and adjusted for significant prognostic factors (sex, age, route of hospitalization, HF class, respiratory failure, CAD, hypertension (HTN), atrial fibrillation (AF), life-threatening arrhythmias, renal failure, shock) was 10,7% compared to 5,4%, 7,0% and 7,1% in hospitals with a staff of ⩾10, 5-9 and 1-4 cardiologists, accordingly [11].There are significant differences in the practice of managing patients with HF: more frequent prescribing of therapy and therapeutic and diagnostic interventions in hospitals with better provision of cardiologists [11].

Another study demonstrated a 30% reduction in the risk of in-hospital mortality for the population of patients hospitalized with HF in hospitals with the highest ratio of cardiologists to 50 inpatient beds [12]. Dividing all hospitals into quartiles, the group with the highest score (16,7) compared with the lowest (4,4) showed an average 59% increase in the use of beta-blockers, a 38% increase in angiotensin converting enzyme inhibitors and a 27% increase in mineralocorticoid receptor antagonists [12]. Thus, better management of patients with HF by cardiologists may lead to improved hospital outcomes, but also, potentially, by a higher frequency of optimal drug therapy, which reduces mortality, to improved long-term outcomes.

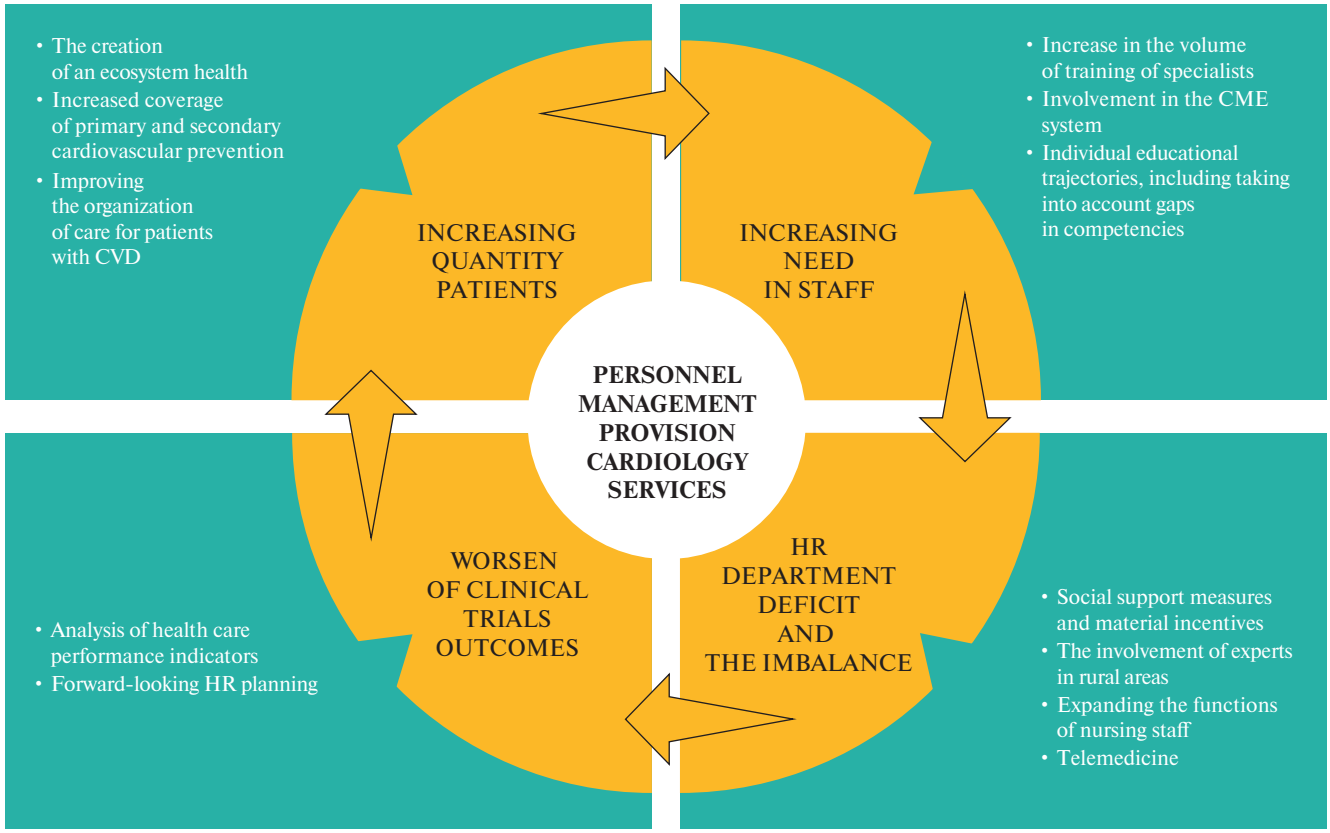


**Figure 1.** Development of human resource capacity and competencies as factors that play a key role in ensuring access and quality of CVD health care.
**Note:** the increasing burden of CVDs is the main factor behind the high demand for qualified cardiac professionals and the growing relative and absolute shortage of staff in the system of care for patients with CVDs, which is reflected in the worsening of clinical outcomes in patients with CVDs. Strategies to both increase the number of specialists and improve the quality of their training can improve the efficiency of the whole system of CVD care. Yellow indicates the main challenges for CVD care, while green indicates ways of addressing the identified challenges.
**Abbreviations:** CVD — cardiovascular disease, CME — continuing medical education.

It is noteworthy that better inpatient management by cardiologists compared to non-cardiologists may be associated with a reduced risk of pneumonia, septicemia and urinary tract infection, in addition to improved survival, as demonstrated in a study using propensity score matching depending on age, sex, income level, diagnosis, presence of HTN, type 2 diabetes (T2D), end-stage chronic kidney disease, cirrhosis, hyperlipidaemia, Parkinson's disease, number of hospital admissions and frequency of emergency department visits [13]. This is particularly important in view of the increasing number of patients with CVD who have non-cardiac disorders at the same time.

Another large national study in Japan (Table 1) has shown that a higher number of cardiologists who are certified as specialists is associated with lower mortality in patients admitted with a wide range of CVDs to an acute care hospital, regardless of equipment, patient demographics and variant of CVD [14]. However, these associations were more pronounced for smaller hospitals. The emergence of a relative shortage of specialists in large hospitals with an increase in the number of beds and physician workload (high "number of beds per certified cardiologist" ratio) was accompanied by an increase in hospital mortality [14]. In contrast, another study (Medicare, USA, 2004-2006) showed a reduction in 30-day mortality from myocardial infarction (MI) and HF when admitted to hospital with a high annual volume of medical services for these conditions [15]. However, the authors set a volume threshold above which there is no reduction in mortality. These results emphasize that the number of specialists and volumes (which determine specialist experience and are important, particularly in percutaneous coronary intervention and coronary artery bypass grafting [16, 17]) are not the only parameters affecting outcomes. It is not so much the number as the workload of specialists that is fundamental, and this must be

Table 1

**Studies on the impact of the availability of inpatient cardiologists on outcomes in patients with MI/acute coronary syndrome, HF**

| Author, year of publication | Analyzed parameters/sample size | Results |
|---|---|---|
| Sasaki, et al., Japan, 2014 [11] | Patients with acute heart failure (n=38668) admitted to emergency care hospitals (n=546) between 2010 and 2011.<br>In-hospital mortality adjusted for sex and age. | Hospitals with a higher staffing of cardiologists have a lower hospital mortality rate (5,4% vs 7,1%, p<0,001 in the group with >10 cardiologists vs the group with 1-4 cardiologists). |
| Kanaoka, et al., Japan, 2019 [12] | Patients with HF (n=154290) admitted to intensive care unit (n=770) between April 1, 2012 and March 31, 2014.<br>Subgroups divided by quartiles according to the ratio of the number of cardiologists per 50 cardiac beds.<br>In-hospital mortality. | Reduction in the in-hospital mortality with an increase in the ratio of cardiologists per 50 cardiac beds.<br>For subgroups with an index value of 9,7 (8,8-10,1) and 16,7 (14,0-23,8), the HR was 0,81 (95% CI, 0,71-0,91; p<0,001) and 0,68 (95% CI, 0,59-0,77; p<0,001), respectively. |
| Wu, et al., Taiwan, 2020 [13] | Patients hospitalized for CVDs (n=6264) between 2008 and 2013.<br>Hospital mortality.<br>Risk of complications during hospital admission. | The mortality rate of patients treated by cardiologists was lower than in the group of patients treated by physicians from other specialties: OR, 0,37, 95% CI, 0,29-0,47.<br>The number of complications, such as pneumonia, septicemia and urinary tract infection, was higher if the treatment was not carried out by cardiologists. |
| Yoneyama, et al., Japan, 2019 [14] | Patients over 18 years of age (n=896171) hospitalized for a wide range of CVDs from between April 1, 2012 and March 31, 2013.<br>Certified cardiologists (n=11687).<br>The specialist workload indicator is the number of beds per certified cardiologist.<br>In-hospital all-cause mortality. | More certified cardiologists were associated with lower in-hospital mortality (HR, 0,980, 95% CI, 0,975-0,986; p<0,01) regardless of hospital facilities and patient characteristics.<br>Increase in hospital mortality with an increase in number of beds per certified cardiologist: HR, 1,012, 95% CI, 1,008-1,015; p<0,01. |
| Kulkarni, et al., USA, 2013 [18] | Patients over 65 years of age hospitalized with MI (n=171126) and HF (n=352853).<br>Number of cardiologists per 100000 population aged over 65 in 306 regions with hospitals in 2010.<br>One-month and 1-year mortality risk. | The risk of death within 30 days and 1 year was higher in regions with fewer cardiologists: for patients with MI, OR was 1,13 (95% CI, 1,06-1,21; p<0,0002) and 1,06 (95% CI, 1,00-1,12; p<0,0571), respectively; for patients with HF, OR was 1,19 (95% CI, 1,12-1,27; p<0,0001) and 1,09 (95% CI, 1,04-1,13; p<0,0001), respectively. |

**Abbreviations:** CI — confidence interval, MI — myocardial infarction, HR — hazard ratio, OR — odds ratio, HF — heart failure, CVD — cardiovascular disease.

taken into account in the territorial planning of specialized health care, the routing of patients with acute CVDs and the rules of interaction between institutions. In particular, a study of the spatial distribution density of cardiologists (the ratio of specialists to the eligible population aged over 65 years) has shown that regions with a low density of cardiologists have higher 30-day and one-year mortality rates in patients with MI (13% and 6%) and HF (19% and 9%) [18].

**Outpatient cardiac monitoring and prognosis of cardiovascular patients**

A seamless model of management of patients with chronic CVDs, especially elderly and comorbid patients receiving care in different institutions and by different specialists, may reduce CVD mortality [19]. One solution is to establish a cardiovascular risk management system in each region, with continuity between inpatient and outpatient care being an important component of this system [20]. Continuity reduces the number of hospital admissions and the risk of death [21]. Studying the role of the professional managing patients discharged from hospital after an acute cardiovascular event can help to plan and organize the most effective model of follow-up.

Several studies have demonstrated that outpatient follow-up by a cardiologist reduces the risk of adverse events (Table 2). Among high cardiovascular risk patients with a history of T2D, previous MI and/or coronary revascularization, other known CVDs discharged from the differential chest pain unit and presenting within 30 days of discharge to an outpatient cardiologist visit, there was a 15% reduced risk of MI or death compared with patients with a general practitioner visit and a 21% reduction

compared with patients without an outpatient visit [22].

These associations were observed, adjusted for a wide range of influencing factors, despite a later visit to the cardiologist (median of 12 (5-20) days after discharge vs 7 (2-15) days for the general practitioner) and a higher proportion of patients with risk factors and previous CVD. For patients in the cardiologist follow-up group, a higher frequency of appointments for diagnostic tests, including stress tests, echocardiography, as well as major classes of cardiovascular drugs and coronary revascularization was found [22]. In a similar analysis of a patient population without diabetes or previous CVD [23], follow-up with a cardiologist together with a primary care physician compared with no visit within 30 days of discharge was associated with a 27% and 19% reduction in risk of death and death or MI, respectively. A cardiologist visit was associated with a tendency to reduce the risk of death by 20% and of death or MI by 13%, whereas no improvement in outcomes was observed with primary care alone versus no follow-up [23]. Patient groups in which the cardiologist was involved in the follow-up were characterized by a higher frequency of use of diagnostic tests, myocardial revascularization and prescription of CAD therapy [23].

Of note, evidence of more frequent adherence to current clinical guidelines, prescription of enhanced screening and optimal drug therapy by cardiologists has been repeatedly confirmed in subgroups of primary and secondary cardiovascular prevention [24], in patients with AF and chronic HF [25-28]. A retrospective cohort study including patients with newly diagnosed AF (n=184161, USA) also found an 11% lower risk of death in the first 90 days of follow-up and more frequent prescribing of anticoagulant and antyarrhythmic therapy, statins and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers [26]. All-cause mortality, as well as stroke and major bleeding rates, were significantly lower among patients with first-diagnosed AF who were followed up for one year by cardiologists compared with patients who did not visit a cardiologist [27]. In another retrospective population-based study of patients with first-time AF presenting to the emergency department (n=2902, Ontario, Canada), mortality was 32% lower in those with cardiac consultation during the subsequent year of follow-up compared with

**Table 2**

**The influence of the specialization of the doctor performing outpatient follow-up on clinical outcomes**

| Author, year of publication | Sample | Groups analysed | Impact on management tactics | Impact on outcomes |
|---|---|---|---|---|
| Czarnecki, Canada, 2013 [22] | Patients over 18 years of age discharged from chest pain differential department (n=56767) with high cardiovascular risk (concomitant T2D, previous CVD, cardiac surgery). | Three groups depending on the visit and the specialty of the outpatient doctor in the first 30 days after discharge:<br>1. Cardiologist<br>2. Primary care physician<br>3. Without a doctor | Frequency in groups 1, 2, 3:<br>echocardiography: 38,9%, 15,8%, 9,9%;<br>PCI: 5%, 1%, 0,7%;<br>statin therapy: 71,5%, 58,9%, 53,4%;<br>ACE inhibitors/ARBs: 72%, 65,1%, 61,7%;<br>BB: 62,2%, 49,7%, 48,6%. | Reduced risk of all-cause mortality or hospital admission for MI:<br>in group 1 vs group 3 (HR, 0,85, 95% CI, 0,78-0,92; p<0,001) and vs group 2 (HR, 0,79, 95% CI, 0,71-0,88; p<0,001).<br>Increased risk of repeat admissions to the pain differential department in group 1 vs group 3: 13,2% and 11,9%. |
| Czarnecki, Canada, 2014 [23] | Patients over 50 years of age discharged from chest pain differential departmeny (n=216527) with low cardiovascular risk (no CVD, cardiac surgery, T2D). | Four groups depending on the visit and speciality of the outpatient doctor in the first 30 days after discharge:<br>1. Cardiologist<br>2. Cardiologist and general practitioner together<br>3. General practitioner<br>4. Without doctor | Frequency in groups 1, 2, 3, 4:<br>Stress tests: 71,8%, 71,9%, 28,4%, 15,6%;<br>coronary revascularisation: 5,4%, 6,4%, 0,8%, 0,9%;<br>Statin therapy: 51,8%, 53,9%, 38,4%, 32,6%;<br>ACE inhibitors/ARBs: 51,4%, 56,2%, 45,5%, 38%. | The risk of all-cause mortality within one year of discharge was lower in group 2 compared with group 4 (OR, 0,73, 95% CI, 0,63-0,85; p<0,001), in group 1 compared with group 4 (OR, 0,80, 95% CI, 0,65-0,99; p<0,042). |

**Table 2. Continued**

| Author, year of publication | Sample | Groups analysed | Impact on management tactics | Impact on outcomes |
|---|---|---|---|---|
| Singh, Canada, 2017 [25] | Patients with newly reported AF (n=2902) aged 20 to 80 years admitted to the emergency department. | Two groups, depending on the specialization of the outpatient doctor for the following year:<br>1. Cardiologist<br>2. General practitioner | More frequent prescribing in group 1 compared to group 2:<br>VKA: 46,8% vs 39,6%;<br>DOAC: 18,1% vs 14,2%;<br>Echocardiography: 51,9% vs 24,5%;<br>Stress tests: 30,6% vs 13,7%;<br>CA: 11,2% vs 0,3%;<br>PCI: 1,6% vs 0%. | Group 1 versus group 2 had lower one-year mortality (5,3% vs 7,7%, HR 0,68, 95% CI 0,55-0,84; p<0,001), higher rates of repeat hospitalizations with AF (17,9% vs 8,2%, HR 2,3, 95% CI 2,0-2,7 p<0,001), stroke (1,7% vs 0,5%, HR 3,4, 95% CI 1,8–6,1; p<0,001), bleeding (3,1% vs2%, HR 1,5, 95% CI 1,1-2,1; p<0,001), HF (3,2% vs 1,4%, HR 2,2, 95% CI 1,5-3,1; p<0,001). |
| Perino, USA, 2017 [26] | Patients with newly reported AF (n=184161) admitted to the emergency department. | Two groups depending on the specialization of the outpatient doctor for the first 90 days after diagnosis:<br>1. Cardiologist<br>2. Primary care physician | In groups 1 and 2:<br>administration of anticoagulant therapy: 70,3% and 58,8% (p<0,0001);<br>drugs to control VCR: 90,1% and 80,5% (p<0,0001);<br>antiarrhythmic drugs: 20,8% and 11,0% (p<0,0001)<br>antiplatelet agents: 42,6% and 28,6% (p<0,0001)<br>statins: 65,6% and 58,1% (p<0,0001). | Reduced risk of death at 90 days in group 1 versus group 2: HR, 0,89, 95% CI, 0,88-0,91, p<0,001. |
| Hawkins, Canada, 2019 [27] | Patients over 18 years of age with newly reported AF (n=7986) presenting to the emergency department. | Groups according to the specialty of the outpatient doctor for the next 90 days after diagnosis:<br>1. Cardiologist<br>2. Therapist<br>3. Non-specialist<br>4. Without follow-up | Frequency at one year follow-up in groups 1, 2, 3, 4:<br>Holter monitoring: 26,5%, 20,5%, 17,2%, 8,5%;<br>echocardiography: 85,1%, 72,4%, 49,5%, 30%;<br>cardioversion 30,3%, 25,9%, 16,9%, 28,1%;<br>angiography: 6%, 5,5%, 2,7%, 1,8%;<br>VKA prescription: 28,8%, 22,1%, 25,2%, 12,2%;<br>BB: 48,9%, 42,9%, 43,1%, 17,5%. | After 12 months, patients seen by a cardiologist had a lower risk of death (HR, 0,72, 95% CI, 0,55-0,93); stroke (HR, 0,60, 95% CI, 0,37-0,96); major bleeding (HR, 0,69, 95% CI, 0,53-0,89) compared with patients without cardiologist follow-up. |

**Abbreviations:** VKA — vitamin K antagonists, BB — beta-blockers, ARB — angiotensin II receptor blockers, CI — confidence interval, ACE — angiotensin-converting enzyme, MI — myocardial infarction, CA — coronary angiography, DOAC — direct oral anticoagulants, HR — hazard ratio, OR — odds ratio, T2D — type 2 diabetes, HF — heart failure, CVD — cardiovascular diseases, AF — atrial fibrillation, PCI — percutaneous coronary intervention, VCR — ventricular contraction rate.

the group without cardiac consultation. However, there was a higher rate of rehospitalizations with AF, HF and stroke [25]. The study was conducted using propensity score matching, taking into account sex, age, socioeconomic status, cardiologist examination during an emergency department stay and in the 2 years prior to admission, cardioversion, repeat admissions to the emergency department, presence of HF, T2D, stroke, HTN, bleeding, comorbidity, risk of thromboembolic complications by $CHA_2DS_2VASc$.

An inverse correlation between the availability of cardiologists per 100 000 population and the frequency of major hospital admissions (r=-0,34, p<0,01) was shown in a large Canadian study, with no relationship between the number of hospital admissions and availability of primary care physicians. However, the availability of cardiologists was also associated with a higher use of different cardiovascular diagnostic tests (relative risk (RR), 1,10, 95% confidence interval (CI), 1,09-1,10, p<0,001), including coronary angiography (RR, 1,03, 95% CI, 1,02-1,04, p<0,001) and echocardiography (RR, 1,16, 95% CI, 1,15-1,17; p<0,001) and non-invasive tests (RR, 1,10, 95% CI, 1,10-1,11; p<0,001) [29]. It is likely that the interpretation of an increased

risk of hospital admission with better therapeutic and diagnostic management in cardiology follow-up should not be seen as a negative trend, but rather as an indication of alertness to prevent the development of adverse outcomes.

A particularly complex population of patients with a high risk of adverse outcomes is represented by patients with HF. The Russian RUS-HF study showed better survival during treatment in specialized departments and subsequent follow-up for 3 years after discharge in groups of cardiologists-specialists in HF and cardiologists of the federal center compared to regional center cardiologists (80,3% and 77,9% vs 52%) [28]. It can be expected that in specialized institutions, the outcomes of HF are better due to the participation of a multidisciplinary team in the treatment, technical capabilities, accumulated experience, high professional level of specialists, as well as a greater frequency of prescribing therapy that affects the prognosis [28]. Foreign studies in this area also demonstrate a more frequent use of the main groups of drugs recommended for the treatment of patients with HF, with joint follow-up after discharge of patients hospitalized with HF in the emergency department, by cardiologists and general practitioners, compared with follow-up only by general practitioners or no outpatient follow-up [30].

The reduction in the risk of death associated with the cardiologist's follow-up after discharge should be interpreted carefully. The very existence of the visit after discharge may reflect several factors such as organizational and related to patient characteristics, greater adherence to treatment and lower severity of the condition. On the other hand, the adjustment for multiple factors that potentially determine the prognosis strongly indicates the presence of a "specialist effect" on improving the quality of health care and prognosis in CVD.

The question of which specialty doctor should observe patients at the outpatient stage, however, cannot be resolved unambiguously. One of the successful areas of personnel policy in the system of care for patients with CVD is the introduction into clinical practice of teams that include nurses with higher education, clinical pharmacologists, and medical assistants. With this approach, a high level of quality of medical services can also be achieved. In particular, a large longitudinal IMPROVE HF cohort study conducted to assess the quality of management of patients with HF or left ventricular dysfunction due to MI at the outpatient stage, which included patients from 162 cardiology practices (n=14891, USA), did not show significant differences in compliance with current clinical recommendations in the groups of patients observed with the participation of medical assistants and nurses and only doctors. In addition, in cardiology practices staffed by medical assistants and nurses with higher education, the training of patients with HF was carried out [31]. In another study of outpatient follow-up of patients after MI by a team or only doctors, there were also no significant differences in mortality within 90 days after discharge (adjusted odds ratio (OR), 1,18, 95% CI, 0,98-1,42), drug treatment (OR, 0,98, 95% CI 0,89-1,08), risk of rehospitalization (OR, 1,11, 95% CI, 0,99-1,26) [32]. At the same time, the patients observed by the team were more likely to suffer from T2D (37% vs 33%), HF (20% vs 16%), were discharged to a medical institution (21% vs 13%), and had more visits during the 90 days of follow-up (median number of visits 6 vs 5) [32].

**Availability of cardiologists and mortality from CVD**

The results of the research indicate that among a wide range of factors that affect the mortality from CVD, an important role is played by the availability of specialists and availability of qualified specialized healthcare. The prognostic significance of a visit to a specialist has been convincingly demonstrated for patients with chronic diseases (HF, CAD, chronic obstructive pulmonary disease or asthma) living in rural areas. A visit to a specialist, compared to one or more visits to a primary care doctor, was associated with a 15,9% reduction in the incidence of potentially preventable hospitalizations and a 16,6% reduction in death [33].

The relationship between CVD mortality and the number of cardiologists was found in a large epidemiological study conducted using data on the availability of primary care physicians in 3142 US districts from 2005 to 2015. It was found that after adjusting for socio–economic and demographic factors, an increase in the provision of 10 cardiologists per 100 thousand population is associated with a decrease in cardiovascular mortality by 49,4 cases per 1 million population (95% CI, from -76,8 to -22,0 deaths per 1 million population). However, the authors also noted a decrease in cardiovascular mortality by 30,4 cases per 1 million population, with an increase of 10 primary care physicians (95% CI, from -52,4 to -8,4). The obtained results emphasize the significant role of human resources, including the primary health care system, in the outcomes of CVD [34].

In a cross-sectional study of associations between various indicators of the availability of regional health systems and population health indicators in 16 federal states of Germany, an inverse correlation was established between the number of cardiologists and the incidence of CVD [β=-0,689, p=0,031], while

no significant associations were found between the availability of general practitioners and endpoints [35]. The total number of residents per 1 department of differential diagnosis of chest pain directly correlated with the incidence of CVD [β=42,730, p=0,036] and related mortality [β=4,962, p=0,002], which can be partially explained by the relative shortage of specialists. The socio-economic characteristics of the federal regions could potentially affect the results, since their impact on mortality rates and demand for medical care has been proven in many studies [36].

## Conclusion

Despite the differences in research methodology and indicators analyzed, the observational nature of studies, the possibility of systematic selection errors and underestimation of potentially influencing factors, the results of most studies are consistent and convincingly emphasize the fundamental role of cardiologist in receiving cardiovascular care. The "specialist effect" on cardiovascular outcomes is shown both for different patient populations and different stages of care. The shortage of cardiologists is critical to achieve a sustainable rate of decline in the CVD rate. While the most important elements of an effective HR policy are to ensure that staffing needs are met, that physician shortages in particular specialties are overcome, that geographic disparities are eliminated and that practitioners have a high overall skill level, further research is needed to identify the most appropriate, science-based approaches for strategically choosing a regional HR service and providing it with the right human resources. The development of regionally specific, integrated and tailored solutions to coordinate assistance and provide at least one specialist consultation can save significantly more lives in a shorter timeframe.

**Relationships and Activities:** none.

## References


1. Wang H, Abbas KM, Abbasifard M, et al. Global age-sex-specific fertility, mortality, healthy life expectancy (HALE), and population estimates in 204 countries and territories, 1950-2019: a comprehensive demographic analysis for the Global Burden of Disease Study 2019. The Lancet. 2020;396(10258):1160-203. doi:10.1016/S0140-6736(20)30977-6.
2. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019 The Lancet. 2020;396(10258):1204-22. doi:10.1016/S0140-6736(20)30925-9.
3. Federal State Statistics Service, https://rosstat.gov.ru.
4. World Health Organization. Health workforce. https://www.who.int/health-topics/health-workforce#tab=tab_1.
5. "Passport of the national project "Healthcare". (In Russ.) http://www.consultant.ru. (21 Nov 2020).
6. D'Souza M, Saaby L, Poulsen TS, et al. Comparison of Mortality in Patients With Acute Myocardial Infarction Accidentally Admitted to Non-cardiology Departments Versus That in Patients Admitted to Coronary Care Units. The American Journal of Cardiology. 2014;114(8):1151-7. doi:10.1016/j.amjcard.2014.07.035.
7. O'Neill DE, Southern DA, Norris CM, et al. Acute coronary syndrome patients admitted to a cardiology vs non-cardiology service: variations in treatment & outcome. BMC Health Services Research. 2017;17(1). doi:10.1186/s12913-017-2294-0.
8. Hall MJ, Levant S, DeFrances CJ, Hospitalization for Congestive Heart Failure: United States, 2000-2010 NCHS Data Brief N108 October 2012 U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Centers for Disease Control and Prevention National Center for Health Statistics https://www.cdc.gov/.
9. Maggioni AP, Dahlström U, Filippatos G, et at. EURObservationalResearch Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). European Journal of Heart Failure. 2013;15(7):808-17. doi:10.1093/eurjhf/hft050.
10. Mercier G, Georgescu V, Bousquet J, Geographic Variation In Potentially Avoidable Hospitalizations In France. Health Affairs. 2015;34(5):836-43. doi:10.1377/hlthaff.2014.1065.
11. Sasaki N, Kunisawa S, Otsubo T, et al. The relationship between the number of cardiologists and clinical practice patterns in acute heart failure: a cross-sectional observational study. BMJ Open. 2014;4(12):e005988. doi:10.1136/bmjopen-2014-005988.
12. Kanaoka K, Okayama S, Nakai M, et al. Number of Cardiologists per Cardiovascular Beds and In-Hospital Mortality for Acute Heart Failure: A Nationwide Study in Japan. Journal of the American Heart Association. 2019;8(18):e012282. doi:10.1161/JAHA.119.012282.
13. Wu Y-M, Liu C-C, Yeh C-C, et al. Hospitalization outcome of heart diseases between patients who received medical care by cardiologists and non-cardiologist physicians: A propensity-score matched study. PLOS ONE. 2020;15(7):235207. doi:10.1371/journal.pone.0235207.
14. Yoneyama K, Kanaoka K, Okayama S, et al. Association between the number of board-certified cardiologists and the risk of in-hospital mortality: A nationwide study involving the Japanese registry of all cardiac and vascular diseases. BMJ Open. 2019;9(12). doi.10.1136/bmjopen-2018-024657.
15. Ross JS, Normand S-LT, Wang Y, et al. Hospital Volume and 30-Day Mortality for Three Common Medical Conditions. New England Journal of Medicine. 2010;362(12):1110-8. doi:10.1056/nejmsa0907130.
16. Bradley EH, Herrin J, Wang Y, et al. Strategies for Reducing the Door-to-Balloon Time in Acute Myocardial Infarction. New England Journal of Medicine. 2006;355(22):2308-20. doi:10.1056/nejmsa063117.
17. Auerbach AD. Shop for Quality or Volume? Volume, Quality, and Outcomes of Coronary Artery Bypass Surgery. Annals of Internal Medicine. 2009;150(10):696. doi:10.7326/0003-4819-150-10-200905190-00007.
18. Kulkarni VT, Ross JS, Wang Y, et al. Regional density of cardiologists and rates of mortality for acute myocardial infarction and heart failure. Circulation: Cardiovascular Quality and Outcomes. 2013;6(3):352-9. doi:10.1161/CIRCOUTCOMES.113.000214.
19. Shlyakhto EV, Zvartau NE, Villewalde SV, et al. Implemented models and elements of the organization of medical care for patients with heart failure in the regions of the Russian Federation: prospects for transformation into regional cardiovascular risk management systems. Russian Journal of Cardiology. 2020;25(4):3792. (In Russ.) doi:10.15829/1560-4071-2020-4-3792.
20. Shlyakhto EV, Zvartau NE, Villevalde SV, et al. Cardiovascular risk management system: prerequisites for developing, organization principles, target groups. Russian Journal of Cardiology. 2019;24(11):69-82. (In Russ.) doi:10.15829/1560-4071-2019-11-69-82.
21. Voss R, Gardner R, Baier R, et al. The care transitions intervention: translating from efficacy to effectiveness. Arch Intern Med. 2011;171(14):1232-7. doi:10.1001/archinternmed.2011.278.

22. Czarnecki A, Chong A, Lee DS, et al. Association Between Physician Follow-Up and Outcomes of Care After Chest Pain Assessment in High-Risk Patients. Circulation. 2013;127(13):1386-94. doi:10.1161/circulationaha.112.000737.
23. Czarnecki A, Wang JT, Tu JV, et al. The role of primary care physician and cardiologist follow-up for low-risk patients with chest pain after emergency department assessment. American Heart Journal. 2014;168(3):289-95. doi:10.1016/j.ahj.2014.05.016.
24. Kumar A, Fonarow GC, Eagle KA, et al. Regional and practice variation in adherence to guideline recommendations for secondary and primary prevention among outpatients with atherothrombosis or risk factors in the United States: a report from the REACH Registry. 2 Crit Pathw Cardiol. 2009;8(3):104-11. doi:10.1097/HPC.0b013e3181b8395d.
25. Singh SM, Qiu F, Webster L, et al. The Relationship Between Cardiologist Care and Clinical Outcomes in Patients With New-Onset Atrial Fibrillation. Canadian Journal of Cardiology. 2017;33(12):1693-700. doi:10.1016/j.cjca.2017.10.003.
26. Perino AC, Fan J, Schmitt SK, et al. Treating Specialty and Outcomes in Newly Diagnosed Atrial Fibrillation. Journal of the American College of Cardiology. 2017;70(1):78-86. doi:10.1016/j.jacc.2017.04.054.
27. Hawkins NM, Scheuermeyer FX, Youngson E, et al. Impact of cardiology follow–up care on treatment and outcomes of patients with new atrial fibrillation discharged from the emergency department. EP Europace. 2020;22(5):695-703. doi:10.1093/europace/euz302.
28. Sitnikova MYu, Lyasnikova EA, Yurchenko AV, et al. The results of 3 years of work of the Russian Hospital Register of Chronic Heart Failure (RUssian hoSpital Heart Failure Registry — RUS-HFR): the relationship between management and outcomes in patients with chronic heart failure. Cardiology. 2018;58(S10):9-19. (In Russ.) doi:10.18087/cardio.2483.
29. Alter D, Stukel T, Newman A. The relationship between physician supply, cardiovascular health service use and cardiac disease burden in Ontario: Supply-need mismatch Canadian Journal of Cardiology. 2008;24(3):187-93. doi:10.1016/S0828-282X(08)70582-8.
30. Avaldi VM, Lenzi J, Urbinati S, et al. Effect of cardiologist care on 6-month outcomes in patients discharged with heart failure: results from an observational study based on administrative data. BMJ Open. 2017;7(11):e018243. doi:10.1136/bmjopen-2017-018243.
31. Albert NM, Fonarow GC, Yancy CW, et al. Outpatient Cardiology Practices With Advanced Practice Nurses and Physician Assistants Provide Similar Delivery of Recommended Therapies (Findings from IMPROVE HF). The American Journal of Cardiology. 2010;105(12):1773-9. doi:10.1016/j.amjcard.2010.01.360.
32. Rymer JA, Chen AY, Thomas L, et al. Advanced practice provider versus physician-only outpatient follow-up after acute myocardial infarction. Journal of the American Heart Association. 2018;7(17). doi:10.1161/JAHA.117.008481.
33. Johnston KJ, Wen H, Joynt Maddox KE. Lack Of Access To Specialists Associated With Mortality And Preventable Hospitalizations Of Rural Medicare Beneficiaries. Health Affairs. 2019;38(12):1993-2002. doi:10.1377/hlthaff.2019.00838.
34. Basu S, Berkowitz SA, Phillips RL, et al. Association of Primary Care Physician Supply with Population Mortality in the United States, 2005-2015. JAMA Internal Medicine. 2019;179(4):506-14. doi:10.1001/jamainternmed.2018.7624.
35. Dornquast C, Willich SN, Reinhold T. Prevalence, Mortality, and Indicators of Health Care Supply — Association Analysis of Cardiovascular Diseases in Germany. Frontiers in Cardiovascular Medicine. 2018;5:158. doi:10.3389/fcvm.2018.00158.
36. Stringhini S, Carmeli C, Jokela M, et al. Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1·7 million men and women. The Lancet. 2017;389(10075):1229-37. doi:10.1016/S0140-6736(16)32380-7.