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ORIGINAL ARTICLES
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Analysis of the information about the incidence of heart failure, associated mortality and burden on the healthcare system, based on the encoding data in 15 subjects of the Russian Federation

Zvartau N. E., Solovyova A. E., Endubaeva G. V., Medvedev A. E., Solovyov A. E., Avdonina N. G., Yakovlev A. N., Apsheva E. A., Duplyakov D. V., Zolotova Y. V., Koloeva H. M., Kostina K. S., Levina E. S., Lomovtseva R. H., Lvov V. E., Nikolaeva I. E., Svetlova N. A., Spasenkov G. N., Fayans I. V., Shkurina N. S., Villevalde S. V., Shlyakhto E. V.

Aim. This study aims to assess the incidence of heart failure (HF) and associated mortality, and also the burden on the healthcare system in the subjects of Russian Federation, based on the HF encoding data.

Material and methods. We made a structured request for the number of patients with HF and the number of cases of providing medical care in 2019. HF was understood to mean the presence of at least one of the codes I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43.0, I43.1, I43.2, I43.8, I50.x (expanded encoding) according to International Classification of Diseases 10th Revision. The code I50.x was considered separately (the standard HF enconding).

Results. The information about the incidence of HF, associated mortality and burden on the healthcare system was obtained from 15 subjects (53,6% from those that gave the data according to the request; the adult population is 18,9% from total adult population of Russian Federation). We noted significant heterogeneity between the regions. The median of the incidence of HF and associated mortality was 2,6 and 3,2% in accordance with the data of the expanded encoding, and 0,21 and 11,3% — according to the standard HF encoding. The presence of the code I50.x was observed in average in 9,4% of all cases of HF and defined the patients who frequently used emergency medical services and were frequently hospitalized (60 (18, 96) and 48 (20, 137) cases per 100 patients versus 9 (5, 24) and 17 (10, 70) cases in the expanded encoding).

Conclusion. According to the encoding, the indicators of the incidence of HF and associated mortality vary greatly between the regions, the median values are 2,6 and 3,2% in expanded and 0,21 and 11,3% in standard approaches. In the standard encoding, there were more frequent use of emergency medical services and less number of outpatient visits. The development and introduction of a unified approach to encoding and recording the cases of HF will provide obtaining objective statistical data and using them for management decisions.

Keywords: heart failure, ICD codes, incidence, load, burden on the healthcare system, prognosis.

Relationships and Activities: none.

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Among a wide range of cardiovascular diseases (CVDs) heart failure (HF) is characterized by the highest risk of death, which reaches 12 and 43% in case of the presence of the symptoms and in case of hospitalization with HF decompensation, respectively [1, 2]. The decrease in mortality rate of patients with HF is potentially the most effective strategy to achieve the goal of federal project "Fight against cardiovascular diseases" by 2030. The project actively discusses the transformations in the system of the organization of medical care and the preferential drug provision of patients with HF, contributing to the improvement of the patients` prognosis [3-6]. It was showed that in ideal conditions of randomized clinical trials, the modern classes of drugs significantly reduce the risk of the HF development and progression, and their combination in patients with HF and low left ventricular ejection fraction (EF) can provide more than two times decrease in general mortality [7]. The additional risk reduction of recurrent hospitalizations for worsening HF and death can be achieved due to multidisciplinary monitoring programs [8]. Planning needs, economic justification and evaluation of subsequent effectiveness in the implementation of these strategies in routine practice is hampered by the lack of data on the epidemiology of HF in the Russian Federation (RF). In the absence of a system of centralized collection of statistical information on HF at the level of regions and the country as a whole [9, 10] and a fully functioning segment "Heart failure" of the vertically integrated medical information system "Cardiovascular diseases" (VIMIS CVD), one of the initial methods for assessing the epidemiology of HF can be the analysis of the frequency of use of codes according to the International Classification of Diseases (ICD) for the list of diseases associated with a high probability of the presence/development of HF. This approach is widely used abroad. The possibility to use the encoding for the studies at the population level is emphasized by the data of the systematic review and meta-analysis [11]. The HF encoding has showed 96,8% specificity and 75,3% sensitivity in relation to the HF diagnosis established during thorough analysis of medical history, the use of symptomatic Framingham criteria 1971 (positive predictive significance up to 94,3%), EF values ⩽55% (specificity 99,5%), criteria of the European Society of Cardiology 1995 (specificity up to 86%) [11]. Since the modern algorithm of HF diagnostics is quite complicated and in particular it may include the invasive estimation of hemodynamics during loading, the scientifically-based possibility of using a simplified approach to assessing epidemiology based on encoding data is of special importance.

Previously, we performed a study aimed to investigate the regional integrated database of electronic medical records of Saint-Petersburg, which was based on the accounting for the ICD codes that potentially characterize the presence of HF, where we obtained the value of the HF prevalence comparable with average European value (1,4 vs 1,7% in Europe) [9, 12]; however, it significantly differed from the assumed prevalence of HF in the European part of the Russian Federation according to the EPOKHA (ЭПОХА) research (7%) [13]. Taking into account the differences in the population characteristics, prevalence and mortality from CVDs and in the features of the medical care organization, it is interesting to perform the similar study in other subjects of RF, in particular, to obtain the information about the possibilities in accounting and assessing the burden of HF for the country as a whole.

The study is aimed to assess the prevalence and lethality in HF as well as the burden on the healthcare system in the regions of RF based on the data of the HF encoding.

Material and methods

We made a structured request to the executive authorities in the healthcare field of 40 subjects of the Russian Federation of the Northwestern, Southern, North Caucasian and Volga Federal districts supervised by V. A. Almazov National Medical Research Centre of the Ministry of Health of the Russian Federation within the framework of the federal project "Development of a network of national medical research centers and the introduction of innovative medical technologies". The structure of the request included the number of the

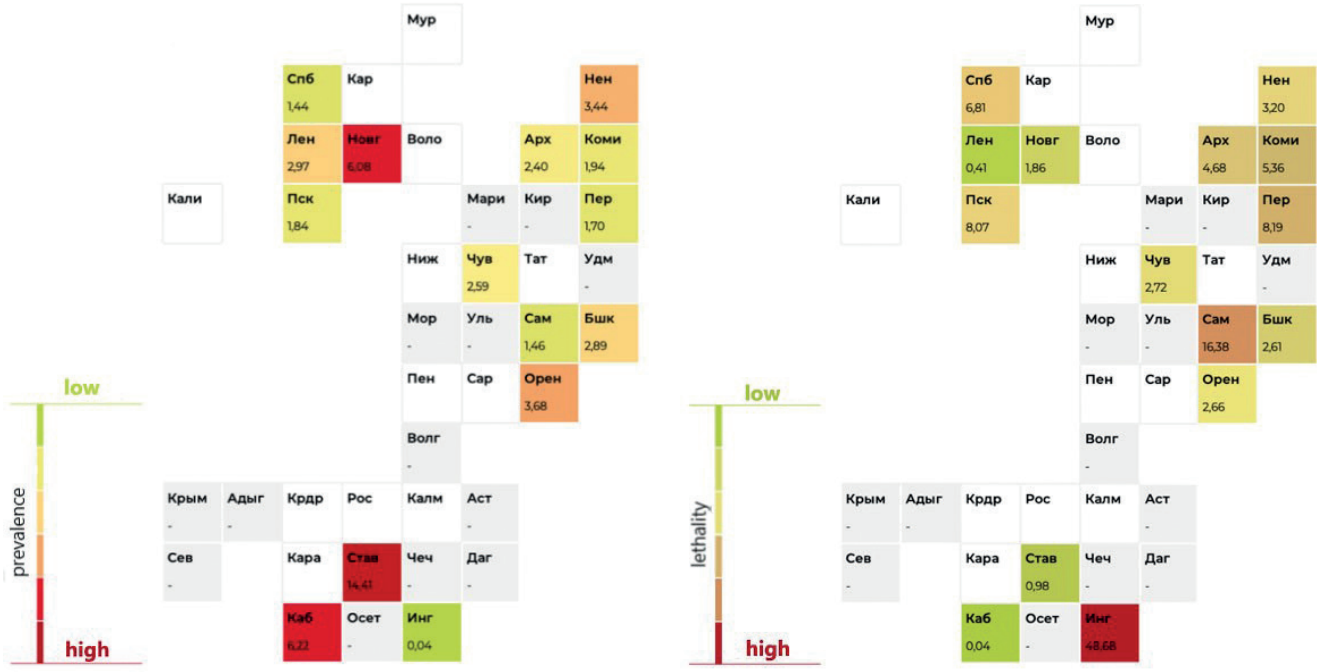

Figure 1. Tile diagrams with gradation of prevalence (**A**) and mortality (**B**) values for HF, established according to encoding data (as a percentage) in the supervised regions. White indicates the regions which did not respond to the request. Grey — regions that did not provide the data on the parameters.

patients and cases of providing medical care in 2019, when at least one of the ICD-10 codes was used in the diagnosis: I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43.0, I43.1, I43.2, I43.8, I50.x (expanded encoding) [9]. The patients with the presence of at least one of these codes were considered as the patients with HF. The indicators with the presence of at least on code I50.x in the diagnosis were considered separately (standard encoding). We made an additional request for the data on the number of adults, the number of cases of seeking medical care among the adult population, including hospitalizations, visits to polyclinics, ambulance calls, deaths in 2019.

Statistical processing of the results was carried out using a software package Stata 16.0 (StataCorp, College Station, TX, USA). Incidence was calculated as the ratio of the number of cases of HF to the adult population for the beginning of 2019; mortality — as the ratio of the number of died people diagnosed with HF to the total number of patients with HF. The indicators were evaluated in groups in the presence of at least one of the analyzed codes and separately in the presence of codes I50.x. Taking into account the small sample size, the data were presented in the form of median and interquartile range (IQR, 25 and 75 percentiles) and absolute numbers (proportions).

The study was performed in accordance with the standards of Good Clinical Practice and the principles of the Declaration of Helsinki.

Results

The information according to the request was received from 28 of 40 subjects of RF, supervised by V.A. Almazov National Medical Research Centre of the Ministry of Health of the Russian Federation. The response was 70%. The total adult population of the subjects of the Russian Federation who responded to the request was 36085763 people in 2019, that corresponds to 31% of the total adult population of the country. The completeness of the response to the request (the proportion of the received indicators from the requested indicators) varied from 13,8 to 100%. Three regions used the data of electronic medical cards as the source of the information, and in other cases — the data of the territorial fund of compulsory medical insurance of subjects.

The data of the prevalence and lethality while using the ICD-10 codes that potentially characterize the presence of HF, were obtained from 15 regions

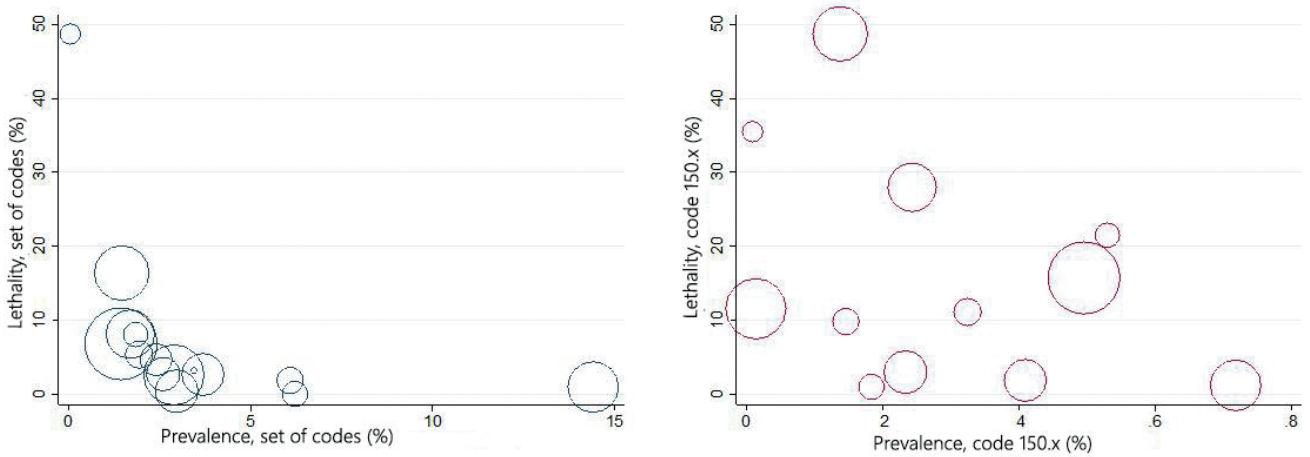

Figure 2. Scatter diagrams of the values of the prevalence of HF and lethality in HF, established according to encoding data, with a weighting factor equal to the proportion of the adult population in a subject of the Russian Federation in relation to the adult population of the Russian Federation as a whole. **A** — expanded encoding, **B** — standard encoding.

Table 1

Indicators of burden on healthcare system, associated with HF

Indicator of burden on healthcare system, associated with HF	Standard encoding	Expanded encoding
Proportion among all seeking medical care, %	0,10 (0,04, 0,18)	0,91 (0,47, 4,04)
Proportion among ambulance calls, %	0,43 (0,06, 0,81)	0,92 (0,40, 2,64)
Proportion among hospitalizations for any reason, %	0,31 (0,03, 0,48)	1,50 (0,98, 5,09)
Proportion among outpatient visits, %	0,02 (0,004, 0,06)	0,77 (0,31, 2,53)
Number of seeking medical care per 100 patients	98 (49, 136)	170 (122, 217)
Number of ambulance calls per 100 patients	60 (18, 96)	9 (5, 24)
Number of hospitalizations for any reason per 100 patients	48 (20, 137)	17 (10, 70)
Number of outpatient visits, per 100 patients	123 (108, 186)	175 (134, 219)

Note: data are presented as median (25, 75 percentiles); taking into account the intersections between the groups, the assessment of the differences in burden indicators between the groups was not performed.
Abbreviation: HF — heart failure.

(53,6% from those who gave the data on the request, the adult population corresponds to 18,9% from the entire adult population of RF) (Figure 1 A, B). In the expanded encoding of HF, the median of the HF prevalence was 2,6% (IQR 1,7-3,7, range from 0,04 to 14,4%), the median of lethality — 3,2% (IQR 1,9-8,1%, range from 0,04 to 48,68%). The maximum and minimum lethality rate was noted in two regions with the minimum and maximum values of the prevalence (Figure 2 A). In accounting all available information, the correlation between the indicators of the prevalence and lethality was absent; in deletion of two extreme values in expanded encoding there was the reverse correlation between the prevalence and lethality (r=-0,67, p=0,013).

In average, the presence of I50.x code was observed in 9,4% of all cases of HF established according to the encoding data (IQR 2,4-19,3%, range from 0,5 to 34,5%). The accounting for I50.x code only corresponded to the median of HF prevalence 0,21% (IQR 0,04-0,44%, range from 0,01 to 0,72%) and lethality 11,3% (IQR 2,42-24,7%, range from 0,99% to 48,70%) (Figure 2 B). The median value of the proportion of patients with the presence of I50.x code in diagnosis in relation to the total number of patients of the expanded encoding group was higher at the inpatient stage of providing medical care than at outpatient stage — 11,8% (IQR 2,8-28,6%) vs 5,4% (IQR 1,1-8,9%).

The proportion of seeking medical care for the cohort of patients with the codes characterizing the presence of HF in relation to the total number of seeking medical care varied greatly between the regions and depending on the approach to the

disease encoding (Table 1). The greatest burden was noted on the ambulance service and the inpatient unit. With a total lower burden on healthcare system in the case of standard encoding, the number of ambulance calls and hospitalizations for any reason per 100 patients was greatly higher than in expanded encoding (Table 1).

Discussion

Using the method of structured collection of information from the subjects of the Russian Federation, the present study showed high heterogeneity of the reported data on the prevalence and mortality in HF established according to the encoding data, different frequency of use of the I50.x code according to ICD-10 and differences in the indicators of the burden on the healthcare system associated with HF. It was established that the predominant source of the information on cases of providing medical care for patients with HF is the databases of the territorial compulsory medical insurance fund of the subjects of the Russian Federation, while in at least half of the cases (in 46% of the regions that gave the data) this information is not used for accounting and operational monitoring. The obtained results indicate existing gaps and the need to develop the common principles of the accounting and encoding of cases of HF in RF that will provide assessing the burden of the disease and monitoring the effectiveness of measures at the regional and federal levels.

The previously performed population studies have demonstrated significant heterogeneity of the indicators of the prevalence and lethality in HF between countries [14]. Apart from the differences in the availability and quality of providing medical care, one of the probable reasons for the heterogeneity of the values of statistical parameters are different disease accounting systems. Data from national statistical services, databases of insurance medical organizations and medical information systems, large population studies, registries are used as the sources of information.

In the present study, despite the similar source of the information in most regions, the differences between extreme values of the parameters showing the prevalence and lethality in HF according to encoding data were more than three hundred- (range from 0,04% to 14,4%) and thousandfold (range from 0,04% to 48,68%) in the case of expanded encoding and greatly lower in the case of standard encoding (prevalence ranges from 0,01% to 0,72%, lethality ranges from 0,99% to 48,70%, respectively). High variability was previously shown for the standardized indicator of mortality rate from HF too [10] that in combination with high variability of other statistical parameters once more emphasizes the importance of the development and implementation in RF of a unified encoding system, in particular, HF. Indeed, the observed associations between the prevalence and lethality indicate the presence of contradictory approaches — the accounting for only severe cases of HF with the highest lethality rate in one regions and the overdiagnostics of HF in CVDs with more favorable prognosis in other regions. In the situation of low availability of analyzing the level of natriuretic peptides which are recommended for the diagnostics of HF with intermediate and preserved EF of the left ventricle [15], the problem of the overdiagnostics of HF can remain relevant.

It is assumed that the prevalence of HF is in average 1-3% of adult population [16], and varies between countries. According to the Heart Failure Atlas of European Society of Cardiologists (HFA ESC), the indicator of the incidence of HF in European countries vary in the range 1,99-6,55 per 1000 patient-years, and the prevalence of HF — in the range 1,2-3,9% (the corresponding information for RF is not presented in the Atlas) [12]. According to the analysis of the expanded encoding data given by the regions, the prevalence of HF in RF in average is 2,6%, with little variability of the indicator in most of the regions and 1-5% range of its value. While using the standard encoding, the prevalence of HF in RF will not exceed 1%, that together with general information about the high prevalence of CVDs in the RF and a very high level of cardiovascular risk, rather indicates an underaccounting of a significant number of HF cases. It should be emphasized that the frequency of the use of I50.x codes differed dozens of times between the regions (the range is from 0,5 to 34,5% among all potential cases of HF) including the large regions that does not allow us to interpret the obtained differences as an error of small sample size only. At the same time, for the analyzed regions, as in our earlier study in Saint-Petersburg [9], it was also noted that the presence of the I50.x code on average characterizes patients of higher risk, with frequent ambulance calls, frequent hospitalizations and high mortality.

Limitations of study. The performed study has a number of limitations. The main of them is the use of the information to analyze, given by the subjects of RF but not the data from official sources of statistical information. Nevertheless, the systematic collection of the information about the prevalence and lethality in HF is not carried out, and the annual statistical digests of Federal State Statistics Service provide the data on only main nosologies (ischemic heart disease and cardiovascular diseases) or on other heart diseases as a set of I30.x-I51.x codes. The extrapolation of data from large Russian studies (with a systematic selection error typical of them) to the entire population of the Russian Federa-

tion also has certain limitations. In addition, taking into account that all main powers for planning and implementing measures in HF, which are planned within the regional programs "Fight against cardiovascular diseases", are assigned to the subjects of RF, it is important to analyze the statistical parameters available today.

Despite the sampling to analyze the prevalence and lethality in HF corresponded to 19% of total adult population of RF, we used the data of just small part of the subject of RF, and in the situation of the insufficiency and high heterogeneity of the data, the median values of the analyzed indicators may not reflect the true average Russian value. Nevertheless, the present study is one of the first attempts to analyze and attract attention to solving the problems of the systematic collection of statistical information for patients with HF at the level of the regions and the country as a whole.

It should be emphasized that there is no a universal approach to the choosing of the codes which should be considered for assessing the burden of HF. The Global Burden of Disease Study 2017 used the list of >50 codes of cardiovascular, pulmonary, endocrine, hematological and other diseases [17]. American Hospital Registry of Heart Failure Get with the Guidelines is based on the key codes of ICD-10 (I11.0, I13.0, I13.2, I50.x), whereas National Heart Failure Audit in the UK — on 7 codes (I11.0, I25.5, I42.0, I42.9, I50.0, I50.1, I50.9); the information of the HF epidemiology is also published based on the data reported by a doctor (SwedeHF) or a patient (NHANES). Despite the fact that in our study we accounted many codes used in earlier performed studies [11], the searching the most optimal approach is required, with high sensitivity and specificity for HF in Russian population, proved in validation studies and in audit of the quality of providing medical care.

Conclusion

According to the information given by 15 regions for 2019, we noted high heterogeneity of the indicators reflecting prevalence and lethality in HF and the burden to the healthcare system, associated with HF. The medians of prevalence and lethality in HF were 2,6 and 3,2% according to expanded encoding (I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43.0, I43.1, I43.2, I43.8, I50.x) and 0,21 and 11,3% — according to standard (the accounting for only I50.x code) encoding of HF. The presence of I50.x code in diagnosis mainly characterizes the cohort of patients with a large number of seeking emergency and inpatient medical care, less number of outpatient visits and greater lethality. It is necessary to develop a unified approach to encoding cases of HF and accounting at the country level in order to obtain objective statistical data and use them for management decisions. The improvement of regional medical information systems and the development of VIMIS CVD with an increase in the number of available data, including the clinical and demographic characteristics of patients, and further analysis of indicators at the country level, including those standardized by gender and age, will further provide a detailed assessment of the burden of HF in the RF and contribute in determination of the necessary steps to reduce it.

Relationships and Activities: none.

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Association of cystatin C with changes of left ventricular structure and function in individuals with different cardiovascular risk

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Aim. This study aims to investigate the association of cystatin C with changes of left ventricular structure and function in individuals with different cardiovascular risk (CVR).

Material and methods. 267 patients with low-moderate (group I, n=58), high (group II, n=80) and extremely high (group III, n=129) CVR were examined. The level of serum cystatin C, creatinine and blood lipid spectrum, filtration rate of the kidneys and echocardiography indicators were estimated.

Results. Among all the study participants (n=267), 194 patients (72,6% of cases) had the increased level of serum cystatin C; 165 patients (61,7% of cases) showed the signs of the left ventricular hypertrophy (LVH). The increased level of serum cystatin C was observed in 51,7% of cases in group I; 75,0% — in group II and 80,6% — in group III. The values of glomerular filtration rate (GFR) calculated using the CKD-EPI and F. Hoek formula were the following: 100,2±17,0 ml/min/1,73 m^2 and 84,8±15,5 ml/min/1,73 m^2, $p<0,05$ in group I; 81,2±21,6 ml/min/1,73 m^2 and 63,1±18,3 ml/min/1,73 m^2, $p<0,05$ in group II; 63,0 (32,0;93,0) ml/min/1,73 m^2 and 55,1 (22,1;70,7) ml/min/1,73 m^2 — in group III. The LVH detection increased with the increase of the CVR degree (43,1% — in group I; 66,2% — in group II and 67,4% in group III). Relative wall thickness (RWT, units) increased significantly from the patients of group I (0,34±0,04 units) to the patients of group II (0,37±0,08 units) and III (0,38±0,06 units). Eccentric variant of LVH significantly prevailed in all the groups. On one side, it was found that the level of serum cystatin C was in direct correlation with left ventricular mass index (LVMI, r=0,268, $p<0,05$) and left ventricular RWT (r=0,190, $p<0,05$), and on the other side, the inverse relationship between LVMI and GFR for cystostatin C was observed (r=-0,324, $p<0,05$).

Conclusion. The results of the study showed that the level of serum cystatin C and LVMI value significantly increase with the increase of the CVR degree. The high levels of serum cystatin C are closely associated with the increase of LVMI and the changes in the RWT value. In turn, the increase of LVMI negatively correlated with filtration rate of the kidneys in patients with different CVR. Concerning the structural changes in the left ventricle, eccentric HLV prevailed in all the three groups.

Keywords: cardiovascular risk, cystatin C, glomerular filtration rate, left ventricular hypertrophy.

Relationships and Activities: none.

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Key messages

- The frequency of the kidney dysfunction increases with the increase of cardiovascular risk (CVR), and the detection of the disorders of excretory renal function in patients with high CVR reliably provides the effective secondary prevention of atherosclerotic cardiovascular diseases.
- In addition to generally accepted markers of CVR, it is important to investigate new and, simultaneously, informative biomarkers, particularly cystatin C, to predict the development of cardiovascular events (CVE).
- Both level of serum cystatin C and values of the left ventricular structure and function changes increase with the increase of CVR degree, and this is an independent predictor of CVE.

The presence of chronic kidney disease (CKD) in a patient significantly increases cardiovascular risk (CVR). In accordance with the studies [1, 2] performed in recent years [3], the frequency of kidney dysfunction occurrence increases in individuals with high and very high CVR. There is a close interrelationship between cardiovascular pathology and functional abilities of kidneys [4]. Accumulated experimental, clinical and laboratory data of a mutual influence between cardiovascular and urinary systems created a basis of the concept of "cardiorenal syndrome" [5]. In this situation, a mutually aggravating lesions of kidneys and heart greatly increases the risk of an unfavorable prognosis [6]. In this regard, in recent years, serum biomarkers of kidney and heart diseases have been actively studied. Glomerular filtration rate (GFR) calculated on the basis of serum creatinine, gives an idea of CKD severity and forecasts the degree of CVR [2, 3]. It should be noted that the biomarker of CKD development in its early stages is cystatin C, the growth of which outstrips the increase in blood creatinine by an average of 5 years. Taking into account this fact, leading experts recommended to use serum cystatin C with the aim to improve the accuracy of the GFR assessment together with creatinine as additional method to analyze the condition of excretory kidney function [2, 7]. A key moment for the practical medicine is a fact that the single measurement of the serum cystatin C level provides a reliable determination of the GFR value [7]. As the data of the performed studies [8, 9] have been shown, the probability of CDR has a reverse correlation with a decrease in GFR. However, the problems of the correlation between the cystatin C concentration and left ventricular (LV) structural and functional condition in different CVR remain unclear.

The study aims to investigate the interrelationship between serum cystatin C and structural and functional changes in LV in individual with different CVR.

Material and methods

A single-stage cross-sectional study was conducted from February 2021 to October 2022. The study included 267 patients who received hospital treatment in the departments of the therapeutic profile of the National Hospital under the Ministry of Health of the Kyrgyz Republic. The patients were from 22 to 86 years of age (the mean age was 55,6±12,2 years). The inclusion criteria were the presence of one and more factors of CVR such as the following: total cholesterol (CS) concentration ⩾5,01 mmol/l, low-density lipoprotein (LDL) CS ⩾3,01 mmol/l, triglycerides (TG) ⩾1,7 mmol/l, smoking, arterial hypertension (AH), stable forms of ischemic heart disease, diabetes mellitus, carotid and femoral atherosclerotic lesions, and also ischemic stroke in anamnesis. The exclusion criteria: the patient`s refusal of the study, acute kidney lesion, acute coronary syndrome, thyroid gland dysfunction, CKD stage V, valvular heart pathologies, persons with malignant neoplasms, feverish patients, morbid obesity. The present study strictly followed the Declaration of Helsinki, and the study methodology and protocol were discussed and approved by the independent local Ethics Committee of "Society of Specialists in Chronic Kidney Disease of Kyrgyzstan" (the protocol № 3 of May 12, 2021). All participants signed a form of informed consent for medical examination. The total CVR was calculated using the scale SCORE. All participants were subdivided into the individuals with low-moderate (from 0 to 4%) (I — group, n=58); high (from 5 to 9%) (II — group, n=80) and very high (>10%) (III — group, n=129) risk of death from cardiovascular diseases (CVDs). The clinical part of the study included the measurement of arterial pressure to all the patients (according to Korotkov`s method), heart rate, body mass index, and the collection of a detailed anamnesis. Echocardiography to all the study participants was performed according to the generally accepted methodology where the linear

LV sizes were determined: end-systolic LV volume, end-diastolic LV volume, stroke volume, thickness of interventricular septum, thickness of posterior LV wall. In addition, we calculated left ventricular mass index (LVMI) and the character of LV structural changes according to the international recommendations [10, 11]. The following variants of LV structural changes were determined: concentric remodeling (relative wall thickness (RWT)) >0,42 U., the LVMI indicator in norm), eccentric LV hypertrophy (HLV) (LVMI above the norm, the RWT indicator <0,42 U.), concentric HLV (LVMI above the norm, the RWT indicator >0,42 U.). HLV was diagnosed in LVMI >115 g/m^2 in men and >95 g/m^2. The laboratory part of the study estimated the levels of total CS, LDL-CS, high-density lipoprotein-CS and TG. The functional state of kidneys was assessed according to the level of serum creatinine and cystatin C using the formulae "Chronic Kidney Disease Epidemiology Collaboration" and F. Hoek, respectively. The reference concentrations of cystatin C in blood serum were 0,40-0,99 mg/l. According to the regulation of the Russian Scientific Society of Nephrology (RSSN) (Научное общество нефрологов России (НОНР)), the categories of the functional state of kidneys were determined [12].

Statistical processing. The data obtained during this study were processed using the program Microsoft Office Excel 2007 (Microsoft Corp., USA) and Statistica 10,0 (StatSoft Inc., USA). The description of the signs different from normal distribution, is presented as Me [Q1; Q3], where Me — median, Q1 and Q3 — the first and third quartiles. To describe the pattern of distribution different from normal, nonparametric methods were used — the Mann-Whitney criterion. The significance of differences between the subgroups was estimated using Student`s t-test (for variables with normal distribution), and Mann-Whitney U-test (for variables with nonparametric distribution). To determine the relationships between different parameters, a correlation analysis was performed. Spearman's nonparametric rank correlation coefficient was used to determine the correlation of parameters that have an incorrect distribution, and Pearson's paired correlation coefficient was used for parameters with a normal distribution. The value of p<0,05 was considered statistically significant.

Results

The present study included 267 patients with low and moderate CVR (58, 21,7%), high CVR (80, 30,0%) and very high CVR (129, 48,3%). In general, the proportion of men and women was 135 (50,6%) and 132 (49,4%), respectively. As shown in Table 1, the number of women was significantly higher in the group with low and moderate CVR (72,4% and 27,6%, p<0,05). Whereas the groups of high (67,5% and 32,5%, p<0,05) and very high (68,4% and 49,6%, p<0,05) CVR contained much more men. The average age of women was a little higher in all the three subgroups. The subgroup II contained the following number and proportion of patients: with AH (n=47; 58,7%), with reduced renal function (n=35; 43,7%) and diabetes mellitus (n=19; 23,7%). Atherogenic dyslipidemia was found in just 10 people in 12,5% of the cases. At the time of the study conduction, the individuals from the subgroup III have had myocardial infarction in the anamnesis (n=54; 41,8%) and ischemic stroke (n=28; 21,7%). 49 patients (37,9%) had more severe decrease in excretory function of kidneys.

The serum cystatin C level above threshold values (>0,99 mg/l) was found in most of examined patients. Among all the study participants (n=267), 194 patients (72,6% of the cases) had raised levels of serum cystatin C. In particular, the increase in this biomarker level was observed in 30 (51,7%) examined patients from the group I (Table 2). As for the

Table 1

Distribution of the study participants depending on the degree of CVR (n=267)

Parameter	Frequency, n (%)
Low and moderate cardiovascular risk, n=58 (21,7%)	
Men/women	16 (27,6%)/42 (72,4%)
Mean age of men, years	45,9±13,4
Mean age of women, years	53,8±13,9
High cardiovascular risk, n=80 (30,0%)	
Men/women	54 (67,5%)/26 (32,5%)
Mean age of men, years	52,2±12,8
Mean age of women, years	53,1±13,8
Arterial pressure, ⩾180/110 mm Hg	47 (58,7%)
Total cholesterol, >8,0 mmol/l	6 (7,5%)
Low-density lipoprotein cholesterol, >4,9 mmol/l	4 (5,0%)
Diabetes mellitus type 2	19 (23,7%)
GFR, 30-59 ml/min/1,73 m^2	35 (43,7%)
Very high cardiovascular risk, n=129 (48,3%)	
Men/women	65 (68,4%)/64 (49,6%)
Mean age of men, years	58,1±10,6
Mean age of women, years	60,4±8,3
Myocardial infarction in anamnesis	54 (41,8%)
Ischemic stroke in anamnesis	28 (21,7%)
Chronic kidney disease, GFR <30 ml/min/1,73 m^2	49 (37,9%)

Abbreviation: GFR — glomerular filtration rate.

Table 2

Comparative laboratory and instrumental characteristics of examined individuals with different CVR

Parameters	Group I, n=58	Group II, n=80	Group III, n=129
Elevation of serum cystatin C	30 (51,7%)	60 (75,0%)**	104 (80,6%)*
Hypercholesterolemia	26 (44,8%)	30 (37,5%)	54 (41,8%)
Hypertriglyceridemia	12 (20,6%)	34 (42,5%)**	49 (37,9%)
Dyslipidemia	27 (46,5%)	40 (50,0%)	53 (41,0%)
Concentric LV remodeling	1 (1,7%)	5 (6,2%)	12 (9,3%)*
Hypertrophy of LV, total	25 (43,1%)	53 (66,2%)**	87 (67,4%)*
Concentric LV hypertrophy	4 (16,0%)	11 (20,7%)	18 (20,7%)
Eccentric LV hypertrophy	21 (84,0%)	42 (79,3%)	69 (79,3%)
LVMI, g/m^2	134,5±38,5	143,3±39,2	162,9±62,0*
LV RWT, U.	0,34±0,04	0,37±0,08	0,38±0,06*

Note: * — p<0,05 between groups I and III, ** — p<0,05 between groups I and II.
Abbreviations: LVMI — left ventricular mass index, LV — left ventricle, RWT — relative wall thickness.

Table 3

Comparative characteristics of renal filtration function

Prameters	Group I, n=58	Group II, n=80	Group III, n=129
Creatinine, μmol/l	66,0±11,1	91,6±27,4**	98,5 (70,6;272,9)*
Cystatin C, mg/l	0,987±0,235	1,307±0,404**	1,255 (1,060;3,010)*
GFR based on creatinine, ml/min/1,73 m^2	100,2±17,0	81,2±21,6**	63,0 (32,0;93,0)*
GFR based on cystatin, ml/min/1,73 m^2	84,8±15,5	63,1±18,3**	55,1 (22,1;70,7)

Note: * — p<0,05 between groups I and III, ** — p<0,05 between groups I and II.
Abbreviation: GFR — glomerular filtration rate.

individuals with high and very high CVR, the elevated serum cystatin C in them was noted in 75,0% and 80,6%, respectively. Hypercholesterolemia (HCS), hypertriglyceridemia (HTG) and dyslipidemia were found in 44,8%, 20,6% and 46,5% of the cases, respectively. The group of the patients with high CVR had HCS, HTG and dyslipidemia in 37,5%, 42,5% and 50,0%, respectively. The prevalence of HCS, HTG and raised level of LDL-CS in the group of very high CVR were 41,8%, 37,9% and 41,0%, respectively.

The analysis of echocardiography results showed that the number of the patients with concentric type of LV remodeling was significantly higher in the group of the individuals with very high CVR (9,3%) compared to high (6,2%), low and moderate (1,7%) CVR. In total sample of our study (n=267), 165 people (61,7% of the cases) had echocardiographic signs of HLV. It should be noted that the frequency of HLV grew with an increase in the degree of CVR, reaching 43,1% in the group I; 66,2% — in the group II and 67,4% in the group III. The same thing was observed in relation to RTW of LV, the value of which greatly increased from the group I (0,34±0,04 U.) to the groups II and III (0,37±0,08 U. and 0,38±0,06 U.). As expected, the value of LVMI was significantly higher among the patients with very high (162,9±62,0 g/m^2) compared to high (143,3±39,2 g/m^2) and low-moderate (134,5±38,5 g/m^2) CVR. The analysis of the LV structural changes showed significant prevalence of eccentric HLV in all the three groups. The frequency of concentric and eccentric HLV in the groups with low and moderate, high and very high CVR was distributed as follows: 16,0% (n=4)/84,0% (n=21), 20,70% (n=11)/79,3% (n=42) and 20,7% (n=18)/79,3% (n=69). We consider it important to note that in our study, HLV was recorded in 23 (88,4%) of women from the group II and 47 (73,4%) — from the group III. Regarding to men, the frequency of HLV in the groups II and III was 30 (55,5%) and 40 (61,5%) of the examined patients, respectively.

According to the criteria of stratification of CVR, the average levels of serum creatinine and cystatin C were significantly higher in the group III (Table 3). It is worth noting that the value of GFR calculated on the basis of serum cystatin C was significantly lower compared to the GFR data determined on the basis of serum creatinine in all the three groups.

Table 4

Comparative characteristics of renal filtration function (F. Hoek)

Parameters	Group I, n=58	Group II, n=80	Group III, n=129
C1, GFR ⩾90 ml/min/1,73 m^2	21 (36,2%)*	7 (8,7%)	8 (6,2%)
C2, GFR 60-89 ml/min/1,73 m^2	37 (63,8%)*	37 (46,3%)	54 (41,9%)
C3a, GFR 45-59 ml/min/1,73 m^2	–	19 (23,8%)**	15 (11,6%)
C3б, GFR 30-44 ml/min/1,73 m^2	–	17 (21,2%)**	5 (3,9%)
C4, GFR 15-29 ml/min/1,73 m^2	–	–	21 (16,3%)
C5, GFR <15 ml/min/1,73 m^2	–	–	26 (20,1%)

Note: * — p<0,05 between groups I and III, ** — p<0,05 between groups II and III.
Abbreviation: GFR — glomerular filtration rate.

In this regard, we investigated the state of the excretory function of kidneys on the basis of serum cystatin (Table 4). Thus, the frequency of C1 and C2 categories of the functional state of kidneys among the individuals with low and moderate CVR was 36,2% and 63,8%, respectively (p<0,05). Moreover, these data differed from those of the patients from the group of high CVR where the prevalence of C1 and C2 categories of the renal filtration function was significantly lower — 8,7% and 46,3%, respectively (p<0,05). A moderate (C3a) and significant (C3б) decrease in the excretory function of kidneys among the patients with high and very high CVR was the following: 23,8% and 11,6%, p<0,05; 21,2% and 3,9%, p<0,05. 21 patients (16,3%) had abruptly reduced (C4) renal filtration. At the time of the study conduction, 26 patients (20,1%) from the group III required renal replacement therapy (Table 4).

As shown in the Table 2, with the elevation of the CVR degree, the serum cystatin C level and the LVMI value significantly increase, i.e. their highest quartiles were observed in the individuals with very high CVR.

We also calculated the indicators of correlation relationship between the LVMI value and the serum cystatin C level. Thus, the serum concentration of cystatin C statistically significantly directly correlated with the value of LVMI (r=0,268, p<0,05) and RTW of LV (r=0,190, p<0,05). Negative correlation relationship was observed between LVMI and GFR determined using cystatin C (r=-0,324, p<0,05).

Discussion

With an increase in the degree of CVR, the frequency of kidney dysfunction increases, that was confirmed by the results of our study. The identification of early disorders of excretory renal function in individuals with high CVR reliably provides effective secondary prevention of atherosclerotic CVDs. It is known that early diagnostics of CKD allows doctors to start timely treatment, to prevent the development of unfavorable complications and to reduce lethality in this category of patients. In this regard, comprehensive search for new and at the same time informative biomarkers of the CBR is relevant. Therefore, scientists have no doubts about the significance of the investigation of cystatin C that may serve as an important biomarker in the stratification of CVR.

The modern studies noted that cystatin C is a low molecular weight protein which freely passes through the glomerular membrane and undergoes breakdown in the tubular system. Besides, it is important that the concentration of this biomarker does not depend on the type of nutrition, muscle mass, physical activity, age, ethnicity and gender [13]. Certainly, all the listed properties of cystatin C make it an informative biomarker both in practical cardiology and neurology [14]. For example, the group of researches headed by Barbarash L. S. (2013) analyzed the prognostic value of serum cystatin C in relation to the risk for the development of complications during hospital period in patients underwent coronary bypass surgery. The authors have demonstrated [15] that the serum cystatin C levels in patients with an adverse outcome were reliably higher compared to individuals with favorable prognosis a day before and on seventh day after coronary bypass surgery. A previously conducted observational study showed [16] that the elevated serum cystatin C level was closely related to the risk of death from all causes including CVDs. Higher levels of serum cystatin C signal not only about the severity of excretory renal function disorders but also forecast the increase in CVR. The study performed by Ekerblom A, et al. [17] showed that the serum levels of cystatin C ⩾1,01 mg/l were independent predictors of cardiovascular death during a year regardless a variant of acute coronary syndrome. According to another data [18], the elevation of serum cystatin C level was associated with the increase in the prevalence of AH, smoking and dyslipidemia. In addition, high serum levels of cystatin C were associated with the growth of the fre-

quency of myocardial infarction and ischemic stroke regardless other traditional risk factors of CVDs [17]. These data coincide with the results of our study too, where with the increase in CVR, the elevation of serum cystatin C level was observed (Tables 2-4). As shown in our study, the concentration of serum cystatin C statistically significantly correlated with LVMI and LV RWT. An interrelationship between the levels of cystatin C and LV structural changes was also shown in the study of Polozov E. I., et al. [18]. Huang Z, et al. (2022) note that in individuals with high CVR, the highest serum levels of cystatin C were associated with the growth of LVMI value as well as the development of LV diastolic dysfunction [19]. As the authors have shown [19], the increase in the serum level provokes the occurrence of concentric and eccentric HLV. A recently published study of Chernyavina A. I., et al. showed [20] that the estimation of GFR based on cystatin C in individuals with high CVR can be used as a marker to forecast the risk for the development of chronic heart failure in patients with non-complicated hypertensive disease without CKD. As the authors have reported [20], in elevated serum cystatin C level, a relative risk for the development of chronic heart failure reaches 2,99. Whereas in reduced GFR according to cystatin C 74 ml/min/1,73 m^2 and lower, a relative risk for the development of CHF is 1,26. A number of studies have shown [21-24], that in the subgroups of patients having left auricular thrombosis with non-valvular atrial fibrillation, the median and the interquartile serum cystatin C levels were clinically significantly higher. It seems, in individuals with high and very high CVR, pathogenesis for the development and progression of cardiovascular events involve, along with cystatin C, inflammation and associated atherosclerotic and fibrotic processes. These data once again emphasize the presence of close pathogenetic, clinico-laboratory and prognostic interrelationships of renal filtration function and the risk for the development of cardiovascular events within the framework of a single cardiorenal continuum.

Limitations of study. Heterogeneity of nosological patterns in patients of a therapeutic profile as well as the absence of analysis of the pharmacological therapy character.

Conclusion

In this study, we demonstrated that with an increase in CVR, there was a significant increase in both the serum cystatin C level and the LVMI value. Regardless the degree of CVR, the indicators of renal filtration function, calculated based on serum cystatin C, are significantly lower compared to blood creatinine. High serum cystatin C levels closely correlated with LVMI value and with the changes of LV RWT values. Among LV structural changes regardless the degree of CVR, eccentric HLV prevailed. Taking into account the advantages of cystatin C compared to serum creatinine, the investigation of the interrelationship between this biomarker and LV structural and functional changes in individuals with different CVR is promising and requires further research.

Relationships and Activities: none.

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Hypertensive disease after moderate coronavirus infection. The results of six-month follow-up

Fedoseeva D. O., Sokolov I. M., Shvarts Yu. G.

Aim. This study aims to assess the clinical specificity of course of hypertensive disease (HD) during the first 6 months after new coronavirus infection (COVID-19) and to investigate prognostic significance of laboratory and instrumental parameters for organ dysfunctions in acute period of COVID-19 in patients with HD.

Material and methods. The study included 82 patients. The main group included 50 patients with HD duration of at least 3 years, who received antihypertensive therapy and had confirmed moderate COVID-19. The control group included 32 patients with HD and without COVID-19. The mean age was 63,6±7,9 years and 66,6±10,3 years, respectively. The standard parameters of carbohydrate and lipid metabolism, inflammatory markers, hematological indicators, glomerular filtration rate (GFR) were measured, and also arterial pressure, Ps, t° C, SpO_2, peak expiratory flow rate (PEFR) were recorded. In 6 months we contacted by phone to conduct a survey concerning the 6-month period after hospitalization or outpatient examination with filling the questionnaire form SF-36.

Results. Before inclusion, 76,5% and 83,3% of the patients in the main and control groups, respectively, took 1 hypotensive drug; 17,7% and 16,6% — 2-3 drugs; 5,9% ($p<0,05$) of the patients from the COVID-19 group took the drugs irregularly before hospitalization. In 6 months, 3% in each group took 1 hypotensive drug, 50% — 2 drugs, and 47% — 3 drugs. For the control group this was: 77% — 2 and 20% — 3, respectively. After analyzing the SF-36 form, we found that the worsening of emotional health in the group with HD and COVID-19 correlated ($p<0,05$) with initial SpO_2 (r=-0,623), t° C (r=-0,371), PEFR (r=0,423), and the degree of improvement — with GFR (r=0,339), total cholesterol (r=0,471) and platelet count (r=0,414). SF-36 also showed that in the main group, the worsening of physical health was associated with lower ALB (r=0,512), the higher increase of lactate dehydrogenase (r=0,342) and RBC (r=0,393).

Conclusion. In 6 months after moderate COVID-19, the patients develop pronounced emotional and physical disorders as well as the worsening of HD clinical course. Regarding to this, the parameters reflecting severity of systemic inflammation, impairment of liver function and changes in brain function in acute COVID-19 possessed the prognostic significance.

Keywords: hypertensive disease, novel coronavirus infection.

Relationships and Activities: none.

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Key messages

- Moderate COVID-19 worsens the course of hypertensive disease: it increases the frequency of hypertensive crisis and causes the requirement of the larger number of the drugs due to development of microvascular damage and imbalance between pressor and depressor mechanisms.
- In 6 months after moderate COVID-19, the patients with HD develop more pronounced emotional and physical disorders.
- The found changes in total cholesterol levels, platelet count, glomerular filtration rate, albumin and lactate dehydrogenase levels may be used as the predictors. The listed indicators are associated with severity of systemic inflammation, impairment of liver function and changes in brain function in acute COVID-19.

Currently, cardiovascular diseases are one of the most common comorbid pathological conditions in patients with novel coronavirus infection (COVID-19); almost every second patient with COVID-19 infection and concomitant cardiovascular diseases has hypertensive disease (HD) [1]. And some authors note the role of HD as a risk factor of more severe course of COVID-19 [1, 2].

To date, relatively little is known about clinical and laboratory-instrumental features of the HD course against the background of COVID-19. In addition, there is no enough understanding of long-term systemic effects, including cardiovascular, of COVID-19 on the organs in HD. The clinical features of the development of HD after COVID-19 infection are not completely clear, in particular, in patients with moderate course of COVID-19.

The data of the fact that the clinical symptoms named Long-COVID can persist after COVID-19 infection from several weeks to several moths are being accumulated [2-6]. It is described that the Long-COVID manifestations may be associated with viral or immuno-mediated disorder of the autonomic nervous system, functional disorders of some organs and endocrine system disorders [5, 6]. The latter may have a relation to HD progression too.

In this regard, our study was mainly aimed to assess the clinical features of the HD course during first 6 months after COVID-19 infection as well as to investigate the prognostic values of laboratory and instrumental parameters which characterize organ dysfunction in acute period of COVID-19 in patients with HD.

Material and methods

The total number of patients involved in the prospective study was 82. The inclusion of patients was carried out from November 2020 to February 2021. The investigated group included 50 patients with HD stages II-III and very high risk of the development of cardiovascular complications (according to SCORE-2), with duration of HD at least 3 years, received antihypertensive therapy and with confirmed moderate COVID-19 according to the criteria of the temporary methodological recommendations for prevention, diagnostics and treatment of COVID-19 (the Ministry of Health of Russian Federation version 9 from 26.10.2020), who received hospital treatment in the infectious department of S. R. Mirotvortsev University hospital № 1 of Saratov State Medical University. The HD diagnosis was verified in accordance with the clinical recommendations "Arterial hypertension in adults 2020" of the Russian Society of Cardiology [7]. The age of patients varied from 38 to 80 years (the mean age was 63,6±7,9 years), of them 28 women and 22 men.

The comparison group included 32 patients (19 women and 13 men) with confirmed HD stages II-III and very high risk of the development of cardiovascular complications, with duration of HD ⩾3 years, received constant basic hypotensive therapy (the diagnosis was verified similarly to the research group) and without COVID-19, who were under outpatient supervision in the Clinical center of Saratov State Medical University at the time of the study conduction and applied for a planned consultation due to various problems, against the background of satisfactory control of arterial pressure (AP) level. The age of patients varied from 39 to 80 years (the mean age was 66,6±10,3 years).

The exclusion criteria for both groups were: uncontrolled or resistant HD, hypertensive crisis (HC) before hospitalization or at admission to the hospital as well as before outpatient supervision, secondary arterial hypertension; acute or decompensated chronic heart failure, acute coronary syndrome and its complications, the rhythm disturbances with hemodynamic impairment, acute cerebrovascular accident and/or transient ischemic attack at the moment of hospitalization or examination of outpatients; the presence of acute inflammatory processes of any other localization; oncological diseases at

Table 1

The main initial laboratory parameters (Me [25%; 75%])

Parameters	Investigated group HD+COVID-19 (n=50)	Control group HD (n=32)	Value p
SpO_2, %	95,5 [94,0; 97,0]	97,0 [96,0; 97,0]	0,001
SAP, mm Hg	121,0 [113,0; 132,0]	135,0 [125,0;143,0]	0,00009
DAP, mm Hg	71,0 [65,0; 84,0]	80,0 [72,0; 89,0]	0,04
Pulse, beats/min	69,0 [60,0; 80,0]	65,5 [60,0; 72,0]	0,1
PEFRmean l/min	223,3 [170,0; 331,7]	255,0 [205,0; 328,3]	0,2
White blood cell count, 10*9/l	8,0 [5,9; 9,8]	7,3 [6,3; 8,5]	0,7
Redd blood cell count, 10*12/l	4,6 [4,1; 4,9]	4,7 [4,4; 5,2]	0,2
Platelet count, 10*9/l	222,5 [184,0; 318,0]	221,5 [183,0; 266,5]	0,2
Hemoglobin, g/l	135,5 [124,5; 141,0]	123,5 [112,5; 138,5]	0,9
Ferritin, µg/l	400,0 [380,9; 400,0]	–	–
Glucose, mmol/l	8,3 [6,0; 10,6]	5,8 [4,7; 6,2]	0,00002
Albumin, g/l	32,1 [28,5; 34,1]	36,0 [33,1; 37,1]	0,00001
Urea, mmol/l	7,0 [5,1; 8,6]	6,8 [5,2; 8,7]	0,9
Creatinine, µmol/l	79,6 [71,2; 90,0]	88,6 [81,4; 100,0]	0,002
LDH, u/l	308,1 [224,2; 363,0]	187,3 [150,5; 233,5]	0,00000001
ALT, u/l	38,7 [19,5; 77,2]	23,6 [14,6; 28,4]	0,00009
AST, u/l	33,2 [26,0; 42,6]	22,6 [18,8; 27,5]	0,0006
Cholesterol, mmol/l	4,9 [4,0; 5,4]	4,5 [3,7; 5,1]	0,00009
Total protein, g/l	67,9 [64,0; 71,0]	69,0 [64,5; 70,1]	0,2
Potassium, mmol/l	5,6 [5,1; 5,9]	5,0 [4,6; 5,5]	0,00000001
Sodium, mmol/l	136,7 [134,7; 139,0]	140,3 [136,9; 141,7]	0,003

Abbreviations: ALT — alanine aminotransferase, AST — aspartate aminotransferase, HD — hypertensive disease, DAP — diastolic arterial pressure, LDH — lactate dehydrogenase, PEFR mean. — peak expiratory flow rate, mean value, SAP — systolic arterial pressure, COVID-19 — novel coronavirus infection, SpO_2 — oxygen saturation.

present and in the anamnesis; severe kidney pathology (including chronic kidney disease stage 3); decompensation of liver diseases.

Blood sampling and measurement of laboratory and instrumental parameters were performed to all hospitalized patients starting from the second day of hospital treatment, in the morning, from 06:30 to 07:30. Blood sampling was performed on an empty stomach and before oral and parenteral administration of drugs.

In 30-40 min after blood sampling, a doctor measured the level of AP in accordance with ESC, pulse, body temperature (t° C), blood oxygen level (SpO_2), peak expiratory flow rate (PEFR). SpO_2 was measured using a pulse oximeter Riester Ri-fox N. PEFR measurement was performed with a peak flow meter Omron PF20 three times for further determination of the mean value and maximum value. The outpatient examination was performed similarly.

The parameters of carbohydrate and lipid metabolism were investigated, and the analysis of inflammatory markers (C-reactive protein, ferritin) was performed. The standard laboratory blood parameters — hematological and biochemical were tested: total protein, albumin (ALB), total bilirubin, urea, glucose, cholesterol, alanine aminotransferase, aspartate aminotransferase, potassium and sodium, creatinine and glomerular filtration rate (GFR).

In 6 months after primary examination, we contacted the patients by phone to conduct a survey concerning the 6-month period after hospitalization or outpatient examination. The patients informed the doctor about significant changes in their health condition: hospitalizations for HD or consultation with doctor for this reason, the development of hypertensive crisis [8], and following recommendations for HD treatment. To record the symptomatic hypotonic episodes (SHEs) we conditionally accepted a temporary decrease in AP level below 100 and 60 mm Hg [8, 9] and the presence of the clinical symptoms (heaviness in the head, headache, dizziness, cardialgia, shortness of breath, general weakness) with duration >10 min [8].

In the hospital and immediately after patient`s consultation with doctor, the received therapy was corrected. In 6 months, a number of antihyperten-

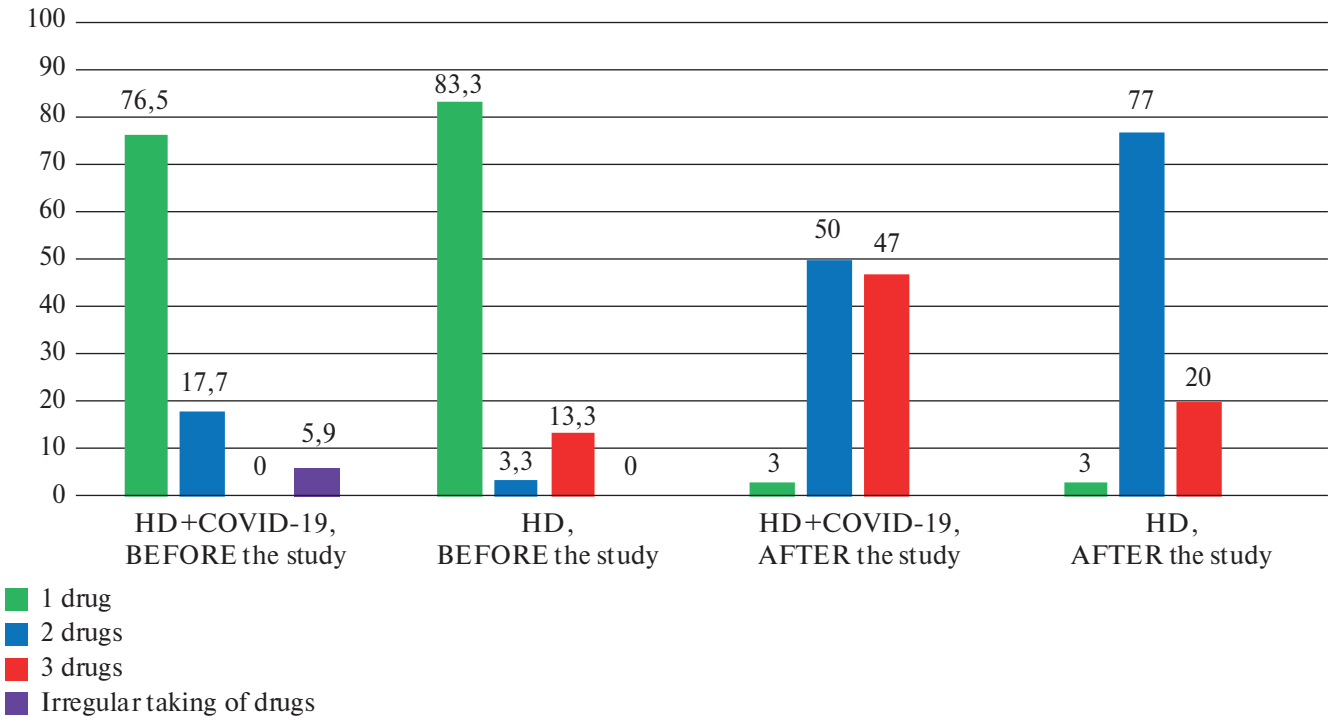

Figure 1. The number of antihypertensive drugs (%) taken by patients before and 6 months after the inclusion into the study in the main (HD and COVID-19) and control (HD without COVID-19) groups.
Abbreviations: HD — hypertensive disease, COVID-19 — novel coronavirus infection.

sive drugs used by a patient at the time of the survey was analyzed. During the telephone contact, the SF-36 questionnaire "Assessment of quality of life" was filled out. The analysis was made on the basis of percentage indicators from 0 to 100 points relative to the maximum possible for each scale, and then the general parameters were calculated: general physical health (physical status) and general mental health (emotional status).

We assessed an improvement or worsening of physical and emotional state, i.e. the assessment of these characteristics by the patients themselves for the last 6 months. When assessing the dynamics of physical state, we considered it appropriate to take into account the increase or decrease in the clinical symptoms of the main disease and the restoration of physical productivity. When assessing the emotional state, we based on the own opinion of the patients in the regard of the presence of changes according to the parameters which are assessed using the SF-36 questionnaire.

Statistical processing of the obtained results using methods of graphical analysis, analysis of variance with the determination of M±SD, with abnormal data distribution — Kruskal-Wallis ANOVA with the determination of Me, Q25 and Q75, cross-tabulation using the Fisher and χ^2 criteria, as well as nonparametric correlation with the determination of the Kendall coefficient, was carried out using the application software package "STATISTICA 10.0" (StatSoftUSA) and MicrosoftExcel. We give and discuss below only statistically significant correlation coefficients ($p<0,05$).

Results

The mean duration of HD in the examined patients in the group with HD and COVID-19 was 11,5±4,72 years. 14 patients from the same group also had a form of chronic ischemic heart disease — exertional angina pectoris (3 patients had myocardial infarction in the anamnesis), 5 patients had atrial fibrillation, 43 — had different degree of obesity (mean body mass index was 29,4±3,5 kg/m^2), and 17 patients had type 2 diabetes mellitus. Most patients were hospitalized in average on the fifth day from the onset of the clinical symptoms of COVID-19. All patients of this group received oxygen therapy; moistened oxygen was delivered through a nasal cannula at a flow rate of 5 l/min. During treatment, glucocorticosteroids were administered parenterally twice a day. The dose varied according to temporary guidelines for prevention, diagnostics and treatment of COVID-19 (the Ministry of Health of Russian Federation version 9 from 26.10.2020).

In the group of patients with HD and without COVID-19, the mean duration of HD was

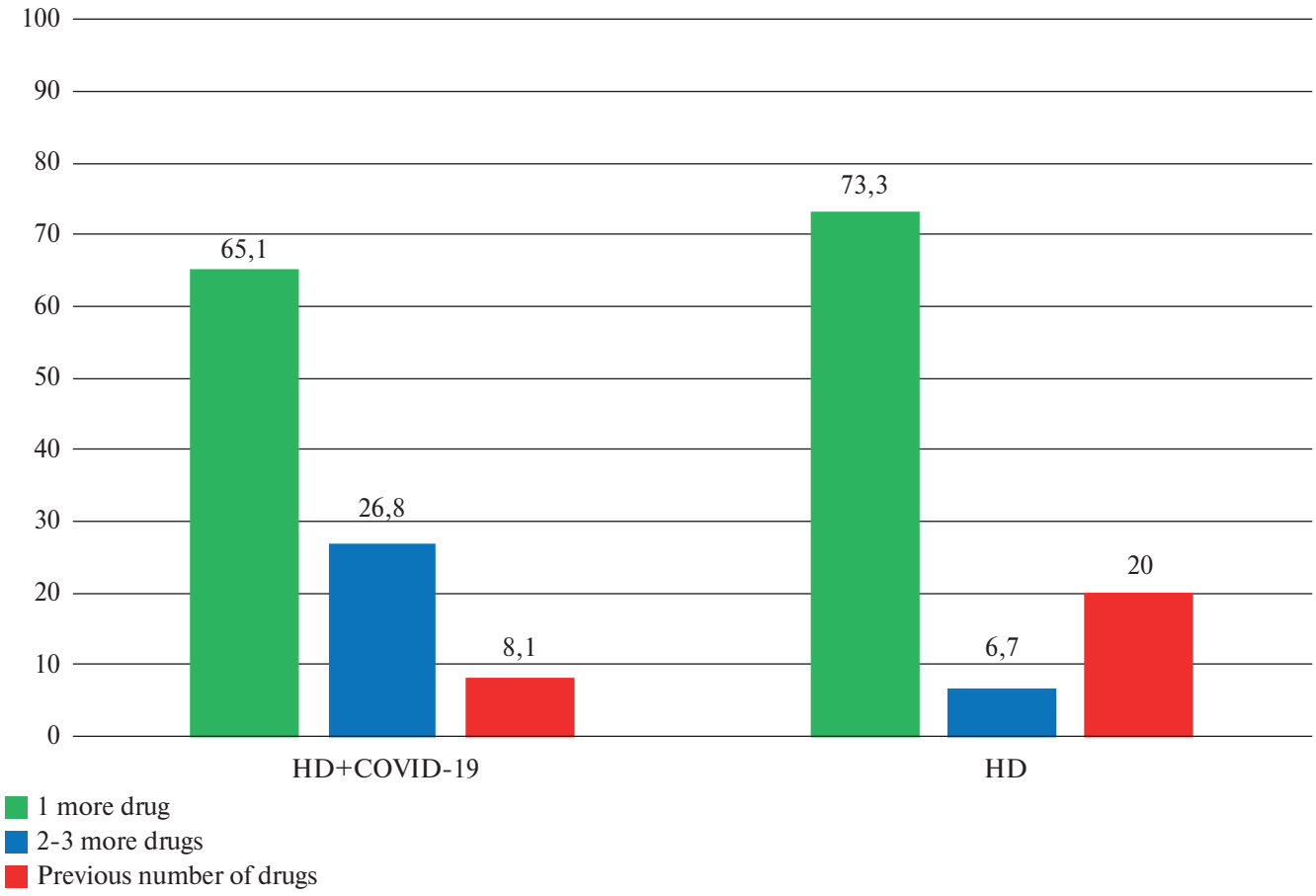

Figure 2. The comparison of the number of antihypertensive drugs (%) taken by patients before and 6 months after the inclusion into the study.
Abbreviations: HD — hypertensive disease, COVID-19 — novel coronavirus infection.

13,25±7,25 years, 20 patients had chronic ischemic heart disease — exertional angina pectoris, 6 of them previously suffered myocardial infarction, 14 patients suffered a different form of atrial fibrillation, 29 had different degree of obesity (mean body mass index was 31,9±4,4 kg/m^2), 8 patients had type 2 diabetes mellitus.

During the first examination in the clinic, 50% patients with HD and COVID-19 had a decrease in SpO_2 up to 87% minimum, 34% — increase in t° C from 37° C to 38,6° C; in 86% of the patients, systolic AP (SAP) was 100-138 mm Hg, and in 80% of the patients, diastolic AP (DAP) was 60-88 mm Hg. We noted the increased level of some laboratory parameters such as ferritin, glucose and potassium level in a significant number of the patients, while the level of ALB and total protein was decreased.

The main initial laboratory parameters are given in Table 1.

All patients in the group with HD and without COVID-19 had stable satisfactory condition, t° C and SpO_2 were normal; in almost half of them, SAP was ⩾140 mm Hg, and in a quarter — DAP was ⩾90 mm Hg. The analysis of the laboratory parameters showed that a significant number of the patients had an increased blood glucose level.

Most of the patients in the main and control groups took one hypotensive drug before the inclusion into the study — 76,5% and 83,3%, respectively, and 2-3 drugs — 17,7% and 16,6%. 5,9% patients of the group suffered COVID-19 did not take the drugs regularly immediately before hospitalization.

According to the results of the conducted survey, in six months after the discharge and outpatient treatment it was found that the mean value of emotional health in the patients with HD and COVID-19 corresponded to 41,7±6,5% based on SF-36, and in the patients without COVID-19 — 42,1±3,9%.

Emotional health in the group of the patients with HD and COVID-19 was improved during 6 months in 65% of respondents according to the assessment by the patients themselves, while in the comparison group, the improvement was noted in significantly larger number of the patients (80%).

The worsening of emotional state after the discharge was associated with relatively high SpO_2 (r=

-0,623), increased t° C (r=-0,371) and lower indicators of PEFR (r=0,423). As for the prognostic value of the laboratory data, emotional state worsened in initially relatively low values of GFR (r=0,339), total cholesterol (r=0,471) and platelet count (r=0,414). While in the group of the patients with HD and without COVID-19, emotional state worsened in initially relatively high values of total cholesterol (r=-0,294).

As for self-assessment of the physical state changes, most of the patients (60%) with HD and COVID-19 noted the worsening of the state in further 6 months after the discharge, while in the group without COVID-19 — just 20%, i.e. significantly less.

The testing of physical health using the SF-36 questionnaire showed the mean value of physical state in the group of the patients with HD and COVID-19 — 46,8±7,5%, and in the patients without COVID-19 — 42,1±3,9%.

The relative decrease in physical state in 6 months was noted in the group of the patients with COVID-19, who initially had the following changes of the laboratory parameters: lower level of ALB (r=0,512), relatively high value of lactate dehydrogenase (LDH) (r=0,342) and relatively increased red blood cell count (r=0,393).

The physical state in the group of the patients with HD and without COVID-19 worsened in relatively low values of the SpO_2 level (r=0,452) and higher values of DAP (r=-0,48).

After the discharge from the hospital during the follow-up period in the group with COVID-19 32% of the patients noted the development of non-complicated HC (p<0,05), that is 2 times larger than in the control group (16%).

SHEs were also a little more frequent (p>0,05) in the group of the patients with HD and COVID-19 (56%) than in the patients with HD and without COVID-19 (47%).

The assessment of the prognostic value of the laboratory parameters in the group with HD and COVID-19 showed that HC occurred more often in those patients who initially had lower platelet count (223,1±62,2*10*9/l) and higher level (450,8±198,5 μg/l) of ferritin than in the patients who did not develop HC (282,4±91,6*10*9/l and 353,7±117,4 μg/l, respectively).

In the group of the patients with HD and COVID-19 in 6 months after the discharge, 50% of the patients took two hypotensive drugs, and 47% had to take 3 drugs. Among the patients with HD and without COVID-19 — 77% took 2 antihypertensive drugs, and just 20% took 3 drugs, i.e. significantly less than after COVID-19. 3% in each group continued to take 1 drug (Figure 1). Compared to the period before the inclusion into the study, 28,6% of the patients of the group with COVID-19 began to take 2-3 more drugs, and 65,1% one more drug. In the control group — 6,7% and 73,3% patients, respectively. Other patients did not change the number of drugs (Figure 2). And almost all the patients said that during last 3 months the basic antihypertensive therapy was not corrected.

Discussion

The performed study was aimed to investigate the prognostic value of the levels of some clinical, laboratory and instrumental parameters in patients with HD after moderate COVID-19. Apart from that, while comparing the features of the clinical parameters in the selected groups after 6-month follow-up period, to a certain extent, we may judge the effect of moderate COVID-19 on the HD course. In general, the studies concerning the monitoring the patients with combination of HD and COVID-19 related to "strict" endpoints during and after the disease [3, 10, 11] or analyzed the problem within Long-COVID, while the present study emphasized the clinical characteristics of the course of HD itself after COVID-19.

In particular, in the group of the patients with HD and COVID-19, we revealed the increase in some laboratory parameters such as ferritin, glucose, potassium, and the decrease in ALB and total protein. The first AP measurement in the group of the patients with HD and COVID-19 showed lower mean value of AP compared to the AP level in the group of the patients without COVID-19 that is quite explainable by the different causes of hospitalization and consultations with doctor. For the main clinical parameters, the groups were comparable.

In six months after COVID-19, the patients with HD more often had the problems with emotional and physical state. We cannot exclude that the presence and absence of these deviations depended on the features of the reaction to COVID-19.

Probably, the disorders we revealed in emotional and physical sphere in 6 months after COVID-19 and associated with that changes in the level of some laboratory and instrumental parameters can be caused by the severity of systemic inflammation in the acute period of infection and its consequences. In particular, this can be indicated by the interrelationship between emotional state in 6 months after the discharge and the changes in such parameters as general level of t° C, PEFR, cholesterol, platelets, GFR in acute phase of the disease. They are the parameters with changes of which the negative tendencies in patients` emotional state were associated. It was described that these parameters react to the power release of pro-inflammatory cytokines in

COVID-19. It is also likely, the worsening of emotional state after COVID-19 during next 6 months is caused by the persistence of autoimmune-mediated dysfunction of the autonomic nervous system, which can play an important role in the disorders of psychoemotional status [10, 11]. We also cannot exclude the association of this with the development of anxiety and depressive disorders which probably may be regarded as the manifestations of Long-COVID, in particular, the changes in the brain work against the background of COVID-19 infection as well as unfavorable symptoms of HC and SHEs.

Besides, we can assume that the changes in physical state in the long-term period are associated with some signs of the liver lesion during COVID-19. [12, 13]. This was evidenced by the relative decrease in the level of ALB, and increase — LDH in patients who developed the worsening of physical state in 6 months after COVID-19.

More significant changes in the platelet count and ferritin level in patients with COVID-19 were subsequently associated with more frequent development of HC. As already noted, these changes in the laboratory parameters may indicate a more active inflammatory process in the acute period of COVID-19 in these patients and probably more severe lesion of significant for HD organs.

In general, the results of the analysis of the clinical characteristics allow us to assume that COVID-19 worsens the course of HD. For example, patients suffered COVID-19, against the background of more intensive therapy, more often developed HC and had a certain tendency to more frequent SHEs than patients who did not have COVID-19. And SHEs were more typical of the patients who developed the crises. Obviously, SHEs are associated with more significant disorder of autoregulation of bloodstream in the internal organs, in particular, brain [8, 14]. Probably, this results in the combination of SHEs and HC in the group of the patients with HD and COVID-19 [8, 15], i.e. these events have the same cause.

In 6 months, the patients with HD and COVID-19 significantly more often took a greater number of drugs. As known, during an acute infection period, the active systemic inflammation causes the lesion of many organs and systems, in particular due to microvascular injury, that aggravates imbalance between the pressor and depressor mechanisms. The latter worsens the course of HD, increases the frequency of HC and as a result requires the taking of greater number of antihypertensive drugs.

Conclusion

In 6 months after moderate COVID-19 patients with HD develop more severe disorders of emotional and physical state that patients after consultation with doctor for HD, who had no COVID-19. These events were revealed to be associated with the parameters reflecting the severity of systemic inflammation, the disorders of the liver function and the changes in the brain work in acute period of COVID-19, such as total cholesterol, platelet count, GFR, ALB, LDH. The latter makes perspective the use of these laboratory parameters as predictors.

The obtained data also indicated that moderate COVID-19 aggravates the course of HD. Among patients with HD during 6 months after COVID-19, the 2 times increase in the frequency of the development of non-complicated HC, a little more frequent SHEs and the requirement of greater number of antihypertensive drugs to control AP were revealed.

Relationships and Activities: none.

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Association of iron deficiency with atrial fibrillation recurrence after pharmacological cardioversion

Valeev M. Kh.[1], Khasanov N. R.[2]

Aim. This study aims to assess the association between iron deficiency (ID) and recurrences of atrial fibrillation (AF) in patients after pharmacological cardioversion with amiodarone within 12 months.

Material and methods. The open-label, prospective, single-center study included 198 patients with non-valvular paroxysmal AF after successful pharmacological cardioversion with amiodarone. Group I included 116 patients with ID, and group II — 82 patients with normal iron status. The primary end-point of the study was the development of symptomatic AF recurrences within 12 months after the cardioversion which was estimated by the Kaplan-Meier method. The differences were considered statistically significant if p-value was <0,05.

Results. Absolute ID was found in patients of group I; anemia was revealed in 85,3% of the patients. The groups did not differ in basic clinical and demographical parameters, concomitant diseases and drug therapy. Along with that, the I group patients were older (the median was 73 (64,8-79) years old and 69 (63-75) years old, respectively, p=0,008), and their left ventricular mass was larger (the median was 145 (115-176) g and 132,5 (118,2-145) g, respectively, p=0,004). The sinus rhythm restoration in group I required less dose of amiodarone (the median was 450 (300-600) mg and 1000 (600-1200) mg, respectively, p<0,001) and less time from the start of the drug administration to the rhythm restoration (the median was 7 (3-10) and 12 (9-18) hours, respectively, p<0,001). During the 12-month follow-up period, 49 (42,2%) patients in group I and 16 (19,5%) patients in group II developed AF recurrences (p=0,0008), hazard ratio 2,64 (95% confidence interval: 1,5-4,65) (p=0,0003).

Conclusion. ID is associated with the increase of the number of symptomatic AF recurrences in patients after pharmacological cardioversion with amiodarone within 12 months.

Keywords: iron deficiency, paroxysmal atrial fibrillation, pharmacological cardioversion, amiodarone.

Relationships and Activities: none.

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Key messages

- Iron deficiency (ID) is associated with increased risk of atrial fibrillation (AF) recurrences within 12 months after pharmacological cardioversion with amiodarone.
- In pharmacological cardioversion with amiodarone, the sinus rhythm restores faster in patients with paroxysmal AF and ID.
- The sinus rhythm restoration in patients with paroxysmal AF and ID requires less dose of amiodarone.

Atrial fibrillation (AF) is one of the most common forms of cardiac rhythm disturbance, reaching 2% in population [1, 2]. Prognostically unfavorable consequences of AF include cardioembolic complications which are frequently associated with AF paroxysms [2, 3]. To date, the main risk factors for the development of AF have been established: they include arterial hypertension, ischemic heart disease, diabetes mellitus, valvular heart defects, chronic heart failure (CHF), the disorders of thyroid gland function, age and other factors [2]. Cardiomyocyte apoptosis and myocardial fibrosis, the disturbance of the regulation of Na^+ and Ca^{2+} ions in cardiomyocytes, myocardial electrical remodeling, the imbalance of cardiac autonomic regulation and inflammation play an important role [4, 5]. During last years the possible role of iron deficiency (ID) in the development of AF is discussed, however, this problem is more often considered in the context of anemia and CHF [6]. Currently, it is well known about the worsening of the forecast in patients with CHF with the presence of ID [7-9]. A possible mutual effect of CHF and ID with participation of ID is probably associated with inflammation accompanying both HCF and AF, with the increased level of hepcidin, the decreased level of ferroportin, the reduced absorption of Fe^{2+} ions in gastrointestinal tract, the disorder of erythropoesis, the development of functional and absolute ID leading to anemia which, in turn, aggravates the course of CHF and AF [6, 10]. A direct role of ID in the development and course of AF, and in influencing the restoration and maintenance of sinus rhythm remains unclear. Taking into account a wide prevalence of ID in population and the severity of AF complications, the investigation of the features of pharmacological cardioversion results and the frequency of recurrent AF paroxysms seems very interesting.

The study aims to assess the association of ID with the development of AF recurrence in patients after pharmacological cardioversion with amiodarone during 12 months.

Material and methods

The open-label, observational, prospective, single-center study included 198 patients (the median age was 71 (63,2-77) years), of them 120 (60,6%) men and 78 (39,4%) women, with paroxysmal form of AF, sequentially hospitalized to the Department of Cardiology in the Kazan Medical-Sanitary Unit in the period from 2019 to 2021 for the paroxysm development. AF was identified using the results of electrocardiography (ECG) in accordance with the current recommendations of the Ministry of Health of Russia (2020) [2]. The criteria of inclusion into the study: age >18 years, the presence of paroxysmal form of non-valvular AF, the duration of AF paroxysm not more than 48 hours at the moment of hospitalization, successful pharmacological cardioversion with amiodarone, a signed informed consent. The study does not include patients with hemoglobin level <90 g/l; valvular heart disease; hypertrophic and dilated cardiomyopathies; patients who suffered acute coronary syndrome within 1 month; clinically significant bleedings accompanied by a fall of hemoglobin level within last 6 months; stroke; patients with an active oncological disease; B_{12}-deficiency and other anemias excepting iron deficiency; patients who have no possibility to be examined during 12 months. The exclusion criteria: the development of a serious cardiovascular event in a patient (cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke), the withdrawal of informed consent by a patient.

The anamnestic data from all the patients, including the presence of the AF symptoms at the moment of the examination and their duration, the past and concomitant diseases, taking of medications were collected; physical examination, ECG, transthoracic echocardiography (EchoCG), clinical and biochemical analysis of blood were performed. ID was identified in a decrease in the level of plasma ferritin <100 μg/l (absolute ID) or 100-299 μg/l in transferrin saturation coefficient <20% (relative ID). The reduced hemoglobin level <130 g/l in men and <120 g/l in women was estimated as a diagnostic sign of anemia according to the criteria of World Health Organization. In accordance with iron status, the patients were divided into the group of ID or the group with normal iron level.

The sinus rhythm restoration was performed by intravenous administration of amiodarone at the rate of 5 μg/kg, and if necessary, the daily dose could be up to 15 μg/kg. The dose of amiodarone and the time from the start of its administration to the sinus rhythm restoration were registered. According to the indications and current recommendations, patients were given recommendations on lifestyle modification and prescribed the necessary drug therapy. Iron sulfate drugs were prescribed to patients with identified ID.

The follow-up period was 12 months. After cardioversion, the patients visited doctors monthly on a planned basis. During each visit ECG was recorded, drug therapy was monitored and, if necessary, corrected. During entire follow-up period, the cases of the development of the symptomatic AF recurrences and adverse cardiovascular complications (cardiovascular death, non-fatal stroke, hospitalization for CHF decompensation) were registered. AF recurrences developed during the follow-up period were treated with amiodarone. All the

Table 1

Clinical and demographic characteristics of patients

Parameter	Group 1, n=116	Group 2, n=82	p
Age, years (Me [Q1; Q3])	73 (64,8-79)	69 (63-75)	0,008
Gender			0,185
Women, n (%)	75 (64,7)	45 (54,9)	
Men, n (%)	41 (35,3)	37 (45,1)	
The first time identified AF, n (%)	58 (50)	36 (43,9)	0,118
AF anamnesis <1 year, n (%)	15 (12,9)	14 (17,1)	0,450
AF anamnesis >1 year, n (%)	43 (37,1)	33 (40,2)	0,762
BMI, kg/m^2 (Me [Q1; Q3])	26,0 (24,0-27,9)	26,5 (24,5-28,9)	0,318
SAP, mm Hg (Me [Q1; Q3])	140 (130-150)	138,5 (120-145)	0,305
DAP, mm Hg (Me [Q1; Q3])	80 (80-90)	80 (80-90)	0,844
AH, n (%)	116 (100)	82 (100)	–
IHD, n (%)	36 (43,9)	48 (41,4)	0,771
MI, n (%)	13 (11,2)	18 (21,9)	0,065
CHF, n (%)	75 (64,7)	53 (64,6)	0,807
FC I, n (%)	9 (12,0)	8 (15,1)	0,808
FC II, n (%)	64 (85,3)	42 (79,2)	0,509
FC III, n (%)	2 (2,7)	3 (5,7)	0,691
FC IV, n (%)	0	0	–
DM, n (%)	47 (40,5)	30 (36,6)	0,658
Stroke, n (%)	8 (6,9)	0 (0)	0,022
COPD, n (%)	8 (6,9)	1 (1,2)	0,084
Hypothyroidism, n (%)	12 (10,3)	9 (11)	0,927

Abbreviations: AP — arterial hypertension, DAP — diastolic arterial pressure, IHD — ischemic heart disease, MI — myocardial infarction, BMI — body mass index, SAP — systolic arterial pressure, DM — diabetes mellitus, FC — functional class, AF — atrial fibrillation, COPD — chronic obstructive pulmonary disease, CHF — chronic heart failure.

patients completed the study. The primary endpoint of the study was the development of AF recurrence during 12 months.

Statistical analysis was performed using the Statistica 13.3 (StatSoft. Inc) program. The quantitative parameters were evaluated for compliance with the normal distribution using the Shapiro-Wilk criterion. In normal distribution, the data obtained are presented in the form of arithmetic averages and their standard deviations ($M\pm\sigma$). In the distribution different from normal the results were described using the median values, 25% and 75% quartiles (Me [Q1; Q3]). in normal distribution, the mean values were compared using the Student`s t-criterion, and in the cases with the absence of normal distribution, the Mann-Whitney U test was used. The statistical significance of differences in quantitative indicators with abnormal distribution was evaluated using the Kraskel-Wallis criterion. The relationship between quantitative indicators having a normal distribution was determined using the Pearson correlation coefficient, and in the absence of a normal distribution — using the Spearman's rank correlation. The nominal data were compared using Pearson's χ^2 criterion with the Yates correction or the Fisher's exact criterion. The development of AF recurrences in the investigated groups was assessed by the Kaplan-Meier method and the Cox proportional hazards model, and the likelihood-ratio test was used for comparison. The differences between parameters were considered statistically significant if the value of $p<0,05$.

The study protocol was approved by the Local Ethics Committee of Kazan State Medical University.

Results

According to the results of identification of the ID presence, the patients were divided into 2 groups. The group 1 included 116 patients with ID, of them 41 (35,3%) men and 75 (64,7%) women; the group 2 included 82 patients with normal iron status, of them

Table 2

Results of patients` blood analysis

Parameter	Group 1, n=116 (Me [Q1; Q3])	Group 2, n=82 (Me [Q1; Q3])	p
White blood cell count (×10^9/l)	7 (5,8-8,3)	7 (6,1-8,3)	0,702
Platelet count (×10^9/l)	270 (212,5-312)	267 (203,2-300,5)	0,404
Red blood cell count (×10^{12}/l)	3,9 (3,6-4,3)	4,6 (4,3-5,2)	<0,0001
Hemoglobin, g/l	107 (99,8-115)	137 (130-143,8)	<0,0001
Hematocrit, %	33 (30,6-35,4)	42 (39,9-44)	<0,0001
TIBC, µmol/l	101 (100,2-101,8)	54,3 (48,7-57,9)	<0,0001
Ferritin, ng/ml	6,6 (5,8-7,3)	57,5 (46-74,3)	<0,0001
Transferrin, g/l	8 (7,9-8,1)	3,3 (2,8-3,5)	<0,0001
TSC, %	8,2 (7,6-8,9)	37,3 (31,7-41,6)	<0,0001
NT-proBNP, pg/ml	284,0 (145,0-497,5)	258,0 (136,0-507,5)	0,737
Glucose, mmol/l	6,4 (5,3-7,9)	6,3 (5,3-7,7)	0,907
Creatinine, µmol/l	68,4 (61,0-79,8)	75,6 (61,2-84,1)	0,1574
Urea, mmol/l	5,8 (4,8-7,0)	6,4 (5,2-7,4)	0,035
Potassium, mmol/l	4,1 (4,0-4,4)	4,2 (4,0-4,4)	0,397
TSH, mU/l	1,4 (0,8-3,0)	2,0 (0,9-3,1)	0,143

Abbreviations: TSC — transferrin saturation coefficient, TIBC — total iron-binding capacity, TSH — thyroid stimulating hormone, NT-proBNP — N-terminal pro-brain natriuretic peptide.

Table 3

EchoCG data

Parameter	Group 1, n=116	Group 2, n=82	p
LVM, g (Me [Q1; Q3])	145 (115-176)	132,5 (118,2-145)	0,004
LA, ml (Me [Q1; Q3])	72,5 (65-89)	72 (62,2-77)	0,103
EF, % (Me [Q1; Q3])	58 (56-61)	58,5 (55-61)	0,999
EDS, cm (M±σ)	5,0±0,5	5,0±0,4	0,878
ESS, cm (Me [Q1; Q3])	3,3 (3,2-3,7)	3,3 (3,1-3,6)	0,475
SPAP, mm Hg (Me [Q1; Q3])	32,5 (28-40)	31,5 (28-37)	0,143
Diastolic dysfunction, n (%)	79 (68,1)	48 (58,5)	0,179

Abbreviations: EDS — end-diastolic size, ESS — end-systolic syze, LA — left atrium, LVM — left ventricular mass, SPAP — systolic pulmonary artery pressure, EF — ejection fraction.

37 (45,1%) men and 45 (54,9%) women. According to clinical and demographic characteristics, both groups were comparable to each other, and at the same time the patients with ID were older (the median age was 73 (64,8-79) years and 69 (63-75) years, respectively, p=0,008). There were no differences in gender, in the frequency of the first time identified AF and various periods of AF identification, in body mass index, arterial pressure level and the frequency of most common concomitant diseases. The prevalence of arterial hypertension, ischemic heart disease, past MI and stroke, CHF, diabetes mellitus, chronic obstructive pulmonary disease was estimated. 8 (6,9%) patients of the group 1 earlier suffered a stroke, and in the group 2 there were no patients with a stroke in the anamnesis (p=0,022). 12 (10,3%) patients of the group 1 and 9 (11%, p=0,927) patients of the group 2 had hypothyroidism (Table 1).

Before hospitalization, 38 (32,8%) patients of the group 1 and 37 (45,1%) patients of the group 2 (p=0,106) received direct oral anticoagulants. None of the patients included into the study received warfarin. There were no differences in the frequency of use of most other classes of drugs, except for blockers of the renin-angiotensin-aldosterone system and β-blockers. The group 1 patients less often received angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers — 71 (61,2%) and 72 (87,8%) patients, respectively (p<0,001). The group 1 patients also less often received and β-blockers — 21 (18,1%) patients vs 29 (35,4%) patients of the group 2 (p=0,030).

Table 4

Drug therapy in patient groups

Drugs	Group 1, n=116, n (%)	Group 2, n=82, n (%)	p
DOACs	116 (100)	82 (100)	–
ACEi/ARBs	116 (100)	82 (100)	–
β-blockers	88 (75,9)	67 (81,7)	0,420
CAs	12 (10,3)	10 (12,2)	0,859
MCRAs	1 (0,9)	0 (0)	0,862
Statins	42 (36,2)	35 (42,7)	0,440
Nitrates	21 (18,1)	13 (15,9)	0,707
L-thyroxine	12 (10,3)	9 (11)	0,927
Hypoglycemic drugs	50 (43,1)	29 (35,4)	0,344
Bronchodilators	7 (6,1)	1 (1,2)	0,185

Abbreviations: CAs — calcium antagonists, MCRAs — mineralocorticoid receptor antagonists, ARBs — angiotensin II receptor blockers, ACEi — angiotensin-converting enzyme inhibitors, DOACs — direct oral anticoagulants.

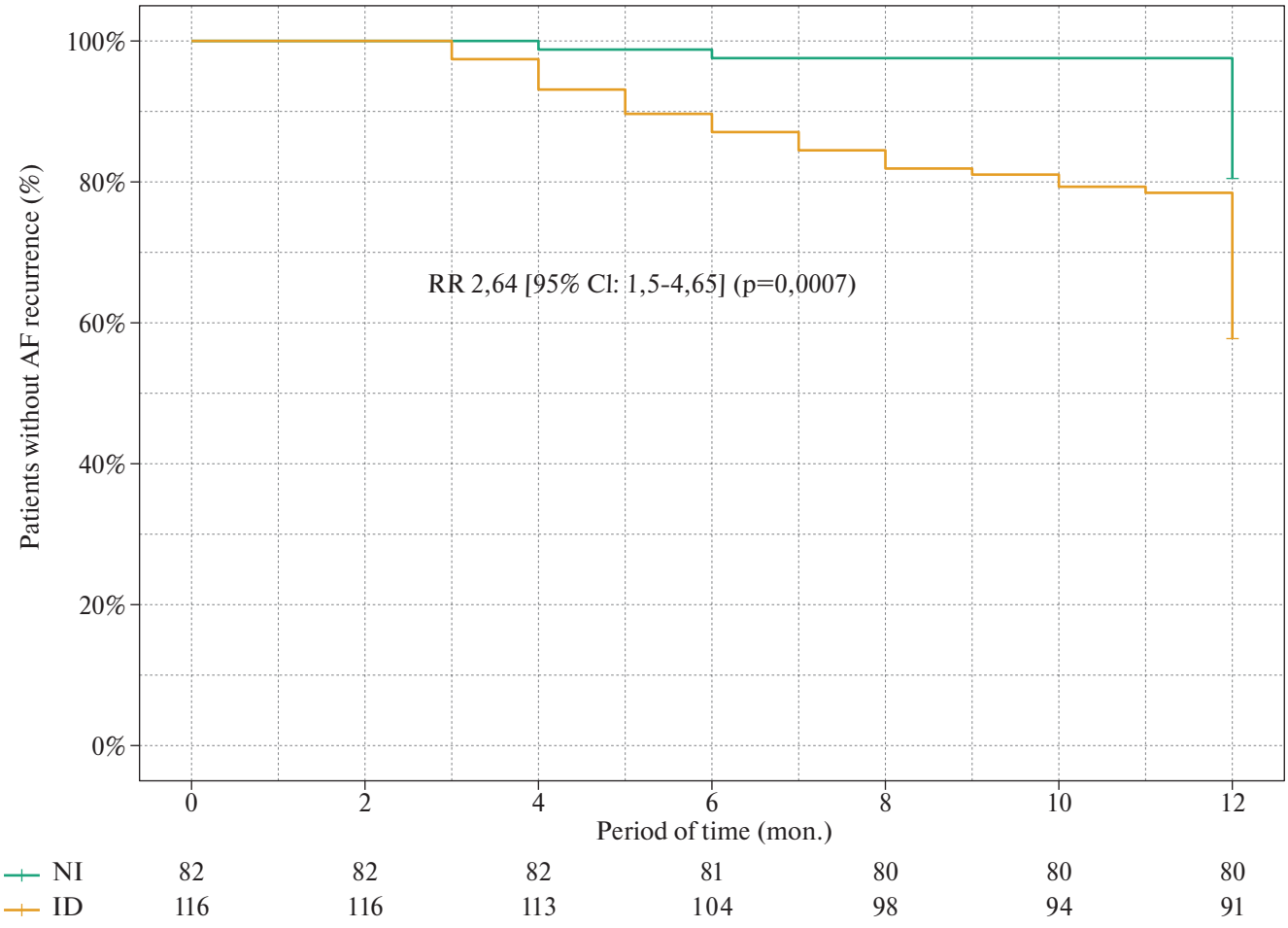

Figure 1. Development of AF recurrences in the patient group 1 and 2.
Abbreviations: ID — iron deficiency (group 1), CI — confidence interval, NI — normal iron level (group 2), RR — risk ratio, AF — atrial fibrillation.

The analyses of blood demonstrated the presence of absolute ID in almost all patients of the group 1 as well as the lower median values of red blood cell count, the level of hemoglobin, hematocrit, plasma ferritin and transferrin, transferrin saturation coefficient and higher total iron-binding

capacity (Table 2). The signs of mild anemia were found in 99 (85,3%) patients of this group. None of the group 2 patients had anemia. But the group 2 had a higher median of the plasma urea level compared to the group 1 (6,4 (5,2-7,4) and 5,8 (4,8-7,0) mmol/l), respectively, p=0,035). White blood cell count and platelet count, the levels of N-terminal pro-brain natriuretic peptide, glucose, creatinine, potassium and thyroid stimulating hormone did not differ between the groups.

A larger mass of left ventricular myocardium (LVM) was found in the patients of the group 1, using EchoCg performed at hospitalization. The median of LVM in the group 1 was 145 (115-176) g, and in the group 2 — 132,5 (118,2-145) g (p=0,004). The groups did not differ in the indicators of the left ventricular volume, end-diastolic and end-systolic sizes of the left ventricle, left ventricular ejection fraction, systolic pulmonary artery pressure and in the frequency of the occurrence of left ventricular dysfunction (Table 3).

The results of pharmacological cardioversion showed that to restore sinus rhythm, the patients of the group 1 required a significantly less dose of amiodarone (the medians of the doses were 450 (300-600) mg and 1000 (600-1200) mg, respectively, p<0,001) and less time from the start of amiodarone administration to the cessation of AF paroxysm compared to the group 2 (the medians of time were 7 (3-10) and 12 (9-18) h, respectively, p<0,001). After the cardioversion performed, all the patients received direct oral anticoagulants, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers; 88 (75,9%) patients in the group 1 and 67 (81,7%, p=0,420) patients in the group 2 received β-blockers. Antiarrhythmic drugs of I, III and IV classes did not use, except for amiodarone to stop AF recurrences. Besides, some patients receive calcium antagonists, mineralocorticoid receptor antagonists, statins, nitrates, bronchodilators, L-thyroxine, hypoglycemic and other medications (the main classes of medications prescribed to the patients in accordance with an individual clinical situation are shown in Table 4).

During 12-month follow-up period, symptomatic recurrences of AF were recorded in 49 (42,2%) patients in the group 1 and in 16 (19,5%) patients in the group 2 (p=0,0008). The risk ratio of the development of AF paroxysms in the patients with ID was 2,64 (95% confidence interval: 1,5-4,65) (p=0,0003). The results of the Kaplan-Meier analysis are shown in Figure 1. Taking into account the differences between the groups of the patients in age and past stroke, we performed the Cox regression analysis with inclusion of age and stroke in anamnesis as correction co-variants. In view of these corrections, a relative risk of the development of AF recurrences in the patients with ID was 3,08 (95% confidence interval: 1,74-5,47) times (p<0,0001). For the follow-up period, there have been no cases of hospitalization for decompensation of CHF, cardiovascular death, non-fatal MI or non-fatal stroke.

Discussion

To date, quite a large amount of information has been accumulated concerning the negative mutual influence of AF and CHF on each other development and course, that forms as though a vicious circle [6]. The effect of CHF on the development of AF paroxysms after cardioversion in patients with ID would have been assumed. In our study, CHF was identified in almost 65% of patients but there were no differences in the frequency of its occurrence in both groups. Both groups did not differ between each other in the main characteristics, except for those parameters which are determined by the presence of ID and its symptoms. In 85,3% of the patients in the group 1 anemia as a result of ID was revealed, that naturally affected the decrease in the values of red blood cell count, and the levels of hemoglobin and hematocrit in clinical analysis of blood. According to existing data, the prevalence of ID increases with age [2], and in our study the patients of the group 1 were older than in the group 2. The review of Sutil-Vega M, et al. (2019) provided the data on a larger LVM in patients with ID [11]. The similar data were obtained in EchoCG performed to the patients of the group 1. In turn, the lower level of urea we revealed in the patients with ID requires further special investigation of the kidney function in patients with different iron status. Thus, we may say about sufficient comparability of both groups between each other for most parameters which are not caused by the wide prevalence of anemia in the group 1. A key distinguishing factor was the presence or absence of ID. ID was associated with the requirement of a less dose of amiodarone and less time needed for the sinus rhythm restoration in pharmacological cardioversion. The obtained results indicate the necessity of further investigation of the influence of ID on the effectiveness of antiarrhythmic therapy. The drug therapy received by the patients after cardioversion does not differ between both investigated groups. 12-month follow-up for the patients showed a great difference in the development of AF recurrences. According to the results of our study, ID is associated with the increased frequency in AF recurrences more than 2,6 times, increasing the risk of their development during 1 years after cardioversion. Currently, there is no certain explanation of the relationship between ID and amiodarone

influence on the sinus rhythm restoration and with further development of AF recurrences we revealed. To some extent, the obtained results can be determined by the influence of ID on the decrease in the production of adenosine triphosphate, the impairment of the control of cellular Ca^{2+}, the development of mitochondrial dysfunction and damage to mitochondrial DNA, oxidative and nitrosative stress, inflammation, autonomic dysfunction, the acceleration of cardiomyocyte apoptosis and myocardial remodeling [12, 13]. It is believed that the dispersion of the P wave of the electrocardiogram can be considered as a simple and reliable marker of the development of AF paroxysms [14]. Simsek H, et al. (2010) showed the relationship between ID with increase in P wave dispersion and myocardial function disorder, that may contribute to the development of AF paroxysms [15]. Thus, a number of changes in cardiomyocytes, caused by ID, may affect both the results of cardioversion and development of AF recurrences.

A certain limitation of our study is a small number of included patients and the assessment of the presence of ID only in the inclusion of patients into the study. In addition, in the study antiarrhythmic drugs of I, III and IV classes were not used for long-term therapy.

Conclusion

The results we obtained indicate the association of ID with decreased ability to maintain sinus rhythm and increased number of symptomatic AF recurrences in patients within 12 months after pharmacological cardioversion with amiodarone. To determine the role of ID as a prognostic factor of the effectiveness of cardioversion and development of AF paroxysms, further investigations on a larger group of patients are needed. New data may influence the existing approaches to the management of patients with AF.

According to the results of open-label, observational, prospective study, ID is associated with the increased frequency of AF recurrences during 1 year after pharmacological cardioversion with amiodarone.

Pharmacological cardioversion in patients with AF paroxysm and ID requires less doses of amiodarone and less time for sinus rhythm restoration.

Relationships and Activities: none.

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Effect of senile asthenia syndrome on cardiovascular mortality within 12 months in patients over 70 years of age with myocardial infarction

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Aim. This study aims to investigate the effect of senile asthenia syndrome (SAS) on the cardiovascular mortality risk within 12 months in patients over 70 years of age with myocardial infarction.

Material and methods. We performed a retrospective study of 92 patients over 70 years of age with myocardial infarction, who agreed to participate. To detect senile asthenia syndrome, we used the questionnaire "Age is not a hindrance". We estimated the anamnestic data, and also laboratory and instrumental parameters. The follow-up period was 12 months. As an end-point, the onset of an adverse event — cardiovascular death was chosen. Statistical non-parametric methods, ROC analysis, Kaplan-Meier survival analysis (p<0,05) were used.

Results. In 12 months, 19 patients (20,65%) met the end-point. The median (25%; 75%-quartile) of the numbers of points according to the questionnaire "Age is not a hindrance" was significantly higher in the group of dead patients than in the group without adverse outcomes — 4 (3; 5) and 2 (1; 4) points (p<0,001). When gaining 3 or more points according to the questionnaire "Age is not a hindrance", risk ratio of cardiovascular death within 12 months was 1,72; 95% confidence interval: 1,28-2,30 (p=0,001). In conduction of ROC analysis to predict adverse outcome when gaining 3 or more points according to the questionnaire "Age is not a hindrance", the area under the curve (AUC) was 0,78 (p<0,001), sensitivity — 89%, specificity — 60%.

Conclusion. The risk of cardiovascular death within 12 months after myocardial infarction in patients over 70 years of age with SAS increases by 72%. The inclusion of the results from the questionnaire "Age is not a hindrance" into prognostic models, and the SAS estimation in this cohort of patients will improve the risk stratification.

Keywords: myocardial infarction, senile asthenia syndrome, frailty syndrome, medium-term forecast, cardiovascular death.

Relationships and Activities: none.

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In recent decades demographic changes in the world are characterized by an increase in the number of elderly and senile people. And one of relevant problems related to human aging is a senile asthenia syndrome (SAS) [1]. SAS is a geriatric syndrome which is characterized by the formation of age-associated decrease in the physiological reserve and functions of many of body systems, that leads to increased vulnerability of elderly people to the effects of endogenous and exogenous factors and to a high risk of adverse health outcomes, loss of autonomy and death. There are two approaches to the etiology of SAS development. The first approach, according to Fried LP, et al., consider senile asthenia as genetically-caused phenotype, while the second approach, according to Rockwood K, et al. — as the collection of accumulated deficiency of functions against the background of polymorbid pathology [2, 3].

Table 1

Clinical and anamnestic characteristics of the groups of the patients depending on the number of the points obtained from the questionnaire "Age is not a hindrance"

Parameter	Group I, N=46 (50%)	Group II, N =46 (50%)	χ^2	p
Age, years, Me (Q25; Q75)	81,50 (77,00; 84,25)	72,00 (70,00; 77,25)		<0,001
BMI, kg/m^2, Me (Q25; Q75)	28,54 (24,38; 30,23)	28,35 (25,23; 30,25)		0,781
In anamnesis:				
Past myocardial infarction, n (%)	22 (48)	13 (28)	2,95	0,086
ACVA, n (%)	10 (22)	3 (7)	3,22	0,073
Atrial fibrillation, n (%)	17 (37)	8 (17)	3,52	0,061
Arterial hypertension, n (%)	46 (100)	45 (98)	0,001	1,000
CHF IIA and more severe, n (%)	45 (98)	33 (72)	10,19	0,001
Diabetes mellitus, type 2 — insulin-dependent, n (%)	15 (33) 4 (9)	11 (24) 2 (4)	1,88	0,390
Peripheral arterial atherosclerosis, n (%)	5 (11)	6 (13)	0,001	1,000
PCI, n (%)	3 (7)	3 (7)	0,001	1,000
PSI (stent implantation) during current hospitalization	16 (38)	33 (72)	8,75	0,003
ACS, n (%)	0	0	–	–
Chronic kidney disease, n (%): C1 C2 C3a C3б	 0 23 (50) 12 (26) 11 (24)	 2 (4) 25 (54) 16 (36) 3 (6)	10,03	0,040
At admission:				
Class of AHF according to Killip, n (%): Killip I Killip II Killip III Killip IV	 29 (63) 5 (11) 7 (15) 5 (11)	 37 (81) 5 (11) 2 (4) 2 (4)	5,03	0,169
ST elevation on ECG, n (%)	9 (20)	21 (46)	5,98	0,014

Abbreviations: ACS — aortocoronary shunting, BMI — body mass index, ACVA — acute cerebrovascular accident, AHF — acute heart failure, CHF — chronic heart failure, PCI — percutaneous coronary intervention, ECG — electrocardiogram.

The diagnostics of SAS is conducted during a comprehensive geriatric assessment, however, the presence of an acute disease, including myocardial infarction (MI), is a contraindication for the comprehensive geriatric assessment [4-6]. In this case SAS is detected by the use of screening questionnaires. The following instruments for SAS diagnostics are used more frequently: Fried Scale based on Cardiovascular Health Study, Frailty Index based on Canadian Study of Health and Aging, Rockwood Clinical Frailty Scale, Edmonton Frail Scale (EFS) and five-component FRAIL scale [7-10]. The most relevant screening questionnaire in our country is "Age is not a hindrance" — domestic analogue of the FRAIL scale [6]. When scoring 0-2 points on the scale "Age is not a hindrance", the absence of SAS in a patient is determined, 3-4 points — pre-asthenia is diagnosed, ⩾5 points — SAS [4, 5]. The prevalence of SAS among individuals older than 65 years is ~10,7%, increasing up to 52% among individuals older than 85 years [11].

The presence of SAS is an unfavorable factor that increases the risk of adverse outcomes. The recent studies indicate an independent prognostic value of SAS in elderly and senile patients with MI [12, 13]. For example, the study of patients older than 70 years having acute coronary syndrome with ST-segment elevation, who underwent primary percutaneous coronary intervention (PCI) in Leiden university, assessed the prognosis of patients depending on the presence of SAS (30-day mortality, major bleeding, renal failure *de novo* (contrastinduced), clinical death within 30 days, acute cerebrovascular accident (ACVA)). Fragile patients were determined using the test consisting of 12 questions Safety Management Program (SMP) when scoring >1 points. The frequency of occurrence of endpoints was reliably higher that in the group of the patients with ⩾1 points [14].

It should be noted that geriatric state of elderly and senile patients with MI is more often not evaluated that makes it difficult to stratify the risk of this

Table 2

Distribution of points according to the scales of assessment of the risk of an adverse event, including bleedings, across the groups of the patients depending on the number of points obtained from the questionnaire "Age is not a hindrance"

Scales	Group I (n=46), Me (Q1; Q3)	Group II (n=46), Me (Q1; Q3)	p
CRUSADE scale, points	43,00 (35,75; 54,50)	35,50 (25,75; 46,75)	0,012
GRACE scale, points	174,00 (154,75; 195,75)	153,00 (142,75; 166,25)	<0,001
PRECISE-DAPT scale, points	26,00 (19,75; 33,75)	19,00 (15,00; 24,00)	0,002
TIMI scale, points	6,00 (4,00; 8,00)	4,00 (3,00; 5,00)	0,001

Table 3

Comparative analysis of EchoCG data between the groups of the patients depending on the number of points obtained from the questionnaire "Age is not a hindrance"

Parameter	Group I (n=46), Me (Q1; Q3)	Group II (n=46), Me (Q1; Q3)	p
EF according to Simpson, %	45,50 (38,00; 54,25)	52,00 (48,00; 56,25)	0,021
LV ESV, ml	50,50 (39,75; 75,25)	55,00 (45,00; 73,25)	0,529
LV EDV, ml	105,50 (81,25; 126,25)	119,50 (99,25; 139,50)	0,028
LV EDV/m^2, ml/m^2	61,00 (47,50; 70,50)	61,00 (53,00; 73,00)	0,385
LVRWT, proportions of the whole	0,44 (0,37; 0,51)	0,43 (0,39; 0,47)	0,264
LAVI, ml/m^2	40,50 (34,00; 47,00)	35,00 (27,75; 41,25)	0,013
ILCD	1,60 (1,38; 1,93)	1,40 (1,20; 1,60)	0,036
IVCD, mm	19,00 (18,00; 20,25)	19,00 (18,00; 20,25)	0,625
SPAP, mm Hg	38,40 (33,93; 47,85)	34,20 (28,75; 41,50)	0,023
E/A	0,70 (0,60; 0,78)	0,70 (0,60; 0,90)	0,734
E/e’	7,35 (6,00; 12,00)	9,00 (6,50; 11,00)	0,864
LVMI, g/m^2	109,00 (85,00; 137,25)	106,50 (91,25; 121,00)	0,663
Mitral valve insufficiency			
Degree	I группа, N (%)	II группа, N (%)	χ^2 (p=0,032)
No	3 (7)	11 (24)	8,84
Degree 1	31 (67)	31 (67)	
Degree 2	11 (24)	4 (9)	
Degree 3	1 (2)	0 (0)	

Abbreviations: IVCD — inferior vena cava diameter, LVMI — left ventricular mass index, ILCD — index of local contractility disorders, LAVI — left atrial volume index, EDV — end-diastolic volume, EDV/m^2 — end-diastolic volume standardized relatively to body surface area, ESV — end-systolic volume, LV — left ventricle, LVRWT — left ventricular relative wall thickness, SPAP — systolic pulmonary artery pressure, EF — ejection fraction, E/A — ratio of early peak velocity of transmitral blood flow to late peak velocity, E/e’ — ratio of late peak velocity of transmitral blood flow to velocity of early diastolic mitral annular motion.

group of patients. And the risk of adverse outcomes in elderly and senile patients is more often associated not with age but with the presence of senile asthenia. Thus, in practice, "frailty" is not only a geriatric syndrome which needs to be diagnosed and treated by itself but a potential component of risk models too. The assessment of the likelihood of the presence and severity of SAS can become an independent marker of high risk of adverse outcomes in elderly and senile patients [15].

The study aims to investigate the influence of SAS on the risk of cardiovascular death (SVD) during 12 months in patients older than 70 years with MI.

Material and methods

Our prospective study included 92 patients with ST-elevation MI and non-ST-elevation MI older than 70 years, who were treated in cardiology departments of the Samara State Medical University Clinics in the period from 2020 to 2021 and gave informed consent to participate in the study. The conduction of the study was approved by Ethics Committee of Samara State Medical University of

Table 4

Comparative analysis of results of assessment of individual geriatric symptoms between the groups of the patients depending on the number of points obtained from the questionnaire "Age is not a hindrance"

Parameter	Group I (n=46), Me (Q1; Q3)	Group II (n=46), Me (Q1; Q3)	p
Questionnaire "Age is not a hindrance", points	4,00 (3,00; 5,00)	1,00 (0,00; 2,00)	<0,001
Charlson comorbidity index, points	6,50 (5,00; 7,00)	5,00 (4,00; 6,00)	<0,001
Time spent on the "Get up and go" test, sec	15,00 (13,75; 18,00)	9,50 (9,00; 10,25)	<0,001
Mini Nutritional Assessment, points	19,00 (18,00; 20,78)	21,00 (20,00; 22,50)	<0,001
Philadelphia Geriatric Morale Scale, points	52,50 (43,75; 60,00)	44,00 (36,00; 55,25)	0,029
Mini-Mental State Examination, points	20,00 (18,00; 23,00)	22,00 (20,75; 24,00)	0,001
Barthel Activities of Daily Living Index, points	80,00 (70,00; 90,00)	95,00 (95,00; 95,00)	<0,001

the Ministry of Health of the Russian Federation from 30.09.2020. The exclusion criteria: the presence of endocrine pathology (except for diabetes mellitus (DM) type 2); oncological diseases with life expectancy <1 years; anamnestic data on the hereditary pathology of the hemostasis system, severe cognitive disorder according to the scale Mini-Mental State Examination (a brief scale for assessing mental state), severe liver failure (the presence of liver cirrhosis, increased activity of alanine aminotransferase and aspartate aminotransferase by more than 5 times), severe renal failure (glomerular filtration rate (GFR) <30 ml/min/1,73 m^2 by CKD-EPI formula), the presence of acute kidney injury and acute kidney disease in current hospitalization. We estimated the data of clinical picture and anamnesis, the results of general clinical and laboratory tests, structural and functional parameters of heart (transthoracic echocardiography (EchoCG) using Philips Affiniti 50 (Netherlands) machine). The patients examined and treated in accordance with the clinical recommendations for the management of patients with acute ST-elevation and non-ST-elevation MI [16, 17]. The patients included into the study had acute disease that is why on this stage we used the screening questionnaire "Age is not a hindrance" [4, 5] that allowed us to make a preliminary conclusion about possible presence of SAS. We also determined the Charlson Comorbidity Index. Based on the result obtained from the questionnaire "Age is not a hindrance", the patients were divided into 2 groups: group I (n=46) — with the number of points ⩾3 ("fragile" and "pre-fragile" patients), group II (n=46) — 0-2 points (the patients without SAS). At admission we assessed the risk of adverse outcomes during hospital stay in the patients with acute coronary syndrome without ST-elevation on ECG according to the GRACE scale, and in the patients with ST-elevation on ECG — according to the TIMI scale. We assessed the risk of bleedings during hospital stay in the patients with acute coronary syndrome according to the CRUSADE scale and the risk of bleedings in the patients after PCI at the use of double antiplatelet therapy (the PRECISE-DAPT scale). The detection and determination of severity of geriatric syndromes including SAS were conducted by a cardiologist using the special scales on 5^{th} day of hospitalization after the stabilization of patients` condition. The motor activity was assessed using the "Get up and go" test with fixation of time; functional activity — according to the scale of the assessment of basic functional activity of Barthel (Barthel Activities of daily living Index); nutritional state — Mini Nutritional Assessment scale (a brief scale of nutritional assessment); moral state — Philadelphia geriatric morale scale; mental state — Mini-Mental State Examination. When performing the "Get up and go" test, the patient was asked to sit on a stable chair, leaning on the back. The patient had to get up from the chair, walk 3 meters, turn around, walk back to the chair and sit on it, leaning on the back. The time spent by the patient on the test was recorded [3, 4]. 12 months after hospitalization, we determined the endpoint achievement by contacting patients` relatives. We accepted CVD to be the endpoint (fatal recurrent MI, ACVA, decompensation of chronic heart failure (CHF)). Then the patients were divided into 2 groups: group A — the patients without the adverse outcome and group B — the patients with the adverse outcome. Statistical nonparametric methods, ROC analysis, Kaplan-Meier survival analysis were used. Quantitative signs are represented in the form of a median (25%; 75% quartile), differences between groups were evaluated by the Mann-Whitney U test. Qualitative signs are represented in the form of an absolute quantity and a percentage of the whole. Comparison of qualitative signs was carried out according to Pearson's χ^2 criterion. P<0,05 is taken as the level of statistical reliability. The Statistica 8.0 program was used for statistical analysis.

Table 5

Differences between the patients depending on an outcome according to clinical laboratory parameters

Parameter	Group A Without adverse outcome, Me (Q1; Q3), n=73	Group B CVD, Me (Q1; Q3), n=19	p
Age, years	76,00 (71,00; 81,50)	82,00 (74,00; 85,00)	0,010
Duration of hospitalization, days	10,00 (8,00; 11,50)	11,50 (8,75; 13,75)	0,170
Questionnaire "Age is not a hindrance", points	2,00 (1,00; 4,00)	4,00 (3,00; 5,00)	<0,001
Charlson comorbidity index, points	5,00 (5,00; 6,00)	7,00 (7,00; 8,00)	<0,001
Time spent on the "Get up and go" test, sec	11,00 (9,00; 15,00)	14,00 (12,00; 18,00)	0,008
Nutritional state, points	20,70 (19,00; 22,00)	19,00 (18,00; 20,00)	0,024
Barthel functional activity, points	95,00 (85,00; 95,00)	80,00 (65,00; 95,00)	0,002
Redd blood cell count, $\times 10^{12}$/l	4,56 (4,18; 4,83)	3,95 (3,52; 4,26)	<0,001
Hemoglobin, g/l	136,00 (125,50; 146,00)	120,00 (108,00; 129,00)	0,001
Glucose, mmol/l	6,15 (5,13; 7,90)	8,96 (6,32; 12,91)	0,002
Urea, mmol/l	6,30 (4,98; 8,13)	9,90 (8,10; 14,40)	0,001
Creatinine, μmol/l	83,00 (71,00; 101,60)	115,30 (74,60; 135,20)	0,006
GFR according to CKD-EPI, ml/min/1,73 m^2	65,00 (52,00; 78,50)	45,00 (39,00; 62,00)	0,001

Abbreviations: GFR — glomerular filtration rate, CVD — cardiovascular death.

Table 6

Differences between the patients depending on an outcome according to clinical laboratory parameters (continuation)

Parameter	Group A Without adverse outcome, n=73 (79,35%)	Group B CVD, n=19 (20,65%)	p
Past MI in anamnesis	21 (29)	14 (74)	0,001
Diabetes mellitus	16 (22)	10 (53)	0,014
The class of acute left ventricular failure at admission:			0,015
Killip I	57 (78)	9 (47)	
Killip II	5 (7)	5 (26)	
Killip III	5 (7)	4 (21)	
Killip IV	6 (8)	1 (5)	
ST elevation	28 (32)	2 (11)	0,042
BLLBH	4 (6)	8 (42)	0,001
Atrial fibrillation/flutter	13 (18)	10 (53)	0,005
PCI during current hospitalization	44 (62)	5 (29)	0,031

Abbreviations: BLLBH — blockage of left leg of the bundle of His, MI — myocardial infarction, CVD — cardiovascular death, PCI — percutaneous coronary intervention.

Results

The mean age of the patients in the investigated cohort was 77,3±2,4 years. Of them men — 47,8% (n=44). The patients were divided into 2 groups according to the number of scored points obtained from the questionnaire "Age is not a hindrance". The group I included the patients with probable SAS and pre-asthenia (⩾3 points), n=46 (50%); the group II included the "non-fragile" patients (0-2 points), n=46 (50%). The clinical and anamnestic characteristics of the patients according to the groups are shown in Table 1. The patients in the group I with probable SAS and pre-asthenia were reliably older, had lower GFR at admission, and more frequently had stagnant CHF in anamnesis. While the patients from the group II reliably more frequently had ST-elevation MI. Reliable differences in the level of red blood cell, hemoglobin, potassium and sodium were observed. The patients with SAS and pre-asthenia had lower level of hemoglobin and red blood cells

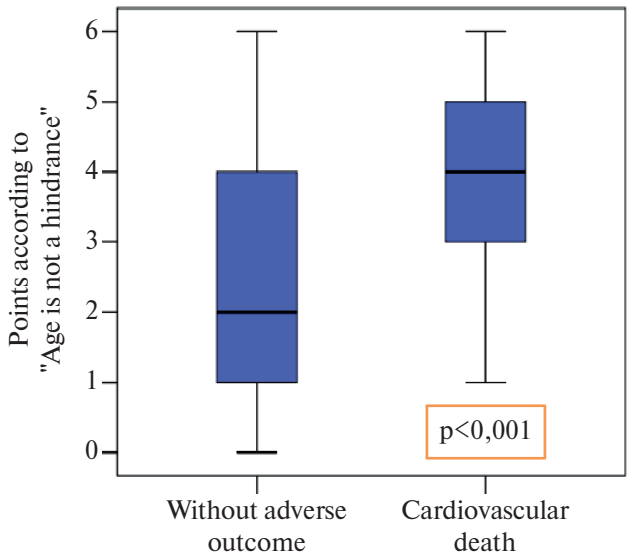

Figure 1. Distribution of points according to the questionnaire "Age is not a hindrance" depending on an outcome of the patients.

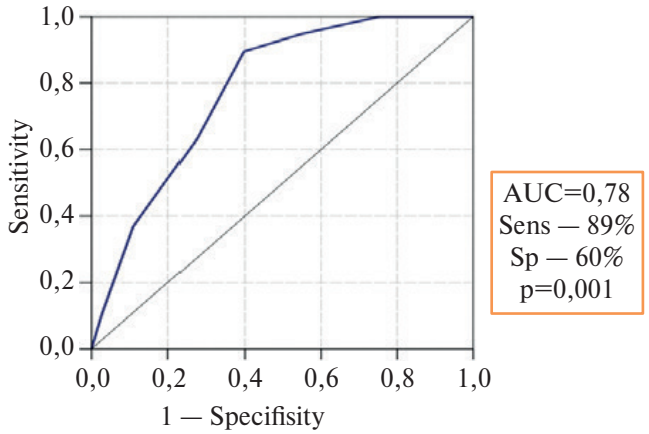

Figure 2. ROC-curve of CVD forecasting during 12 months after MI in patients older than 70 years when scoring ⩾3 points according to the questionnaire "Age is not a hindrance".

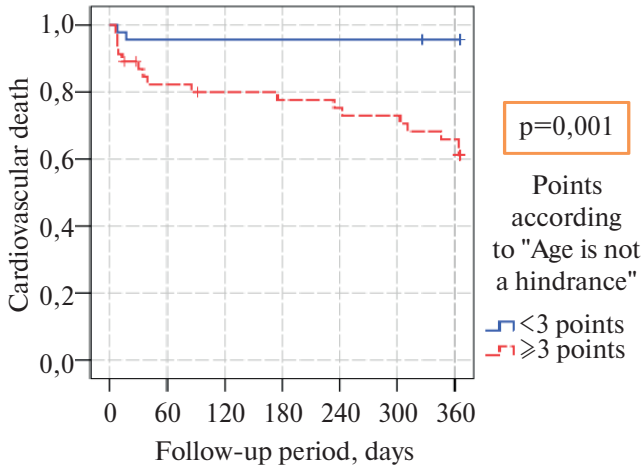

Figure 3. Analysis of survival of the patients depending on the number of points obtained from the scale "Age is not a hindrance".

compared to the group II. Thus, the medians (25%; 75% quartiles) of the level of red blood cells were in the groups 4,21 (3,84; 4,68) $\times 10^{12}$/l and 4,58 (4,24; 4,84) $\times 10^{12}$/l, respectively, p=0,004, and of the level of hemoglobin — 125,00 (109,75; 138,25) g/l and 137,00 (129,50; 147,00) g/l, p=0,001. Along with this, a quarter of the patients from the group I had mild anemia. There were no reliable differences in the level of hf-troponin T, the lipid profile components, creatinine and other laboratory parameters. The medians (25%; 75% quartiles) of GFR by CKD-EPI at admission in the groups were 61,00 (42,50; 70,25) ml/min/1,73 m^2 and 65,00 (52,00; 78,25) ml/min/1,73 m^2, respectively (p=0,102).

The patients of the group I both with and without ST-elevation had a reliably higher risk of in-hospital adverse cardiovascular events. The risk of bleedings during hospital stay as well as in taking double antiaggregating therapy was also reliably higher than in the group of the patients with SAS and pre-asthenia compared to the "non-fragile" patients. The distribution of the number of points according to the scales of the assessment of the risk of adverse outcomes and bleedings depending on the presence of SAS is shown in Table 2.

The patients included into the study received a standard medication therapy in accordance with relevant clinical guidelines including double antiaggregating therapy. However, in the group I clopidogrel was preferred in 70% of cases, and loop diuretics were also reliably more often prescribed for this group.

Structural and functional condition of myocardium was evaluated using transthoracic EchoCG in all patients during 24 hours from the moment of admission to the hospital. Comparative analysis of EchoCG data is shown in Table 3. Reliable differences in the values of left ventricular (LV) end-diastolic volume (p=0,028) and ejection fraction (p=0,021) between the groups were observed. Thus, in the patients of the group II preserved and moderately decreased EF was detected more frequently (the median of EF was 52%), whereas in the patients of the group I — moderately decreased and decreased EF (the median — 45,5%).

The group I compared to the group II had reliably higher left atrial volume index (the medians were 45,5 ml/m^2 and 35,0 ml/m^2, respectively, p=0,013) and pulmonary artery pressure (the medians were 38,4 and 38,2 mm Hg, respectively, p=0,023).

There were no significant differences in severity of diastolic dysfunction, left ventricular mass index, left ventricular relative wall thickness as well as in inferior vena cava diameter. The patients in the

group I had reliably higher degree of mitral regurgitation (p=0,032).

During the first 24 hours from the moment of hospitalization all patients underwent coronary angiography with probable PCI in roentgen operating room (using the angiography machine General Electric Innova 3100IQ). And this showed no reliable differences between the groups of the patients in the number of injured vessels. However, the frequency of performing PCI was reliably higher in the group I — 72% vs 38% in the group II, p=0,003. The most often reasons of the refusal from PCI in both groups were the presence of three-vascular diffuse lesion as well as the technical impossibility to perform PCI. The estimation of the PCI complications revealed no reliable differences between the groups of the patients.

Comparative analysis of geriatric syndromes is shown in Table 4. In the group I compared to the group II, reliable difference in severity of all geriatric syndromes and the level of comorbidity index was observed. The patients of the group I had reduced motor activity in a moderate degree. Mild dementia was revealed in both groups but it was expressed in a greater extent in "fragile" and "pre-fragile" patients (p=0,001). Also, these patients were reliably more dependent on outside care (moderate extent of dependence according to Barthel index). The patients in the group I had satisfactory moral state with the risk of developing depression, and in the group II — good moral state without the risk of developing depression; the differences in moral state were reliable. As for nutritional state, both groups were in the risk zone of nutritional deficiency, and these disorders were reliably more expressed in the group I.

12 months later, by a method of phone contact with patients` relatives, it was ascertained that 19 patients achieved the endpoint. Then, depending on the presence of the adverse outcome, the following groups were made: group A included 73 patients (79,35%) without the adverse outcome, group B — 19 with the adverse outcome (20,65%). The individuals with the adverse outcome included 18 patients from the group I.

When comparing the clinical and laboratory parameters depending on an outcome (Tables 5 and 6), the following reliable differences were obtained. The patients from the group with the adverse outcome were older and more often had past MI, DM and atrial fibrillation (AF) in anamnesis. In this group, ST-segment elevation was found less frequently, and blockage of left leg of the bundle of His was recorded more frequently at admission as well as the class of heart failure was higher. The laboratory indices showed reliable differences in the level of hemoglobin, red blood cells and GFR. Also, the individuals in the group with the adverse outcome had higher Charlson comorbidity index and more pronounced geriatric syndromes.

Distribution of points according to the questionnaire "Age is not a hindrance" depending on the outcomes is shown in Figure 1. Thus, the medians (25%; 75% quartiles) in the groups were, 2 (1-4) and 4 (3; 5), respectively, at p<0,001.

The data of ROC analysis performed to forecast CVD during 12 months after MI in the patients older than 70 years showed an unfavorable result obtained from the questionnaire "Age is not a hindrance", equal to 3 points. The area under curve (AUC) was 0,78, at sensitivity of 89% and specificity of 60% (p=0,001). The risk ratio (95% confidence interval) when scoring ⩾3 points by the questionnaire "Age is not a hindrance" for the adverse outcome onset for the investigated category of patients was 1,72 (1,28-2,30) at p=0,001. When constructing survival Kaplan-Meier curves for the patients in the general cohort, the forecast of CVD during 12 months was higher in the patients who scored ⩾3 points by the questionnaire "Age is not a hindrance" (p=0,001) (Figure 2). The Figure 3, which presents the survival curves, shows that this population of the patients reduces by 40% by 1 year after MI.

Discussion

The data we obtained on the prevalence of probable SAS in the investigated population do not contradict the literature data — 17,4%. We revealed a reliably higher level of comorbidity and risk of adverse outcomes as well as bleedings in this category of individuals that coincides with the data obtained by other researchers [11]. The patients with adverse outcome reliably more frequently had past MI in anamnesis (p=0,001) and DM (p=0,014); at admission, ST-segment elevation was recorded more frequently (p=0,042) or blockage of left leg of the bundle of His (p=0,001), atrial fibrillation or flutter (p=0,005). In the group with the adverse outcome compared to survival patients, the median (25%; 75% quartiles) of EF according to Simpson was 37,00% (34,00; 44,00) and 52,00% (47,00; 56,00), left ventricular volume index — 42,00 (35,00; 53,00) ml/m^2 and 36,00 (30,00; 42,50) ml/m^2; systolic pulmonary artery pressure — 45,70 (38,60; 63,30) mm Hg and 35,00 (31,50; 40,50) mm Hg, respectively (p<0,05).

It should be also noted that in our study the patients with probable senile asthenia and pre-asthenia were treated mostly conservatively. According to the literature data such patients undergo PCI really less frequently. In particular, this is associated with unfavorable comorbid background in this category

of patients. Past MI, ACVA, AF and peripheral arterial atherosclerosis are met in anamnesis of elderly people with high frequency that coincides with the results of our study [18, 19]. Some researchers have found that the probability of the successful use of invasive diagnostic and therapeutic interventions is significantly lower in elderly people, and therefore, there is a high risk of adverse outcomes and complications [20]. However, currently, many studies have shown an advantage of invasive strategy for the improvement of the prognosis in elderly and senile patients with MI [21]. Regarding to the duration of hospital stay, in our study we obtained no reliable differences between the patients depending on an outcome, that indicates the inexpediency of unjustified prolongation of hospitalization.

We found that the patients older than 70 years with probable SAS and pre-asthenia have a worse prognosis of SAS onset during 12 months after MI. According to our data, the survival rate during a year after MI in patients older than 70 years is ~60%, that also does not contradict the literature data [22]. The data we obtained showed that when scoring ⩾3 points by the screening questionnaire "Age is not a hindrance", the risk of CVD during a year after MI in the patients was higher on average by 72%. According to the literature data this indicator is at the same level, and the risk of general lethality during 3 years increases by 2,5-4 times [23].

It should be noted that severe comorbid pathology worsens prognosis in elderly and senile patients. For example, Rockwood K, et al. consider SAS as a collection of accumulated deficiency of functions against the background of polymorbid pathology [3]. In our study, the presence of probable SAS and pre-asthenia is also associated with more severe comorbid background. The Charlson comorbidity index was reliably higher in the patients of the group I. But the development of SAS is considered as an independent predictor of the adverse outcome in patients with MI of this age category. This gives the possibility to build mathematical models for predicting the risk of the adverse outcome in this category of patients taking into account the presence of SAS and/or the number of points obtained from the screening questionnaire "Age is not a hindrance". The work in this direction seems promising for the improvement of the risk stratification in elderly and senile patients with MI and will be continued by the authors.

Thus, SAS is an important marker of adverse cardiovascular events in patients with MI older than 70 years. In managing elderly and senile patients with MI it is important to assess geriatric state and take it into account when stratifying risk of this category of patients. Treatment and monitoring of these patients should be carried out by a multidisciplinary team of doctors together with a geriatrician. The correction of SAS will contribute to the improvement of outcomes in this category of patients. The limitation of this study may be a small sample size.

Conclusion

According to the results of the survey of the patients older than 70 years with MI using the questionnaire "Age is not a hindrance", the proportion of the patients scored 0-2 points (without SAS) was 50% (n=46), patients with supposed pre-asthenia (3-4 points) — 32,6% (n=30) and patients with probable SAS (⩾5 points) — 17,4% (n=16). The patients with probable SAS had reliably higher comorbidity level (chronic kidney disease, DM, anemia, stagnant CHF, AF) and the risk of adverse outcomes at the high risk of bleedings. When scoring ⩾3 points by the questionnaire "Age is not a hindrance", the risk of CVD during 12 months in the patients older than 70 years with MI increased by 72%.

Relationships and Activities: none.

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Retrospective analysis of outcomes in patients with myocardial infarction in late admission to PCI center

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Aim. This study aims to determine the impact of invasive treatment strategy on long-term outcomes in patients with ST-segment elevation myocardial infarction (STEMI) in late admission to PCI center (12-48 hours from the symptom onset) in comparison with conservative management.

Material and methods. The study population included 154 people with STEMI, admitted to V. P. Polyakov Samara Regional Clinical Cardiology Dispensary during 12-48 hours after onset of myocardial ischemia symptoms, for the period of inclusion (2013-2017). The mean age of the patients was 57,2±9,2 years old. The study evaluated two time periods: intrahospital and long-term (during 4 years from the index hospitalization). The primary end-point: cardiovascular death. The secondary combined end-point included: myocardial infarction recurrence, life-threatening rhythm disturbances, acute bleeding, heart failure NYHA III-IV functional class. The patients were divided into two groups depending on initially chosen management strategy: invasive (I) (n=113; 73,4%) or conservative (II) treatment (n=41; 26,6%).

Results. Comparing frequency of occurrence of cardiovascular death depending on chosen treatment tactics, we found that the probability of lethal outcome from cardiovascular causes in conservatively treated patients increased by 20,64 times (95% confidence interval (CI): 1,04-408,61), p=0,018 during intrahospital period of the study. The analysis performed using the Kaplan-Meier method showed the medians of the time of lethal outcome occurrence: in conservative group — 76,5 months (95% CI: 67,6-85 months), in invasive group — 92,1 months (95% CI: 88,9-95,3 months), p=0,014.

Conclusion. This study presented the results of our own retrospective study which confirms that revascularization in late-presenting patients with STEMI (12-48 hours from the symptom onset) results in improving the outcomes in both intrahospital and long-term periods.

Keywords: acute myocardial infarction, ST-segment elevation acute coronary syndrome, percutaneous coronary intervention, revascularization.

Relationships and Activities: none.

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Key messages

- The relevance of the present study is caused by the absence of complete clarity regarding the management tactics of patients with ST-segment elevation myocardial, admitted between 12 and 48 hours after onset of myocardial ischemia symptoms.
- To date, there has been little research on this issue, and the obtained results are contradictory.

Restoration of blood flow through infarct-related artery (IRA) in early stages of ST-elevation myocardial infarction (STEMI) is the basis for treatment of patients of this profile. That is why the vast majority of the patients immediately after verification of STEMI diagnosis (regardless of age and gender) should be considered as the candidates for reperfusion therapy. Currently, this type of treatment involves the use of two strategies: primary percutaneous coronary intervention (PCI) and pharmacoinvasive approach [1].

There are the clear indications for the performance of primary PCI and thrombolysis in patients admitted within 12 hours from the onset of ischemia symptoms. So, in clinical recommendations of the Ministry of Health of Russian Federation (MH RF) "Acute ST-elevation myocardial infarction", the level of reliability of evidences (LRE) and the level of persuasiveness of recommendations (LPR) reach the highest values — LRE A and LPR 1 [1]. In similar document of European Society of Cardiology (ESC), the class of recommendations and the level of reliability for this treatment tactics also correspond to the maximum — IA [2]. Besides, primary PCI is indicated to patients with STEMI, having the duration of the symptoms >12 hours and the signs of ongoing ischemia, the clinical picture of heart failure (HF), and the signs of shock or life-threatening rhythm disturbances (Ministry of Health of Russian Federation — LRE A; LPR 2; ESC — IA) [1, 2].

Currently there is no common opinion on the benefits of PCI performed in patients with STEMI beyond 12 hours from the onset of symptoms in the absence of the evidences of ongoing ischemia (Ministry of Health of Russian Federation — LRE A, LPR 2; ESC — IIA) [1, 2]. However, a certain number of patients with STEMI seek medical help quite late — for example, in countries with economies in transition and developing countries the number of such patients reaches 20% [3]. Accordingly, this influence the choice of the management strategy, and is directly related with the absence of reperfusion in patients [4].

By now, the register data have been published, proving that delayed revascularization (>12 hours from the onset of symptoms) performed in patients with STEMI, leads to improvement of their survival both in hospital and long-term periods [5-7].

Kim C and Braunwald E [8] proposed a hypothesis of "open artery", according to which even quite late blood flow restoration through IRA contributes to the reduction of severity of post-infarctional myocardial remodeling. On our opinion, it is this hypothesis that may explain the improvement of the life prognosis in patients who underwent PCI.

Taking into account the contradictory data on expediency of surgical reperfusion in patients with STEMI, who admitted during 12-48 hours after the onset of myocardial ischemia symptoms, we conducted a retrospective analysis of the outcomes in patients of this profile using the materials of Samara regional register of acute coronary syndrome. The analysis included patients admitted to V. P. Polyakov Samara Regional Clinical Cardiology Dispensary (SRCCD) in the period from 2013 to 2017. We assessed short-term and long-term (during 4 years) outcomes in patients of this profile depending on the management tactics.

The aim of the study: to determine the influence of invasive treatment strategy on immediate and long-term outcomes in patients with STEMI in late admission to PCI center (12-48 hours from the onset of symptoms), in comparison with conservative treatment tactics.

Material and methods

During 2013-2017 6368 patients with MI were admitted to V. P. Polyakov SRCCD, 4333 of them had STEMI. We selected the patients admitted within 12-48 hours after the onset of myocardial ischemia symptoms, the total number was 746 people. Then we assessed these patients according to the presence of the exclusion criteria such as: 1) the presence of indications to primary PCI performance (hemodynamic instability, life-threatening arrhythmias, signs of ongoing ischemia); 2) impossibility of PCI performance; 3) administration of a thrombolytic drug; 4) age ⩾75 years old; 5) taking of oral anticoagulants; 6) severe concomitant pathology (moderate and severe anemia (hemoglobin <90 g/l), malignant neoplasms, severe thrombocytopenia ($<75\times10^9$/l) or severe blood clotting disorders in the anamnesis, renal failure with glomerular filtration rate <30 ml/min/1,73 m^2 (CKD-EPI), aortic dissection). The criterion of exclusion from the analysis was also the use of ticagrelor or prasugrel as a component of double antiplatelet therapy for leveling of additional benefits for the outcomes obtained in patients who took these $P2Y_{12}$ blockers in the randomized controlled trials PLATO and TRITON-TIMI38 [9, 10].

Finally, the study population reached 154 people, that was 2,4% of the total number of patients with STEMI admitted to V. P. Polyakov SRCCD for the inclusion period (2013-2017). Of them men — 114 (74%), women — 40 (26%). The average age of the patients was 57,2±9,2 years old. The diagnosis of STEMI was made on the basis of the recommendations valid at the moment of admission to the hospital. All patients included into the study received optimal drug therapy (ODT) [11, 12]. At hospitalization,

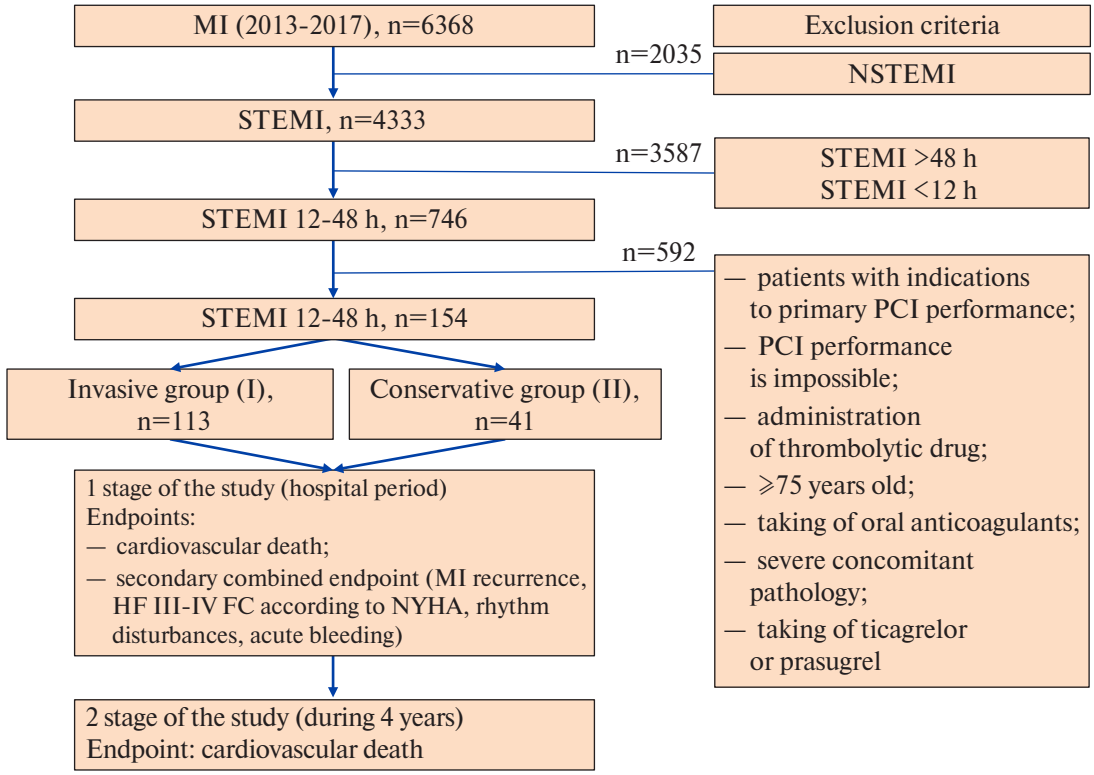

Figure 1. Study design.
Abbreviations: MI — myocardial infarction, NSTEMI — non-ST-elevation myocardial infarction, STEMI — ST-elevation myocardial infarction, HF — heart failure, FC — functional class, PCI — percutaneous coronary intervention.

the patients signed a standard form of informed voluntary consent to medical intervention and processing of personal data. The conduction of this study was approved by Local Ethics Committee.

Depending on the chosen management tactics, the patients were divided into two groups: invasive (I) or conservative (II) treatment. The group I patients underwent coronary angiography with revascularization of IRA (n=113; 73,4%), in addition to ODT. The group II received ODT only, and did not undergo PCI (n=41; 26,6%). We tried to analyze the reasons due to which the patients were managed conservatively. 8,1% of the patients signed the refusal of coronary angiography, 32,4% of this group were recommended to undergo planned coronary angiography, and 40,5% — to undergo load testing in 3-6 months followed by cardiologist consultation to determine the further management tactics. In 19% of the cases we could not find an obvious reason of choosing conservative management tactics. On our opinion, PCI was not performed exactly because of the time factor, i.e. late admission of patients.

The study design is presented in the Figure 1. The data given in the Table 1 show that the groups of conservative or invasive treatment were comparable for the basic statistical parameters.

The study estimated two time periods: hospital and long-term (during 4 years from the index hospitalization). Following the hospital period results, we accepted cardiovascular death as the primary endpoint; the secondary combined endpoint included: MI recurrence, life-threatening rhythm disturbances, acute bleeding developed during the index hospitalization period, and heart failure III-IV functional class according to NYHA at discharge. Following the long-term observation results, we accepted cardiovascular death as the primary endpoint. Taking into account the retrospective design of the present study, it was not possible to reliably establish the frequency of the occurrence of the secondary endpoints that is why they were excluded from this stage of the analysis.

The study materials were subjected to statistical processing using the parametric and nonparametric methods. Accumulation, correction and systematization of the initial information were carried out in spreadsheets Microsoft Office Excel 2019. Statistical analysis was performed using the program IBM SPSS Statistics v.26 (the software developer — IBM Corporation) and program MedCalc (the software developer — MedCalcSoftware Ltd).

The quantitative indicators were evaluated for compliance with the normal distribution using the

Table 1

Characteristics of groups at the moment of admission to hospital

Characteristics	Invasive tactics, Me [Q1; Q3] or n (%)	Conservative tactics, Me [Q1; Q3] or n (%)	p
Total number of patients	113	41	–
Male	88 (77,9)	26 (63,4)	0,071
Female	25 (22,1)	15 (36,6)	0,071
Age	56 [50; 64]	61 [51; 65,5]	0,150
MI in anamnesis	12 (10,6)	3 (7,3)	0,760
Anterior MI	56 (49,6)	16 (39,0)	0,247
Inferior MI	50 (44,2)	17 (41,5)	0,758
Another MI localization	4 (3,5)	4 (9,8)	0,210
Hypertensive disease	98 (86,7)	37 (90,2)	0,557
Obesity	29 (25,7)	10 (24,4)	0,872
Diabetes	15 (13,3)	11 (26,8)	0,055
Hyperlipidemia (total cholesterol >5 mmol/l)	83 (73,5)	27 (65,9)	0,356
Tobacco smoking	43 (38,1)	11 (26,8)	0,197
Diabetes mellitus	16 (14,1)	11 (26,8)	0,068
Acute cerebral circulatory disorder in the anamnesis	6 (5,3)	6 (14,6)	0,084
Chronic obstructive pulmonary disease in the anamnesis	7 (6,2)	3 (7,3)	0,726
Gastrointestinal diseases	4 (3,5)	1 (2,4)	0,724

Abbreviations: MI — myocardial infarction, Me — median, Q1; Q3 — lower and upper quartiles.

Kolmogorov-Smirnov criterion, as well as the indices of asymmetry and kurtosis. The sets of qualitative indicators, the distribution of which differed from normal, were described using the values of the median (Me), as well as the lower and upper quartiles [Q1-Q3]. Nominal data were described indicating the absolute values and percentages.

To compare the independent sets in the cases of the absence of normal data distribution signs, the Mann-Whitney U-test was used.

The comparison of the nominal data was performed using the Pearson χ^2 criterion. In the case of the analysis of four-field tables with the expected phenomenon in at least one cell less than 10, we calculated the criterion χ^2 with the Yates correction.

As a quantitative measure of the effect, when comparing relative indicators, the odds ratio indicator (OR) was used, defined as the ratio of the likelihood of an event occurrence in the group exposed to the factor to the likelihood of an event occurrence in the control group. With the purpose to project the obtained OR values onto the general set, we calculated the limits of the 95% confidence interval (CI). If zero values caused calculation problems, 0,5 was added to all cells. Based on the obtained data, the significance of the relationship between the outcome and the factor was considered proven if the CI was found outside the no-effect limit, taken as 1.

The survival function of patients was estimated using the Kaplan-Meier method, and the significance of the differences in survival between the groups — using the long-rank criterion of Mantel-Cox.

Results

When comparing the frequency of cardiovascular death occurrence depending on the chosen treatment tactics, it was established that the likelihood of lethal outcome from cardiovascular causes in the conservative group patients increased by 20,64 times (95% CI: 1,04-408,61), p=0,018 during hospital period of the study.

In addition, in the selected groups the frequency of the secondary combined endpoint during hospital period was analyzed. This indicator was statistically significantly higher in the conservative treatment group — 10 (24,4%) compared to group I of invasive treatment — 9 (7,96%) (OR 3,73; 95% CI: 1,39-9,99), p=0,006. The data obtained in the comparison of the frequency of different outcome occurrence during the index hospitalization, are shown in Table 2. During the study, we revealed that the patients in ODT group we more often prescribed additional medications (nitrate and diuretics) — 18 (43,9%) and 27 (23,9%), respectively (OR 2,49; 95% CI: 1,17-5,29), p=0,018, and this indirectly points to

Table 2

Hospital outcomes depending on chosen management tactics

Indicator	Invasive group, n (%)	Conservative group, n (%)	OR (95% CI)	p
Death during index hospitalization	0 (0)	3 (7,3)	20,64 (1,04-408,61)	0,018
Secondary combined point	9 (7,96)	10 (24,4)	3,73 (1,39-9,99)	0,006
CHF 3-4 according to NYHA	8 (7,1)	7 (17,1)	–	0,119
MI recurrence	0 (0)	2 (4,9)	–	0,070
Rhythm disturbance	0 (0)	1 (2,4)	–	0,266
Bleeding	1 (0,9)	0 (0)	–	1,000
Prescription of nitrates and diuretics at discharge	27 (23,9)	18 (43,9)	2,49 (1,17-5,29)	0,018

Abbreviations: CI — confidence interval, MI — myocardial infarction, OR — odds ratio, CHF — chronic heart failure.

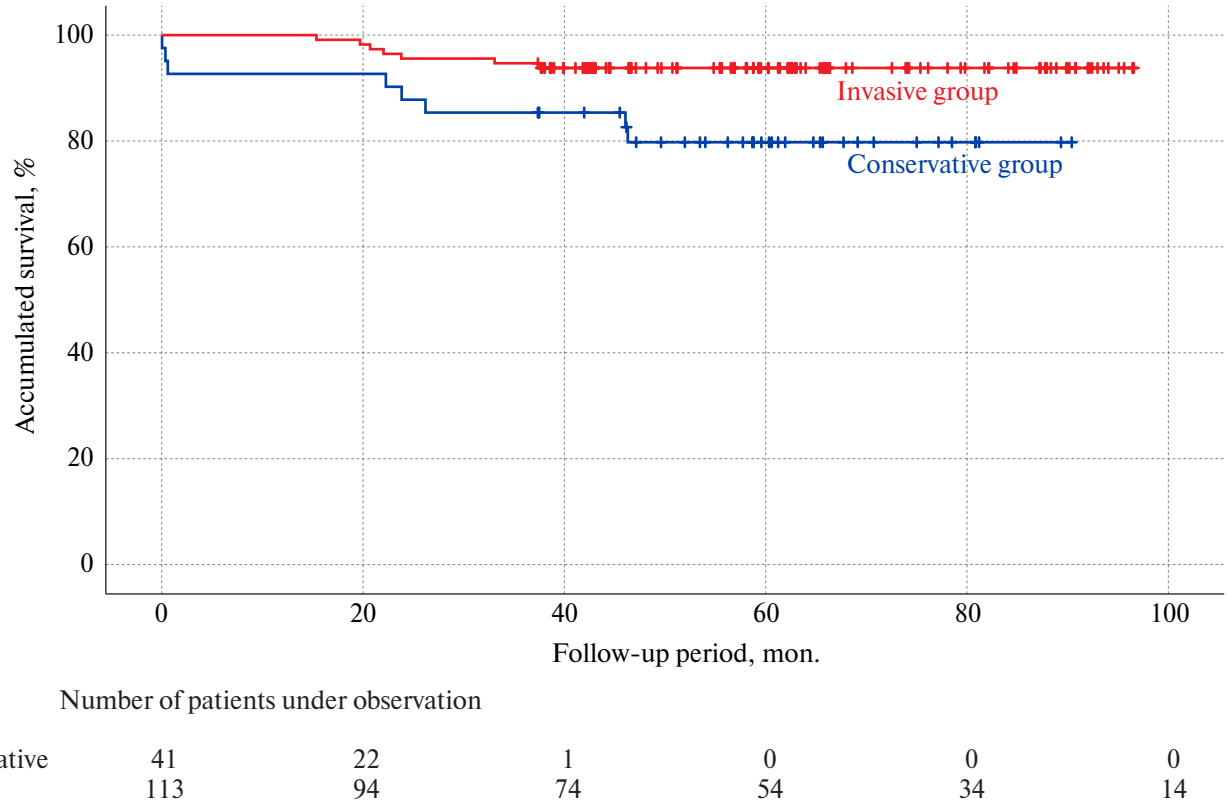

Figure 2. Chart of survival function of patients in conservative and invasive groups during 4 years.

the development of angina pectoris and HF in the patients of this group.

The Kaplan-Maier analysis showed that the medians of time of death occurrence were: in conservative group — 76,5 months (95% CI: 67,6-85 mon.), in invasive group — 92,1 mon. (95% CI: 88,9-95,3 mon.), p=0,014 (Figure 2).

Discussion

The relevance of this study is caused by the absence of complete clarity regarding the management tactics of patients with STEMI, admitted within the period of 12-48 hours after the onset of myocardial ischemia symptoms. It is known that patients of this profile have an adverse prognosis of life compared to patients admitted in more early time from the onset of myocardial infarction symptoms [13].

To date, there has been little research on this issue, and the obtained results are contradictory. For example, in the BRAVE-2 research (2005) the authors came to conclusion that the late PCI (12-

48 hours from the onset of ischemia symptoms) increase the volume of viable myocardium, improve the long-term outcomes decreasing frequency of cardiovascular complications and lethal cases. In the first research stage the primary endpoint was the final size of MI, measured using single-photon emission computed tomography with 99m technetium in 5-10 days after randomization. The results showed that the size of MI was reliably smaller in the surgical group patients compared to the ODT group — 8,0% (2,0-15,8) and 12% (3,2-25,0) of the left ventricular size; p=0,004. The index of myocardial viability was 0,44 (0,13-0,8) in the invasive group and 0,23 in the conservative group (0,0-0,5); p<0,001. In the long-term period of the BRAVE-2 research (during 4 years), the frequency of death from cardiovascular causes was estimated. In the invasive group, 20 patients died (11,1%; 95% CI: 7,3-16,7), and in the ODT group — 34 patients died (18,9%; 95% CI: 13,9-25,4) (adjusted risk ratio (RR) 0,55; 95% CI: 0,31-0,97); p=0,04 [5, 14].

The effect of reperfusion on the survival rate within 12 months in patients with STEMI, admitted during 12-24 hours from the onset of myocardial ischemia symptoms, was studied in Polish register of acute coronary syndromes in the period from June 2005 to August 2006. Total number of patients included into the analysis was 2036. The study results showed that mortality among patients with invasive treatment tactics in 12 months was lower than in patients with conservative strategy (9,3% vs 17,9%, p<0,0001) [15].

The meta-analysis performed by Hai-TaoYang, et al. (2019) investigated the results of 18 studies which were both randomized controlled and observational and cohort trials according to design. All the studies assessed the outcomes in patients with MI depending on the management tactics — only ODT or its combination with late reperfusion (>12 h). The results showed that late revascularization was associated with the decrease of mortality rate from all causes (RR 0,60; 95% CI: 0,44-0,83), p=0,002; main cardiovascular outcomes (RR 0,67; 95% CI: 0,50-0,89), p<0,001 and HF (RR 0,76; 95% CI: 0,60-0,97), p=0,03, compared to the ODT group. Besides, in the invasive treatment group, the frequency of MI recurrences tended to decrease (RR 0,70; 95% CI: 0,47-1,05), p=0,08. But late PCI significantly improved the prognoses, when performed in 12-48 hours, while revascularization performed between 2 and 60 days after the onset of ischemia symptoms, had no a positive effect [16]. The limitation of this meta-analysis was the inclusion of patients with non-ST elevation MI that might influence the final outcomes because such patients have initially more favorable prognosis compared to patients with STEMI [17].

In retrospective analysis conducted by Russian authors, they came to the results that PCI performed to patients with STEMI, admitted later than 12 hours from the onset of symptoms, may improve the long-time prognosis. This study analyzed the data of 178 patients admitted with STEMI later than 12 hours from the onset of angina attack, in period 2008-2009. The average time from the onset of symptoms was 96,6 hours. 83 patients underwent PCI with coronary stenting, — these patients were included into the invasive treatment group. 95 patients received conservative therapy only. According to the results of coronary angiography, 51 patients had initial IRA occlusion. During 3-year follow-up period, the mortality rate was 13,2% in the surgical treatment group and 35% — in the conservative therapy group (RR 0,23; 95% CI: 0,10-0,53), p=0,0004. And the survival rate was reliably higher in revascularized patients both with occluded and stenosed IRA compared to the conservative treatment group [18].

The importance of the time factor in performance of even late PCI was also confirmed in the OAT research (2006) which found no benefits regarding the outcomes in the invasive group in PCI performance during 3-28 days after the onset of myocardial ischemia symptoms. The primary endpoint of the research — death, MI, hospitalization with HF IV NYHA class, collectively. For 4 years the frequency of the primary endpoint has been 17,2% in the PCI group vs 15,6% in the OMT group (RR 1,16; 95% CI: 0,92-1,45), p=0,2 [19].

In 2022, the data of the retrospective register were published, that showed ambiguous results. The authors analyzed the medical histories of 274 patients with STEMI, admitted to hospital in ⩾12-48 hours after the onset of myocardial ischemia symptoms without the signs of ongoing ischemia, in period from October 2010 to December 2019. The proportion of men was 67,5%, the average age of the patients was 68±13 year old. The patients were divided into two groups depending on the management tactics (primary PCI or conservative approach). Statistical processing of the obtained data revealed the tendency to the decrease in the frequency of the occurrence of severe clinical outcomes such as recurrent MI (0 vs 0,4%, p=1,0), mechanical complications (0 vs 2,2%; p=1,0), stable ventricular tachycardia (0 vs 0,9%, p=1,0) and hospital death (0 vs 4,4%, p=0,37) in the primary PCI group, in contrast to the patients with conservative management. However, none of the differences reached statistical significance [20].

In our study we came to conclusion that the surgical strategy improves the survival rate in patients

with STEMI, admitted in 12-48 hours from the onset of ischemia symptoms. These results are consistent with the conclusions of a number of studies described above [5, 14-16, 18], along with that for the first time in our work it was shown that in the conservative management group, patients more often needed the prescription of drugs such as nitrates and diuretics. The additional therapy was required because of the persistence of the morphological substrate — atherosclerotic plaque in the coronary artery as well as HF progression.

Pathophysiological basis of the expediency of the intervention within 12-48 hours can be the fact that in 12 hours from the onset of myocardial ischemia symptoms, the viable myocardium may be saved in the IRA bed. Accordingly, even late restoration of blood flow through IRA, beyond the standard time limit for saving the myocardium from necrosis, has a positive effect of "hibernating" cardiomyocytes [8]. Reperfusion performed in a late phase of MI, contributes to acceleration of the tissue repair process due to the increase in population of infiltrating cells which play significant role in the lysis of necrotized myocardium and in collagen synthesis. Myocardial revascularization in the zone of infarction contributes to proliferation of cardiomyocytes and protects from apoptosis [21]. Collateral circulation is one more factor that preserves coronary blood flow necessary to maintain myocardial viability after coronary artery occlusion. Due to this, in late mechanical reperfusion, the left ventricle has the possibility of functional recovery [22].

Our study shows that invasive tactics in patients with STEMI in late admission improves the hospital outcomes and also has a positive effect on the long-term prognosis of life. The monitoring of patients is continuing.

Limitations of the study. The limitations of the present study are the retrospective design and participation of patients from one medical center.

Conclusion

Thus, currently there is no common opinion about the time period during which PCI has a positive effect on the prognosis of patients with STEMI in their late admission to PCI center (>12 hours from the onset of the disease). The clinical studies and meta-analyses published to date have shown contradictory results regarding to the prognosis of patients with STEMI, who underwent late PCI. According to the results of our retrospective analysis, statistically significant increase of the survival rate in the invasive treatment group was revealed, both during hospital and long-term period. We also observed the tendency to the decrease in the frequency of MI complications during the index hospitalization. Besides, the conservative group patients were more often prescribed additional medications necessary for treatment and correction of HF and angina attacks, and this most likely indicates to the presence of a substrate for the development of these pathologies in patients who did not undergo PCI. To definitively determine the effect of delayed PCI on patient outcomes and determine the time period during which invasive treatment statistically significantly increases survival in patients of this profile, it is advisable to perform a clinical trial with a prospective design and randomization procedure at the moment of admission of patients to hospital.

Relationships and Activities: none.

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Assessing the significance of some biomarkers in perioperative period after thoracic aortic reconstruction

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Aim. This study aims to assess the association between levels of biomarkers and postoperative complications in patients after thoracic and thoracoabdominal aortic reconstruction.

Material and methods. This study included 132 patients. The most of them underwent ascending aortic and aortic arch reconstruction (65 and 57, respectively). The concentrations of proadrenomedullin, presepsin, procalcitonin, troponin I and N-terminal brain natriuretic peptide were measured before induction anesthesia, at the end of the surgical operation and in 6 hours after surgery.

Results. 69 patients had postoperative complications. Among them, inflammatory (27,3%) and cardiovascular complications (12,1%) prevailed. At the end of the surgical operation, the levels of the biomarkers in patients without postoperative complications and with postoperative complications were for presepsin 326 [206; 451] и 620 [332; 829] p<0,00001, troponin I 0,77 [0,46; 1,39] and 1,49 [0,59; 3,39], p=0,01, proadrenomedullin 0,894 [0,683; 1,221] and 1,201 [0,944; 1,762], p=0,0002, procalcitonin 0,206 [0,147; 0,452] and 0,563 [0,307; 2,107], p=0,0002, respectively. According to log-linear regression model, the level of prepepsin at the end of the surgical operation >459,5 (odds ratio (OR) 6,84, 95% confidence interval (CI): 3,14-14,87) or proadrenomedullin >0,788 (OR 5,47, 95% CI: 1,52-19,68) are associated with the increased risk of postoperative complications. The level of presepsin >519,5 pg/ml at the end of the surgical operation (OR 4,55, 95% CI: 1,97-10,47) is associated with the increased risk of inflammatory complications. Regarding the prognosis of the risk of prolonged cardiotonic drug infusions, threshold values for troponin were >1,04 at the end of the surgical operation (sensitivity 75%, specificity 71,3%, AUC 0,785), >1,57 in 6 hours after surgery (sensitivity 81,3%, specificity 71,6%, AUC 0,794).

Conclusion. High levels of presepsin at the end of the surgical operation may be useful to predict the postoperative complications in patients who underwent the aortic surgery however, the low levels of presepsin do not exclude the development of postoperative complications. The increased level of troponin I at the end of the surgical operation and in 6 hours after surgery can be a predictor of the need for cardiotonic support in the postoperative period.

Keywords: biomarkers, presepsin, proadrenomedullin, procalcitonin, troponin I, N-terminal brain natriuretic peptide, cardiosurgery, aortic arch, ascending aorta.

Relationships and Activities: none.

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Key messages

What is already known about the subject?

- Biomarkers are widely used to predict adverse cardiosurgical outcomes.
- Perioperative dynamics of the biomarker levels may influence the tactics of treatment of cardiosurgical patients.

What might this study add?

- Dynamics of the presepsin levels allows doctors to predict both inflammatory complications and the overall adverse events in postoperative period.
- Troponin I levels may be used to predict cardiovascular insufficiency in postoperative period in patients who underwent thoracic aortic surgery.

How might this impact on clinical practice?

- The parameters of intraoperative biomarker dynamics together with the findings obtained with other methods, allow doctors to determine the ways to correct the postoperative complications. The levels of biochemical parameters in intraoperative period of thoracic aortic reconstruction will become a criterion to correct the tactics of treatment of patients in early postoperative period.

Over the past decade, the level of cardiac surgical care has increased significantly; complex combined surgical interventions are performed in patients with severe cardiovascular and other concomitant diseases. This became possible due to the improvement of preoperative preparation, surgical technique, anesthesiological support and treatment of patients in the postoperative period. Despite the modern achievement in anesthesiology-resuscitation and surgical technique, lethality (during 30 days after operation) in all cardiosurgical patients is still ~3% [1].

Currently, forecasting of intensive care unit length of stay and outcome after cardiosurgical operations is based on the clinical parameters and concomitant diseases of different organs and systems and their severity (Parsonnet model, EuroSCORE II etc). Cardiosurgical operations include the use of artificial blood circulation which activates the different ways of systemic inflammatory response of body, and extensive surgical trauma also contributes to this. Systemic inflammatory response is characterized by systemic disorders of a number of bodies`s natural defense mechanisms from traumas and infections: fibrinolysis, coagulation, complement activation, immune cell activation, and oxidative stress in addition to inflammation. The damage to target organs arises as a result of the interaction between patient`s activated defense systems and the lesion of a regional vessel wall due to either physical trauma or ischemia/reperfusion [2].

With the aim to improve clinical results and to decrease mortality in cardiosurgical patient population, new biomarkers are being investigated for the improvement of the quality of prognostic models. In particular, presepsin (PSP) and procalcitonin have a comparable prognostic value in regard to unfavorable renal, cardiovascular and respiratory outcomes in cardiosurgical patients. Besides, PSP has a prognostic value in relation to intrahospital, 30-day and 6-month mortality [3], and it also highly effective for early diagnostics of sepsis in intensive care and resuscitation unit patients [4]. Some biomarkers are routinely used in cardiosurgery including preoperative assessment, such as troponins and cerebral natriuretic peptides [5, 6], while others are still under investigation.

Currently, cardiospecific troponins (cTnI, cTnT) localized mainly in the myocardium, are widely used as a marker of cardiovascular lesion [7]. The markers can reflect the damage to cardiomyocytes not only in the occurrence of irreversible pathological conditions (myocardial infarction) but also in the potentially reversible pathophysiological mechanisms (myocardial ischemia-reperfusion injury, mechanical impact during surgical operation, sepsis, acute renal failure and other processes) [8].

Adrenomedullin (ADM) is expressed in many organ systems including cardiovascular, renal, pulmonary, cerebrovascular, gastrointestinal and endocrine [9]. ADM affects the cardiovascular system causing vasodilation, natriuresis and inhibition of aldosterone production thereby, providing a general optimization of cardiac pre-load [10]. It was found that ADM provides prognostic information in cardiac failure (CF) [9]. Unfortunately, the ADM peptide is unstable and not suitable for use in clinical practice. But MR-proADM, a protein fragment reflecting the ADM levels in the bloodstream, was stable and suitable for use in clinical practice [11].

The study aims to assess the relationship between the level of biomarkers and development of postope-

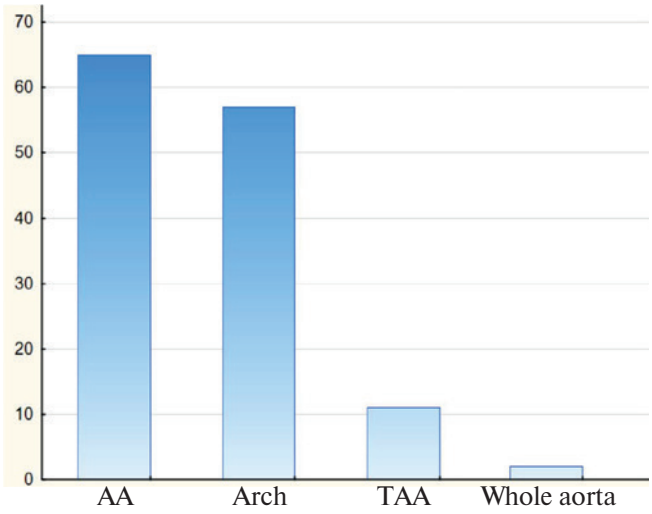

Figure 1. Types of surgical interventions.
Abbreviations: AA — ascending aorta, TAA — thoracoabdominal aorta.

Table 1

Initial pathology

Pathology	All patients (n=132)
Aortic insufficiency of the 3rd degree, n (%)	32 (24%)
Aortic insufficiency of the 4th degree, n (%)	8 (6%)
Aortic valve stenosis of the 3rd degree, n (%)	15 (11%)
Aortic valve stenosis of the 4th degree, n (%)	5 (4%)
Mitral insufficiency of the 3rd degree, n (%)	5 (4%)
Mitral insufficiency of the 4th degree, n (%)	1 (1%)
Ascending aortic aneurysm, n (%)	66 (50%)
Aortic arch aneurysm, n (%)	21 (16%)
Aortic root aneurysm, n (%)	44 (33%)
Connective tissue dysplasia syndrome, n (%)	17 (13%)
Thoracoabdominal aortic aneurysm, n (%)	27 (20%)
Aortic dissection type 1, n (%)	20 (15%)
Aortic dissection type 2, n (%)	6 (5%)
Aortic dissection type 3, n (%)	13 (10%)
Aortic dissection neither A nor B type, n (%)	3 (2%)
Thrombosis of the ascending aorta, aortic arch, n (%)	1 (1%)

Table 2

Anthropometric patient data, M±SD

Parameter	Value (n=132)
Women, n (%)	45 (34%)
Men, n (%)	87 (66%)
Age, years	56±13
Height, cm	174±14
Weight, kg	86±20
Body surface area, m^2	2±0,22

Table 3

Concomitant diseases and transthoracic echocardiography data, M±SD

Parameter	All patients (n=132)
LV EF, %	57±7,6
LV EDV, ml	171±88
CHF 3 FC according to NYHA, n (%)	9 (7%)
CHF 4 FC according to NYHA, n (%)	2 (2%)
COPD, n (%)	14 (11%)
CVD, n (%)	18 (14%)
DM, n (%)	7 (5%)
CKD C2, n (%)	16 (12%)
CKD C3, n (%)	21 (16%)
CKD C4, n (%)	2 (2%)
Constant form of AF, n (%)	9 (7%)
Paroxysmal form of AF, n (%)	17 (13%)
ACVA in the anamnesis, n (%)	9 (7%)
Leriche syndrome, n (%)	6 (5%)
Hypertensive disease stage 3, n (%)	64 (48%)
IHD, n (%)	27 (20%)
VDLE, n (%)	15 (11%)
Repeated cardiac surgery, n (%)	16 (12%)
Hereditary thrombophilia, n (%)	1 (1%)
Multiple organ failure, n (%)	5 (4%)
IDA, n (%)	5 (4%)
Obesity degree 1, n (%)	13 (10%)
Obesity degree 2, n (%)	7 (5%)
Obesity degree 3, n (%)	3 (2%)

Abbreviations: VDLE — varicose disease of lower extremities, IDA — iron deficiency anemia, IHD — ischemic heart disease, LV EDV — left ventricular end-diastolic volume, ACVA — acute cerebrovascular accident, DM — diabetes mellitus, LV EF — left ventricular ejection fraction, AF — atrial fibrillation, CKD — chronic kidney disease, COPD — chronic obstructive pulmonary disease, CHF FC according to NYHA — chronic heart failure according to functional classification of New York Heart Association, CVD — cerebrovascular disease.

rative complications in patients after thoracic and thoracoabdominal aortic reconstruction.

Material and methods

The study was performed in accordance with the standards of Good Clinical Practice and the principles of the Declaration of Helsinki. The study protocol was approved by the Ethic committee of B.V. Petrovsky Russian scientific center of surgery. We obtained written informed consent from all participants prior to inclusion into the study. The study is registered on ClinicalTrials.gov. NCT04689139 Protocol ID039420200002.

The prospective non-randomized cohort study included 132 patients who underwent surgical interventions aimed to restore and reconstruct the thoracic aorta (Figure 1). In the spectrum of surgical interventions, the reconstruction of the ascending aorta prevails.

The inclusion criteria: 18-75 years of age, reconstruction surgery in aneurysms of thoracic and/or thoracoabdominal aorta.

The exclusion criteria: impossibility to analyze at least one of three patient samples due to pre-analytic errors (hemolysis).

Blood sampling aiming to determine the biomarker concentrations was performed in three consecutive stages:

1. Before induction anesthesia;
2. At the end of surgical operation;
3. In 6 hours after surgery.

The patients included into the study underwent surgical interventions for aneurysm/dissection of ascending aorta, aortic arch and/or thoracoabdominal aorta (Table 1). Anthropometric data are given in the Table 2. Initially, most of patients had preserved left ventricular ejection fraction and increased left ventricular end-diastolic volume. Among concomitant pathology, arterial hypertension, chronic kidney disease, ischemic heart disease, rhythm disturbances in the form of atrial fibrillation and other nosology prevailed (Table 3).

To collect intraoperative data, we used a unique scientific system "Collection of electronic anesthesia cards of cardiosurgery patients of the B.V. Petrovsky Russian scientific center of surgery"[1].

Before surgery, patients received premedication with drugs from the benzodiazepine group (sibazone 10 mg/m or alprazolam 0,25-0,5 mg orally) on the eve of surgery and opioids (trimeperidine 20 mg/m), H_1-histamine receptor blockers (chloropyramine hydrochloride 20 mg/m). Introduction anesthesia was performed using propofol 2,0-2,5 mg/kg, fentanyl 2-3 mcg/kg and cisatracurium bezilate 0,15 mg/kg. Anesthesia was maintained by inhalation of sevoflurane 0,7-1,0 MAC and fentanyl using a perfuser at a dosage of 2-3 mcg/kg×h. Myoplegia was maintained by continuous infusion of cisatracurium bezilate at a rate of 0,06-0,1 mg/kg×h. Monitoring included: electrocardiography of 7 leads (I, II, III, avL, avR, avF, V5), invasive arterial pressure, central venous pressure, pulse oximetry and capnography. Surgical interventions on the aortic arch were performed under circulatory arrest with a target temperature of 27° C, selective mono- and/or bihemispheral antegrade cerebral perfusion with control of the volumetric perfusion rate (8-12 ml/kg) according to transcranial dopplerography and cerebral oximetry. Surgical interventions on the thoracoabdominal aorta were performed in the conditions of selective perfusion of the renal arteries, superior mesenteric artery and coeliac trunk. During intra- and postoperative periods, the cerebrospinal fluid pressure with target values 8-12 mm Hg was constantly monitored.

According to the protocol, the period of observation and collection of the information within the present study was 10 days or until discharge from hospital, depending on which event occurs earlier.

The inclusion criteria of these or those biomarkers into the study were: the availability of technical capability to determine the biomarker concentration and the turnaround time not more than 40 min. Thus, the following parameters were included into the study:

- procalcitonin, PSP — biomarkers of inflammation,
- proadrenomedullin — marker of organ dysfunction,
- troponin I TnI-hs — marker of myocardial injury,
- N-terminal pro-brain natriuretic peptide (NT-proBNP) — marker of HF.

The determination of procalcitonin and proadrenomedullin concentrations was performed using the analyzer Kryptor Compact Plus (Thermo Fisher Scientific), troponin I, NT-proBNP, PSP — using the analyzer PATHFAST (LSI Medience Corporation).

Statistical processing of the obtained data was carried out using a software package "Statistica 10 for Windows". The parameters were checked for the normality of the distribution considering the chi-square criterion. The comparative analysis was performed using the Student's t-test or Mann-Whitney U test, depending on the results of the previous normality test. In $p<0,05$ the difference between the groups were considered statistically significant. The search for predictors of the development of complications in the postoperative period was carried out using log-linear regression, ROC analysis; logistic regression coefficients were used to estimate the odds ratio (OR) for each dependent variable of the model. To identify the influence of a set of nominal and non-nominal values on the quantitative response of biomarkers, the regression analysis was performed.

[1] A unique scientific installation "Collection of electronic anesthesia cards of cardiac surgery patients of the B.V. Petrovsky Russian National Research Center" B.V. Petrovsky Russian Scientific Center of Surgery (Moscow), Head of UNU: Axelrod B.A., MD, Professor of the Russian Academy of Sciences, https://med.ru/ru/unikalnaa-naucnaa-ustanovka.

- Lethal outcomes — 2 patients (2,9%)
- Extracorporeal detoxification — 7 (10,1%)
- Inflammatory complications — 36 patients (27,3%)
  - Pneumonia — 29 (22,0%)
  - Wound infection — 7 (5,3%)
  - Mediastinitis — 3 (2,3%) Sepsis — 5 (3,8%)
- Myocardial infarction — 5 (3,8%)
- Cardiac rhythm disturbances — 24 (18,2%)
- Acute renal failure — 11 (8,3%)
- Need in cardiotonic support — 16 (12,1%)
- Need in vasopressor support — 14 (10,6%)

Figure 2. Spectrum of complications (n=69).

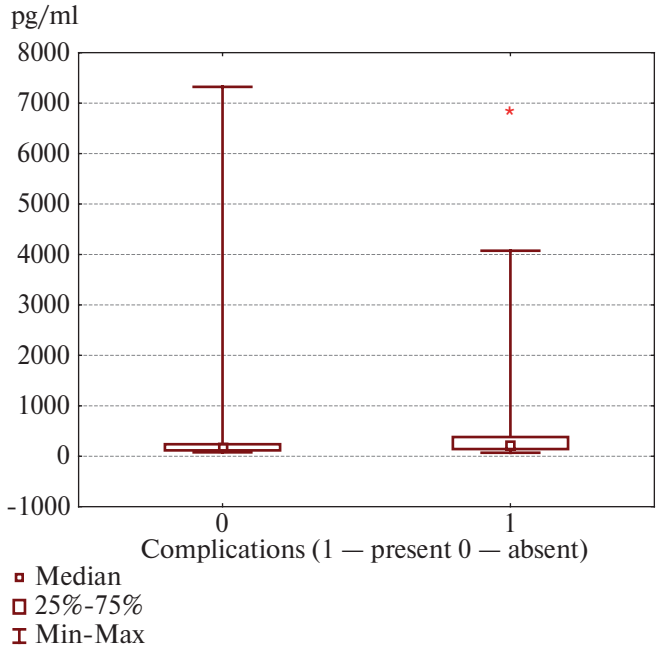

Figure 3. Initial values of PSP.
Note: * — p<0,01.

Results

A complicated course (the presence of at least one of the complications given below) of the postoperative period was observed in 69 patients of 132 (Figure 2).

The criterion of the increased need in cardiotonic support — the need for dopamine/dobutrex infusion >3 mcg/kg×min and/or duration >24 hours from the moment of surgery. The criterion of vascular insufficiency is the need for norepinephrine infusion >150 ng/kg×min and/or the duration of administration >24 hours from the moment of surgery, acute renal failure — an increase in serum creatinine level ⩾26,5 mmol/l during 48 hours, an increase in serum creatinine by ⩾1,5 times compared to the previous 7 days, urine volume <0,5 ml/kg×h during 6 hours.

According to the results of comparative analysis between the groups with non-complicated and complicated postoperative periods at the stage "before induction anesthesia", statistically significant differences were revealed only for PSP concentrations (Figure 3), and at the same time, the group of the patients with complicated postoperative period course had statistically higher PSP levels.

At the stages "at the end of surgical operation" and "in 6 hours after surgery", the patients with complicated postoperative period course had higher values of PSP, troponin I, procalcitonin and proadrenomedullin (Figure 4).

To search for possible predictors, we used the analysis of log-linear regression, according to results of which we found that at the end of surgical operation only the increased levels of proadrenomedullin are associated with the increased risk of complicated postoperative period course (OR 6,23, 95% CI: 1,78-21,86).

To determine the level of proadrenomedullin, the ROC-analysis was the most effective (with the maximum possible simultaneously sensitivity and specificity) allowing us to separate groups of patients with complicated and non-complicated postoperative period. It was found that the optimal cut-off level for proadrenomedullin at the end of surgical operation is 0,788 (sensitivity 43,75%, specificity 88,89%). The proadrenomedullin concentrations at the end of surgical operation >0,788 are associated with the increased risk of the complicated postoperative period course (OR 5,47, 95% CI: 1,52-19,68).

When analyzing the results of the determination of PSP, it was noted that despite statistically higher PSP levels in patients with complicated postoperative period course, the low values of PSP do not allow us to exclude the development of complications with sufficient confidence. Most likely, this feature of the distribution of PSP concentrations in the groups of patients with normal and complicated postoperative periods was a reason why, according to the log-linear regression results, the increase in the PSP level at the end of surgical operation is not associated with the increased risk of the development of complications in postoperative period.

At the same time, according to the nature of the distribution of PSP concentrations at the end of surgical operations, it was noticed that the complicated postoperative period course is characterized by such high values of this biomarker, which were not

Parameter	Stage	Non-complicated course of p/o period (M (Q1-Q3); minimum-maximum values)	Complicated course of p/o period (M (Q1-Q3); minimum-maximum values)	P
Presepsin pg/ml	Before surgical operation	171 (117-239) 78,8-7323	216 (143-381) 70,4-4074	0,0072
	At the end of surgical operation	326 (206-451) 119-1263	620 (332-829) 145-2531	0,000007
	In 6 hours after surgery	450,5 (269-716) 151-3337	627,0 (382-1015) 132-3480	0,0147
Troponin I ng/ml	At the end of surgical operation	0,4510 (0,202-0,957) 0,006-17,6	0,755 (0,345-1,81) 0,009-23,9	0,0133
	In 6 hours after surgery	0,77 (0,46-1,39) 0,008-17,9	1,49 (0,59-3,39) 0,008-23,5	0,0278
Proadrenomedullin nmol/l	At the end of surgical operation	0,894 (0,683-1,221) 0,234-2,098	1,201 (0,944-1,762) 0,484-3,254	0,0018
	In 6 hours after surgery	1,009 (0,772-1,235) 0,351-2,682	1,475 (1,135-1,894) 0,484-3,534	0,0002
Procalcitonin ng/ml	At the end of surgical operation	0,094 (0,064-0,131) 0,027-0,98	0,137 (0,102-0,234) 0,057-4,523	0,0033
	In 6 hours after surgery	0,206 (0,147-0,452) 0,080-6,278	0,563 (0,307-2,107) 0,112-17,33	0,0002

Figure 4. Dynamics of markers and course of p/o period.
Abbreviation: p/o — postoperative.

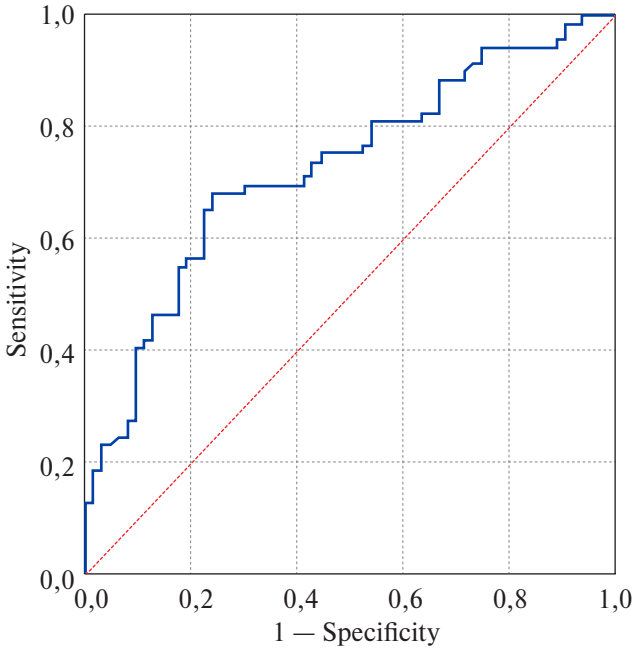

Figure 5. ROC-analysis of PSP at the end of surgical operation and risk of complications.

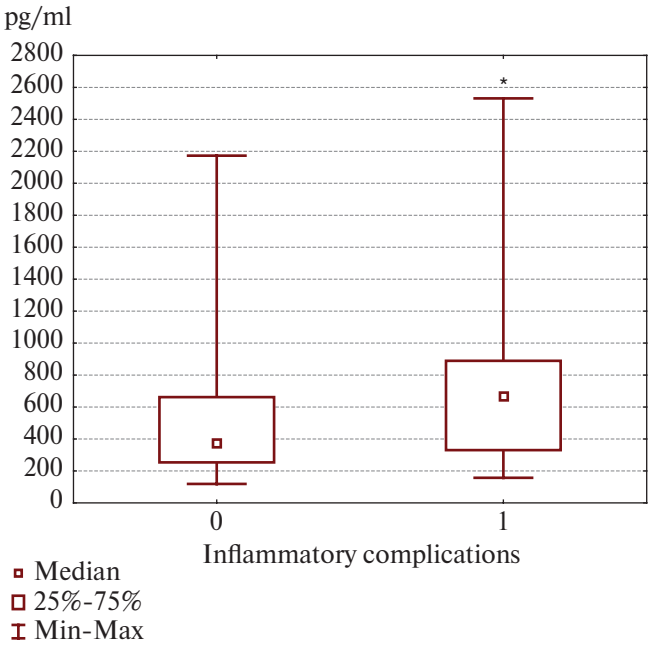

Figure 6. PSP level at the end of surgical operation in patients with inflammatory complications.
Note: * — p<0,01, 1 — complicated postoperative period, 2 — non-complicated postoperative period.

found in patients with non-complicated postoperative period. This fact allowed us to assume that probably the increased PSP levels can be associated with the increased risk of complications in postoperative period, however, low or slightly raised PSP levels do not allow us to exclude the development of complications.

According to the ROC-analysis results, the most acceptable cut-off level for PCP at the end of surgical operation is 459,5 (sensitivity 68,1%, specificity 76,2%). The PSP levels at the end of surgical operation >459,5 are associated with the increased risk of

Parameter	Stage	Non-complicated course of p/o period (M (Q1-Q3); minimum-maximum values)	Complicated course of p/o period (M (Q1-Q3); minimum-maximum values)	P
N-terminal pro-brain natriuretic peptide, pg/ml	Before surgical operation	229 (123-871) 13-30001	1160 (280-7054) 39-11871	0,0025
	At the end of surgical operation	213 (86-668) 11-23734	684 (351-3971) 51-10803	0,0014
	In 6 hours after surgery	421 (203-1270) 26-14616	1305 (626-7159) 224-27346	0,0011
Troponin I ng/ml	At the end of surgical operation	0,548 (0,202-1,29) 0,006-7,58	1,74 (0,833-5,41) 0,317-23,9	0,0001
	In 6 hours after surgery	0,858 (0,453-1,825) 0,008-23,5	2,275 (0,317-23,9) 0,833-5,410	0,0001

Figure 7. Markers and prolonged infusion of cardiotonic drugs in postoperative period.
Abbreviation: p/o — postoperative.

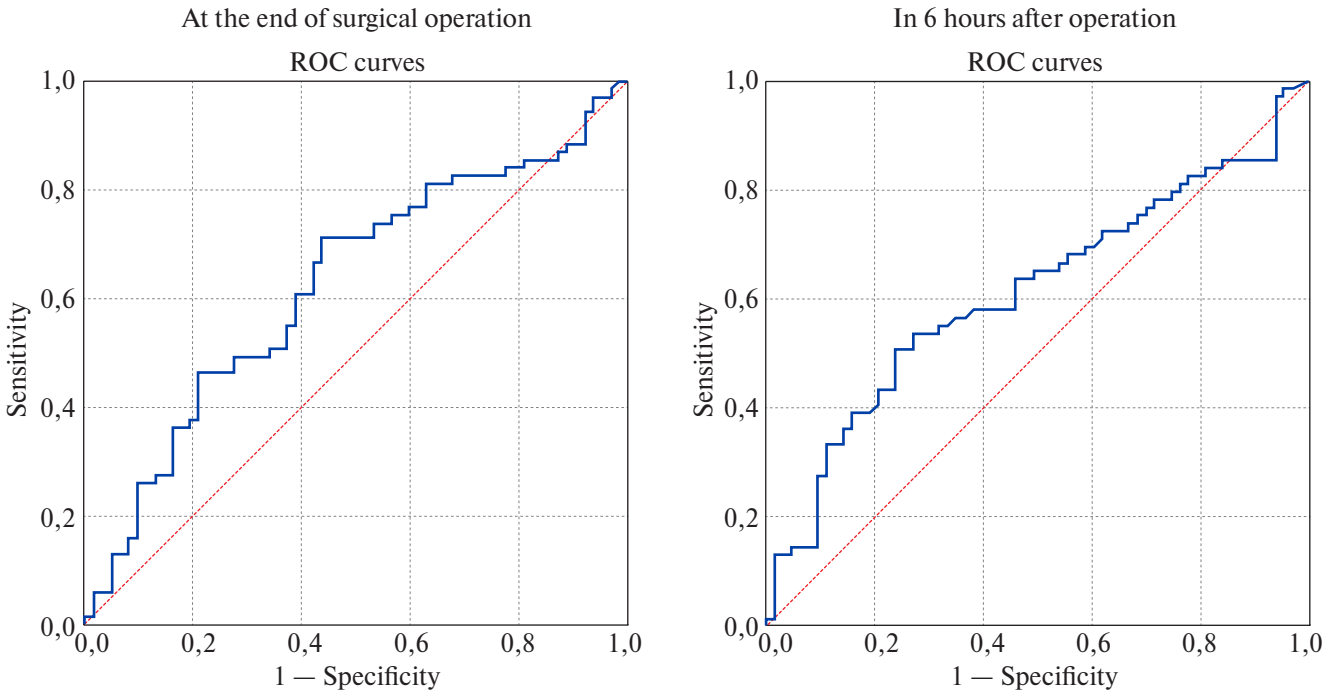

Figure 8. ROC-analysis for Troponin I.

the complicated postoperative period course (OR 6,84, 95% CI: 3,14-14,87) (Figure 5).

As for the PSP concentrations in 6 hours after surgery, the noted tendency was no longer observed in this period. For this period, despite statistically reliably higher PSP values in the group of patients with complicated postoperative period, the PSP values in general were so heterogeneous that it was not possible to identify the predictor.

Thus, the high PSP levels (>459,5) at the end of surgical operation can be useful regarding the prognosis of the development of complications in postoperative period in patients after aortic surgery but at the same time, the low PSP levels cannot exclude the development of complications in postoperative period in such patients, that is important to take into account while interpreting the results of this biomarker in postoperative period.

The inflammatory complications in postoperative period were observed in 36 patients of 132. Of them:

- pneumonia — 29;
- wound infection — 7;
- mediastinitis — 3;
- sepsis — 5.

According to the comparative analysis results, the most suitable biomarker for forecasting the development of inflammatory complications in postoperative period is the level of PSP at the end of surgical operation (Figure 6). The group with inflammatory complications in postoperative period had higher values of PSP (the median of the values in the group with normal postoperative period course was 372,5, range 119-2173 the median of the values in the group with complicated postoperative period course — 668,5, range 157-2531, p=0,0029). Using the ROC-analysis, we found that the most acceptable threshold value of the biomarker is the level of 519,5 pg/ml (sensitivity 69,4%, specificity 66,7%, area under ROC-curve (AUC) 0,669, 95% CI: 0,563-0,775), above which the risk of inflammatory complications is increased (OR 4,55, 95% CI: 1,97-10,47) with the same statement that low or slightly raised PSP levels do not allow us to exclude the development of complications.

High need in the infusion of cardiotonic drugs, indirectly indicating HF, was observed in 16 patients of 132. The comparative analysis outlined the range of possible predictors — the levels of NT-proBNP before surgical operation, at the end of surgical operation and in 6 hours after surgery, and the levels of troponin I at the end of operation and in 6 hours after surgery (Figure 7). But the log-linear regression results showed that only increase in the troponin levels directly after operation and in 6 hours after operation can be the predictors of prolonged infusion of cardiotonic drugs in postoperative period (OR 1,53, 95% CI: 1,15-2,04 and OR 1,23, 95% CI: 1,08-1,40, respectively).

Using the ROC-analysis, we determined the optimal cut-off levels for troponin I (Figure 8):

- at the end of surgical operation >1,04 (sensitivity 75%, specificity 71,3%, AUC 0,785),
- in 6 hours after surgery >1,565 (sensitivity 81,3%, specificity 71,6%, AUC 0,794).

According to the long-linear regression analysis results, the risk of high need in prolonged infusion of cardiotonic drugs in postoperative period is associated with the raised troponin levels >1,04 at the end of surgical operation (OR 7,45, 95%, CI: 2,22-25,07) and the troponin level >1,565 (OR 10,90, 95%, CI: 2,88-41,25) in 6 hours after surgery.

Discussion

The ideal indicator of biological processes in the modern clinical conditions should have sufficient sensitivity and specificity, be informative, accessible, reproducible and timely, since the dynamics of an indicator may be used not only to forecast unfavorable events in postoperative period but also to control treatment. In this study, we used both the biomarkers which have been used in routine practice for a long time and relatively new peptides, the use of which can be quite perspective (PSP) in forecasting postoperative complications. We used proadrenomedullin as a marker of organ dysfunction, PSP, procalcitonin as the markers of inflammation, troponin I as an indicator of myocardial injury, and NT-proBNP as an indicator of HF. The concept of the complex evaluation of biomarkers, which was used in the present study, coincide with the studies of other authors. For example, Vershinina MG, et al. [4] showed the advantages of using a combination of biomarkers (the model of the use of the PSP and proadrenomedullin combination is the most effective) for early diagnostics of sepsis in intensive care and resuscitation unit patients in critical state.

It should be noted that most of the studies dedicated to the prognostic significance of the biomarkers in cardiosurgery were performed in valvular pathology surgery and/or in myocardial revascularization. The study performed by Clementi A, et al. showed a high prognostic value of PSP and procalcitonin for the estimation of postoperative renal, cardiovascular and respiratory complications. PSP was also effective for forecasting intrahospital, 30-day and 6-month lethality [3].

Despite the significance of the problem of thoracic and thoracoabdominal aortic reconstructive surgery, the publications dedicated to the use of biomarkers for forecasting postoperative complications are sporadic.

In our study, we found significant differences before the main stage of the surgical intervention in PSP only. However, even in the presence of statistically reliable differences, the values of this biomarker concentrations were so overlapping both in the region of high values and in the region of normal values, that it was not possible to use this indicator to forecast the development of inflammatory complications.

A revealed regularity that the high values of this biomarker are typical of complicated postoperative period course and were not observed in patients with non-complicated postoperative period course, also seems interesting. This fact allowed us to assume and then to prove that the increased PSP levels at the end of surgical operation are associated with the increased risk of the postoperative complications but low or slightly raised PSP levels do not allow us to exclude the development of complications. It is necessary to consider the revealed characteristic when interpreting the PSP determination results: high PSP levels (>459,5 pg/ml) at the end of surgical opera-

tion can be useful for forecasting the development of complications in postoperative period in patients who underwent aortic surgery, but at the same time low PSP levels at the end of operation cannot exclude the development of complications.

Regarding to forecasting inflammatory complications, it was found that according to the comparative analysis results, the most suitable biomarker for forecasting inflammatory complications in postoperative period is the PSP level at the end of surgical operation. But the pattern of distribution of PSP values in the analyzed groups also showed that even in statistically reliable differences, the values overlapped both in the region of high values and in the region of normal values, and according to the log-linear regression analysis results, the increased PSP level is not associated with the increased risk of complicated postoperative period course.

We found that the most acceptable threshold value of the biomarker is the level of 519,5 pg/ml (sensitivity 69,4%, specificity 66,7%, AUC 0,669, 95% CI: 0,563-0,775), above which the risk of inflammatory complications is increased (OR 6,84, 95% CI: 3,14-14,87), but at the same time the low PSP levels at the end of surgical operation (<519,5 pg/ml) cannot exclude the development of complications.

When investigating the dynamics of the changes in the levels of the analyzed biomarkers, we found that the auxiliary calculated parameters reflecting the dynamics of the changes in PSP levels can be also attributed to the predictors of inflammatory complications.

The 2-times and more increase in PSP level during time of surgical operation is associated with the increased risk of the development of complicated postoperative period course (OR 3,05, 95% CI: 1,34-6,95). The absence of the increase in PSP level during first 6 hours after surgery is associated with the increased risk of the development of complicated postoperative period course (OR 4,15, 95% CI: 1,83-9,41). And the combination of these two risk factors — PSP level at the end of surgical operation >519,5 pg/ml and the absence of the increase in PSP level during first 6 hours after surgery — is associated with the increased risk of the development of complicated postoperative period course (OR 5,80, 95% CI: 2,19-15,35).

Thus, for forecasting the development of inflammatory complications in postoperative period it is appropriate to use not only absolute PSP values at the end of surgical operation but also the monitoring of the dynamics of this indicator.

Highly sensitive troponin I has proven itself well in the diagnostics of not so much myocardial infarction as cardiovascular lesion [12]. It is an independent predictor of postoperative complications and lethality in patients with acute aortic dissection, and patients with initially elevated value of the marker had a greater number of cardiovascular complications [13]. In this regard, troponin I has some advantage over classical assessment scales (EuroSCORE, VA) in cardiosurgical patients [14].

In aortic surgery, the diagnostics of myocardial lesion is especially important because myocardial infarction in postoperative period is diagnosed quite rare. Our study revealed it in just 5 (3,8%) patients, while the need in cardiotonic and vasopressor support in 16 (12,1%) and 14 (10,6%), respectively. The evaluation of troponin I level will speed up the start of inotropic support because the myocardial damage during surgical operations on the thoracic aorta more often has a subclinical character and its causes are indirect (circulatory arrest, ischemia-reperfusion syndrome and other factors).

It should be also noted that the publications dedicated to the dynamics of highly sensitive troponin I in cardiosurgical patients emphasize a great role of a type of surgical intervention. In the study performed by Mastro F, et al., patients underwent mitral and aortic valve surgery, thoracic aortic surgery, myocardial revascularization and combined operations were examined. The maximum growth of the indicator was found in patients underwent mitral valve surgery as well as after combined operations [15]. These facts may be important in interpreting the laboratory results and making clinical decisions in postoperative period.

The limitation of our study is that its results cover the patients who underwent reconstructive surgery on the thoracic and thoracoabdominal aorta. The study included 132 patients that is also one of its limitations. To extend the use of these biomarkers as the predictors of complications in other categories of patients, further investigations will be required.

Conclusion

- High PSP levels at the end of surgical operation can be useful for forecasting the development of complications in postoperative period in patients underwent aortic surgery however, low PSP levels do not exclude the possibility of the development of complications.
- PSP showed greater informativity in forecasting of complications in general than precisely inflammatory complications.
- The increased troponin I level immediately after surgical operation and in 6 hours after operation can be a predictor of the need in cardiotonic support in postoperative period.

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Single-stent strategy for left coronary artery bifurcation lesions in patients with chronic ischemic heart disease: protocol of a randomized trial

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Aim. This study aims to compare the intraoperative, immediate postoperative and long-term postoperative results of stenting followed by final kissing balloon angioplasty (FKB) and without FKB for left coronary artery (LCA) bifurcation lesions in patients with chronic ischemic heart disease.

Material and methods. We plan to perform an open-label, prospective, randomized, single-center, cohort trial that will include 40 patients with left main coronary artery bifurcation lesion, who will undergo stenting procedure followed by FKB or without FKB, using the second-generation drug-eluting stents. Randomization into two groups will be done after performing coronary angiography, confirming the inclusion criteria and the absence of non-inclusion criteria and signing a written consent in 2 copies. Group 1 — stenting followed by FKB. Group 2 — stenting without FKB. The total follow-up period is 24 weeks. It is planned to contact by phone on 30th and 180th day (±7 days) of postoperative period to obtain the information about patient condition, general survival rate, the events of combined controlled points and drug therapy. During 2nd phone contact, on 180th day (±7 days), a patient will be invited to undergo multispiral computed tomography of the coronary arteries.

The primary combined end-point: cardiac death, nonfatal myocardial infarction, acute cerebrovascular accident and the repeat target vessel revascularization.

The secondary combined end-point: thrombosis and stent restenosis.

Conclusion. Our study will optimize the approach to the choice of stenting strategy (with or without FRB) for left main coronary artery bifurcation lesions in patients with chronic ischemic heart disease.

Keywords: stenting of left main coronary artery, final kissing balloon angioplasty, true bifurcation lesion, false bifurcation lesion.

Relationships and Activities: none.

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Key messages

- The type of left main coronary artery bifurcation lesion may influence the choice of optimal single-stenting technique to treat left main coronary artery bifurcation lesions in patients with chronic ischemic heart disease.
- The stenting without final kissing balloon angioplasty may be used in false bifurcation lesion with the main coronary artery caliber Ø⩾4 mm and regardless of the angle of the lateral branch origin.

Hemodynamically significant bifurcation lesion of left main coronary artery (LMCA) in patients with chronic ischemic heart disease (IHD) is the absolute indication for surgical intervention [1]. The choice of the optimal interventional treatment method is still under discussion in professional communities [2]. It is recommended to use this or that approach to percutaneous coronary intervention (PCI) depending on the type of LMCA bifurcation lesion [3]. The single-stent strategy (provisional-stenting) is recommended in case of true or false lesion, while the double-stent approach is justified for a complex case determined according to the criteria of the DEFINITION II research [4, 5]. The stenting algorithm is presented in the final 16th document of European Bifurcation Club, published in 2022, which once again raises the question of the need of the routine final kissing balloon angioplasty (FKB) in single-stent strategy [6].

The study aims to compare the immediate and long-term results of LMCA bifurcation lesion stenting followed by FKB and without FKB in patients with chronic IHD.

Material and methods

Study design. We plan to perform an open-label, prospective, randomized, single-center, cohort trial that will include 40 patients with LMCA bifurcation lesion, who will undergo stenting procedure (followed by FKB or without FKB), using the second-generation drug-eluting stents. Randomization will be done after performing coronary angiography (CA), confirming the inclusion criteria and the absence of non-inclusion criteria. Group 1 — stenting followed by FKB. Group 2 — stenting without FKB. The timing for PCI will be determined individually by a multidisciplinary team according to international relevant recommendations.

The study meets the standards of Good Clinical Practice and ethical aspects of Helsinki Declaration created by the World Medical Association, paragraph 15 of Article 37 of Federal Law № 323-FZ of November 21, 2011 "On the basics of Public Health protection in the Russian Federation". The Local Bioethics Committee has examined the objectives and plan of the study conduction and has given its positive opinion about the study. We will obtain written informed consent from all participants prior to inclusion into the study.

Criteria of inclusion. Gender (any); age ⩾18 years old; chronic IHD (stable exertional angina pectoris, painless form of ishemia) with proven myocardial ischemia according to non-invasive and/or invasive (determination of fractional flow reserve (FFR) and/or instant flow reserve (IFR)) methods of functional assessment of blood flow; presence or absence of myocardial infarction (MI) in the anamnesis; left ventricular ejection fraction >35%; "unprotected" LCA trunk — the absence of working aortocoronary shunts; the presence of true or false bifurcation lesion; technical possibility and good anatomical conditions for the PCI conduction; informed patient consent to participate in the study.

Criteria of non-inclusion. The diagnosis of acute coronary syndrome (ST-segment elevation MI, MI without ST-segment elevation, early postinfarctional angina pectoris, unstable angina pectoris); left ventricular ejection fraction ⩽35%; "protected" LCA trunk; local lesion of the ostium, proximal or middle third, not affecting the bifurcation and requiring PCI within the limits of LCA trunk; multivascular lesion in the coronary bed with SYNTAX Score >32; patients with diabetes mellitus and multivascular lesion in the coronary bed with SYNTAX Score >22; impossibility to receive double antithrombotic or double/triple antithrombotic therapy (antiplatelet + anticoagulant) in case of atrial fibrillation and/or valvular prosthesis in the anamnesis; severe chronic obstructive pulmonary disease: III-IV stage; acute heart failure II-IV (Killip); mental disorders; oncological diseases that limit life expectancy; pregnancy and lactation.

Inclusion into the study. At admission, the standard drug therapy in accordance with the clinical recommendations will be prescribed to a potential study participant, all necessary examinations will be conducted, and after confirming the non-invasive inclusion criteria and the absence of the non-inclusion criteria with suspected the left main coronary artery bifurcation lesion, a patient will undergo CA. After performing CA, in case of confirmation of the invasive inclusion criteria and the absence of the non-inclusion criteria, a patient will receive full information about the study, and he will be asked to sign the informed consent in 2 copies (one of them will be given to him). The information of each study participant will be recorded to specially designed individual registration patient cards.

Randomization. Randomization will be carried out by the envelope method in 1:1 ratio intraoperatively, after performing CA and confirming all inclusion criteria and the absence of non-inclusion criteria, into two groups, with 20 patients in each. Group 1 — stenting followed by FKB. Group 2 — stenting without FKB. The surgical approach to perform PCI will be determined by a radiosurgeon. Drug-eluting stents used in routine practice will be implanted. Predilation of the target lesion is at the discretion of an operating surgeon. Proximal optimization with noncompliant balloon is mandatory step. It is mandatory to protect the lateral branch (LB) with the second coronary conductor. If in group 1 LB is com-

	During hospital period		Observation after discharge from hospital	
	Before CA, after CA conduction	After PCI	Phone contact on 30th day	Phone contact on 180th day and face-to-face visit
Informed consent, inclusion/non-inclusion criteria	✓			
Anamnesis, clinical status	✓	✓	✓	✓
Laboratory methods	✓	✓		
ECG	✓	✓		
EchoCG	✓	✓		
MSCT				✓
Load testing	✓			✓
Drug therapy	✓	✓	✓	✓
Evaluation of intraoperative results		✓		
Evaluation of combined control points		✓	✓	✓

Figure 1. Research flowchart.

Abbreviations: CA — coronary angiography, MSCT — multispiral computed tomography, PCI — percutaneous coronary intervention, ECG — electrocardiography, EchoCG — echocardiography.

promised according to QCA (Qualitative comparative analysis) angiographic data and the results of invasive functional examination methods (FFR and IFR), it needs to pass to forced stenting with FKB. At the end of the operation, the category of angiographic result of PCI will be given, based on the designed method for determination of postoperative management tactics of patients with IHD according to classification of PCI angiographic results. Double antiplatelet therapy will be prescribed for 6 months.

Telephone contact and face-to-face visit. The total follow-up period will be 24 weeks (Figure 1). The research personnel will contact the patients on 30th and 180th (±7 days) day after the operation. The information about patient condition, general survival rate, the events of combined controlled points and drug therapy will be collected. On the 6th month after operation a patient will be invited to undergo multispiral computed tomography of the coronary arteries. If the participants inform that an event has occurred, it is recorded in special event reporting form with the source documents collected by the research personnel.

End-points. The intraoperative results and combined points will be assessed. The primary combined end-point was determined as MACEs: cardiac death, nonfatal myocardial infarction, acute cerebrovascular accident and the repeat target vessel revascularization. The secondary combined end-point: thrombosis and hemodynamically significant stent restenosis.

Statistical analysis. It is supposed to evaluate the comparable results of the two methods (non-inferiority). Statistical processing of the obtained data will be carried out using a software package Statsoft Statistica 8 (USA). Quantitative variables will be described by the number of the patients, mean ± standard deviation and the median (95% confidence interval (CI)). Qualitative variables will be presented in the form of absolute and relative (percentage) frequencies. To study the relationship between categorical variables, the Fisher exact test will be used, and the reliability of differences between quantitative indicators will be evaluated using non-parametric Mann-Whitney and Wald-Wolfowitz criterion. In all statistical analysis procedures, the achieved significance level (p) will be calculated, and the critical significance level will be assumed to be <0,05. The log-rank test will be used to compare before-event time. Freedom from events will be estimated by constructing a curve using the Kaplan-Meier method.

Current study status. Currently, patients are being recruited into the study.

Discussion

The improvement of PCI techniques and the introduction of modern drug-eluting stents allowed endovascular surgery to occupy its niche in operative treatment of LMCA bifurcation lesion along with aortocoronary shunting in patients with chronic IHD [7]. By now, the LCA trunk stenting has shown its safety and efficacy in patients without diabetes mellitus and with the SYNTAX Score value ⩽32 [8]. A number of clinical studies aimed to compare the different stenting methods have been conducted and showed that the choice of the strategy and technique in stable patients largely depends on the type of bifurcation lesion [3, 4, 6, 9]. European

Bifurcation Club as the main vector of bifurcation stenting development recommends routine use of provisional stenting which is the simplest from the technical point of view and does not limit a surgeon in implanting the second stent if necessary, in true and false lesions [4, 6]. However, the issue of application of FKB which is classic technique aimed to optimization of bifurcation stent and carina, remains relevant. Various studies dedicated to this problem were conducted, the largest of them are RAIN-CARDIOGROUP VII (n=2742) and the analysis of the study database EXEL (n=948), which show the comparable results of the two stenting methods (with FKB and without FKB) [10, 11]. Based on the world tendency, in 2022 European Bifurcation Club came to conclusion that it is not mandatory to perform FKB in case of the optimal angiographic result achieved by stent implantation into the main branch (the most hemodynamically significant branch of the bifurcation — the anterior interventricular branch or the circumflex artery in case of the bifurcation of the LCA trunk), and regardless of the angle of the LB origin [6]. It should be noted that this is primarily referring to the bifurcation lesions that do not affect the LCA trunk therefore, the issue of routine FKB in the immediate bifurcation lesion of the LCA trunk itself remains poorly studied and relevant.

In our study, we propose a hypothesis that the two single-stenting strategy methods (with FKB and without FKB) of LMCA bifurcation lesions in patients with chronic IHD will have comparable immediate and long-term results by the control points. The stenting without routine FKB which reduces the amount of the necessary consumable material and instruments, and reliably reduce the surgical operative duration according to a previously performed retrospective analysis, can be recommended in false bifurcation lesion with the LCA trunk caliber Ø⩾4 mm and regardless of the angle of the LB origin upon condition of the absence of LB compromise confirmed by QCA angiographic data and by the results of invasive functional examination methods (FFR and IFR). But FKB must remain mandatory in case of true LMCA bifurcation lesions regardless of the angle of the LB origin due to the high risk of the LB compromise development.

As you can see from the above, such a hypothesis of single-stent strategy envelopes true and false LMCA bifurcation lesions only. Other lesions in stable patients, which can be referred to the criteria of complex cases according to DEFINITION II research [5], may require the applying double-stent strategy [4] or are recommended to revascularization by aortocoronary shunting method.

Limitations of the study. The main limitations will be single-center study type and small patient sampling, and the factors of diversity in structure of cells of the stents from different manufactures will not be taken into account, that is the important predictor of possible LB compromise.

Conclusion

The planned study will optimize and systematize the approach to routine performance of FKP in single-stent strategy depending on the type of LMCA bifurcation lesion in patients with chronic IHD.

Relationships and Activities: none.

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Experience of conducting the first Russian cardiology hackathon Cardio data hack

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This article is about the experience in organizing and conducting the first Russian cardiology hackathon Cardio data hack UFA 2022 which took place in Ufa in November 2022. It describes the preparation stages and organizational conditions of the hackathon conducting, the ways of interacting between the event organizer and participants, and the methods of evaluating the tasks. The first hackathon case was the recognition of ventricular bigeminy in patients with 24-hour ECG recording; the second case was performing a meta-analysis of the studies which assessed efficacy and safety of oral anticoagulants in atrial fibrillation and chronic renal failure stages IV and V. The hackathon attracted 179 registered participants who formed 42 teams, but further only 37 of them confirmed their participation and formed 8 teams. 7 teams gave the final solution of the tasks, and 5 of them presented their results with 3 of them giving solutions for both cases. Eventually, there were obtained the prototypes of solution for bigeminy recognition during Holter monitoring and high-quality meta-analyses evaluating the efficacy and safety of oral anticoagulants.

Keywords: hackathon, cardiology, Holter monitoring, meta-analysis.

Relationships and Activities: none.

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In the last decade hackathon has gained wide popularity as a way of collaborative solution of a certain problem using modern information technologies (IT) over a limited period of time. Usually, within the framework the hackathon, participants received a task based on an existing problem, often formulated by a quite certain customer interested in solving it. Despite the fact that sometimes hackathon allows the specialists of various economic sectors to get an informational solution of their problem, basically it is a pedagogical practice [1], designed, among other things, to practically consolidate the formation of professional skills in students [2]. Also, many authors who study the hackathon practices refer to its ability to form competencies related to soft-skills, for example, ability to work in a team or project management skills [3]. Despite the popularity of hackathons in Russia and support for their conduction at the state level, in particular, a series of hackathons "Digital Breakthrough" within the framework of the national project "Digital Economy", their use for solving medical problems is rare.

The practice of conducting hackathons specifically on medical topics, on the contrary, is quite popular abroad. This is largely due to the fact that within the framework of the hackathon, you can

present your own idea of an innovative startup in the field of public health [4]. Many researchers of the practice of conducting hackathons on medical topics note that, firstly, this is a great opportunity to participate in interdisciplinary projects that combine the competencies of IT specialists and medical professionals, that contributes to interprofessional training (for example, [5]), secondly, the opportunity to grow a generation of innovators capable of using innovative and entrepreneurial approaches to solve the complex problems of the modern healthcare system [6], thirdly, the possibility of introducing new methods of active training in the field of medicine, contributing to the development of skills in setting and solving problems in the field of digitalization of the healthcare system [7]. Moreover, the hackathon topics in the field of medicine can be various: from epidemiological studies and virology, to genomics and bioinformatics [8]. However, conducting medical hackathons is associated with a number of emerging problems for the organizers. One of the problems is the formation of teams of specialists in various fields, for example, clinicians, scientific researchers, IT specialists, medical statisticians, etc. In this regard, the organizers are required to provide extensive coverage of the hackathon not only in specialized professional "publics" but in the media, and the use of an electronic platform capable of bringing together the specialists from different regions as well as maintaining operational communication between them. Another problem is a keeping the participants motivated to perform the tasks of the hackathon. To solve this problem, it is required to form the prize fund or find alternative non-material ways to encourage participants. The third problem is the formation of a competent jury including the experts from various fields of knowledge (medicine, IT, statistics, pharmacoeconomics, etc.) and the development of methods for coordinating expert opinions to obtain transparent and reliable results of the evaluation of competition participants. Thus, the problem of the development of the methods for organizing and conducting medical hackathons is relevant.

As you know, cardiology/cardiosurgery is a fairly high-tech healthcare industry and is associated with a large number of modern technical and IT solutions. Despite numerous hackathons in the field of healthcare, according to our data, a hackathon in the field of cardiology has not yet been held.

In this article we present the experience of organizing and conducting the first Russian cardiology hackathon Cardio data hack UFA 2022 in Ufa in November 2022.

It should be noted that almost all hackathons have similar principles of organization, and the key point in hackathon conducting is the use of the modern electronic platform that provides the online support for all the event stages: from the team registration and expert consultations to downloading completed solutions and broadcasting participants' speeches. In our case, for conduction of the first hackathon on cardiovascular issues Cardio data hack UFA 2022 within the frameworks of III Eurasian (Russian-Chinese) Congress on the Treatment of Cardiovascular Diseases, the platform codenrock was used. This platform was chosen in particular due to the possibility of chat-communication of both the organizers with participants and participants between each other as well as the support for video broadcasting of all intermediate procedures and the final presentation of works to the jury through its own service.

The first stage in the hackathon organization is the development of the rules of its conducting regarding to general regulations (requirements for participants, requirements for teams), requirements for the final result of completing tasks, the order and timing of the event, the order of registration for the hackathon, requirements for the protection of personal data and the security of the event. The developed rules for the hackathon conduction were posted on the platform which was the main platform for its online holding.

The second stage of the hackathon is the selection of companies which will become the task "providers". It should be noted that the tasks should meet the following requirements: to be modern and interesting for participants, to correspond to the hackathon topic, i.e. to be from the field of cardiology, implying the creation of a prototype in the form of a software product. "The providers" themselves should decide about the valuable prizes that will be presented to hackathon participants as well as the criteria for evaluating tasks.

The third stage of the hackathon organization concerns the creation of organizational conditions for its conduction: expert consultations, determining the format for presenting results, developing a methodology for coordinating expert opinions.

Formally, the hackathon was held in two stages: the first stage was correspondence, when the registered teams of participants do the tasks proposed by the organizers (15 days), and the full-time stage (online), where the participants defended their solution of the proposed cases. It should be noted that participants downloaded the complete task solutions in the form of reports for the tasks, scripts with codes and presentation on the platform in the last day of the correspondence stage, and while performing face-to-face (online), the authors could no longer change the downloaded solutions. The correspondence stage included 2 online consultations with

the experts and case developers (checkpoints), and the participants could also ask questions to both the hackathon organizers and task developers in the chat on the competition platform.

The first task was a practical arrhythmia recognition case — ventricular bigeminy on a test set (dataset) in patients with 24-hour electrocardiogram recording (ECG). The participants received the sets of labeled ECG data where the corresponding type of arrhythmia was marked by the specialists, and also a set of "raw" (unmarked) ECG data on which it was recommended to check the correctness of the resulting solution. The ECG data represented the 7 lead-ECG parameters written to a line (I, II, V5, III, aVL, aVR, aVF). The participants also received the information on the time of the recorded complex in milliseconds from the beginning of the day, on the time of the recorded complex in milliseconds from the beginning of recording, "type of complex" — S-supraventricular, V#-ventricular, X and Z — artifacts, "code of arrhythmia" — a brief designation of the recorded arrhythmia and "arrhythmia" — name of arrhythmia. The participants were required to develop a software solution, download it on the platform, and also to make a presentation in the form of a report on the results obtained and methods used. The case was proposed by the manufacturer of the daily ECG monitoring complex Normocard (Kemerovo).

The second task required the participants to conduct the meta-analysis of the data sources where the efficacy and safety of oral anticoagulants in atrial fibrillation and chronic renal failure stages IV-V were assessed. And it was explained that the participants are not limited either by the choice of the studies or by the source of their search, or by the number of studies, or by the statistical meta-analysis tool used, or by the modeling environment. Along with that, the participants had to make a decision on the inclusion/exclusion of the studies into the meta-analysis independently. The participants were required to present the results of the meta-analysis in the form of an expanded report and provide a script in the form of a code for its performance.

The main difficulty faced by the organizers is that in fact the jury had only one day to check the results obtained by the teams of the hackathon participants. This was complicated by the position of the experts in 4 different time zones of Russia (Moscow, Samara (+1), Ufa (+2), Novosibirsk (+4)). In this regard, the experts filled out the expert evaluation sheet in accordance with the established evaluation criteria developed in advance.

The evaluation criteria of the first task were: the presence of correctly performed preprocessing of the original information (20 points), the presence of the calculated values of classification quality metrics (balanced accuracy not <75% on the test dataset) (25 points), the presence of a ready-made prototype for automatic recognition of bigeminy on an ECG in the form of a software solution (50 points), correctly designed program script with comments (5 points).

The evaluation criteria of the second task were: the presence of a statistically competently well-founded assessment of the heterogeneity of the results of the drug effect in the selected studies (10 points), the presence of correctly well-founded choice of the model with fixed or random effects, all corresponding statistical tests were conducted (10 points), the presence of a correct choice of statistical approach to the meta-analysis performance depending on the criteria of inclusion/exclusion of the studies and their number with justification for such a conclusion (10 points), correct justification for the criteria of inclusion/exclusion (5 points), the conduction of the analysis the stability of the obtained generalized evaluation of the magnitude of the effect (5 points), the presence of correctly and statistically competently conducted analysis of the completeness of the studies included in the meta-analysis (10 points), the presence of graphical support of meta-analysis results (10 points), the presence of correctly designed meta-analysis script with comments and report on the meta-analysis (20 points), the presence of a well-written article on meta-analysis (20 points).

Each expert assigned points to each participating team in accordance with the evaluation criteria, then the points assigned by all the experts were summed up, and based on the ratings received, the teams were ranked. It should be noted that to assess the consistency of expert opinions, the Kendall concordance coefficient was used, the significance of which was checked on the basis of the Friedman criterion at the level of $p<0,05$.

One of the advantages of the hackathon Cardio data hack UFA 2022 was the absence of limitations in the application of the development environment, which is quite rare for Russian events. As prizes for the first task, it was planned to give a Holter for the prize-winner's medical organization, an annual subscription to the Holter software, Yandex station, souvenirs and merch events. For the second task, the best meta-analysis was published in the journal "Russian Journal of Cardiology. Education".

Finally, the hackathon attracted 179 registered participants who formed 42 teams, but further only 37 of them confirmed their participation and formed 8 teams. 7 teams gave the final solution of the tasks, and 5 of them presented their results with 3 of them giving solutions for both cases.

The jury of the hackathon consisted of experts from Saint-Petersburg (professor Villevalde S. V.),

Samara (professor Duplyakov D. V.), Kemerovo (Gribov A.) and Ufa (professor Zagidullin N. Sh. and associate professor, c.t.s., Lakman I. A.).

The three prize — winners were the following teams: 1st place — team Delta (Saint-Petersburg, Moscow, Astrakhan, Tomsk), 2nd place — team No. 3 (Saint-Petersburg, Ulyanovsk, Kemerovo, Moscow), 3rd place — team Samara cardiology (Samara).

When solving the first task, all 5 teams conducted high-quality data preprocessing, exactly, they conducted an analysis of time series, which in fact are the results of the recorded ECG. To solve the task of bigeminy classification, 4 teams of these 5 used artificial neural networks, one team used machine learning algorithms (random forest, boosting). As a metric to assess the quality of classification, all teams chose the area under the ROC curve (AUC). In result, the AUC of all teams when recognizing bigeminy was not less than 60%.

When solving the second task, all 3 teams used the PRISMA methodology in conducting systematic review and meta-analysis. As an inclusion criterion, all 3 teams used for the studies a condition of comparing the results of the efficacy and safety of any oral anticoagulant at any dose (dabigatran, rivaroxaban or apixaban) compared with warfarin for patients with chronic kidney disease stage 4-5, and one of the teams additionally considered only the results of randomized clinical trials.

Finally, one team selected 6 studies, another — 4 and the third — 3, and 2 studies were considered by all the teams. All 3 teams used and analyzed the forest-plots for endpoints (stroke, infarction, death), and 2 teams also built funnel plots to estimate the sufficiency of the studies for the meta-analysis. To assess the quality of the selected studies, one team used the "traffic light" chart, and the other two teams calculated the indicators I^2 and Q to assess the heterogeneity and homogeneity of the studies. All 3 teams used R for the meta-analysis conduction; moreover, one of the teams wrote its own software.

After the hackathon conduction, on the basis of the collected data from the expert evaluation sheets, the consistency of expert opinions was checked: for the second task, the concordance coefficient of expert opinions was 0,66 ($p<0,001$), for the first task, such an analysis was not performed. This indicates the consistency of expert opinions that is a marker of their competence in the field of conducting expertise.

The choice of online hackathon conduction technology made it possible to significantly expand the geography of participants and attract specialists from various fields of knowledge necessary to solve practical tasks (cardiologists, doctors of functional diagnostics, developers of software applications and specialists in the field of data analysis and statistics). As a result, the teams turned out to be not only interdisciplinary but also interregional. For example, the team that won in the hackathon included participants from Saint-Petersburg, Moscow, Astrakhan and Tomsk, the second-place team — participants from Saint-Petersburg, Moscow, Ulyanovsk and Kemerovo. Interestingly, many hackathon organizers set the possibility of international and interregional cooperation as one of the goals of its holding. For example, in the hackathon SIIM 2021 (USA), where it was required to develop an experimental concept of a radiology training module with gamification elements, participants contacted specialists from five different countries, which allowed them to complete an operational check of the developed concept [9]. Another advantage of the hackathon, especially within the framework of major scientific events, is the opportunity to combine the efforts of both experienced participants and novices to find creative solutions to complex problems. For example, the work [10] says that the hackathon held within the framework of the International Research Congress of Nurses in Calgary (Canada) has become an excellent method of bringing together novices and experts with different experiences to develop technological solutions to healthcare system problems. We hope that the experience gained in the first cardiology hackathon in the Russian Federation will be in demand in the future and will lead to greater integration of cardiologists and IT specialists.

Relationships and Activities: none.

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Specificity of long-term management of a woman patient of reproductive age after surgical mitral valve repair against the background of infective endocarditis

Dren' E. V., Lyapina I. N., Ganyukov V. I., Ivanova A. V., Stasev A. N., Barbarash O. L., Barbarash L. S.

As a clinical case, we present the "portrait" of a woman patient with acquired mitral valve (MV) defect against the background of infective endocarditis which was diagnosed during the third trimester of pregnancy. The patient underwent mitral valve replacement surgery with biological prosthesis "KemKor" followed by two successful deliveries. In 18 years after the correction of the mitral valve defect, she developed valve prosthesis dysfunction therefore, she underwent endovascular transcatheter implantation of bioprosthesis by method "prosthesis-into-prosthesis" in the mitral position.

This clinical case is unique in terms of the reasoning the biological prosthesis choice to correct acquired MV defect in a patient of reproductive age, the long-term period of the bioprosthesis functioning and the correction of further developed valve dysfunction using the techniques of transcatheter implantation.

Keywords: heart valve bioprosthesis, mitral valve, infective endocarditis, prosthesis-into-prosthesis.

Relationships and Activities: none.

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Key messages

- This clinical case demonstrates the uniquely long period of the biological mitral valve prosthesis functioning in a woman patient of reproductive age against the background of infective endocarditis.
- The use of the techniques of transcatheter implantation by the method "prosthesis-into-prosthesis" to correct the heart valve dysfunction.

The prevalence of acquired heart defects in general population is from 2 to 5%, with regular increase in the frequency of their detection with age [1]. The mitral valve (MV) lesion which can occur as isolated or combined defect, is one of the main causes of interventions in cardiosurgery. The traditional methods of treating MV defects is valve replacement or plasty under conditions of artificial blood circulation [2].

According to the data of Russian researches, the proportion of patients with an infectious lesion of MV requiring surgical correction, increased by 2 times over the period from 2015 to 2020 [3, 4].

Infectious endocarditis (IE) in pregnant women occurs quite rare (0,006% of cases) [5], has mainly a secondary nature and subacute course, develop on the valves which are initially damaged by rheumatic process, or in congenital valve defects, and is usually detected in III trimester of pregnancy [6].

In case of the presence of a MV defect requiring surgical correction in women of reproductive age, the implantation of biological prostheses (BP) of heart valves with low thrombogenicity is the most preferable due to the absence of the need for lifelong anticoagulant therapy (ACT). This allows not to increase the risk of uterine bleedings during pregnancy and childbirth, and also to carry a healthy baby [7]. However, low durability of BP xenogenic tissue further leads to severe valve dysfunction. Xenogenic tissue of the prosthesis undergoes calcification which is accompanied by infiltration of recipient cells with subsequent repopulation and remodeling of valve structures [8, 9].

Currently, the search of the causes of BP dysfunction continues. This is important from the view of the modification of the BP dysfunction risk factors, that will allow to prolong the time of the prosthesis functioning. There are several theories of the dysfunction formation — natural aging (wearing) of BP, prosthesis-related dysfunctions (fatigue strength, bioinertness, resistance to mineralization), recipient-associated factors (modified/unmodified), prosthetic endocarditis. But recently the role of the traditional for atherosclerosis risk factors of BP dysfunction — dyslipidemia, obesity — has been actively discussed. It is known that adipose tissue is a source of pro-inflammatory mediators (interleukin-16, tumor necrosis factor-alpha), and in this regard, obesity can contribute to the limitation of the valve service life too [10].

In repeated surgical interventions for the correction of prosthesis dysfunction, the perioperative risks are much higher than in initial valve reconstruction. Therefore, the use of minimally invasive approaches for the correction of prosthesis dysfunction is actively discussed. Endovascular MV replacement is an alternative method of treatment in patients with high surgical risk including patients who have already undergone MV prosthetics under conditions of artificial blood circulation [11].

The present clinical case demonstrates a long period of BP life in a young woman patient of reproductive age as well as the use of transcatheter technologies to correct the dysfunction of the prosthesis that has occurred.

Description of clinical case

A woman patient L. consulted a cardiologist for the first time in 1998 at the age of 21 years, being on 7th month of pregnancy, after a respiratory viral infection. In that period for the first time the patient developed the symptoms of heart failure (HF) (complaints of shortness of breath during physical activity (PA) (NYHA III), increased fatigue). The patient had not had any cardiovascular diseases before. Of concomitant diseases she had autoimmune thyroiditis (compensated) and mild chronic iron deficiency anemia.

IE with MV lesion was diagnosed — the rupture of the anterior mitral leaflet with formation of severe regurgitation (degree IV) and the presence of mobile vegetation on the posterior leaflet. The patient was followed up by a cardiologist, cardiosurgeon and gynecologist during the entire pregnancy; in 39th week of pregnancy she delivered a healthy baby by caesarean section, and further she was actively treated for HF with suppression of septic process in cardiosurgical department. After discharge from the hospital, the patient continued to be monitored by a cardiosurgeon with dynamic echocardiographic (EchoCG) examination. In 2000, 2 years after delivery, the patent underwent MV replacement surgery with BP "KemKor-30" (epoxytreated). The choice of the valve prosthesis was agreed with the patient and was caused by her desire to have children in the future. After the operation, the symptoms of HF regressed and PA tolerance (PAT) restored at a high level. It should be noted that at the time of surgical intervention performance, the patient`s weight was 46 kg with the height of 168 cm (body mass index (BMI) =16,3 kg/m^2).

In 6 months after surgical intervention, against the background of good functioning of the prosthesis, the absence of cardiac rhythm disturbances and HF symptoms as well as other indications for the use of ACT, indirect anticoagulant phenylin was cancelled.

In 2001 and 2002, the patient had unplanned pregnancies despite she used barrier methods of contraception. The pregnancies were terminated by medical abortion. In 2002 (2 years after the operation), the patient had her 4th pregnancy. At that time

Table 1

Parameters of transthoracic EchoCG in the dynamics from 2013 to 2022

Parameters according to EchoCG data	06.2013	07.2014	09.2015	12.2016	2017	2018	05.2019	09.2019	03.2020	03.2020 after surgery	03.2020 before discharge	10.2021	08.2022	11.2022
Trans-prosthetic regur-gitation (degree)	II	II	II	II	II	I-II	II-III	III-IV	III (according to TO EchoCG III-IV)	0-I	I	0-I	I	I
OA LV (cm^2)	2,3	3	–	2,7	2,5	2,3	2,6	2,7	1,8	1,6	1,75	1,65	1,7	1,5
Vmean (cm/sec)	114	120	128	131	136	146	134	165	124	108	152	122	176	163
Vmax (cm/sec)	165	180	–	210	–	229	192	–	244	161	194	207	222	214
Pmax (mm Hg)	11	13	–	18	–	21	15	–	24	10,4	15	17	20	18
Pmean (mm Hg)	6	6,2	7	8	8	9	8	12	8	5,2	10	7	13	11
LV EF (%)	70	72	72	78	75	72	74	79	85	64	66	69	71	67
LA (cm)	3,6	3,6	3,8	3,6	3,9	3,7	3,8	4,3	4,5	–	4	4,2	4,1	4,1
LV EDV (ml)	108	88	97	135	108	113	102	130	124	88	88	124	102	66
LV ESV (ml)	32	25	27	30	27	35	27	27	18	32	30	38	30	22
LV SV (ml)	76	63	70	105	81	81	75	103	106	56	58	86	72	44
RVOT prox. (cm)	2,2	2,4	2	2,2	2,1	1,9	1,6	2,2	2	–	–	1,5	2,5	2,9
RA (4AC) cm×cm	4,2×4,2	3,6×4,1	4,2×4,9	4,1×4,5	4,4×4,5	3,7×4,4	4,2×4,3	4,1×4,3	3,9×5	–	4,3×4,6	4,7×4,8	4,2×5,0	4,3×5,3
PAPsyst (mm Hg)		25	28	22	30	28	28	55	60	20	45	34	38	41
PAP mean (mm Hg)	12	15	–	–	–	–	–	–	–	–	–	23	26	26
Degree of regurgi-tation on TV	–	–	–	–	–	I	–	II-III	I	0-I	–	I	I	I

Abbreviations: RVOT prox. — proximal size of the right ventricular outflow tract, PAPsyst/mean — systolic/mean pulmonary artery pressure, EDV — end-diastolic volume, ESV — end-systolic volume, LV — left ventricle, LA — left atrium, MV — mitral valve, RA — right atrium size, TV — tricuspid valve, SV — stroke volume, TO EcoCG — transoesophageal echocardiography, EF — ejection fraction, EchoCG — echocardiography, OA — orifice area, Vmean — mean mitral valve flow velocity, Vmax — maximum mitral valve flow velocity, Pmax — maximum transmitral gradient, Pmean — mean transmitral gradient.

the examination results showed no contraindications for pregnancy. During the entire pregnancy, the patient was monitored by a team included cardiosurgeons, cardiologists and obstetricians-gynecologists. In 2003 she delivered a healthy baby by caesarean section.

After delivery the patient underwent annual control examination in particular to exclude the disorder of BP function. The patient`s state remained stable, PAT was high, shortness of breath and heartbeat in PA did not worry her.

In 2010, 10 years after MV replacement, transthoracic EchoCG revealed moderate degenerative changes in the form of thickening of prosthetic valve leaflets. This is natural and expected process for BP heart valves. In dynamic examination of the patient, the EchoCG parameters met to the criteria of the normal function of the prosthetic valve, however, a moderate decrease in the effective orifice area, the increased mean diastolic gradient and blood flow velocity on the BP were observed (Table 1).

At 34 years of age (2011), the patient became pregnant for the fifth time, and despite informing her about the risks of prosthetic complications, taking into account >10 years functioning of the prosthesis, the patient wished to carry the pregnancy. During the entire pregnancy she was under observation, and neither cardiac rhythm disturbances or HF

symptoms were noted. The patient`s coagulogram parameters were within normal values, and there was no need to prescribe her an additional ACT.

During pregnancy, there was noted the increase in sizes and volumes of the left cardiac chambers due to an increased volume of circulating blood and increased pre-loading. On the 8th week of pregnancy, as a result of the mechanism described above, the central regurgitation on MV BP occurred. By the time of the delivery transprosthetic regurgitation increased by 2 times. There were no significant changes in the indicators of blood flow velocity and diastolic gradient on the prosthetic valve during pregnancy, that reflected a good functional condition of the prosthesis (Table 1). Thus, the morphological and functional parameters of cardiac remodeling underwent physiological changes throughout pregnancy.

During the pregnancy the patient gained 7 kg in weight. The pregnancy proceeded against the background of mild anemia of a pregnant woman, with the courses of taking iron medications. A term healthy boy was born by caesarean delivery. According to the data of control EchoCG performed before the discharge, intracardiac hemodynamics has returned to normal with a decrease in the regurgitation on MV BP up to I degree.

The dynamic EchoCG examination in the period from 2011 to 2013 showed transprosthetic regurgitation of II degree, and the areas of thickening of the prosthetic valve leaflets (Table 1). PAT remained sufficient. Since 2014 a moderate MV BP dysfunction has been revealed; the regurgitation on the prosthesis was close to II degree (directed obliquely), and the dynamics showed the growth of pressure gradient on MV. In May 2019 a planned EchoCG detected a moderate dysfunction of BP; transprosthetic regurgitation on MV has increased up to moderate-severe (II-III degrees) (Table 1).

It is important to note that since 2013 the patient has begun to gain in weight, and by 2019 her weight was 78 kg (the weight gain was 32 kg from the time of the surgical intervention), BMI was 27,6 kg/m^2.

Starting from September 2019, the patient began to complain of palpitations both at rest and PA, interruptions in the work of the heart, the appearance of inspiratory shortness of breath when walking with acceleration, climbing to the 2nd floor. EchoCG showed an increase in orifice area of MV, non-uniform leaflets with the areas of thickenings on BP, severe transprosthetic regurgitation — up to III-IV degree, the increase in the velocity of transmitral flow and in pulmonary artery pressure compared to May 2019г (Table 1). The physical examination showed — heart rate 90 beats/min, systolic-diastolic murmur at the point of MV auscultation, BMI =28,9 kg/m^2. According to electrocardiography — sinus rhythm, single ventricular extrasystole; according to multispiral computed tomography with angiopulmonography — no data for pulmonary embolism. Laboratory examination revealed mild iron deficiency anemia (hemoglobin 111 g/l; hematocrit 34,6%; red blood cells 4,27*10^{12}, ferritin 80 μg/l, iron level 5,8 μmol/l), hyperbilirubinemia 27,1 μmol/l (direct bilirubin 12,2 μmol/l; indirect bilirubin 14,9 μmol/l).

Taking into account increasing BP dysfunction and HF progression, collegially with a cardiosurgeon and roentgenendovascular surgeon, a decision on the need to correct the dysfunction of the prosthesis was made. In a high surgical risk, endovascular MV prosthesis is a method of treatment alternative to "open surgery" and is suitable in particular for patients who have already undergone MV prosthetics under conditions of artificial circulation (techniques "prosthesis-into-prosthesis"). Open re-replacement of implanted biological MV, especially in individuals with severe concomitant pathology, is associated with high lethality [11]. To assess morphometry of BP and interatrial septum (IAS) and to detect the additional factors (calcinosis etc) with the aim to consider the possibility of endovascular MV reimplantation, in November 2019 the patient underwent multispiral computed tomography of heart with contrast and electrocardiographic synchronization, which detected calcifications at the periphery of the MV BP [11, 12]. Taking into account a high surgical risk of repeated open intervention — EuroScore II — 5,6% (at the time of examination, the age of the patient was 43 years, the patient had pulmonary hypertension (systolic pulmonary artery pressure was 55 mm Hg), functional class III according to NYHA, cardiosurgical intervention in the anamnesis), due to patient`s refusal from a repeated intervention on an open heart under conditions of artificial blood circulation and from lifelong ACT, at that moment a decision was made to perform a planned transcatheter endovascular MV prosthetics (prosthesis-into-prosthesis) with application of endovascular constructions used for the aortic valve prosthesis.

As a medical treatment, it was recommended to take: acetylsalicylic acid 75 mg, pantoprazole 20 mg 1 time/day, torasemide 5 mg in the morning, metoprolol succinate 12.5 mg in the morning, ivabradine 5 mg 2 times/day, spironolactone 25 mg in the lunch time, oral iron drugs.

In March 2020 the patient was admitted to the hospital for a planned surgical treatment.

In March 12, 2020, under conditions of roentgen operating room, endovascular implantation of transcatheter valve Edwards SAPIEN XT 26 mm was performed in the mitral position (prosthesis-into-prosthesis) using right transfemoral approach. The

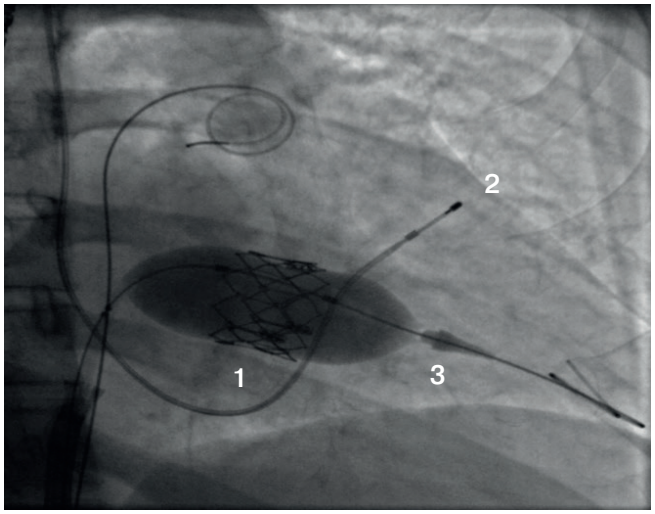

Figure 1. Transcatheter endovascular implantation "Edwards SAPIEN XT 26 mm" in mitral position (prosthesis-into-prosthesis) 2020. Full balloon inflating of the implanted prosthesis in the MV position.
Note: 1 — the straightened frame of the prosthesis, 2 — the electrode of the pacemaker in the right ventricle; 3 — the delivery system.

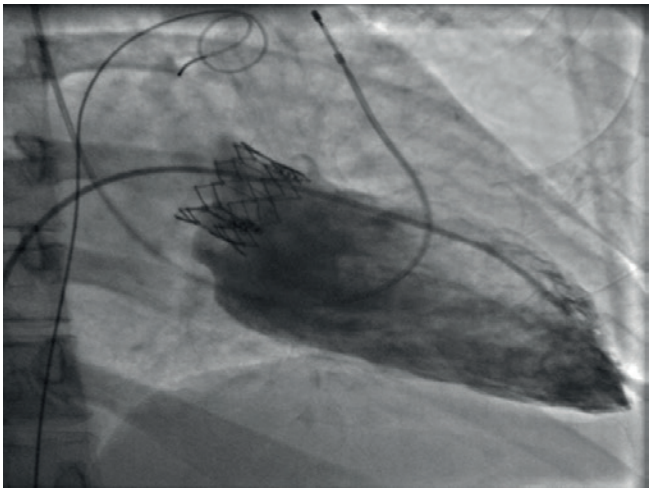

Figure 2. Competent work of the implanted transcatheter valve Edwards SAPIEN XT 26 mm in the MV position using the technique prosthesis-into-prosthesis.

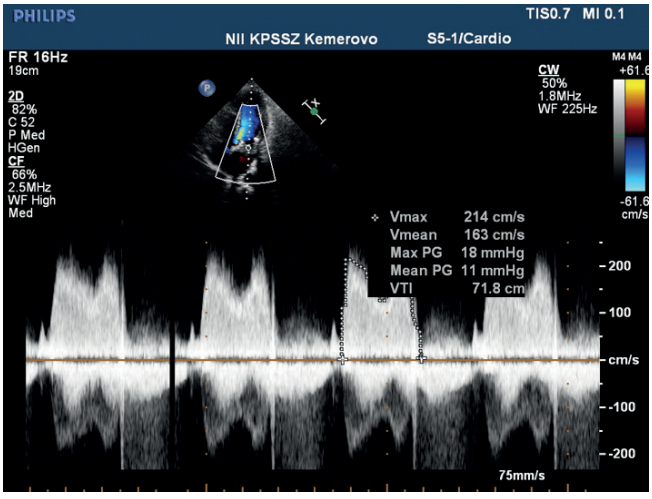

Figure 3. Velocity indicators and pressure gradient on MV (November 2022).

course of the operation: using right jugular approach, the electrode of the temporary pacemaker was installed into the right ventricle. Under conditions of artificial lung ventilation with the use of intravenous anesthesia, puncture access was provided (common femoral vein). Transseptal puncture was performed, through the left atrium and prosthesis in the mitral position the first super-rigid conductor was installed, in the left atrium the second conductor was installed, a balloon catheter with a diameter of 10 mm, then 16 mm was installed along the conductor, and IAS pre-dilation was performed. The attempts to pass with the conductor through IAS and BP in the mitral position were technically difficult (due to rigidity of IAS), the introducer was installed into the common femoral vein 18F, under conditions of ultra-frequent stimulation (180 per minute), the Edwards SAPIEN XT balloon-expandable transcatheter valve with a size of 26 mm was positioned into the position of the BP in the mitral position with a volume of liquid in a high-pressure syringe of 24 ml (Figures 1, 2).

Postoperative EchoCG control from 12.03.2020 — there is a correct position of the valve, no atrioventricular conduction disorders and compromise of paravalvular structures; peak and mean gradient, the degree of regurgitation and blood flow velocity of MV diminished (Table 1). The data of multispiral computed tomography from March, 17, 20202, before the discharge: the state after transcatheter MV implantation (prosthesis-into-prosthesis), the prosthesis is installed in MV position, diameter up to 24 mm, height ~19,5 mm. There is a IAS defect, up to 4,5 mm in width.

The patient was discharged in a stable condition, she had no any complaints; the medications recommended: torasemide 10 mg, warfarin 2,5 tablets (6,25 mg) under the control of an international normalized ratio (target values 2,5-3,5) for 3 months, spironolactone 25 mg in the morning and lunch time, ivabradine 5 mg 2 times/day. The patient was regularly observed in the cardiology dispensary polyclinic.

29 months after the surgical intervention (August, 2022), she once again consulted the doctors of the cardiology center, complaining of reduced PAT, the occurrence of heaviness in the precardial region and shortness of breath in PA (NYHA III).

The additional examination showed the hemoglobin level 92 g/l, ferritin — 78 μg/l, iron level in blood — 7,8 μmol/l. The EchoCG data — the prosthesis function is satisfactory, transprosthetic regurgitation is of 0-I degree, Vmax — 214 cm/sec, Vmean — 163 cm/sec, Pmax — 18 mm Hg, Pmean — 11 mm Hg on MV, stroke volume of the left ventricle (LV) — 44 ml, LV ejection fraction — 67%, LV end-diastolic volume — 66 ml, LV end-systolic volume — 22 ml, discharge into the right atrium through the IAS defect is 0,15 cm (Figure 3). Transoesophageal EchoCG from November, 01, 2022 — no data for degenerative changes of the prosthesis. Thus, the EchoCG data allowed to assume the development of prosthesis-patient mismatch in the patient, without any structural changes on the bioprosthesis.

Bioimpedance analysis was performed: weight — 79 kg, height 168 cm, the content of fat in the body is higher than in norm — 36% (N<32%), percentage of water content in the body 41% — below the norm (N 45-60%), muscle mass 43,9% — the norm, physical development 2 — indicates obesity; bone mass 2,3 kg — the norm, the level of visceral fat in the body 8 — the norm.

Since December 2021, the patient started taking combined oral contraceptives according to the recommendation of a gynecologist due to abundant *mensis*, which was accompanied by a decrease in hemoglobin to 87 g/l. The patient herself associated the worsening of her condition with taking hormonal medications since when they were canceled, she noted a positive tendency (she herself canceled the use of combined oral contraceptives in April 2022).

After the consilium, taking into account the satisfactory function of the prosthesis, the reduction of the patient's weight, compensation for existing anemia and subsequent dynamic monitoring were recommended. Upon discharge from the hospital, hemoglobin has increased in dynamics and was maintained at the level of 115 g/l against the background of taking iron drugs (iron (III) hydroxide polymaltosate 100 mg 2 times/day) for 10 days.

The patient was discharged from the hospital with the clinical diagnosis:

Acquired valve defect. Replacement of MV by BP "KemKor" from 2000. MV prosthetic dysfunction, insufficiency (severe transprosthetic regurgitation, degree II-III). Transcatheter endovascular implantation "Edwards SAPIEN XT 26 mm" in the mitral position (prosthesis-into-prosthesis) from 2020. Defect of IAS. Tricuspid valve insufficiency, degree I. Ventricular extrasystole, gradation III according to Lown. Chronic HF, stage IIA. Pulmonary hypertension. Functional class II.

Concomitant diseases: autoimmune thyroiditis, euthyroidism. Chronic gastritis, remission. Chronic iron deficiency anemia of mild severity.

Recommendations for taking medications are given: acetylsalicylic acid 75 mg in the morning, bisoprolol 5 mg in the morning, ramipril 2,5 mg in the evening, spironolactone 25 mg in the morning, torasemide 2,5 mg in the morning. It is recommended to compensate for iron deficiency anemia by course taking of iron drugs (iron (III) hydroxide polymaltosate 100 mg 2 times/day) for 2-3 months, monitoring of total blood count, iron and ferritin levels in dynamics after 1 month, gynecologist consultation, weight loss, annual transthoracic echocardiography, observation by a cardiologist in a place of residence.

Discussion

There are the data indicating that the risk of BP dysfunctions correlates with age and the dysfunctions more frequently occur in young patients. The study performed by Astapov D.A., et al. [13] established that the implantation of BP in younger age is associated with more likelihood of an adverse outcome in dynamic monitoring. It seems, the reproductive age of women is one of a small number of exclusions used as an argument for the implantation of BP in young individuals. The period of normal functioning of heart valve BP is within the limits of 8-15 years but there are the observations of a longer period of BP service life without the signs of its dysfunction [14-16].

The publication of Kondyukova N.V., et al. from 2015 [17] described a case of MV re-replacement with the use of BP to a young man, where at 33 years of age the patient developed hemodynamically significant mitral regurgitation (degree IV) against the background of IE, and he underwent xenoaortic BP "KemKor-32" implantation. At that moment, the choice of the prosthesis was caused by the presence of sinus rhythm, the possibility of refusal from lifelong anticoagulant treatment, and the presumed resistance of the prosthesis to calcium degeneration. However, after the surgical intervention, due to satisfactory well-being and low compliance, according to the patient, he did not visit a cardiosurgical clinic to control the function of BP during 11 years. 11 years later, due to an increase in HF symptoms, the patient came to the clinic where the BP dysfunction was revealed and then he underwent the re-replacement of MV with implantation of BP "Uniline-28" with the use of implantation technique "valve-in-valve". In this case there were no prosthetic complications due to the chosen type of implanted valve because BP does not require lifelong anticoagulant treatment and monitoring the effectiveness of medi-

cal hypocoagulation. A personalized approach is needed to choose an implanting prosthesis, taking into account a patient compliance too, because this affects the long-term prognosis, patient life quality and the reduction of the risk of prosthetic complications.

In the case of our patient, when in 2019 the BP dysfunction was detected, to determine the further tactics, the scale EuroScore II was calculated; taking into account the presence of pulmonary hypertension (systolic pulmonary artery pressure — 55 mm Hg), cardiosurgical intervention in the anamnesis, NYHA III functional class and the patient`s age of 43 at the time of the examination, the risk according to EuroScore II was 5,6%. And also due to patient`s refusal from "open" surgery and lifelong taking warfarin in mechanical valve implantation, the decision was made to perform the planned transcatheter endovascular MV replacement (prosthesis-into-prosthesis) with application of endovascular constructions used for aortic valve replacement.

Low-traumatic technique of re-replacement has a number of advantages over traditional repeated surgical intervention due to the preservation of the fibrous rings. In favor of the preferred use of BP was a long period of the previous valve functioning (19 years). While choosing a type of prosthesis, it is also necessary to consider the opinion of a potential recipient upon condition of his full awareness about possible risks of the use of this or that valvular prosthesis.

As for the frequency of the repeated operations on prosthetic valves according to the study of Chiang YP, et al. [18], the patients with BP more frequently underwent re-implantation due to prosthetic valve dysfunction compared to mechanical valves. It was showed that 15-year total frequency of repeated operations in the group of patients with BP significantly prevails over the number of re-operations in the group of patients with mechanical prostheses (12,1% vs 6,9%, respectively). But for the patients with BP, the lower likelihood of the development of bleedings (6,6%) is typical compared to the patients with mechanical prostheses (13%) [19].

Currently, the influence of dyslipidemia on the rate of the progression of calcification and degenerative changes in BP valves is investigated [20-23]. For example, in the study of Farivar RS, et al. [20], the patients who developed calcium-associated dysfunction of xenovalves, had an increased level of cholesterol in blood. The study of Mahjoub H, et al. [22] established an increase of the ratio ApoB/ApoA-1 which reflects the qualitative composition of pro-antiatherogenic lipoprotein particles, as an independent factor of BP degenerative changes. Thus, there are the complicated, mutually-mediated interactions between prosthesis and recipient, which affect the BP function. A change in patient`s body physique may affect the prosthetic structural changes and contribute to the progression of its dysfunction.

In case of young reproductive age of a woman patient with acquired MV defect requiring surgical correction, preference is given to BP of the heart valves due to their low thrombogenicity and the absence of the need for long ACT therapy. In turn, the risks associated with the need for ACT therapy are reflected by hemorrhagic complications and possible embryopathy during pregnancy [24]. In this regard, despite the limited service life and the need for repeated operations in future, many specialists are inclined to implantation of valve BP to women of reproductive age [24]. The choice of BP for our patient allowed her to carry and deliver two healthy babies. In addition, the unique period of successful functioning of the BP — 19 years draws attention.

The causes of prosthetic dysfunction can be anatomical and functional; currently, a role of obesity and dyslipidemia in the dysfunction is actively discussed. The study of Kim S, et al. showed that an increase in BMI by one unit is accompanied by an increase in the risk of the chronic HF development in males and females by 5% and 7%, respectively [25]. Obesity itself and resulting increase of body area can cause prosthesis-patient mismatch that is associated with a decrease in survival after MV replacement and with pulmonary hypertension. It is also known that adipose tissue produces adipokines having pro-inflammatory (leptin, interleukins and tumor necrosis factor-α) effects, and with an increase in BMI, adipose tissue starts to become a metabolically dysfunctional phenotype. In this condition adipocytes are forced to produce higher concentrations of pro-inflammatory adipokines which contribute to inflammation and damage to open tissues [26]. Metabolic disorders lead to the processes such as chronic non-specific inflammation and lipid peroxidation which in turn cause calcium degeneration of BP [9].

In our patient, excess body weight occurred before the prosthesis–into-prosthesis implantation, with a dynamic increase in weight almost 2 times since the initial correction of the defect. Additional development of prosthetic calcification and twofold increase of patient`s body weight collectively created the conditions resulted in BP structural changes and appearance of prosthesis-patient mismatch (severe prosthesis-patient mismatch: prosthetic orifice area 1,5/body surface area (1,9) =0,78).

Long existing iron deficiency anemia in the anamnesis also contributed to lower PAT and hemodynamic disorders. Anemia is one more of

the most common causes complicating the course of chronic HF and leading to its aggravation. There are the data indicating that anemia is an independent factor worsening life quality, increasing the risk of repeated hospitalization and mortality in chronic HF [27-29]. It is known that compensation of tissue hypoxia which is developed as a result of anemia occurs with the help of hemodynamic mechanisms. Low hematocrit causes a decrease in blood viscosity and in post-loading, anemia is accompanied by an increase in venous return (pre-loading) that leads to volume overload of heart, and enhanced sympathetic tone results in myocardial contractility and heart rate increase. Due to increased myocardial contractility and heart rate, work overload occurs. These mechanisms lead to myocardial hypertrophy, increasing dilation of heart chambers and development of relative insufficiency of heart valves [30]. Accordingly, the correction of an additional factor such as anemia in this patient is a key moment to compensate the symptoms of chronic HF and to improve life quality.

Currently, there are the alternative to open surgery approaches to correct BP dysfunction [12, 31]. Transcatheter endovascular prosthesis is used for patients with high surgical risk and BP dysfunction, who have already undergone MV replacement under condition of artificial circulation. In this method of surgical correction, transcatheter valves designed for aortic position and specially designed valves are used [11, 12]. The existing register observations in most cases are based on off-label application of SAPIEN valves. The use of a series of SAPIEN constructions initially designed for aortic valves demonstrate good results when they are installed by a method prosthesis-into-prosthesis in interventions on degenerative changed BP in the mitral position [31].

A key aspect in the success of transcatheter prosthesis-into-prosthesis method is a complex assessment of morphometric features of valve, patient`s concomitant pathology, perioperative risk in the use of open or endovascular intervention, and certainly, a detailed planned course of the transcatheter procedure. Thus, transcatheter technologies can become a serious alternative to open surgery for repeated interventions in dysfunction of previously installed prosthetic valves, including those in the mitral position.

The uniqueness of the presented clinical case lies in the long period of MV BP functioning in a young woman, that improved the life quality of the patient and allowed her to successfully carry and deliver two babies. One more childbirth, in turn, contributed progression of transprosthetic regurgitation that required endovascular valve re-implantation "prosthesis-into-prosthesis" 20 years after the initial valve replacement. The persistence of complaints of shortness of breath in PA, insignificant regurgitation after the intervention with prosthesis-into-prosthesis implantation is not a criterion for repeated interventions, however, it requires changes in lifestyle, correction of concomitant anemia and a decrease in the patient's body weight because of the development of the "prosthesis-patient" mismatch.

Conclusion

Thus, the presented clinical case is unique and relevant from the point of view of investigating the course of the disease in women patients of reproductive age who underwent surgical correction of acquired MV defect, whose life quality is improved due to modern diagnostics, correction of therapy and surgical intervention. The use of heart valve BP in this cohort of patients is caused mainly by the absence of the need for ACT therapy that improves the prognosis of childbearing and childbirth. BP installed to the woman patient at the age of 23, for the correction of MV defect of infectious genesis, worked during 19 years, and only 19 years after initial intervention, significant dysfunction of prosthesis occurred, requiring valve re-implantation "prosthesis-into-prosthesis". The long life period of the prosthesis allowed the patient during this time to endure two deliveries against the background of a satisfactory condition. The persistence of insignificant regurgitation after endovascular intervention with implantation "prosthesis-into-prosthesis" is cause by "prosthesis-patient" mismatch against the background of twofold dynamic increasing in patient`s body weight from the time of initial BP implantation and the presence of iron deficiency anemia that requires changes in the life style, decrease in the patient`s body weight and thorough dynamic observation with correction of anemia.

Relationships and Activities: none.

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LITERATURE REVIEWS
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Comparing the efficacy and safety of direct oral anticoagulants with vitamin K antagonist in patients with atrial fibrillation and chronic kidney disease stages IV and V: systematic review and meta-analysis

Skorodumova E. G.[1], Suvorov A. Yu.[2], Enginoev S. T.[3,4], Kercheva M. A.[5], Grebenyuk M. A.[2]

Aim. This study aims to compare efficacy and safety of direct oral anticoagulants (DOAC) with vitamin K antagonist (VKA) in patients with atrial fibrillation (AF) and chronic kidney disease (CKD) stages IV and V.

Material and methods. We systematically searched the PubMed, Google Scholar, Web of Science databases from 1990 to 2022 and included all published studies that compared DOACs with VKA in patients with atrial fibrillation and chronic kidney disease stages IV and V. To search the articles, we used the PICO strategy: Patient, Intervention, Comparison, Outcome of Interest. Data extraction was undertaken by five independent researches, and then a meta-analysis was performed.

Results. Out of all, 6 studies were included in the meta-analysis: 3 randomized controlled trials (n=353) and 3 retrospective analyses (n=37470). The efficacy of DOACs was comparable with VKA. In terms of safety, DOACs and VKA also showed no statistical differences: hemorrhagic stroke, major/minor/gastrointestinal bleeding, general mortality.

Conclusion. In terms of efficacy and safety, the indicators of DOACs and VKA were generally comparable.

Keywords: vitamin K antagonist, direct oral anticoagulants, rivaroxaban, terminal renal failure, atrial fibrillation, chronic kidney disease.

Relationships and Activities: none.

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Chronic kidney disease (CKD) is complicated by atrial fibrillation (AF) in every fourth patient [1]. In case of combination of these two pathologies, the risk of thromboembolic complications increases against the background of equally high risk of bleedings [2]. Decrease in glomerular filtration rate (GFR) is an independent predictor of ischemic stroke/systemic embolism and bleeding [3], whereas anticoagulant treatment of patients with AF is a foundation of the prevention of thromboembolic complications. This makes it important to search the most effective and safe anticoagulant therapy in patients with CKD stages IV-V. Before the advent of alternative anticoagulants with different renal excretion, safety and efficacy parameters, vitamin K antagonist (VKA) served as the drug of choice in patients with AF [4]. However, a number of the clinical trials such as ROCKET [5], ARISTOTLE [6], RE-LY [7],

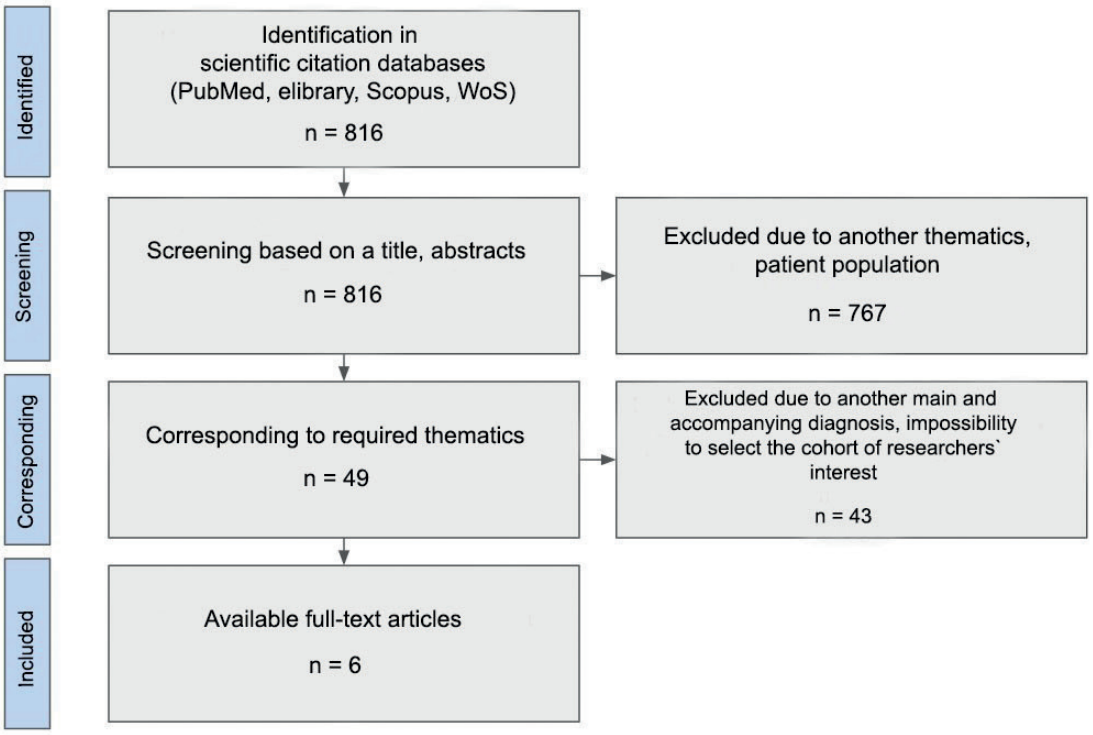

Figure 1. PRISMA-diagram of the selection.

showed the advantage or comparability of direct oral anticoagulants (DOACs) compared to VKA in patients with CKD stages I-III [3]. Meanwhile, patients with CKD stages IV-V were mainly excluded from these studies because of high risks of lethal outcome and development of complications including bleedings [8, 9]. Besides, taking of VKA is associated with calcification of vessels that additionally worsens the course of the disease, being a motivation to search an alternative therapy [10]. The modern position of experts regarding to the prescription of anticoagulants and choice of a certain drug in patients with CKD stages IV-V is that the use of DOACs in patients with CKD stage IV (creatinine clearance 15 — <30 ml/min) can be considered as to use with "caution" in reduced doses taking into account the clearance in these patients; in patients with CKD stage V (creatinine clearance <15 ml/min) as well as in patients who receive renal replacement therapy with hemodialysis, the prescription of these drugs is not approved [10] because the results of the observational studies cast doubt on the benefit of DOACs in this group of patients, while randomized controlled trials (RCT) were not carried out [11].

The paucity of the data on the use of DOACs in patients with CKD stages IV-V, on the one hand, and acceptability of their use in patients with GFR 15-30 ml/min/1,73 m^2 [9] against the background of more effective and safe use of this group of drugs in patients with CKD stages I-III, on the other hand, make the conduction of the studies on their comparison with warfarin relevant. Our meta-analysis was aimed to compare efficacy and safety of DOACs and VKA in patients with AF and CKD stages IV-V.

Material and methods

Systematic review and meta-analysis were performed in accordance with international recommendations (PRISMA)[1] (Figure 1). PICO strategy was used for the search of the studies:

- Patient — patients older than 18 years with AF and CKD stages IV-V;
- Intervention — the use of DOACs;
- Comparison — the use of VKA;
- Outcomes — the number of the endpoints: ischemic stroke, major hemorrhages, minor hemorrhages, gastrointestinal hemorrhages, total mortality.

The data sources. Literature search was conducted in the following databases: PubMed, Google Scholar, Web of Science from 1990 to 2022 for all studies where it was used terminology such as "kidney renal failure" or "terminal kidney failure", or

[1] R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/.

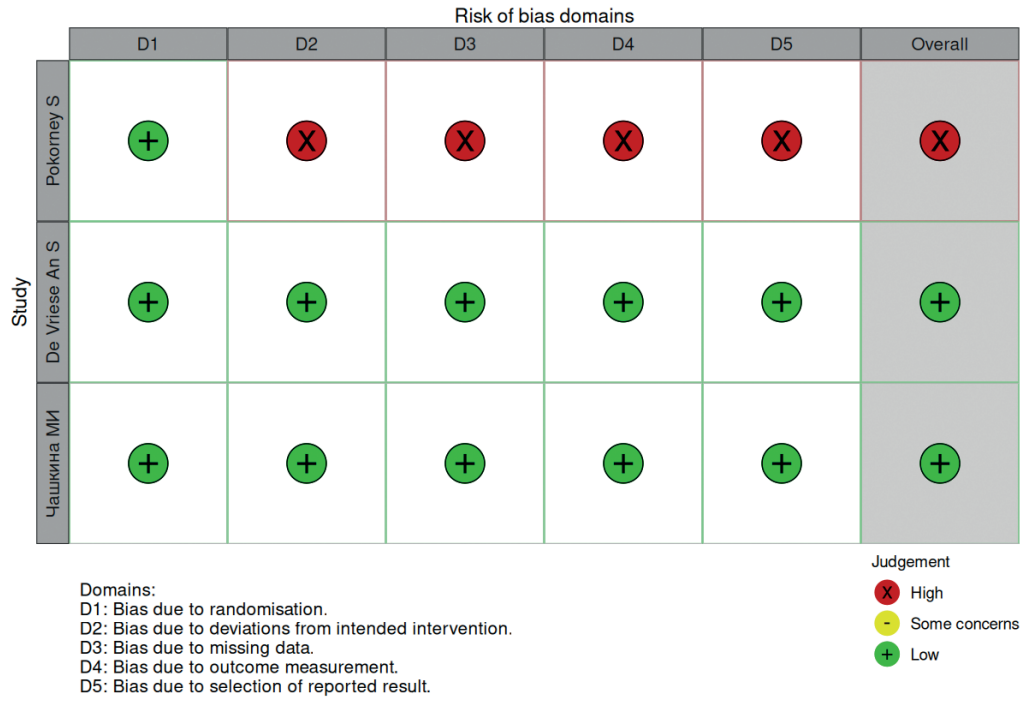

Figure 2. RCT traffic light plot.

"terminal chronic kidney disease", or "end-stage chronic kidney disease", or "Hemodialysis Patients", or "chronic kidney disease";

• and "Atrial fibrillation" (AF);

• and "NOAC" (new oral anticoagulants) or "DOAC";

• and "warfarin" or "Vitamin K antagonist" in the title or abstract.

The selection of the studies. All studies comparing DOACs and VKA in individuals with CKD IV-V stages and AF were included into our study. The Figure 1 showed the PRISMA-diagram of the selection.

The exclusion criteria:

• The studies which did not inform on clinical outcomes;

• The articles in which not the whole group had AF;

• The articles in which patients had GFR >29 ml/min/1,73 m^2.

The data extraction and quality assessment. Five reviewers independently of each other extracted the data including the details of the publications, criteria of inclusion/exclusion, demographic data of patients, sample size and results obtained. Systematic errors of publications were estimated using a funnel plot. Plot asymmetry indicated a systematic error of publication.

The data analysis. The present meta-analysis included 6 studies which documented efficacy and safety of DOACs in patients with AF and CKD stages IV-V. Three of them were RCTs, and the other 3 — large non-randomized retrospective cohort trials (non-RRCTs). All the studies contained a subgroup of patients who received VKA as well as a subgroup received one or several DOACs. Thus, the subgroup received VKA was chosen as reference; the subgroups received DOACs were main within the framework of this meta-analysis.

The investigated criteria of efficacy and safety included the following endpoints: total mortality for the time period of the study conduction, systemic arterial embolisms, newly emerged ischemic stroke, hemorrhagic stroke, major and minor hemorrhages, and when it was possible, gastrointestinal bleedings were selected separately.

The analytical data processing and meta-analysis were performed using R v.4.2 with connection of meta, metafor, dmetar libraries.

To estimate the different types of potential bias, traffic light plots were used separately for RCTs (RoB) and non-RRCTs (ROBINS-I).

Due to retrospective character of a half of the studies, odds ratio (OR) was used to estimate weighted effect size.

Due to significant differences in the sizes of the studies, different time period of their conduction, different types of the study designs (RCT/non-RRCT) as well as the differences in the goals stated in the research, we used the random effects model as the main model for the meta-analysis conduction.

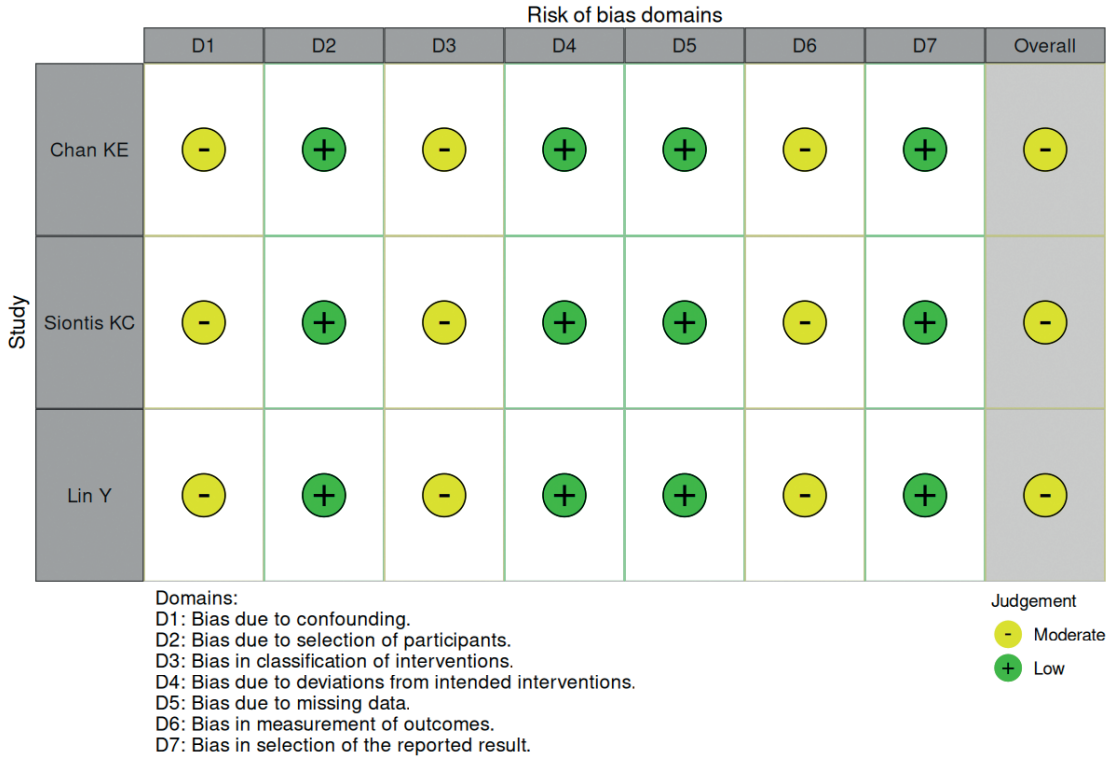

Figure 3. Non-RRCT traffic light plot.

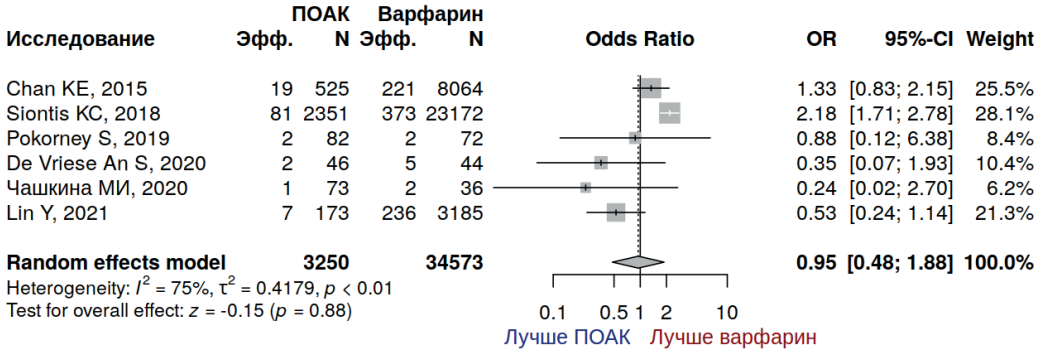

Figure 4. Forest plot for comparison of the effect regarding to the ischemic stroke prevention.
Abbreviation: ПОАК — прямые пероральные антикоагулянты (DOAC — direct oral anticoagulants).

Heterogeneity was estimated by the reverse dispersion method; to estimate dispersion of distributional effects in the random effects model (τ^2), restricted maximum-likelihood method (restricted maximum-likelihood estimator (REML)) was used. The estimation of heterogeneity was conducted by calculating Q-statistics and its significance, and I^2-Higgins and Thompson statistics.

Sensitivity analysis was carried out according to the principle *leave-one-out* with estimation of the impact of the exclusion of each study on the weighted effect and heterogeneity.

The potential publication bias was conducted visually using the funnel plots, and also when calculating the Peters test (at the same time, the results of this test are doubtful taking into account the small number of studies).

To make possible subgroups we considered the type of the study and the type of the anticoagulant used as well as their combination. Because of small number of the studies included into the meta-analysis, the results of the subgroup analysis are generally hypothesis-forming in nature; the results of the traditionally used Q-test (Omnibus test) and its significance are also

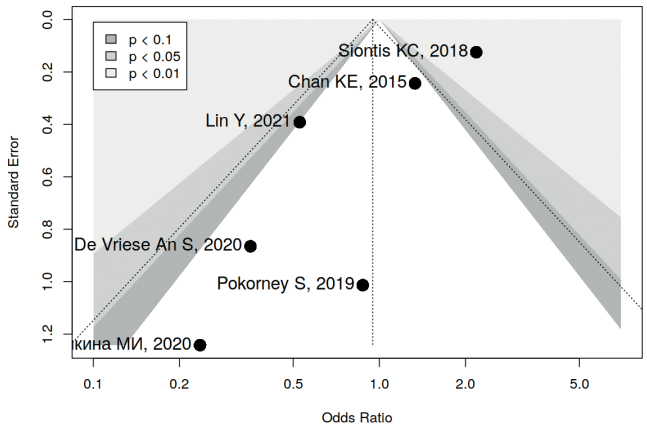

Figure 5. Funnel plot for comparison of a publication bias.

questionable, which is a limitation of this study [12, 13]. In the subgroup analysis, a common across all the studies without recalculation across the subgroups was used; such an approach is recommended for this type of analysis under condition of small number of studies in meta-analysis [13, 14].

Due to the significant above-mentioned differences in the studies as well as their small number in the meta-analysis, it was decided to refrain from conducting a network meta-analysis (this contradicts the basic postulate of transitivity of included studies according to the Cochrane recommendations[2] until the greater number of analogous studies appears).

Results

The quality assessment of the studies included into the meta-analysis

The 6 studies included into the meta-analysis contain the information on 34573 patients.

Among 3 RCTs one study was conducted in Russian Federation. The Pokorney S[3] study was stopped because of the lack of funding but its results are partly available. Other RCTs are conducted in accordance with protocols and included small size samples. Thus, the probability of bias at different stages of the conduction of these studies is assessed as quite low. Below, the RCT traffic light plot is given (Figure 2). The three included cohort studies declared the endpoint evaluation and consideration of safety

[2] Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from https://www.training.cochrane.org/handbook.

[3] Pokorney S. RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation — RENAL-AF Poster in AHA-2019 Some information about research in https://clinicaltrials.gov/ct2/show/results/NCT02942407.

Table 1

Clinical characteristics of patients

Author and link to the study	Type of study	Year of study	Number of included patients	DOAC drug	Mean age, years	Women, %	CHA_2DS_2-VASc mean point	Stroke %	Embolisms, %	HF, %	AH, %	DM, %
Chan K [15]	non-RRCT	2015	VKA — 8064 D — 281 R — 244	dabigatran, rivaroxaban	VKA — 70,6 D — 68,4 R — 66,9	VKA — 38,8 D — 26,9 R — 39,5	VKA — 2,4 D — 2,3 R — 2,2	VKA — 12,7 D — 12,5 R — 16,0	VKA — 12 D — 11,2 R — 14,6	VKA — 20,8 D — 14,6 R — 14,1	No data	VKA — 67,9 D — 70,4 R — 67,8
De Vriese A [16]	RCT	2020	VKA — 44 R — 46	rivaroxaban	VKA — 80,3 R — 79,9	VKA — 43,3 R — 23,9	VKA — 4,8 R — 4,7	VKA — 36,4 R — 32,6	No data	VKA — 20,5 R — 37,0	No data	VKA — 45,5 R — 45,5
Lin Y [8]	non-RRCT	2021	VKA — 3185 R — 173	rivaroxaban	VKA — 69 R — 75	VKA — 49 R — 45	VKA — 3,7 R — 4,0	VKA — 13 R — 19	No data	VKA — 37 R — 33	No data	VKA — 51 R — 41
Siontis K [4]	non-RRCT	2018	VKA — 23172 A — 2351	apixaban	VKA — 68,9 A — 68,1	VKA — 54,3 A — 54,1	VKA — 5,24 A — 5,27	No data	No data	VKA — 77,5 A — 79,5	VKA — 99,6 A — 99,6	VKA — 74,9 A — 75,4
Pokorney S[3]	RCT	2019	VKA — 72 A — 82	apixaban	No data	VKA — 30,5 A — 41,5	No data	No data	No data	No data	No data	No data
Chashkina M [8]	RCT	2020	VKA — 36 R — 73	rivaroxaban	VKA — 78 R — 77	VKA — 61 R — 56	VKA — 4,7 R — 4,6	VKA — 36 R — 10	VKA — 28 R — 8,2	VKA — 44 R — 56	VKA — 96 R — 98	VKA — 44 R — 37

Abbreviations: A — apixaban, VKA — vitamin K antagonist, AH — arterial hypertension, D — dabigatran, non-RRCT — non-randomized cohort retrospective trial, DOAC — direct oral anticoagulants, R — rivaroxaban, RCT — randomized controlled trial, DM — diabetes mellitus, HF — heart failure.

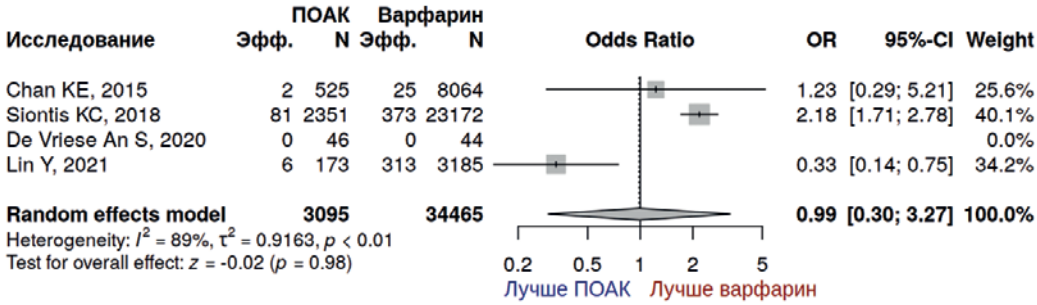

Figure 6. Forest plot for comparison of the effect regarding to systemic embolism prevention.
Abbreviation: ПОАК — прямые пероральные антикоагулянты (DOAC — direct oral anticoagulants).

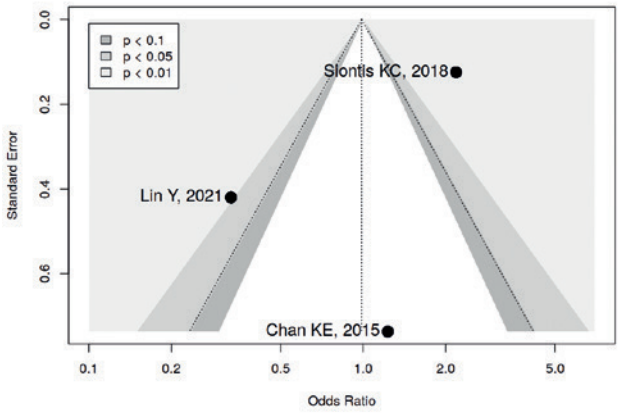

Figure 7. Funnel plot for comparison of a publication bias.

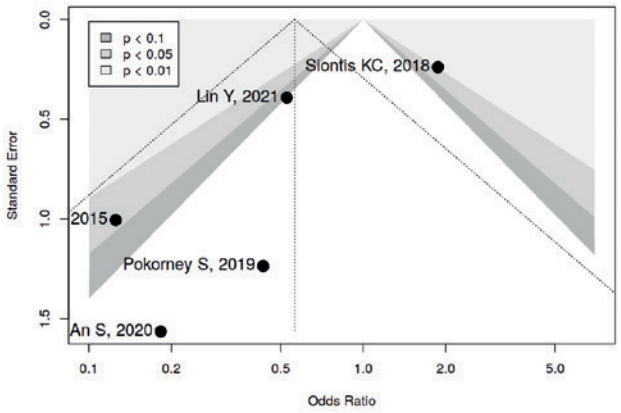

Figure 9. Funnel plot for comparison of a publication bias.

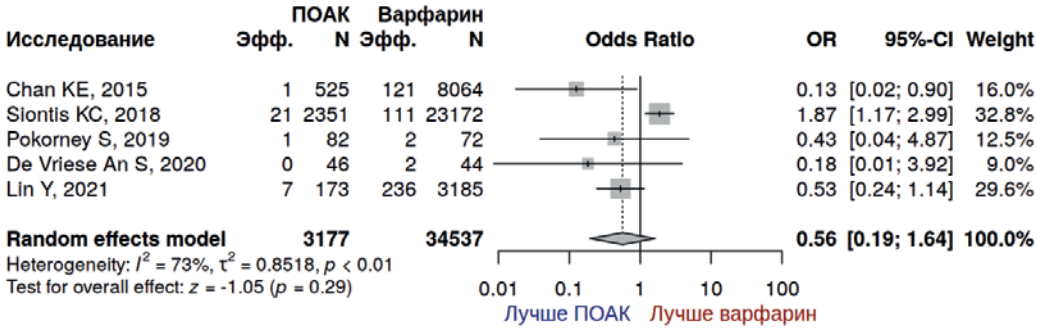

Figure 8. Forest plot for evaluation of odds of the hemorrhagic stroke development in patients.
Abbreviation: ПОАК — прямые пероральные антикоагулянты (DOAC — direct oral anticoagulants).

and efficacy criteria in different ways. The aims of these studies were also a little bit different that can potentially lead to confounding when estimating a weighted effect. In general, the authors of the meta-analysis assess all non-RRCTs as having these of those sources of bias up to moderate (Figure 3).

The clinical characteristics of patients

The clinical characteristics of patients are presented in Table 1.

The studies included 34573 patients who received VKA therapy, 281 — dabigatran, 2433 — apixaban and 536 — rivaroxaban therapy. In general, the groups were comparable in the main demographic parameters.

The quality assessment of efficacy

The main purpose of taking anticoagulants in patients with AF is the prevention of thrombotic and thromboembolic complications. Among the efficacy

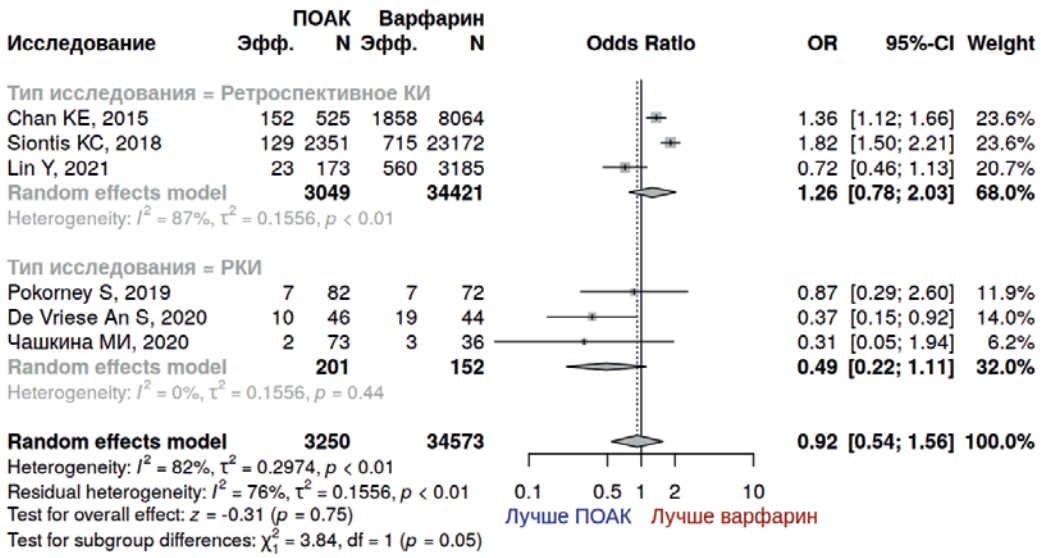

Figure 10. Forest plot for assessment of safety regarding to major hemorrhage depending on the type of the study.
Abbreviations: ПОАК — прямые пероральные антикоагулянты (DOAC — direct oral anticoagulants), РКИ — рандомизированные контролируемые исследования (RCT — randomized controlled trials).

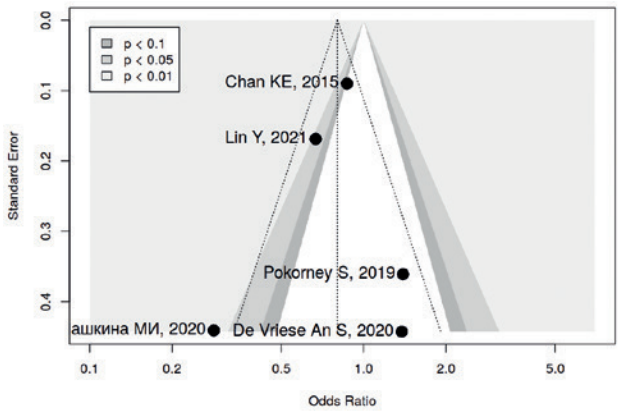

Figure 11. Funnel plot for comparison of a publication bias.

criteria newly occurred ischemic stroke and systemic arterial embolisms were evaluated.

Ischemic stroke

Regarding to ischemic stroke, DOACs were generally comparable with VKA, OR =0,95 (0,48; 1,88), p=0,88 (Figure 4). The only study where VKA had more beneficial effect was the study of Siontis KC, et al. [4]. Visually, on the funnel plot, the RCT results are more displaced to the side of the DOAC advantage, however, 2 large non-RRCTs balance their influence. The Peters test results also speak rather about the absence of a publication bias (Figure 5).

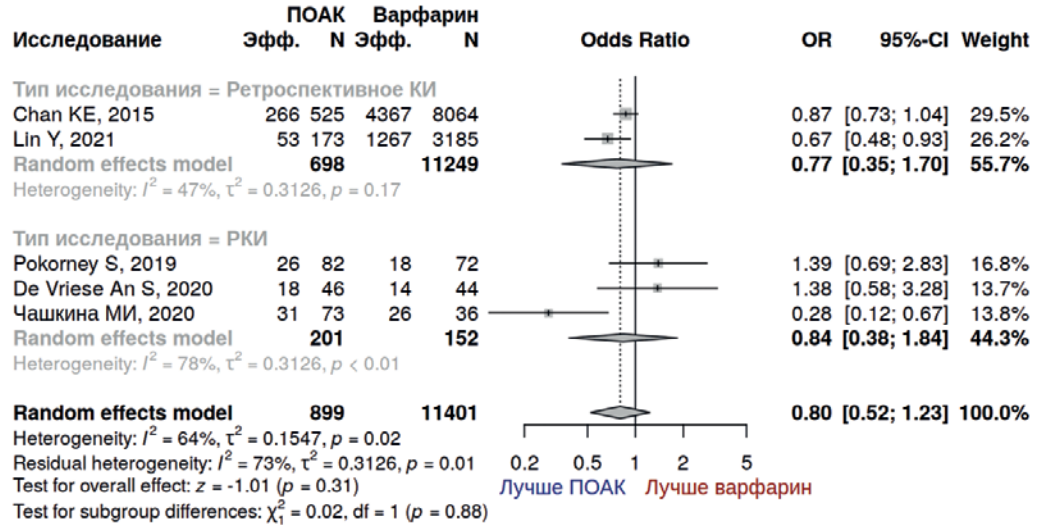

Figure 12. Forest plot for assessment of safety regarding to minor hemorrhage depending on the type of the study.
Abbreviations: ПОАК — прямые пероральные антикоагулянты (DOAC — direct oral anticoagulants), РКИ — рандомизированные контролируемые исследования (RCT — randomized controlled trials).

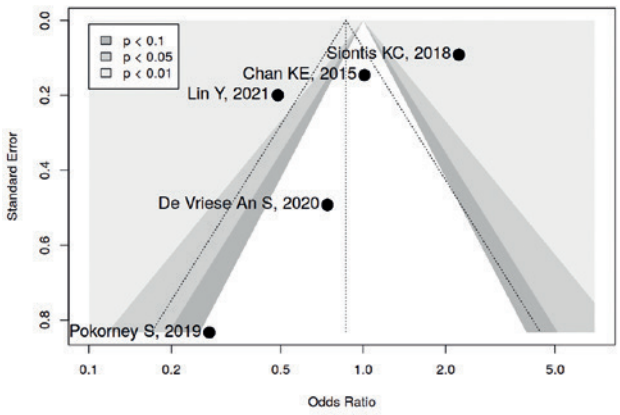

Figure 13. Funnel plot for comparison of a publication bias.

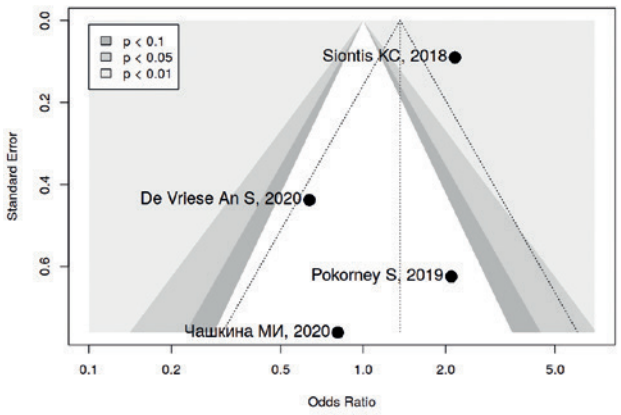

Figure 15. Funnel plot for comparison of a publication bias.

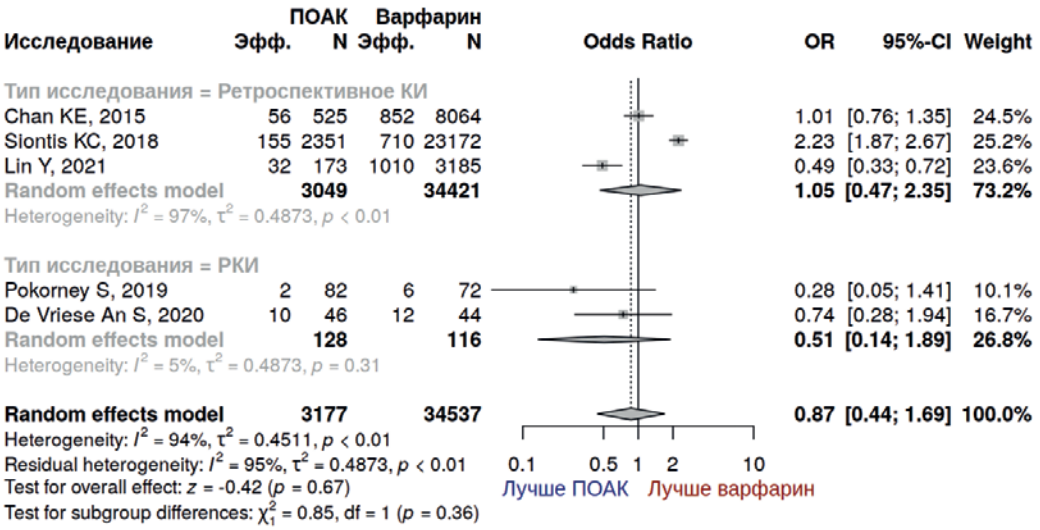

Figure 14. Forest plot for assessment of safety regarding to gastrointestinal bleeding depending on the type of the study.
Abbreviations: ПОАК — прямые пероральные антикоагулянты (DOAC — direct oral anticoagulants), РКИ — рандомизированные контролируемые исследования (RCT — randomized controlled trials).

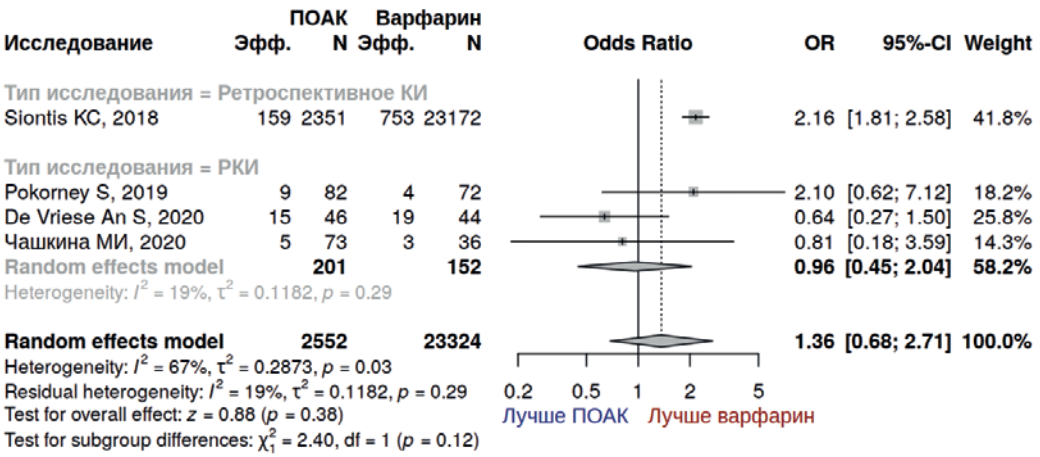

Figure 16. Forest plot for assessment of safety regarding to total mortality depending on the type of the study.
Abbreviations: ПОАК — прямые пероральные антикоагулянты (DOAC — direct oral anticoagulants), РКИ — рандомизированные контролируемые исследования (RCT — randomized controlled trials).

Systemic embolisms

The information on systemic embolisms were available in 4 studies where the effect was multidirectional. Of these 4 studies only one was RCT (De Vriese AS, et al. [16]), in which, however, the achievement of the endpoint was not noted. A weighted effect indicates an equivalent efficiency of DOACs and VKA, OR =0,99 (0,30; 3,27), p=0,98 (Figure 6). To estimate a potential publication bias with 3 studies, only funnel plot was used; the studies are placed relatively symmetrically, and there is no foundation to talk about signs of an obvious bias (Figure 7).

Assessment of safety criteria

Among the safety criteria, we evaluated both those that are directly related to the use of anticoagulants in the form of hemorrhagic complications and indirectly — in the form of total mortality. Certainly, patients with CKD stages IV-V can develop coagulopathy of this or that degree apart from anticoagulant-induced, and, taking into account the burden associated with cardiac rhythm disturbance, the mortality is induced by well-known causes.

Hemorrhagic stroke

The information on such a formidable complication as hemorrhagic stroke was available in 5 studies. The study of Slontis KC, et al. [4] noted the advantage of VKA, and as for the other studies, the endpoint was shifted to the side of the advantage of DOACs that was significant only in the study of Chan KE, et al. [15]. A weight effect showed significant advantage of neither DOACs or VKA, OR =0,56 (0,19; 1,64), p=0,29 (Figure 8). Visually, the larger studies with an insignificant error are grouped near the weight effect, while the small RCTs are shifted to the left. The Peters test demonstrates a low likelihood of publication bias (Figure 9).

Major hemorrhages

The large non-RRCTs of Chan KE, et al. [15] and Siontis KC, et al. [4] demonstrate the advantage of VKA over DOACs, and as for the other studies which all are RCTs, DOACs are more benefit, moreover, in the RCT of De Vriese AS, et al. [16], DOACs are significantly more benefit than VKA. The weighted effect shows an obvious advantage of neither DOACs or VKA, OR =0,92 (0,54; 1,56), p=0,75 (Figure 10). The Peters test results show low likelihood of publication bias but visually, it can be noted that the results are concentrated at the side where DOACs have an advantage in the effect (Figure 11).

Minor hemorrhages

The interpretation of this endpoint was somewhat different from the study to study. It was possible to conduct the analysis of this complication for 5 studies. In general, in comparison of DOACs to VKA, the results of the studies demonstrate multidirectional character, and the weighted effect indicates an advantage of neither DOACs or VKA, OR =0,80 (0,52; 1,23), p=0,31 (Figure 12). The visual analysis and Peters test results indicate the low likelihood of publication bias (Figure 13).

Gastrointestinal bleedings

The results of 5 studies were available to estimate the endpoint in the form of gastrointestinal bleedings. The comparison of safety of DOACs with VKA revealed no any advantages, OR =0,87 (0,44; 1,69), p=0,65 (Figure 14). Visual assessment demonstrates a certain tendency to the displacement to the side of the DOACs advantage, however, the Peters test results are not significant (Figure 15).

Total mortality

The total mortality results were available for all RCTs and 1 non-RRCTs. In general, an advantage of neither VKA or DOACs was noted, OR =1,36 (0,68; 2,71), p=0,38 (Figure 16).

Discussion

As far as we know, this is the first meta-analysis which investigates the efficacy and safety profiles of DOACs compared to VKA in patients with AF and CKD stages IV-V. Unlike other meta-analyses [15, 17] which included patients with different CKD stages or patients who received renal replacement therapy with hemodialysis, we focused precisely on patients with CKD stages IV-V and AF who are not presented separately in the previous studies and, in detailed analysis of the included studies, we notice that they involved patients not only with AF but also with deep vein thrombosis and pulmonary thromboembolism.

Our meta-analysis is a comprehensive review of the current data of six clinical trials for the use of DOACs and VKA in patients with AF and CKD stages IV-V regarding their safety and efficacy as well as separate analysis of DOAC drugs in the subgroups. It included 3 RCTs (one of them was carried out by Russian authors) and 3 retrospective studies. This systematic review included 37823 patients with AF and CKD stages IV-V, 3250 (8,6%) of which took DOACs and 34573 (91,4%) took VKA. The result showed that DOACs were as effective as warfarin in prevention of stroke and systemic embolism and safe regarding to hemorrhagic stroke, major, minor and gastrointestinal hemorrhages, and lethal outcomes.

The results of a previously published meta-analysis [17] comparing DOACs with VKA in patients with AF who received renal replacement therapy with hemodialysis showed that DOACs were as effective as VKA in prevention of stroke and safe regarding to the development of hemorrhagic stroke,

major and gastrointestinal hemorrhages. However, DOACs were associated with higher frequency of systemic embolism, minor hemorrhages and lethal outcomes compared to VKA.

One of the main advantages of DOACs over VKA is the absence of the need in laboratory control. But for some patient cohorts including patients on hemodialysis, it can be important to determine either actual concentration of DOACs (quantitatively), or the effect of DOACs (qualitatively). None of the included studies evaluated the level or effect of DOACs that may reflect the real situation with DOAC monitoring.

The study limitations. Our systematic review included small number of the studies and patients, and the lesser part of them is RCT. Consequently, it is difficult to come to definitive conclusions because of the limited data. In particular, the data of observational studies should be interpreted carefully because even in consistent cohorts, probably, there is a high degree of systematic selection error in distribution of patients using one of methods. Besides, the different DOAC drugs in different doses were used. In addition, the included studies had heterogeneous criteria of inclusion/exclusion and different determinations of each outcome and duration of follow-up. Like in other meta-analyses, endpoint determination can vary depending on the results of the safety and efficacy investigation. Some studies do not give a clear determination of the subtypes of stroke, systemic embolism and subtypes of hemorrhage (major or minor). And also, the etiology of bleeding, especially cerebral hemorrhage, is not specified.

Conclusion

According to the conducted systematic review and meta-analysis in patients with AF and CKD stages IV-V: there was no statistically significant superiority of DOACs or VKA in efficacy regarding to decrease in the risk of stroke or systemic embolism. As for safety in this category of patients, neither DOACs or VKA had a superiority regarding to hemorrhagic stroke, major hemorrhages, minor hemorrhages, gastrointestinal bleedings and total mortality. Thus, DOACs and VKA were comparable in efficacy and safety.

Relationships and Activities: none.

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The problem of cross risk of arterial hypertension progression, obstructive sleep apnea syndrome and COVID-19

Popov K. A., Bulaeva Yu. V., Ermasova S. A., Shvarts Yu. G.

This review considers the risk factors for arterial hypertension (AH) progression, obstructive sleep apnea syndrome (OSAS) and novel coronavirus infection (COVID-19) as potential variables for the prognostic models of estimating the probability of destabilization of the mentioned conditions. The most published studies consider AH and OSAS as the risk factors influencing the course of COVID-19, while moderate and mild COVID-19 can be destabilizing factor regarding to AH and OSAS. In addition, COVID-19, AH and OSAS are interrelated with sleep quality. The worsening of sleep quality often can be both a consequence of these diseases and a factor aggravating their course, and also can cause the increased vulnerability to acute diseases. An increased body mass index is a universal risk factor for many diseases and clinical conditions, and the monitoring of body mass increases the degree of the control of the diseases associated with obesity. In addition, the worsening of sleep quality can be both a consequence of any of above-mentioned conditions and a factor aggravating their course. Also, a promising direction for improving prognostic models is the analysis of autonomic dysfunction in patients.

Keywords: COVID-19, arterial hypertension, obstructive apnea sleep syndrome, prognosis estimation.

Relationships and Activities: none.

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Key messages

- An association between COVID-19, hypertensive disease and obstructive apnea sleep syndrome as well as the mechanisms of mutual worsening between them exist.
- Potential predictors of adverse outcomes are proposed; a comprehensive approach estimating prognosis of course of chronic diseases during and after COVID-19 is needed.
- Additional study of COVID-19 as a potential risk factor for decompensation and more severe course of arterial hypertension and obstructive apnea sleep syndrome as well as respiratory disorders during sleep is required.

Novel coronavirus infection (COVID-19) is associated with cardiovascular complications in the acute and long-term periods. In addition, COVID-19 often provokes the worsening of the course of already existing cardiovascular system (CVS) diseases. At the same time, arterial hypertension (AH), cardiovascular diseases (CVDs), obesity, diabetes and others are the risk factors (RFs) of more severe course of COVID-19. Among hospitalized COVID-19 patients, ~40% have at least one chronic disease. The proportion of comorbid patients in the cases ended with a lethal outcome is over 70%. According to data obtained by Gold MS, et al., AH was more common in patients with severe course of COVID-19 (47,65%) and in lethal cases (47,90%) [1]. According to ACTIV registry, most hospitalized COVID-19 patients have chronic diseases among which the CVDs prevail [2]. It also should be noted that severe and critical complications of COVID-19 are significantly more common in patients with obstructive sleep apnea syndrome (OSAS). It is also known that OSAS is one of the RFs of AH development [3], which adversely affects the course and control of AH and other CVDs [4]. We may judge of the incidence of OSAS in patients with COVID-19 using just indirect signs because this issue is not covered in the literature found according to the specified criteria. In general, we may suppose that there are bidirectional and mutually aggravating interrelationships between CVDs, including AH, and COVID-19 [5], and obesity, autonomic imbalance, changes in the renin-angiotensin-aldosterone system (RAAS) and hypoxia can be the connecting links between OSAS, HD and COVID-19. Taking into account a high incidence of polymorbidity in patients with COVID-19 as well as a distinct mutual aggravation, a complex approach to assess the prognosis of the course of chronic diseases during and after COVID-19 is required. The review is aimed to analyze the published data concerning the interrelations and possible mechanisms of mutual aggravation between hypertensive disease, OSAS and COVID-19.

Methodology of study

We systematically searched the PubMed, Google Scholar, Web of Science databases from 2000 to 2022 in accordance with the following keywords: "arterial hypertension", "obstructive sleep apnea", "COVID-19", "risk assessment", "outcome predictors", "risk factors", "comorbidity". We selected 48 publications concerning the possible mechanisms of mutual aggravation between the mentioned diseases as well as the assessment of the possible predictors of adverse outcomes. The type of study was not a selection criterion. Apart from RFs of severe COVID-19 course, the present review discusses characteristics such as the quality of night sleep, body mass index (BMI), and the state of the autonomic nervous system (ANS). They are considered as potential predictors of the destabilization of AH and OSAS against the background of COVID-19 pandemic. We found a limited number of studies considering COVID-19 as a potential RF of the decompensation and more severe course of AH as well as respiratory disorders during sleep. That is why the use of meta-analysis techniques was impossible. Based on the literature data, it is possible to make just preliminary conclusions and to propose hypotheses on the problem under consideration.

Role of OSAS and AH in the prognosis of COVID-19

OSAS is characterized by recurrent partial or complete obstruction of the airways during sleep, leading to shortness of breath, desaturation and arousals from sleep. A high incidence of OSAS is associated with the increased incidence of AH, obesity, depression, gastroesophageal reflux disease, diabetes mellitus, hypercholesterolemia, asthma [6]. OSAS is also associated with the increased risk of CVDs [4]. Many conditions associated with OSAS coincide with the RFs of severe course and adverse outcome in COVID-19 [7]. Some authors identify the additional predictors of the presence of OSAS for example, the hypertonic load time index [8] that emphasizes an interrelationship between OSAS and the state of CVS. Several pathophysiological mechanisms contribute to the interrelationships between OSAS and vascular risk, including neurohormonal dysregulation, endothelial dysfunction and inflammation [9]. The latter are also typical of the acute course and consequences of COVID-19. CPAP therapy, in turn, decreases arterial pressure (AP) but there were no proves that it decreases the risk of CVDs and serious cardiovascular events. At the same time, the decrease of body weight improves the indicators of AP and lipids in blood against the background of OSAS, whereas the addition of CPAP showed no significant improvement in the indicators of AP or lipids in blood [10].

According to the results of the studies, CPAP may independently affect the level of AP. There are two basic mechanisms of the increase in AP in OSAS, which can be prevented by CPAP. Periodic sympathetic activation accompanied by vasoconstriction caused by the repeated episodes of desaturation and hypoxia, is one of the key mechanisms responsible for the increase in AP in OSAS [11]. Another possible mechanism explaining pathophysiology of AH in OSAS, is the activation of RAAS. The release of renin is associated with the increase in the sympa-

thetic nervous system activity and the loss of sodium due to increased nocturnal diuresis provoked by an increase in the concentration of natriuretic peptide in response to excessive negative intrathoracic pressure during apnea [12].

Thus, a number of the studies have shown the interrelationship between AH, OSAS and COVID-19. However, the issue of the independent effect of confirmed OSAS and AH on the forecast of COVID-19 remains disputable. Besides, at the time of writing the review, the most published studies were focused on the factors affecting the course of COVID-19. The characteristics of the COVID-19 course, which could be the prognostic criteria for the AH and OSAS destabilization, are still under discussion as hypotheses. Meanwhile, the loss of the control of AH due to COVID-19 is often observed in inpatients [13], and can be a serious RF of CVD development, affecting the patients` quality and duration of life.

Decrease of sleep quality in the prognosis of the AH and OSAS destabilization against the background of COVID-19

OSAS is closely interrelated with the quality of sleep. At the same time, sleep quality is one of the basic factors in the control of AH and normal functioning of all body systems. The meta-analysis results showed that people with sleep deficiency had higher values of average systolic and diastolic AP. According to questionnaires, it was also shown that patients with AH had statistically significant decrease in sleep quality [14].

A lot of empirical data of sleep disorders against the background of COVID-19 pandemic have been accumulated. Many hypotheses of the potential mechanisms of these disorders were proposed. A number of authors believe that psychological health is the determining RF of insomnia development in COVID-19 because the results of the studies show correlation between development of depression, anxiety disorders and sleep disorders [15]. But the decrease in the level of physical activity and number of social contacts because of the pandemic limitations or the disease can be themselves the independent RFs for the development of psychological disorders [16]. The exact mechanisms of the direct influence of SARS-CoV-2 on sleep quality are not found. However, the long-term persistent sleep disorders can be considered as the manifestations of post-COVID syndrome following the disease [17]. It should be noted that post-COVID syndrome can be caused by both cerebral disorders due to vascular lesions [18] and the cerebral lesions due to direct influence of COVID-19 virus [19] or indirect mechanism through the formation of immune complexes [20]. In turn, sleep quality can affect the prognosis of the COVID-19 course as well as destabilization of chronic diseases such as AH and OSAS. An open randomized clinical trial which investigated the use of melatonin in addition to basic therapy of COVID-19, has showed more than 2% higher blood saturation in the affected group compared to the control group [17]. Obviously, it is possible to improve the course of this virus infection by normalizing sleep that indirectly confirms the negative role of sleep disorders in COVID-19. Thus, COVID-19 leads to sleep worsening which can be caused by indirect or direct influence of infectious process.

BMI as an independent predictor of adverse outcomes of AH, OSAS and COVID-19

Mutual influence of AH, obesity, COVID-19 and OSAS may look obvious but the identification of the independent predictors of adverse outcomes is possible only within large studies with an appropriate design. Using single-factor analysis, the CORONADO research revealed several characteristics associated with the risk of death on the 7th day of hospitalization for COVID-19. They included age, AH, micro- and macrovascular diabetic complications and concomitant diseases: heart failure and OSAS. But multiply factor analysis revealed no statistically significant independent relationship between severe course of COVID-19 and age, gender, the glucose level control, hypertension or the use of AH and diabetes basic therapy, including RAAS blockers. Only BMI was independently related to a primary outcome. Dyspnea, lymphopenia and increased levels of aspartate aminotransferase and C-reactive protein at admission to hospital were also independent prognostic factors of severe course of COVID-19 [21]. The evidences of the influence of obesity on the course of infectious diseases are not new. For example, during H1N1 pandemic, obesity was independently associated with higher risk of hospitalization, severe course and adverse outcome of influenza. In COVID-19, obesity is also serious independent RF of adverse outcome and severe course. In addition, obesity is associated with decreased immune response to vaccination that can potentially make these patients more susceptible to infection [22]. Obesity is associated with metabolic syndrome (MS) but some authors express doubt whether it is possible to use parameters such as glycemic profile and insulin resistance to build prognostic models for assessing the risk of COVID-19 severity [23].

The role of obesity in the occurrence of AH and its resistant form is well-known. There is an opinion that obesity and MS are the predisposing factors of post-COVID syndrome [24]. Starting from the pandemic, a lot of studies investigated relationship between cardiometabolic syndrome and COVID-19 have been published. Most studies stated such RFs

of severe COVID-19 as CVD, insulin resistance, MS, type 2 diabetes mellitus and increased BMI [25]. Along with this, the risk of cardiac and vascular complications in the nearest months after acute COVID-19 is equally increased in both obese and non-obese individuals [26].

Obesity is also a key factor for OSAS development. In patients with normal BMI, a 10% increase in weight is associated with a sixfold increase in the risk of OSAS [27]. And conversely, a 10% weight loss results in 26% decrease in the apnea-hypopnea index. Like in the case of hypertension, the relationship between obesity and OSAS is mutually increasing. One of the explanations for this interrelationship can be the association of obesity with chronic subclinical inflammation, the "unifying" role of which was mentioned above. Inflammation predisposes people to OSAS, and OSAS itself is a pro-inflammatory process [28]; consequently, an excessive body weight is a common RF for many diseases and clinical conditions, and the control of body weight increases the degree of the control for diseases associated with obesity.

Apart from clinical and pathophysiological features, obesity creates additional difficulties in managing this group of patients: features of intubation, the need for higher positive pressure during CPAP therapy, problems of transportation and performing a number of diagnostic procedures. All these difficulties may also affect the prognosis because they lead to the delay in diagnostics, require more advanced skills of personnel and potentially increase the risk of a variety of complications.

Significance of the phenomenon of mute hypoxia for an adequate clinical assessment of the patient's condition

One more universal pathogenetic factor in many diseases including OSAS and COVID-19 is hypoxia. Both diseases can have a mutually aggravating effect in particular due to the induction of hypoxia. And hypoxia does not always have obvious clinical manifestations. It is known that AP rising can be a reaction to hypoxia. Mute hypoxia in patients with SARS-CoV-2 infection is diagnosed using a pulse oximeter, blood gas level in and six-minute walk test. Mute hypoxia itself is not a RF for more severe course of COVID-19 or an adverse outcome. Nevertheless, the absence of specific complaints during desaturation and the registration of only raised blood pressure or routine diagnosis of a hypertensive crisis can lead to incorrect clinical assessment of the patient's condition and untimely assistance. The causes of mute hypoxia in patients with COVID-19 have not been clear so far. The existing data indicate a probable lesion of the central nervous system and also the probable absence of hypoxic vasoconstriction in these patients [29]. The compensation of CVS hypoxemia is crucial for maintaining oxygen delivery to tissues. The compensatory reserve of cardiovascular system for hypoxemia is more likely to determine the clinical outcomes in COVID-19 than the degree of hypoxia itself [30].

There are some contradictions on this issue. On the one hand, hypoxemia and altered hemodynamics in OSAS against the background of AH may contribute to the increased coagulopathy in COVID-19 and accordingly worsen the prognosis [31]. On the other hand, according to the results of the existing studies there are no data confirming a significant effect of mute hypoxia on the prognosis of the course of a main disease. And there are no unambiguous data on an increase in the risks of an unfavorable COVID-19 prognosis in the presence of a compensated chronic disease, in particular AH, as mentioned above. At the same time, severe form of COVID-19 is associated with polymorbidity. The cause of this seeming contradiction is probably explained as follows. The prevalence of AH and OSAS in patients with COVID-19 can be caused by the common predictors of the development of these diseases. Thus, the prognosis of COVID-19, OSAS and AH can be determined not so much by mutual effect of the diseases as the collection of the common predisposing factors: obesity, chronic inflammation, physical inactivity, stress and others.

Benefits of CPAP therapy in the era of COVID-19

When considering the role of hypoxia in mutual aggravation of OSAS, AH and COVID-19, it is impossible not to note the value of CPAP. The results of the CORONADO research showed that the patients required CPAP for the OSAS treatment, have a higher risk of death from COVID-19 [21]. Probably, this is caused by more severe course of OSAS and combined pathology typical of such patients. According to the data of the RECOVERY-RS research, the use of CPAP in patients with severe hypoxemia in COVID-19 significantly decreases the risks of tracheal intubation and death compared to oxygenation with moistened oxygen through nasal cannulas or a mask [32]. Miller MA, et al. performed a systematic review of the studies concerned with CPAP therapy and COVID-19. They noted that the most prevalent RFs of lethal outcome were common to COVID-19 and OSAS. These RFs include elderly age, hypertension, CVDs, pulmonary diseases and diabetes mellitus. The authors also pay special attention to obesity as a prevalent RF, common to many diseases [7]. This review served as a starting point for a qualitative meta-analysis of 13 cohort studies where Hu M, et al. showed that OSAS was independently associated with a significantly increased risk of death among patients with COVID-19 [33].

There is no enough data yet based on which it would be possible to unambiguously determine the recommendations for the use of CPAP in the combination of OSAS and COVID-19. At the same time, the use of CPAP as non-invasive mechanical lung ventilation seems promising in such comorbid patients.

Autonomic imbalance as a predictor of clinical outcome in combined pathology

One of general causes of the development and worsening of the discussed conditions can be also the changes in the ANS. Obesity and AH naturally determine a number of specificities in the ANS regulation. And the ANS plays an important role in the regulation of the whole body homeostasis including immune system, CVS and coagulation system [34, 35]. Considering the role of autonomic dysfunction in morbidity and mortality from COVID-19 [36], it is suggested to use the monitoring of the vagal tone in patients with COVID-19 as a prognostic marker of COVID-19 disease course [37].

Sleep fragmentation and chronic intermittent hypoxia in OSAS may cause an inflammatory reaction and sympathetic activation [38]. Besides, it is important to note that OSAS manifests in particular in the fluctuations of the ANS tone and disturbance of sleep architecture, and is accompanied by the increased negative intrathoracic pressure which directly affects cardiac function including the heart rate variability (HRV) [39].

The HRV analysis is a reliable non-invasive instrument reflecting the autonomic tone. When analyzing HRV, patients with severe COVID-19 course demonstrated significantly lower values of SDNN ($P<0,001$) and SDANN ($P<0,001$) and higher values of LF/HF than patients with mild course. HRV correlates with COVID-19 disease severity. Patients with severe COVID-19 disease course have more pronounced disorders of HRV, which demonstrate a linear correlation with the N-terminal pro-brain natriuretic peptide, D-dimer and immune function. The data of HRV measurement can be used as a non-invasive predictor of the time to virus elimination as well as a clinical outcome as this is showed in the study of Pan Y, et al. [40]. An underlying mechanism of these changes is still not completely known. The design of the mentioned study did not take into account the presence or absence of chronic CVDs, whereas the autonomic cardiac rhythm regulation significantly differs between patients with COVID-19 and without concomitant cardiovascular pathology and patients having both AH and COVID-19. Another study showed that patients with both COVID-19 and AH have higher sympathetic tone compared to patients with COVID-19 and without concomitant CVDs [41]. According to the design of the study performed by Skazkina VV, et al., severe course of COVID-19 was a criterion of exclusion. Thus, the results can be interpreted only regarding patients with mild and moderate COVID-19. Despite quite significant results, the data of all mentioned studies are obtained on a limited patient sampling and require confirmation on large samples with using more perfect design. In addition, the HRV values would be advisable to combine with other clinical predictors for the complex assessment of the disease status and for prognostic evaluation.

Value of RAAS and its blockers in combination of AH, OSAS and COVID-19

Along with autonomic dysfunction, patients with AH have a disturbed regulation of RAAS, that is also observed in patients with OSAS and COVID-19. Angiotensin-converting enzyme 2 (ACE2) receptors are mainly expressed in the CVS organs, and ACE2 was identified as a receptor for the entry of SARS-CoV-2 [42]. Both in patients with OSAS and with AH and obesity, an increased expression of ACE2 receptors is observed that would favor the viral invasion [43]. The cardiac complications in COVID-19 include myocarditis, acute coronary syndrome, heart failure and arrhythmias [44]. OSAS can potentiate the severity of these complications that obviously increases the risk of adverse outcomes.

However, there is some uncertainty in this regard. It is known that the ACE2 expression is more pronounced in patients with CVDs [45]. At the beginning of the pandemic, the different authors made an assumption that the ACE inhibitors may negatively affect the prognosis in patients with CVDs and AH. However, later this assumption has been disproved by a series of studies. By 2022 no reliable data has appeared, confirming that the ACE inhibitors cause the increase in ACE 2 receptors in the human tissues [46] or otherwise affect the COVID-19 course and outcomes [47].

In this context, it seems interesting that a meta-analysis performed by Gold MS, et al., revealed no statistically significant relationship between CVDs and mortality in COVID-19 [35].

It should be noted that all given results are obtained on relatively small samples therefore, there is a need in further large studies to prove or disprove an interrelationship between the condition of RAAS, CVDs, AH, OSAS and COVID-19.

Features of post-COVID syndrome and probability of destabilization of AH and OSAS

One of the most discussed topics is post-COVID syndrome and/or long-COVID. Currently, there is no common opinion whether to consider these two terms as synonyms or different clinical conditions. This makes a literature review on the given issue difficult because the criteria of determination of

post-COVID syndrome and the endpoints vary from study to study. Most authors agree on two criteria: 1) the symptoms last >4 weeks in the absence of any other potential causes; 2) the symptoms develop or persist after acute confirmed or probable COVID-19. Thus, patients with post-COVID syndrome are united by persistence or occurrence of the symptoms after COVID-19 [48]. At the same time, it remains unclear whether to consider the persistence of symptoms such as increased fatigue, shortness of breath, sleep disturbance, blood pressure fluctuations that have arisen or intensified after infection, as post-COVID syndrome or decompensation of the mentioned diseases. Moreover, the effect of the presence and character of post-COVID syndrome on the probability of AH and OSAS destabilization remains poorly studied. There is no much literature concerning direct physiological impact of COVID-19 on sleep but it highlights the negative synergy between the immune response to COVID-19, including prolonged, and the pro-inflammatory condition caused by OSAS. Obviously, post-COVID syndrome is of the greatest interest precisely regarding to the prognosis of the course of existing chronic diseases, after the acute period of COVID-19 has passed.

Conclusion

Thus, the literature data analysis dedicated to the problem of cross risk of AH, OSAS and COVID-19, in general confirmed bidirectional mutually aggravating interrelationships between these conditions. Most studies consider AH and other chronic diseases as RFs of more severe COVID-19 but only a limited number of researchers studied COVID-19 and post-COVID period as a destabilization factor of AH and OSAS.

It should be noted that at the time of writing the review, the studies based on the multiply factor models established no a reliable relationship between the presence of compensated AH and OSAS and unfavorable COVID-19 prognosis, despite a significantly higher incidence of these conditions in patients with COVID-19 than in the general population.

Also, there were no reliable confirmations of the hypotheses of the association between any methods for the treatment of AH and OSAS with higher/lower risk of infection or more severe/mild course and outcome of COVID-19 disease.

At the same time, we may consider established that obesity is a significant independent RF of both unfavorable prognosis of COVID-19 and the presence of AH and OSAS and their unfavorable course. In obesity there are the "mechanisms-candidates" that can negatively affect the development of these diseases. Besides, obesity can complicate the management of patients and indirectly affect the prognosis of this group of patients.

We can also assume that COVID-19 and its consequences may negatively affect the characteristics of AH and OSAS due to numerous pathogenic factors including hypoxia and aggravating of autonomic imbalance. In this regard, the diagnostics of autonomic dysfunction in patients after COVID-19 aimed to determine the probability of post-COVID syndrome development and AH destabilization, seems perspective. In turn, the study of sleep quality seems perspective regarding to the building of multifactorial prognostic models for both long-term COVID-19 outcomes and the clinical course of AH.

Relationships and Activities: none.

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