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Economic damage of risk factors associated with morbidity and mortality from major chronic non-communicable diseases in Russia in 2016

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Aim. To assess the socioeconomic damage of risk factors associated with morbidity and mortality from major chronic non-communicable diseases (CNCDs) in the Russian population in 2016.

Material and methods. The following RF were included in the analysis: smoking, alcohol abuse, high salt intake, insufficient consumption of vegetables and fruits, consumption of processed red meat, low physical activity, obesity, hypertension (HTN), which have a significant causal relationship with the major CNCDs: cardiovascular diseases (CVDs), type 2 diabetes, chronic obstructive pulmonary disease (COPD), cancer of 10 locations (lung, breast, cervix, ovary, prostate, kidney, stomach, liver, pancreas, colon). Based on the data on the RF prevalence in the Russian population by ESSE-RF study and relative risks by large studies, the population attributable risk for each CNCD was estimated. We used the data of the Federal State Statistics Service, annual forms of Federal Statistical Observation, as well as the results of the Government Guarantee Program for free medical care and the corresponding diagnosis-related groups for 2016. The direct costs of the healthcare system and economic losses due to morbidity and mortality from the major CNCDs associated with the considered RF are determined. The calculations were performed in Microsoft Excel 10.0.

Results. Indirect losses due to premature mortality prevail over direct costs of medical care and disability benefits in the economic damage structure of each RF. The largest damage of four major CNCDs was associated with HTN — 869,9 billion rubles, which is equivalent to 1,01% of gross domestic product (GDP). The next places were taken by obesity — 605,8 billion rubles (0,7% of GDP), smoking — 421,4 billion rubles (0,49% of GDP) and low physical activity — 273,0 billion rubles (0,32% of GDP). The contribution of improper feeding (high salt intake, insufficient consumption of vegetables and fruits, consumption of processed red meat) amounted to 0,17% of GDP (145,3 billion rubles), 0,19% of GDP (160,9 billion rubles) and 0,10% of GDP (83,4 billion rubles), respectively. Alcohol abuse made the smallest contribution to CNCD-related damage — 82,5 billion rubles (0,1% of GDP). This is due to the low prevalence of alcohol abuse in the Russian population according to ESSE-RF study.

Conclusion. Assessment of the economic damage of CNCD RF allows determining the priority areas in healthcare and substantiating the effectiveness of CNCD preventive measures aimed at reducing the RF impact, and, consequently, the burden on the healthcare system and the national economy.

Key words: economic damage, risk factors, chronic non-communicable diseases, relative risk, population attributive risk.

Relationships and Activities: none.

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Introduction

According to the World Health Organization (WHO), the following four groups of chronic noncommunicable diseases (NCDs) make the largest contribution to morbidity and mortality worldwide (71% of 57 million of all deaths in the world): cardiovascular disease (CVD), type 2 diabetes (T2D), cancer and chronic obstructive pulmonary disease (COPD) [1]. These diseases have common proven behavioral risk factors (RFs): smoking, excessive alcohol consumption (EAC), sedentary lifestyle (SL), unhealthy diet (UD) and metabolic RFs such as hypertension (HTN) and obesity [2].

According to the Prospective URban Epidemiological (PURE) study, 70% of cardiovascular morbidity and mortality is due to modifiable RFs, with the greatest contribution of HTN (22,3%). In general, behavioral RFs significantly contribute to all-cause mortality [3].

Globally, smoking is responsible for ~71% of lung cancers, 42% of chronic respiratory diseases, and ~10% of CVDs [2]. HTN is responsible for 51% of strokes and 45% of coronary artery disease (CAD) cases in the world [2]. According to the INTERHEART study, 90% of acute myocardial infarctions are associated with 9 RFs [4]. According to various estimates, inadequate fruit and vegetable consumption is the cause of ~14% of deaths from gastrointestinal cancer, 11% — from CAD, and 9% — from stroke [2]. The SL is related to ~21-25% of the breast and colon cancers, 27% of the T2D, and ~30% of the CAD in the world [2]. Alcohol contributes

to the development of >60 diseases and injuries and is the cause of ~30% of deaths from esophageal and liver cancers worldwide [2].

The contribution of RFs to the morbidity and mortality from NCDs is specified by their prevalence in a particular population and the associated risks of morbidity and mortality, which can also vary in different populations depending on socio-economic factors, ethnic characteristics, and other factors [3]. Assessment of the contribution of RFs to morbidity and mortality from NCDs will allow to determine the economic losses caused by these RFs and to identify priorities to improve public health, as well as justify the allocative efficiency of implemented measures.

A comparative analysis of the economic burden of RFs is carried out in many countries [5, 6], as well as on a global scale [7, 8]. Thus, the McKinsey&Company experts have shown that, on a global scale, the economic cost (EC) of smoking and obesity is comparable to all wars, terrorism and armed conflicts in the world [7].

In Russia, the EC of individual RFs was analyzed earlier [9-11]. A comparative analysis of EC of behavioral and metabolic RFs based on their contribution to morbidity and mortality from four main NCDs has not been performed previously.

The aim was to assess the socioeconomic damage of risk factors associated with morbidity and mortality from major NCDs in the Russian population in 2016.

Material and methods

The analysis included the RFs (smoking, EAC, high salt intake, inadequate fruit and vegetable consumption, consumption of processed red meat, SL, obesity, HTN), which have a causal relationship with the main NCDs — CVD, T2D, COPD, cancer of 10 localizations (lung, breast, cervix, ovary, prostate, kidney, stomach, liver, pancreas, colon).

The prevalence of the considered RFs in the Russian population was determined in a multicenter ESSE-RF study [12-13]. The prevalence of smoking was 23,6%, EAC — 3,8%, inadequate fruit and vegetable consumption — 41,9%, high salt intake — 49,9%, daily consumption of processed red meat — 22,5%, SL — 38,8%. The prevalence of HTN and obesity was 44% and 29,7%, respectively.

The relative risk (RR) of morbidity and mortality from NCDs associated with RFs was determined using the literature data. Based on the RF prevalence and RR, the population attributive risk (PAR) was calculated for each analyzed disease using the following formula:

$$PAR\,(\%) = \frac{P_{exp}\,(RR - 1)}{[P_{exp}\,(RR - 1)] + 1},$$

where: P_{exp} — proportion of individuals exposed to RF; RR — relative risk of a certain outcome for a given RF exposure.

For RR <1, PAR was determined by the reduction formula:

$$PAR = \frac{P_1 + P_0 / (RR - 1)}{P_1 + P_0 / RR},$$

where: P_1 — proportion of individuals with RF; P_0 — proportion of individuals without RFs; RR — relative risk of the disease development in accordance with literature data.

PAR, calculated for each analyzed NCDs, was used to determine the proportion of morbidity/mortality associated with RF. To assess the EC of RFs, the proportion of RFs in the morbidity and mortality from NCDs and then the proportion of the disease in EC was determined. By way of example, the calculation formula of CVD is shown below:

$EC_{RF} = (PAR_{morbidity\_CVD} \times DC_{CVD} + PAR_{mortality\_CVD} \times IC_{CVD})$, where: EC_{RF} — EC of RFs; $PAR_{morbidity}$ — PAR of RFs in CVD morbidity; DC_{CVD} — direct costs, associated with CVDs; $PAR_{mortality}$ — PAR of RFs in CVD mortality; IC_{CVD} — economic losses associated with premature mortality in economically active age due to CVDs.

The methodology for calculating the EC of CVD, T2D and COPD, as well as the results used in this analysis, were published earlier [14-16].

For the above-mentioned NCDs, direct medical costs for out- and inpatient and emergency care were calculated, as well as direct nonmedical costs for disability pensions and indirect costs due to the short-received contribution to GDP due to illness and premature termination of working practice.

Data on direct costs of the healthcare system for 2016 was determined on the basis of previously conducted studies. Based on the literature data on the cost of treating cancer patients, the direct costs were recalculated for 2016. The costs of the healthcare system on pancreatic cancer were not included in the calculation due to the lack of information.

To calculate treatment costs in 2016, the current direct medical costs was indexed to the actual inflation rate using the formula:

$COST_{dmc16} = COST_{dmc0} * In0 * In1 * ... * In16$,

where: $COST_{dmc16}$ — direct medical costs for 2016; $COST_{dmc0}$ — direct medical costs at the study time; In0 — growth rate of consumer price indices in the Russian Federation, following the year of analysis of direct medical costs; In1 and In16 — growth rates of consumer price indices up to 2016.

The healthcare costs per patient in 2016, calculated as described above, were multiplied by the number of people with corresponding cancer in 2016.

Indirect costs included the value of short received contribution to GDP due to premature mortality and disability at working age.

The analysis of mortality was carried out using WHO data and information on cancer mortality of the National Medical Research Radiological Center (Russia). Economic losses associated with premature mortality at the economically active age included GDP gap due to lost life years due to death from cancer, taking into account the employment rate. Future losses were calculated using a net present value of future losses with discounting of 3%.

GDP gap due to disability were defined as follows: first, the number of individuals with permanent disability in each of the disability groups was calculated, taking into account the employment rates. Then the estimated number of non-working disabled people of working age is multiplied by the net present value of GDP per capita.

MS Excel 10.0 software (Microsoft, USA) was used for statistical analysis.

Results

At the first stage, a review of large epidemiological studies was carried out to determine RR of morbidity

Table 1

PAR of RFs included in the analysis

Outcome	Smoking	EAC	High salt intake	Inadequate FVC	PRM	SL	Obesity	HTN
CVD: morbidity	0,088	0,044	0,065	0,048		0,070	0,229	0,306
CVD: mortality	0,128	0,030	0,048	0,048		0,070	0,229	0,346
CAD: morbidity	0,115	0,024		0,048	0,086	0,200	0,308	0,284
CAD: mortality	0,106	0,040		0,048	0,039	0,091	0,308	0,381
Stroke: morbidity	0,096	0,006	0,103	0,100	0,037	0,162	0,279	0,143
Stroke: mortality	0,056	0,004	0,166	0,100	0,037		0,279	0,599
COPD: morbidity	0,096	0,009				0,155		0,238
COPD: mortality	0,191	0,009				0,155		
T2D: morbidity	0,094	0,0005	0,177	0,012	0,090	0,248	0,461	0,183
T2D: mortality	0,115	0,001	0,177	0,012	0,090	0,248		0,013
Stomach cancer: morbidity	0,056	0,011	0,070	0,030	0,092	0,147		
Stomach cancer: mortality	0,078	0,011	0,070	0,030	0,092	0,147		
Colorectal cancer: morbidity	0,107	0,022		0,222	0,039	0,064	0,211	
Colorectal cancer: mortality	0,075	0,022		0,222	0,039		0,211	
Liver cancer: morbidity	0,068	0,004		0,141		0,051	0,209	
Liver cancer: mortality	0,072	0,004		0,141		0,051		
Pancreatic cancer: morbidity	0,039	0,044		0,030				
Pancreatic cancer: mortality	0,152	0,044		0,030				
Lung cancer: morbidity	0,253			0,086		0,133	0,029	0,117
Lung cancer: mortality	0,170			0,086		0,133	0,029	0,117
Breast cancer: morbidity	0,039	0,004				0,091	0,241	0,062
Breast cancer: mortality	0,109	0,005				0,091	0,241	0,062
Cervical cancer: morbidity	0,191						0,067	
Cervical cancer: mortality	0,047						0,067	
Ovarian cancer: morbidity	0,014					0,084	0,077	
Ovarian cancer: mortality	0,078						0,077	
Prostate cancer: morbidity	0,009	0,005				0,051	0,074	0,034
Prostate cancer: mortality	0,032	0,005					0,074	0,034
Kidney cancer: morbidity	0,109	0,004		0,042		0,147	0,082	
Kidney cancer: mortality	0,191	0,004		0,042		0,147	0,082	

Note: EAC — excessive alcohol consumption, FVC — fruit and vegetable consumption, PRM — processed red meat, SL — sedentary lifestyle, HTN — hypertension.

and mortality from the main NCDs associated with RFs. Based on the prevalence of RFs and the RR of morbidity and mortality from NCDs associated with RFs, the PAR of these RFs were calculated (Table 1). Smoking was associated with all NCDs included in the analysis, specifying 13% of mortality from CVD, 19% of mortality from COPD, 17% of mortality from lung cancer, and a significant proportion of mortality from other cancers included in the analysis. EAC was associated with CVD, T2D, COPD and some cancers included in the analysis, in particular, with pancreatic and colorectal cancer. By 4% and 4,4%, alcohol contributed to mortality from CAD and pancreatic cancer, respectively. High salt intake was associated with a high risk of CVD, T2D, and gastric cancer. The contribution of this RF to mortality from stroke was 16,6%, T2D2 — 17,7%, and gastric cancer — 7%. Inadequate fruit and vegetable consumption significantly contributed to the morbidity and mortality from gastrointestinal cancers (colorectal cancer — 22,2%, liver cancer — 14,1%) and CVD (stroke — 10%, CHD ~5%). Daily consumption of processed red meat contributed to morbidity of CAD and T2D in 8,6% and 9%, respectively. Among cancers, the largest contribution of this RF to morbidity and mortality from stomach (9,2%) and colorectal cancers (3,9%) was found. SL was associated with most of the analyzed NCDs, making a significant contribution to the morbidity of CVD, T2D, COPD and cancer of various localization (stomach, kidney, breast). Obesity was associated with a high risk of T2D, CVD, and colorectal, liver and breast cancers, also making a significant contribution to mortality from major NCDs (CVD — 22,9%, colorectal cancer — 21,1%, breast cancer — 24,1%). HTN as an independent metabolic RF was associated with an increased risk of CVD, T2D, COPD, and lung cancer. Hypertension accounts for almost 60% of the contribution to death from stroke.

Table 2

EC of RFs due to their contribution to the development of NCDs

Costs	Smoking	EAC	High salt intake	Inadequate FVC	PRM	SL	Obesity	HTN
Direct medical costs, million rubles	44 446,4	11 841,4	19 406,4	28 787,3	14 062,7	36 402,4	82 089,9	84 606,3
Disability benefits payments, million rubles	1 686,3	267,9	309,7	1 074,7	284,8	1 480,3	2 308,2	1 540,3
Direct costs, total, million rubles	46 132,7	12 109,3	19 716,1	29 862,0	14 347,5	37 882,7	84 398,1	86 146,6
Proportion of direct costs in the general EC pattern	10,9%	14,7%	12,3%	20,5%	17,2%	13,9%	13,9%	9,9%
GDP gap due to premature mortality, million rubles	375 276,1	70 385,6	141 208,4	115 456,6	69 066,3	235 263,4	521 375,7	783 789,5
EC, total, million rubles	421 408,8	82 494,9	160 924,5	145 318,6	83 413,9	273 146,1	605 773,8	869 936,0
EC per capita, rubles	2 876,51	563,11	1 098,46	991,94	569,38	1 864,48	4 134,97	5 938,13

Note: EAC — excessive alcohol consumption, FVC — fruit and vegetable consumption, PRM — processed red meat, SL — sedentary lifestyle, HTN — hypertension.

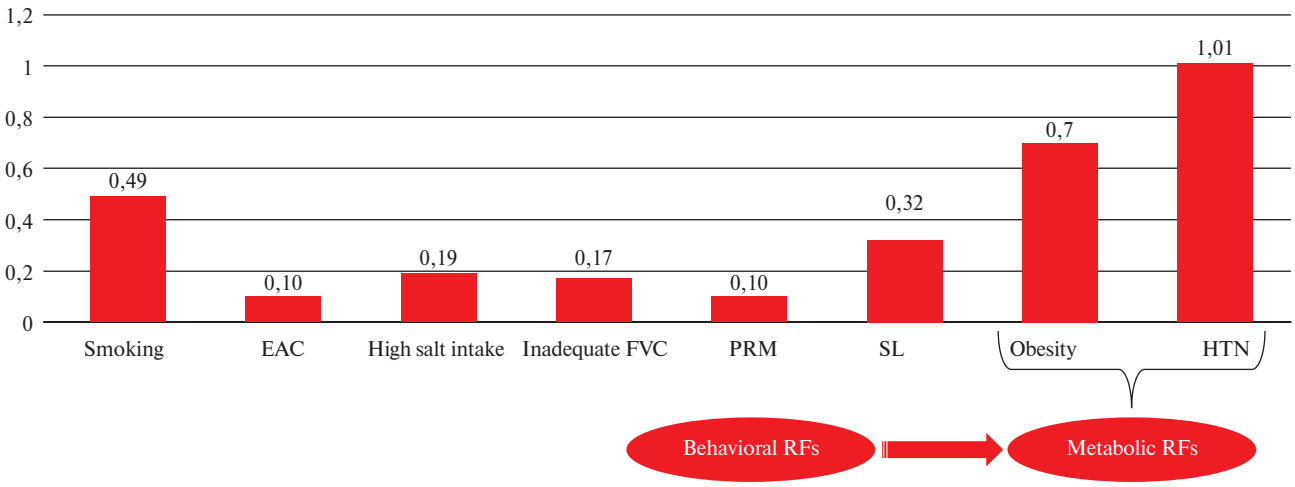

Figure 1. EC of RFs in Russia for 2016 (% of GDP).
Note: EAC — excessive alcohol consumption, FVC — fruit and vegetable consumption, PRM — processed red meat, SL — sedentary lifestyle, HTN — hypertension.

Table 2 and Figure 1 show the EC of RFs based on their contribution to the development of NCDs. In the EC pattern of each RF, indirect losses prevail over direct costs. The greatest damage from the four main NCDs is associated with HTN — 869,9 billion rubles, which is equivalent to 1,01% of GDP. Direct costs for HTN amounted to 86,1 billion rubles, while indirect costs — 783,8 billion rubles. The next largest contribution to EC was associated with obesity (605,8 billion rubles; 0,7% of GDP), smoking (>421,4 billion rubles; 0,49% of GDP) and SL (273,0 billion rubles; 0,32% of GDP). EC of inadequate fruit and vegetable consumption, high salt intake and daily consumption of processed red meat amounted to 0,17% of GDP (145,3 billion rubles), 0,19% of GDP (160,9 billion rubles) and 0,10% of GDP (83,4 billion rubles), respectively. Of all the analyzed RFs, the EAC had smallest contribution — 82,5 billion rubles (0,1% of GDP).

Discussion

RFs significantly contributed to the development of NCDs [3]. In the present study, we analyzed the contribution of behavioral and metabolic RFs to morbidity and mortality from the main NCDs — CVD, T2D, COPD and cancer of 10 localizations. Behavioral RFs specifies the development of metabolic RFs. For example, obesity is associated with diet and SL. The greatest contribution to CVD morbidity is made by such RFs as HTN (30%) and obesity (23%). Mortality from CVD in the Russian population is determined to the greatest extent by HTN (35%), obesity (23%) and smoking (13%). Smoking makes the largest contribution to mortality from COPD (19%). The morbidity of T2D was largely specified by such RFs as obesity (46%), SL (24,8%) and HTN (18%). The largest contribution to the morbidity and mortality of lung cancer was made by smoking (25,3% and 17%, respectively). The morbidity of colorectal cancer was largely determined by inadequate fruit and vegetable consumption (22%), obesity (21%), and smoking (10,7%), while mortality was determined by inadequate fruit and vegetable consumption (22%) and obesity (21%).

Similar studies carried out in other countries had comparable results. In the UK, tobacco smoking was

mostly associated with cancers and obesity (15,1% and 6,3%, respectively). More than 70% of cancers, including two of the five most common cancers (lung and skin cancers), were associated with behavioral RFs [17]. The greatest contribution to CVD morbidity in the populations of Iran, United States and Spain is made by HTN — 11,37%, 54% and 60%, respectively [18].

EC of NCDs all over the world is estimated from 60% to 75% of world GDP, while 30-60% of all NCDs are caused by behavioral RFs [19]. Accordingly, the contribution of the RFs to the EC of NCDs is significant.

According to our study, the highest EC associated with NCDs was caused by HTN and amounted to 869,9 billion rubles (5938,13 rubles per capita). Obesity and smoking were the next largest contributors to EC due to NCDs. EC due to obesity and smoking in Russia in 2016 amounted to 605 (4134,97 rubles per capita) and 421,4 billion rubles (2876,51 rubles per capita), respectively.

According to a large Canadian study assessing the five RFs in 2015 [5], the EC of overweight was the highest, amounting to $2,7 billion (34%). In second place was tobacco smoking ($2,1 billion (27%)), which coincides with the results of this study.

According to a literature review of 18 Australian studies in last 10 years, the highest EC was observed in obesity, ranging from $840 million to $14,9 billion in 1 year. The second position was occupied by tobacco smoking ($10,5 billion), while the lowest EC was observed from unhealthy diet, amounting to $561 million per year [6], which also generally coincides with the presented study.

In the present study, the EC of individual components of unhealthy diet, such as inadequate fruit and vegetable consumption, high salt intake and daily consumption of processed red meat, amounted to 145,3 billion rubles, 160 billion rubles and 83 billion rubles, respectively. In some studies, the EC of unhealthy diet was assessed by individual components, such as the inadequate fruit and vegetable consumption [6], and in others by the integral index [8]. Direct medical costs associated with excessive intake of saturated fat, salt and sugar in Germany in 2008 amounted to €16,8 billion, which is equivalent to 7% of the total treatment cost (€254 billion). Excessive consumption of saturated fatty acids led to losses of €2,9 billion, mainly due to treatment of diabetes, obesity, CAD, COPD [20]. The annual EC due to inadequate fruit and vegetable consumption is $4,39 billion in Canada [21]. Cadilhac AA, et al. estimated that inadequate fruit and vegetable consumption resulted in health care costs of $243,5 million, production losses of $75 million, 55000 disability adjusted life years (DALYs) and 5000 deaths in Australia [22, 23].

In the present study, the EC of EAC was relatively small compared to other RFs, since the prevalence of harmful alcohol consumption was low, and only this component of alcohol damage was included in the analysis. In Australia, the EC due to EAC ranged from $1,1 to 6,8 billion, and was in fourth place after obesity, tobacco smoking and SL, while in Canada — $10,7 billion and was in third place after obesity and smoking.

Losses due to premature mortality prevailed in the EC pattern in Russia and the proportion of direct costs was significantly lower (from 9,9% for HTN to 20,5% inadequate fruit and vegetable consumption). In the Canadian study, direct costs also accounted for a smaller share of losses compared to indirect losses, which included losses due to premature mortality, temporary and permanent disability, as in the present study, but overall, the proportion of direct costs was higher [5]. It is impossible to summarize the obtained EC due to the analyzed RFs of NCDs in Russia for 2016, since the analysis includes behavioral and metabolic RFs, and the former make a significant contribution to the development of the latter.

The results obtained can serve as an economic justification for population-based preventive measures aimed at reducing the RFs of NCDs, and, as a result, underline the priorities of public health programs.

Study limitations

During analysis of the contribution of RFs to morbidity and mortality from CVD, COPD, T2D, and cancers, we used the RRs from international studies, mainly meta-analyzes and large studies on the European population, since there are no large prospective long-term Russian studies, which could affect the accuracy of the PAR calculation. Russian prospective studies are needed to obtain an RR for the Russian population.

These costs cannot be considered completely to RFs, since many RFs are associated with the development of other diseases, injuries, etc. For example, EAC is associated with road traffic accidents, external cause mortality, etc. Smoking also contributes in an increased risk of tuberculosis. However, this was not the purpose of this study. Also, possible interactions of RFs (for example, high salt intake and HTN) were not taken into account.

Conclusion

For the first time, a comparative assessment of EC due to RFs (smoking, EAC, high salt intake, inadequate fruit and vegetable consumption, daily consumption of processed red meat, SL, obesity, HTN) associated with NCDs was carried out in the Russian Federation. Assessment of the economic damage of NCD RFs allows determining the priority areas in healthcare and substantiating the effectiveness of NCD preventive measures aimed at reducing the RF impact, and, consequently, the burden on the healthcare system and the national economy.

Relationships and Activities: none.

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Factors associated with in-hospital mortality in patients after acute cerebrovascular accident (according to the REGION-M register)

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Aim. To determine the main factors associated with in-hospital mortality in patients after acute cerebrovascular accident based on the medical history data.

Material and methods. The study used the data of retrospective hospital part of the REGION-M register, which included all patients hospitalized in one Moscow city clinical hospital from January 1, 2012 to March 30, 2017 with stroke and transient ischemic attack. We analyzed the presence of following parameters' information in case histories of patients who died in hospital and those who were discharged: risk factors (RF), socio-demographic factors, history of cardiovascular and concomitant diseases. The association of factors recorded at hospital admission with mortality rate was studied, and multivariate logistic regression was constructed. A combination of factors significantly associated with in-hospital mortality was determined.

Results. Of 900 patients (365 (40,6%) men and 535 (59,4%) women) included in the REGION-M register, 216 (24,0%) died in the hospital. Assessment of the RF information presence showed that the smoking data was disclosed in 54,3% of case histories, family history — 1,1%, education level — 8,6%, alcohol consumption — 7,4%, disability — 79,1%, hypercholesterolemia — 6,4%. However, there were no significant differences on the completeness of the data collection on the listed RF between deceased and discharged patients. Factors such as gender, age, and outcome were described in all case histories. Univariate analysis of factors significantly associated with patients' mortality marked out age and history of cardiovascular diseases (coronary artery disease (CAD), atrial fibrillation (AF), venous thrombosis) and/or concomitant diseases (diabetes, anemia). Multivariate logistic regression identified factors associated with increased in-hospital mortality as follows: CAD, AF, diabetes, venous thrombosis.

Conclusion. Hospital-based physicians pay little attention to the recording of cardiovascular RF and socio-demographic parameters in patients with stroke, regardless of the condition severity and outcome. In-hospital mortality is associated with age, CAD, AF, diabetes, and venous thrombosis.

Key words: stroke, register, risk factors, in-hospital mortality.

Relationships and Activities. The study was financially supported by a Pfizer grant, which did not affect the study management, analysis of the results and conclusions made.

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Introduction

Among cardiovascular diseases (CVD) and their complications, for several decades, stroke has been one of the leading deaths causes in the adult population in many countries [1].

Registries are now widely used to study the clinical and demographic characteristics of patients after stroke, its risk factors (RF) and factors affecting the clinical course of disease, the development of complications, death, and to assess the quality of treatment at various management stages.

The registry is a type of observational study carried out in accordance with certain rules for the inclusion of patients, collection, storage and processing of data, which helps in solving a number of research and practical issues of modern health care [2, 3]. One of the largest stroke registries today is the Get With The Guidelines-Stroke (GWTG-Stroke) program created in 2003 with the participation of the American Heart Association/American Stroke Association, which by 2016 had included >4 million patients with stroke [4, 5]. In various regions of the Russian Federation, registries of patients with stroke are also maintained [6-9]. However, not all registries assessed the prognostic value of various factors, as well as long-term prospective follow-up was rarely carried out. More often, the significance of various factors on the stroke development was studied in the registers.

It should be emphasized that the mortality rate in stroke is extremely high both in the acute phase and in the long-term follow-up of patients. According to Russian registries, in-hospital mortality with stroke is ~20% or more, while in foreign registries it varies from 5% to 16%, and in recent years this parameter has decreased [10, 11]. During the first year after stroke, almost every second patient dies, and after 5-8 years, the mortality rate reaches 60-80% [12-14]. Despite the high mortality rate, the significance of various factors influencing the death risk of such patients may vary at different stages of the disease course and differ in different regions.

The aim was to identify the main factors associated with hospital mortality in stroke patients in the retrospective hospital part of the REGION-M registry and which is included in the REGION registry [15].

Material and methods

The design and protocol of the REGION study, carried out in the Moscow and Ryazan, were described in detail in the earlier publications [15, 16].

The REGION-M registry, conducted in Moscow, consisted of 2 stages of patient follow-up: retrospective in-hospital and prospective out-of-hospital.

This article analyzes the results of the in-hospital retrospective part of the REGION-M registry, which included all patients hospitalized in I. M. Inozemtsev City Clinical Hospital of Moscow from January 1, 2012 to March 30, 2017 with stroke and transient ischemic attack. Patients discharged from the hospital were included in the second, prospective, inpatient part of the registry.

The registry protocol was approved by the Independent Ethics Committee of the National Medical Research Center for Preventive Medicine.

The main attention was paid to the analysis of medical history. The registry records contained the patient's passport data, information about the disease onset and the characteristics of hospitalization, as well as data on physical examination and diagnostic tests. A large section of records was devoted to collecting information about the prior CVDs, their RFs, complications, surgical interventions, and data on concomitant diseases. A special section of the records was devoted to information on the results of diagnostic tests performed in the hospital. We collected data on drug therapy taken by patients before hospitalization, in the hospital and recommended to the patient at discharge. Data on the surgeries performed during hospitalization was also collected.

A feature of the retrospective registry is inability to clarify information. However, the authors considered that no information about a disease is one thing, while no data on the RF is another. Therefore, if in-patient records did not contain information about previous CVDs and concomitant diseases, these diseases were considered absent. If there was no information about any RFs, then it was considered that there was no information about it.

Information from the registry records was entered into a specially developed electronic database.

The analysis of the obtained indicators of patients who died in hospital and were discharged was carried out.

In the presented article, for the analysis, we selected the factors registered at the prehospital stage and studied their contribution to mortality rate with the creation of a multiple logistic regression model.

Statistical processing of the obtained data was performed using the IBM SPSS Statistics 23 software (IBM Corp., USA).

At the first stage, using the descriptive statistics, the main characteristics of patients included in the registry were presented: patients who died during hospitalization and patients discharged from the hospital. Absolute values and percentages for qualitative traits were determined. Quantitative indicators were analyzed for distribution normality. Mean values and standard deviations for normally distributed quantitative traits were calculated. Median and interquartile range for non-normally distributed traits were calculated.

At the second stage, the completeness of data collection was assessed. If the prevalence of studied trait was <80%, it was not included in further analysis, since this could lead to false results.

At the third stage, using the Pearson's chi-squared test or Fisher's exact test (for 2×2 contingency tables), factors were identified that were significantly associated with in-hospital mortality.

At the fourth stage, a logistic regression model was created to determine a combination of factors with adjustment for sex and age that have a significant effect on in-hospital mortality. Data are presented as odds ratios with 95% confidence intervals.

Results

The REGION-M registry included 900 patients after stroke: 365 (40,6%) men and 535 (59,4%) women. The mean age of patients was 70,6±14,0 years. The age of women was significantly higher than in men (73,3±13,9 vs 66,5±13,2 years, respectively ($p<0,001$)) (Figure 1). In the hospital, 216 (24,0%) patients died, and 684 (76,0%) patients were discharged.

The mean age of the deceased patients was 76,8±11,5 years, while of those discharged from the hospital — 68,6±14,2 years ($p<0,001$). Among the deceased patients, there were 133 (24,9%) women and 83 (22,7%) men (mean age, 80,1±9,1 years and 71,4±12,8, respectively ($p<0,001$)). Among the patients

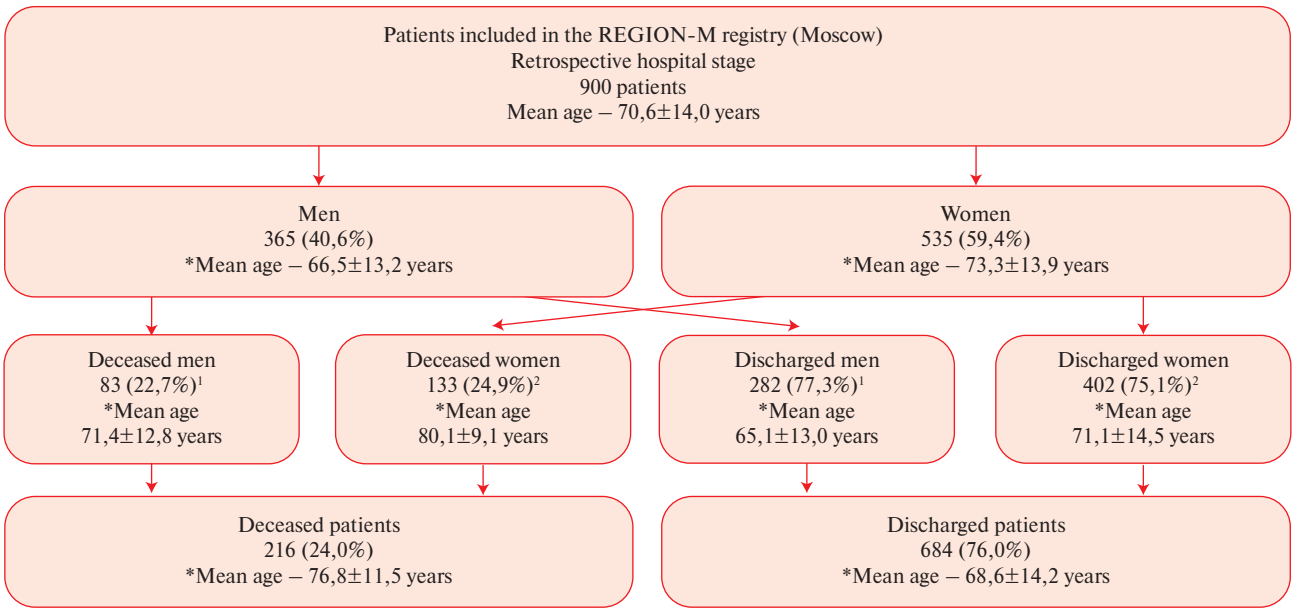


Figure 1. General characteristics of patients.
Note: * — p<0,001; [1] and [2] — indication of the group composition and comparison of the reliability of the difference in average age by sex.

Table 1

Frequency of indicating medical history data (n=900)

Parameter	Survived (n=684)	Deceased (n=216)	Total (n=900)
Sex	684 (100%)	216 (100%)	900 (100%)
Age	684 (100%)	216 (100%)	900 (100%)
Smoking status	394 (57,6%)	95 (44,0%)	489 (54,3%)
Family history of CVD	7 (1,0%)	3 (1,4%)	10 (1,1%)
Education level	56 (8,2%)	21 (9,7%)	77 (8,6%)
Hypercholesterolemia	53 (7,7%)	5 (2,3%)	58 (6,4%)
Alcohol	52 (7,6%)	15 (6,9%)	67 (7,4%)
Disability	552 (80,7%)	160 (74,1%)	712 (79,1%)

who were discharged, there were 402 (75,1%) women and 282 men (77,3%) (mean age, 71,1±14,5 years and 65,1±13,0 years, respectively (p<0,001)) (Figure 1).

Data on the completeness of information collection are presented in Table 1. Sex and age were indicated in all patients. Smoking status was noted in 489 (54,3%) patients, of which only 104 patients smoked (21,3%) and 385 did not. The presence of information about disability was in 79,1% of patients, about hypercholesterolemia — in 58 (6,4%) patients, about alcohol consumption — in 67 (7,4%) patients, about heredity — in 10 (1,1%) of patients. It is important to note that the prevalence of the studied factors practically did not differ between deceased and surviving patients (Table 1).

Due to the fact that the prevalence of the studied factors was complete only by sex and age, and data on other indicators did not exceed 80%, they were not included in further analysis.

Tables 2 and 3 present data on CVDs and comorbidities in history. Among CVDs, the most common were hypertension (HTN) in 856 (95,1%) patients and coronary artery disease (CAD) in 517 (57,4%) patients. Less commonly indicated were atrial fibrillation (AF) (29,8%), heart failure (HF) (18,2%), single myocardial infarction (MI) (19,7%), and stroke (25,7%). The presence of thrombosis was noted in 3,4%, heart defect — 3,0%, MI ⩾2 times — 2,2%, TIA — 2,5% of patients. The results demonstrated higher rates of in-hospital mortality in patients with stroke with a history of CVD and/or concomitant disease. In patients with a combination of CAD, prior MI and AF, in-hospital mortality was 30%. The mortality rate of patients with a history of stroke, HF, and HTN was slightly lower (~25%).

Every fifth patient had diabetes (n=181 (20,1%)) and obesity (n=193 (21,4%)). Moreover, approximately a third of patients (33,1%) with diabetes and every fifth (22,3%) patient with obesity died in the hospital (Table 3).

Chronic lung diseases were indicated in 120 (13,3%) out of 900 patients, cancer — in 90 (10%),

Table 2

Data on CVDs

CVD	Total (% of n=900)	Deceased n=216 (% **)	Discharged n=684 (% ***)	p (χ^2)
Stroke	216 (25,7%)	59 (27,3%)	157 (23,0%)	0,191
TIA	21 (2,5%)	3 (1,4%)	18 (2,6%)	0,292*
CAD	517 (57,4%)	166 (76,9%)	351 (51,3%)	<0,0001
Single MI	177 (19,7%)	58 (26,9%)	119 (17,4%)	0,002
MI ⩾2 times	20 (2,2%)	6 (2,8%)	14 (2,0%)	0,525*
HF	164 (18,2%)	39 (18,1%)	125 (18,3%)	0,942
HTN	856 (95,1%)	209 (96,8%)	647 (94,6%)	0,406
AF	268 (29,8%)	94 (43,5%)	174 (25,4%)	<0,0001
Heart defect	27 (3,0%)	11 (5,1%)	16 (2,3%)	0,075
Thrombosis	31 (3,4%)	16 (7,4%)	15 (2,2%)	<0,0001

Note: * — Fisher's exact test, ** — % of deceased patients, *** — % of discharged patients.

Table 3

Data on comorbidities

Concomitant disease	Total (% of n=900)	Deceased n=216 (% **)	Discharged n=684 (% ***)	p (χ^2)
IGT	81 (9,0%)	14 (6,5%)	67 (9,8%)	0,138
Diabetes	181 (20,1%)	60 (27,8%)	121 (17,7%)	0,001
Anemia	74 (8,2%)	28 (13,0%)	46 (6,7%)	0,004
Obesity	193 (21,4%)	43 (19,9%)	150 (21,9%)	0,528
Cancer	90 (10,0%)	26 (12,0%)	64 (9,4%)	0,252
Chronic kidney disease	80 (8,9%)	21 (9,7%)	59 (8,6%)	0,744
Massive bleeding	3 (0,3%)	1 (0,5%)	2 (0,3%)	0,705*
Chronic lung disease	120 (13,3%)	30 (13,9%)	90 (13,2%)	0,783

Note: * — Fisher's exact test, ** — % of deceased patients, *** — % of discharged patients.

impaired glucose tolerance (IGT) — in 81 (9,0%), chronic kidney disease — in 80 (8,9%), anemia — in 74 (8,2%). In 3 (0,3%) patients, there was prior massive bleeding. The mortality rate among patients with the listed comorbidities was also high: from 17,3% in patients with IGT to 37,8% in patients with a history of anemia.

According to statistical analysis, the presence of CAD, prior MI, AF, venous thrombosis, diabetes and anemia was associated with a higher in-hospital mortality (p<0,05) (Tables 2 and 3).

Figure 2 shows the fourth stage of statistical processing with the creation of a multivariate logistic regression model adjusted for sex and age. Factors such as age, history of CAD, AF, diabetes, venous thrombosis increase in-hospital mortality. The presence of HF in patients was associated with mortality decrease (p<0,008).

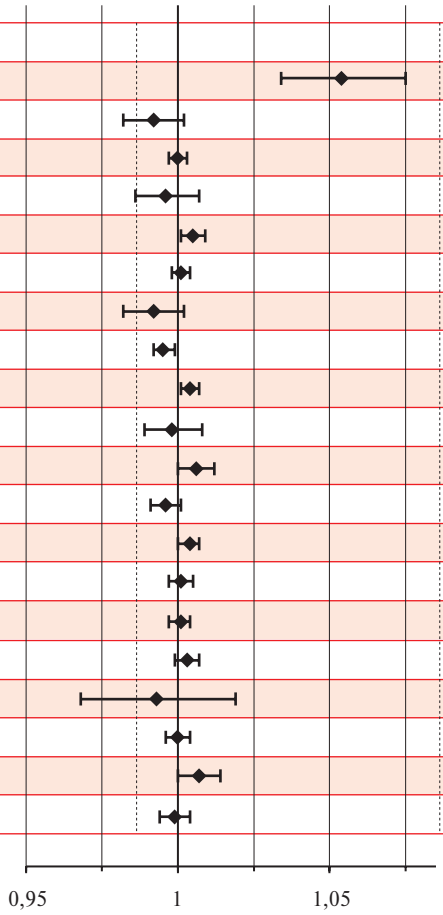
Discussion

According to REGION-M registry, in-hospital mortality remains extremely high: almost every fourth patient hospitalized with stroke dies in the hospital (24,0%). The mortality rate in the groups of men and women differed insignificantly (22,7% vs 24,9%, respectively), however, the mean age of deceased patients was ~9 years higher (p<0,001) in women compared to men. The mean age of the deceased men and women was significantly higher (p<0,001) compared with the mean age of discharged patients (Figure 1).

The obtained indicators coincide with another in- and out-of-hospital registry of patients with stroke (LIS-2), according to which in-hospital mortality was 21,6% [5]. The sex and age ratios of patients who died and were discharged from the hospital were approximately the same as in REGION-M [5]. Women accounts for most of both deceased patients (65,7%) and all those admitted to the hospital (61,6%).

In another Russian registry of inpatients with stroke, conducted in the Smolensk Oblast [6], approximately the same results were obtained: the predominance of women among both admitted and discharged (~60%) patients. Moreover, the mean age of deceased women was >8 years higher than the mean age of deceased men.

In comparison with foreign studies, it was found that in-hospital mortality in stroke patients in Russia is higher: 21-24% vs 5,2-5,6% [3, 12]. The authors of foreign registries emphasize that in the middle of



Parameter	OR (CI 95%)	p
Age	1,054 (1,034-1,075)	p<0,0001
Sex	0,992 (0,982-1,002)	p=0,117
Stroke	1,000 (0,997-1,003)	p=0,953
TIA	0,996 (0,986-1,007)	p=0,492
CAD	1,005 (1,001-1,009)	p=0,006
Primary MI	1,001 (0,998-1,004)	p=0,61
Recurrent MI	0,992 (0,982-1,002)	p=0,127
HF	0,995 (0,992-0,999)	p=0,008
AF	1,004 (1,001-1,007)	p=0,006
HTN	0,998 (0,989-1,008)	p=0,719
Heart defect	1,006 (1,000-1,012)	p=0,069
IGT	0,996 (0,991-1,001)	p=0,14
Diabetes	1,004 (1,000-1,007)	p=0,031
Chronic lung disease	1,001 (0,997-1,005)	p=0,654
Obesity	1,001 (0,997-1,004)	p=0,687
Anemia	1,003 (0,999-1,007)	p=0,16
Massive bleeding	0,993 (0,968-1,019)	p=0,589
Cancer	1,000 (0,996-1,004)	p=0,993
Thrombosis	1,008 (1,000-1,014)	p=0,038
Chronic kidney disease	0,999 (0,994-1,004)	p=0,675

Figure 2. Parameters associated with in-hospital mortality in patients with stroke.
Note: sex adjusted for age; other factors adjusted for sex and age.

the first decade of 21st century, in-hospital mortality in patients with stroke, even in developed countries, was 15-17%, and such a significant decrease in mortality was achieved only after creation of special stroke departments [6, 12]. It should be emphasized that in the Moscow hospital, on the basis of which REGION-M was carried out, a special center was also created. As shown in Russian studies, a set of measures implemented in stroke centers has significantly reduced the rate of stroke mortality in total mortality pattern from 19,2% in 2010 to 15,9% in 2016 [17].

Since the hospital part of REGION-M was retrospective, the studied indicators from the medical records reflect the data actually noted by the doctors. It was impossible to clarify information, respectively, with a quantitative and qualitative analysis of these indicators. It is clear that not all of factors could be included in the logistic regression.

An example of insufficient diagnosis and/or insufficient data on the patient's anamnesis can be the analysis of hypercholesterolemia, which was not included in the logistic regression model, since the information on it was only in 58 out of 900 patients. At the same time, out of 900 patients with stroke, 216 patients had prior stroke, 177 patients — MI, 517 patients — CAD. Such indicators suggest the presence of a greater number of lipid metabolism disorders in patients with a history of severe cardiovascular disease.

The study showed that only sex, age, and outcome of the disease were indicated in all patients, since this information is required when filling out the medical records. The presence of other indicators is significantly lower, which may be partly due to the impossibility of a qualitative history collection by doctors in patients with stroke upon admission and/or due to insufficient attention to these RFs. The smallest number of patients included in REGION-M had data on heredity, alcohol consumption, hypercholesterolemia, and educational level. Smoking is indicated a little more than half of the patients. Information on disability was noted in 80% of patients. It can be seen that data on RFs did not always depend on the disease outcome (mortality), and hence on the patient's condition during hospitalization. For example, information on smoking status was available in 394 (57,6%) survived and 95 (44%) deceased patients, while the data on hypercholesterolemia was noted in 53 (7,7%) and 5 (2,3%) patients, respectively. For the

rest of RFs, the difference in deceased and discharged patients did not exceed 1% (Table 1).

REGION-M registry was the closest to the LIS-2 registry in terms of objectives and methods. According to the LIS-2 registry, there was also a significant amount of unknown data on studied factors and diseases. For example, a history of hypercholesterolemia was unknown in 67,5% of all patients, while the obesity status was not indicated in 36,3% of patients. The proportions of patients with diabetes in the LIS-2 and REGION-M registries differed insignificantly — 20,6% and 20,1%, AF — 26,8% and 29,8%, HTN — 86,8% and 95,1%, stroke — 20,7% and 25,7%. The proportion of patients with CAD (15,6%) and myocardial infarction (12,8%) in the LIS-2 registry were significantly less.

The univariate analysis revealed the following factors associated with hospital mortality: age, CAD, MI, AF, HF, venous thrombosis, diabetes and anemia. When the selected factors were included in the multivariate analysis, it was found that the age of patients, a history of AF, diabetes, CAD, and thrombosis were associated with an increase in in-hospital mortality (Figure 2). The presence of HF in patients was associated with a decrease in mortality.

The factors associated with a high in-hospital mortality in the REGION-M registry in some cases coincided with those in foreign registers (age, AF, diabetes). However, the revealed negative relationships between mortality and HF were not confirmed in foreign studies. Perhaps this indicates that the doctors in the REGION-M registry did not always correctly diagnose HF. It is also possible that the treatment of patients with HF was more complete.

In the LIS-2 registry, indicators influencing in-hospital mortality were the age of patients, stroke type, the severity of impaired consciousness upon admission, a history of HF and AF. When compared with REGION-M, the indicators were slightly different. This is probably due to some difference in the parameters associated with in-hospital mortality included in the multivariate logistic regression model.

Conclusion

Hospital-based physicians pay little attention to the recording of cardiovascular RF and socio-demographic parameters in patients with stroke, regardless of the condition severity and outcome. In-hospital mortality is associated with age, CAD, AF, diabetes, and venous thrombosis.

Relationships and Activities. The study was financially supported by a Pfizer grant, which did not affect the study management, analysis of the results and conclusions made.

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Angioplasty and carotid artery stenting: clinical and morphological factors affecting long-term outcomes

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Aim. To identify clinical and morphological factors affecting the long-term outcomes of endovascular angioplasty and carotid artery stenting.

Material and methods. The analysis included 198 patients after carotid artery stenting between 03.2014 and 05.2018. There were following inclusion criteria: (1) 50% of symptomatic or 70% of asymptomatic carotid artery stenosis of according to NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria; (2) follow-up for each patient for at least 1 year. Using the univariate and multivariate logistic regression, risk factors associated with adverse events were determined.

Results. The incidence of major adverse events during the 12-month follow-up was 9,6% (n=19), including 4 (2%) major and 6 (3%) minor strokes, 7 (3,5%) cases of transient ischemic attack; one (0,5%) patient had transient blindness and one (0,5%) died in the long-term follow-up period due to acute cerebrovascular accident in the target arterial territory. Also, 11 (5,6%) patients had restenosis >50% after 12-month follow-up. Multivariate analysis showed that long-term outcomes were significantly affected by: age >70 years (odds ratio (OR)=1,27, 95% confidence interval (CI): 1,07-1,61 (p=0,01); using of open-cell stents (OR=1,02, 95% CI: 1,01-1,03 (p=0,034)); contralateral stenosis (OR=1,28, 95% CI: 1,05-1,57 (p=0,01); lesion length >15 mm (OR=1,46, 95% CI: 1,12-1,89 (p=0,01)); residual stenosis <30% (OR=1,38, 95% CI: 1,09-1,49 (p=0,012)); complicated atherosclerotic plaque (OR=1,78, 95% CI: 1,21-2,34 (p=0,007)). The development of in-stent restenosis was significantly influenced by factors such as the residual stenosis <30% (OR=1,26, 95% CI: 1,1-1,65; p=0,017) and severe plaque calcification (OR=1,24, 95% CI: 1,04-1,31; p=0,02).

Conclusion. The results obtained indicate the need for more careful preparation for endovascular intervention. Such factors as the use of open-cell stents, contralateral stenosis, lesion length >15 mm, and residual stenosis <30% may be associated with an increased risk of adverse events.

Key words: carotid artery atherosclerosis, stenting, restenosis, calcification.

Relationships and Activities: none.

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Introduction

Stroke is the leading cause of death and disability in the developed countries of the world [1, 2]. Until recently, the carotid endarterectomy (CE) was the gold standard in the treatment of carotid artery stenosis as a primary and secondary prevention of stroke. Today transluminal balloon angioplasty and carotid artery stenting (CAS) are becoming an alternative to CE [3, 4]. Studies such as CREST (Carotid Revascularization Endarterectomy versus Stenting Trial), ACT1 (The Asymptomatic Carotid Trial-1), SAPPHIRE (Stenting and Angioplasty With Protection in Patients at HIgh Risk for Endarterectomy), the purpose of which was to compare long-term outcomes after CE and CAS, although did not reveal significant differences in long-term outcomes after these interventions, they pointed to the weak point of CAS — intraoperative and early postcomplications complications. For example, in the CREST study, which included 2502 patients and compared the results of CE and CAS, the incidence of large and minor strokes in the intraoperative period was significantly higher in the CAS group, which were caused by intra- and postoperative microembolization [5]. The development of such adverse clinical events can be facilitated by clinical, anatomical, morphological and technical factors. The aim was to study the efficacy of angioplasty and CAS and to identify risk factors affecting the results of endovascular treatment in the long-term follow-up period.

Material and methods

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The medical ethics committee approved this study.

We analyzed the treatment results of 198 patients who underwent CAS in the period from March 2014 to May 2018 was carried out. There were following inclusion criteria: presence of 50% symptomatic or 70% asymptomatic carotid artery stenosis (as calculated in NASCET); patient follow-up for at least 1 year.

All patients were examined by a neurologist before and after the intervention. To assess the degree of carotid lesions, all patients underwent duplex ultrasound, computed tomography, or angiography of the brachiocephalic arteries.

Within 12 months after stenting, complications were recorded: large and minor strokes, transient ischemic attack (TIA), Amaurosis fugax, myocardial infarction and death; in-stent restenosis was also assessed during 12 months after intervention.

To identify factors associated with adverse events after CAS, the following variables were analyzed: (1) anatomical and morphological parameters — stenosis degree, contralateral stenosis >50%, plaque calcification, complicated plaque, plaque length and signs of parietal thrombosis; (2) clinical parameters — age, sex, smoking, hypertension, diabetes, heart failure (HF), neurological symptoms 6 months prior intervention ("symptomatic stenosis"), (3) technical parameters — use of distal/proximal cerebral protection device, various implantable stents, dilation, residual stenosis after stenting.

CAS was performed under local anesthesia with blood pressure monitoring. All patients received dual antiplatelet therapy (clopidogrel 75 mg/day, aspirin 100 mg/day) for at least 3 days before surgery. To prevent postoperative hypotension, antihypertensive therapy was missed on the day of surgery [6]. According to the generally accepted Seldinger technique, an 8-Fr introducer was inserted into the femoral artery, followed by a JR-4 guide catheter into the target common carotid artery. After puncture of the femoral artery and introducer installation, heparin was injected intravenously at the rate of 100 U/kg. In the postoperative period, heparin was not injected. In all patients included in this study, depending on the individual anatomical and angiographic features, we used distal or proximal cerebral protection system. Pre- or post-dilation balloon angioplasty was performed as needed. During stenting, only self-expanding stents with different cell designs were used: closed-cell — WALLSTENT (Boston Scientific, USA), XACT (Abbot, USA) (35%), Adapt (Boston Scientific, USA); open-cell — PRECISE (Cordis, USA), Protégé (Medtronic, USA); hybrid design — Cristallo Ideale (Medtronic, USA) (40%).

Statistical analysis was performed using the SPSS 21.0 software (SPSS Inc, Chicago, IL, USA). To compare the two groups, the Mann-Whitney U test was used for quantitative variables and the two-tailed Fisher's exact test or Pearson's chi-squared test — for qualitative variables. To identify the association of blood pressure lowering factors with other variables, we used univariate and multivariate analysis — binary logistic regression with the calculation of odds ratio (OR) and 95% confidence interval (CI). The multivariate analysis included variables with $p<0,05$, selected based on the univariate analysis.

Results

The main demographic and clinical characteristics of patients are presented in Table 1. It can be seen that 76 (38,4%) patients were with symptomatic carotid lesions (48 patients with stroke, 25 patients with TIA, 3 patients with amaurosis fugax within the last 6 months). Age of 46% (n=91) of patients were >70 years. Anatomical and morphological characteristics of the lesions are presented in Table 2. All patients underwent surgery using cerebral protection systems. In 34 (17,2%) patients, >50% carotid stenosis on the contralateral side was observed. In 39 (20%) patients, a complicated plaque was noted. In 42 (21,2%) patients, the conservative strategy was used with residual minor

Table 1

Clinical characteristics

	n=198
Age, years	67±8,3
Age >70 years	91 (46%)
Women	55 (27,8%)
Hypertension	169 (85,4%)
Diabetes	54 (27,3%)
Smoking	97 (49%)
Coronary artery injury	48 (24,2%)
Peripheral artery disease	19 (9,6%)
HF	13 (6,6%)
Symptomatic carotid artery stenosis	76 (38,4%)
Large or minor stroke	48 (24,2%)
TIA	25 (12,6%)
Amaurosis fugax	3 (1,5%)
Uric acid, mg/dl	5,6±1,9
Total cholesterol, mmol/l	4,9±1,6
Triglycerides, mmol/l	1,69±0,42
Low density lipoprotein cholesterol, mmol/l	3,4±0,4
High density lipoprotein cholesterol, mmol/l	0,96±0,14
Creatinine, μmol/L	97,2±35,3

Table 2

Anatomical and morphological characteristics of the lesions

	n=198
Stenosis >70%	174 (87,9%)
Contralateral stenosis >50%	34 (17,2%)
Contralateral occlusion	12 (6,1%)
Cerebral protection system	198 (100%)
Distal protection system	179 (90,5%)
Proximal protection system	19 (9,5%)
Predilation	60 (30,3%)
Postdilation	119 (60,1%)
Close-cell stent design	138 (69,7%)
Open-cell stent design	22 (11,1%)
Hybrid stent design	38 (19,2%)
Lesion length, mean, mm	10
Complicated plaque	39 (20%)
Parietal thrombosis	5 (2,5%)
Residual stenosis <30%	42 (21,2%)

stenosis (<30%). The number of major adverse events within 12-month follow-up was 9,6% (4 (2%) large and 6 (3%) minor strokes; 7 (3,5%) TIAs; 1 (0,5%) amaurosis fugax; 1 (0,5%) patient died in the long-term follow-up). Also, in 11 (5,6%) patients, in-stent restenosis >50% was verified after 12-month follow-up (Figure 1).

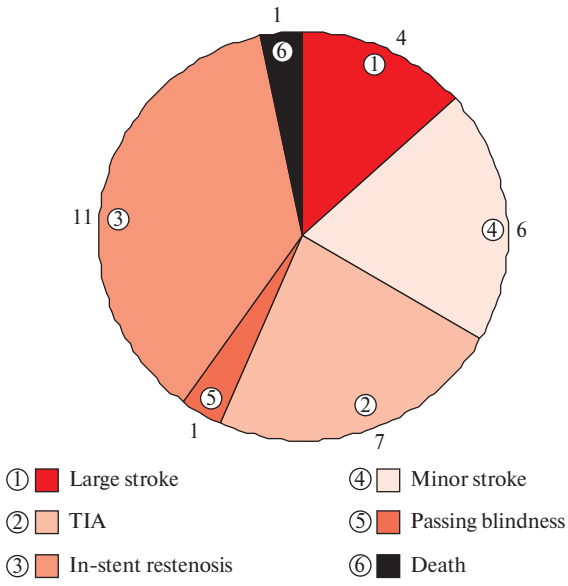

Figure 1. Complication structure (12 months).

Univariate analysis was used to determine the relationship of clinical, anatomical, morphological and technical characteristics with the development of adverse events (Table 3) and in-stent restenosis 12 months after the intervention (Table 4). Multivariate analysis showed that the long-term results were significantly influenced by the age of patients >70 years (OR, 1,27, 95% CI, 1,07-1,61; p=0,01), using open-cell stents (OR, 1,02, 95% CI, 1,01-1,03; p=0,03), contralateral stenosis (OR, 1,28, 95% CI, 1,05-1,57; p=0,01), lesion length >15 mm (OR, 1,46, 95% CI, 1,12-1,9; p=0,01), residual stenosis <30% (OR, 1,38, 95% CI, 1,09-1,49; p=0,01) as well as the complicated plaque (OR, 1,78, 95% CI, 1,21-2,34; p=0,01) (Figure 2). The development of in-stent restenosis was significantly influenced by such factors as the residual stenosis <30% after CAS (OR, 1,27, 95% CI, 1,1-1,65; p=0,02) and severe calcification of plaques (OR, 1,24, 95% CI, 1,04-1,31; p=0,02).

Discussion

Present study with 198 patients revealed that the following characteristics are associated with an increased risk of adverse events: age, contralateral lesions, open-cell design of the stent, and plaque morphology. The incidence of 12-month complications in the presented study was 9,6%, which is consistent

Table 3

Comparison of characteristics of patients with/without major adverse cardiac and cerebrovascular events

	MACCE, n=19	No MACCE, n=179	p
Age, years	73,4±6,8	67,9±8,6	
Age >70 years	16 (84,2%)	92 (51,4%)	0,04
Women	12 (63,2%)	43 (24,1%)	0,01
Hypertension	16 (84,2%)	153 (85,5%)	0,72
Diabetes	12 (63,2%)	42 (23,5%)	0,04
Smoking	9 (47,4%)	88 (49,2%)	0,83
Coronary artery injury	4 (21%)	44 (24,6)	0,73
Peripheral artery disease	2 (10,5%)	17 (9,5%)	0,62
HF	4 (21%)	9 (5%)	0,21
Symptomatic carotid artery stenosis	11 (57,9%)	65 (36,3%)	0,31
Stenosis >90%	8 (42,1%)	29 (16,2%)	0,28
Contralateral stenosis >50%	14 (73,7%)	20 (11,2%)	0,01
Contralateral occlusion	3 (15,8%)	9 (5%)	0,17
Cerebral protection system			
Distal protection system	18 (94,7%)	161 (89,9%)	0,49
Proximal protection system	1 (5,3%)	18 (10,1%)	0,22
Predilation	6 (31,6%)	54 (30,2%)	0,91
Postdilation	15 (78,9%)	104 (58,1%)	0,87
Close-cell stent design	7 (36,8%)	131 (73,2%)	0,24
Open-cell stent design	10 (52,6%)	12 (6,7%)	0,02
Hybrid stent design	2 (10,5%)	36 (20,1%)	0,43
Lesion length >15 mm	7 (36,8%)	9 (5%)	0,01
Complicated plaque	15 (78,9%)	24 (13,4%)	<0,01
Parietal thrombosis	2 (10,5%)	3 (1,7%)	0,07
Residual stenosis <30%	15 (78,9%)	27 (15,1%)	<0,01

Table 4

Comparison of characteristics of patients with/without restenosis

	With restenosis, n=11	Without restenosis, n=187	p
Diabetes	2 (18,2%)	52 (27,8%)	0,64
Smoking	4 (36,4%)	93 (49,7%)	0,58
Symptomatic carotid artery stenosis	4 (36,4%)	68 (36,3%)	0,88
Stenosis >90%	4 (36,4%)	33 (17,6%)	0,08
Severe plaque calcification	9 (81,9%)	27 (14,4%)	<0,01
Close-cell stent design	7 (63,3%)	131 (70%)	0,38
Open-cell stent design	2 (18,2%)	20 (10,7%)	0,28
Hybrid stent design	2 (18,2%)	36 (19,2%)	0,43
Lesion length >15 mm	1 (9,1%)	15 (8%)	0,58
Complicated plaque	2 (18,2%)	37 (19,8%)	0,73
Parietal thrombosis	9 (81,9%)	33 (17,6%)	<0,01

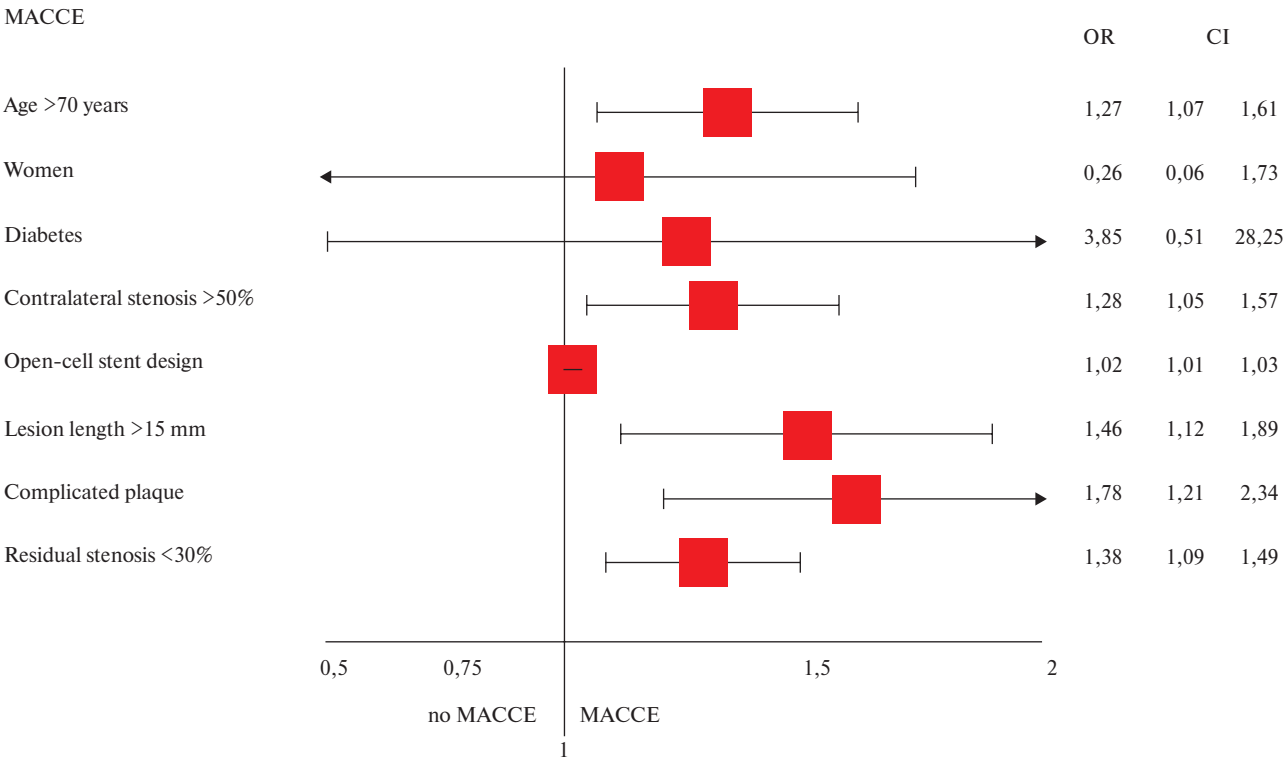

Figure 2. Independent risk factors associated with adverse events (multivariate analysis).

with other studies. For example, in the ARCHer, BEACH, and SAPPHIRE studies, the incidence of major adverse cardiac and cerebrovascular events amounted to 9,6%, 9,1%, 9,9%, respectively [7-9]. Clinical, anatomical, morphological, and technical factors can play an important role in the development of adverse events. The study by Lee HJ, et al. [10] showed that the routine use of open-cell stents significantly increases the number of intraoperative neurological events. In the present study, multivariate analysis also showed the relationship of this factor with the development of adverse clinical events. In our opinion, at present, the use of open-cell stents is advisable only in rare cases of pronounced convoluted lesion. According to the presented study, it was revealed that the lesion length >15 mm and the complicated nature of the atherosclerotic plaque are independent predictors of adverse events. This is due to the large volume of atherosclerotic plaque and the high risk of intraoperative microembolization of cerebral arteries in patients who underwent the intervention with a distal cerebral protection system. Another independent factor that increases the number of adverse clinical events is the conservative angioplasty, in which, after stent implantation and residual stenosis <30%, it is customary to complete the intervention without use of aggressive strategy. This is due to the fact that dilatation in the carotid sinus area is often accompanied by transient

bradycardia with episodes of asystole and syncope, which psychologically strongly affects the operating surgeon. According to the study by Harada K, et al. [11], dilatation in stent area significantly increases the frequency of microembolization and worsens the prognosis in patients. However, according to the results of the presented study, residual stenosis <30% (OR, 1,38, 95% CI, 1,09-1,48; p=0,01) was an independent factor in increasing the risk of adverse events. This may be due to the technological characteristics of stents, which are made of an alloy containing nitinol, which in the postoperative period contribute to stent expansion to the factory setting dimensions. At the time of additional deployment, the residual atherosclerotic plaque covered with a stent can prolapse through the stent cells into the artery lumen, which can cause cerebral embolization and neurological deficit. This theory was supported in the study by Ruffino MA, et al. [12], which, according to the data of diffusion-weighted magnetic resonance imaging, showed the new microembolizations in the period from 24 h to 30 days after the intervention [12, 13].

Also in the present study, it was shown that the development of in-stent restenosis was significantly influenced by such factors as the residual stenosis <30% (OR, 1,26, 95% CI, 1,09-1,64; p=0,01) and severe plaque calcification (OR, 1,24, 95% CI, 1,04-1,31; p=0,02), which was also confirmed in the study by Daou B, et al. [14].

Conclusion

The results obtained indicate the need for more careful preparation for endovascular intervention. Such factors as the use of open-cell stents, contralateral stenosis, lesion length >15 mm, and residual stenosis <30% may be associated with an increased risk of adverse events.

Relationships and Activities: none.

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Intermediate results of the prospective randomized study on the effect of *lamina vastoadductoria* dissection after superficial femoral artery stenting on the restenosis incidence in TASC-II type C and D lesions

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Aim. To compare the effectiveness of superficial femoral artery (SFA) stenting with/without *lamina vastoadductoria* dissection.

Material and methods. The study included are 70 patients with TASC-II type C and D lesions. All patients were divided onto 2 groups: group 1 (n=35) — conventional SFA stenting, group 2 (n=35) — SFA stenting with *lamina vastoadductoria* dissection. The average lesion length in group 1 was 22,92±5,62 cm, in group 2 — 21,2±5,42 cm. The primary endpoint was the absence of binary restenosis and reocclusion. Secondary composite endpoint was procedural success, limb salvage, secondary patency of the operated segment, intraoperative complications. The groups were comparable in age, sex, risk factors and comorbidities.

Results. The procedural success in both groups was 100%. Primary patency after 24 months was 28,5% in group 1 and 60% in group 2. During the 24-month follow-up period, we recorded 1 death in group 2 due to myocardial infarction. In group 1, 2 deaths due to myocardial infarction and pancreatic cancer metastasis were recorded. Limb salvage was 100% in both groups. There were no intraoperative complications in both groups.

Conclusion. *Lamina vastoadductoria* dissection is safe and does not lead to limb functional limitations. Biomechanical changes in the distal SFA segment contribute to the improvement of primary patency after stenting of SFA long lesions. Preliminary results of the single-center pilot study demonstrate the safety and efficacy of SFA stenting with *lamina vastoadductoria* dissection, emphasizing the need for further larger studies to compare it with conventional stenting and to assess the effectiveness during the long-term follow-up.

Key words: superficial femoral artery, TASC-II type C and D, biomechanical forces.

Relationships and Activities: none.

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Introduction

Peripheral arterial disease (PAD) is a global problem that continues to grow and is the cause of disability/mortality in the population. In the population aged 65 and over, the prevalence of PAD varies from 12% to 20%, while the risk of disease increases with the age [1].

PAD ranks third in cardiovascular mortality [2]. Superficial femoral (SFA) and popliteal arteries (pP) are the most common areas of PAD (>50%) [3, 4].

With long SFA, open surgical interventions are the first-line strategy [5]. However, endovascular interventions are widely implemented for infrainguinal arterial reconstruction, which is associated with lower mortality and complication rates. The success and limb-sparing rates are comparable and, if necessary, open surgery can be the definitive treatment.

Endovascular treatment options are: angioplasty (with and without drug-eluting balloons), stenting (bare-metal and drug-eluting stents), and cytoreduction techniques (atherectomy, laser). For SFA revascularization, the technical success of percutaneous transluminal angioplasty reaches 95%. But reliable data from large randomized, controlled trials are still lacking for SFA TASC II types C, D lesions, although this type is prevalent [6].

The restenosis rate after primary stenting is quite high — from 30% to 40%. About 65% of patients after primary revascularization of SFA return with in-segment restenosis [7]. With long lesions, after implantation of first generation stents, fracture was observed in 50% of patients within 1 year [8]. The reason for this is often associated with physiological deformities of the operated artery [9], but the question

of the effect of stent fracture on the restenosis development is controversial [10].

Percutaneous transluminal angioplasty or first-generation peripheral stent implantation had a high percentage of restenosis during 1-year follow-up (>60%) and an increase in the lesion extent. And within 2 years, the primary patency is 26% with long lesions of the femoral-popliteal segment [11].

The combination of re-narrowing of the operated arterial segment with implant fracture contributed to the further study of the mechanical properties of nitinol stents [8].

The main directions in stent modification were as follows: stent architecture, material composition and coating. The new generation stents are more durable, but more adaptable and longer (up to 25 cm) [11].

At the same time, there remains a significant risk of second-generation stent fracture after their implantation in patients with long SFA lesions, which leads to a higher rate of restenosis and reocclusion — up to 37% within a year [9].

The arteries of the femoral-popliteal segment are located in the fascial canals, where in some places they are fixed, and in others they are mobile. These features give the arterial wall unique biomechanical, anatomical and hemodynamic forces that cause changes in the artery geometry the during limb movement. Walking induces axial compression. Musculoskeletal interactions cause radial compression and cyclic deformations, while pulsating blood flow induces repeated radial expansion. This unique biomechanical environment is not observed in other vascular systems and may explain the predisposition of SFA to atherosclerotic lesions, which are usually diffuse and complex, do not respond well to standard revascularization methods, and also tend to recur, which requires reinterventions [12].

To improve long-term results, studies are focused on changing the properties of the stent, while there are no works on changing the biomechanical properties of SFA. Taking into account the above, the search for the optimal method for treatment of long SFA lesions is an urgent issue.

According to the hypothesis of current study, an increase in the mobility of the distal SFA area will contribute to a decrease in the curvature of operated arterial segment in this area, which, in turn, will reduce the risk of stent fracture.

To increase the physiological mobility of SFA and reduce the restenosis rate, it is proposed to supplement the standard SFA stenting with a dissection of the anterior wall of anteromedial intermuscular septum. It is suggested to clip and disinsert 2 proximal arteries around the knee joint. This procedure is standard for accessing the distal SFA for femoral-to-popliteal surgery. Dissection of the fascia in this area and ligation of above arteries does not lead to functional limitation of operated artery.

The aim was to evaluate the effect of *lamina vastoadductoria* dissection with the intersection of collateral branches on the stented SFA patency in patients with long lesions.

Material and methods

This prospective, single-center, randomized, study included 70 patients after repair of 70 vessels due to TASC II type C, D SFA lesions (Rutherford category 3-6 ischemia), who agreed to participate in the study. Patients with acute limb ischemia were not included in the study. Inclusion and exclusion criteria are presented in Table 1.

The demographic characteristics of groups and comorbidities are shown in Table 2. Patients were randomized into 2 groups using sealed code envelope method. The groups were comparable in age, sex and comorbidities. In the first group, the standard SFA stenting was performed; in the second group, the SFA stenting was supplemented by *lamina vastoadductoria* dissection.

Characteristics of lesions and limb ischemia according to Rutherford-Becker in groups are shown in Table 3.

During hospitalization, all patients were measured for the ankle-brachial index (ABI) and underwent duplex ultrasound of lower limb arteries using a VOLUSON 730 system (GE Healhtcare, Zipf, Austria). We also performed contrast-enhanced (Iomeron 400 (Bracco, Milan, Italy)) multislice computed tomography (MSCT) angiography of lower limb arteries using a Aquilion One scanner (Toshiba, Tokyo, Japan) to clarify the anatomy and the volume of the lesion.

Drug preparation included pre-procedure aspirin (300 mg/day), starting at least one day after the procedure. All subjects took aspirin (100 mg/day) for a long time and clopidogrel (75 mg/day) for 3 months.

In both groups, we performed ipsilateral or contralateral arterial access. Recanalization was performed with a hydrophilic 0,035-inch guidewire. Before the start of procedure, heparin (5000 U) was injected intravenously. Primary angioplasty was performed with bare balloon catheters. After angioplasty, a self-expanding nitinol bare metal stent was implanted in accordance with the American College of Cardiology/American Heart Association guidelines [13]. Stents were not implanted the middle or distal third of popliteal artery.

After SFA stenting in the second group under local anesthesia, on day 1 after surgery, access to its distal area at the exit from the Hunter's canal and 1 segment of the popliteal artery was performed. The anteromedial intermuscular septum was dissected, the arteries were ligated and cut off: *a. superior medialis genus, a. superior lateralis genus* (Figure 1).

In most cases, one stent implantation was required to repair the arterial lesion, however, due to long lesion or artery dissection, multiple stents were required. Stent overlap was ~5-10 mm (Table 4).

There were following follow-up periods: in-hospital stage, 6 and 12 months after discharge from the hospital. At the same time, the assessment of clinical symptoms, measurement of ABI and ultrasound of the operated segment were performed. If during the observation period stenosis/occlusion of the operated segment, confirmed by ultrasound, was detected, the patients additionally underwent MSCT angiography.

The primary endpoint is assessed as primary vascular patency, namely the absence of binary restenosis (⩾50%) and reocclusion.

The secondary composite endpoint included: success, limb-sparing, secondary patency of the operated segment, and intraoperative complications.

Statistical analysis. Distribution normality of quantitative data was assessed using the Shapiro-Wilk W test was used. Normally distributed quantitative traits are presented as mean±standard deviation. Non-normally distributed quantitative traits are presented as a median with a 95% confidence interval (CI). The quantitative differences between the groups were determined using the Mann-Whitney U-test. For qualitative traits, the exact two-tailed Fisher's test was used. Comparative analysis of survival curves and freedom from clinically significant events was performed using the log-rank test using the Kaplan-Meier method. Simple and multiple logistic regression was used to identify predictors of a significant event. Cox proportional-hazards regression was used to assess the relationship between one or more continuous or categorical variables and the time to an adverse event. The differences were considered significant at $p<0,05$.

Results

The surgical success in both groups was 100%; there were no intraoperative complications. There were no deaths in the 30-day period. During the follow-up period, we recorded 1 lethal outcome in group 2 from myocardial infarction. In group 1, 2 deaths from myocardial infarction and metastasis of a pancreatic cancer were recorded. In the postoperative period, an increase in ABI was noted in both groups. The ABI dynamics in control points between the

Table 1

Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
45-80 years of age	NYHA class III-IV HF
Primary TASC II type D SFA lesion	Decompensated pulmonary heart disease
Rutherford category 3-6 ischemia	Severe hepatic or renal failure (bilirubin >35 mmol/L, glomerular filtration rate <60 ml/min)
Informed consent	Multiple drug hypersensitivity
Satisfactory outflow channel	End-stage cancer
	Stroke
	Severe calcification of lower limb arteries
	Patients with significant lesion of the common femoral artery
	Patient refusal to participate or continue to participate in the study

Table 2

Characteristics of groups

	Group 1 (n=35)	Group 2 (n=35)	p-value
Sex, M/F	25/10	24/11	N/A
Mean age (±standard deviation)	65±6,62	66,7±9,39	0,256
Mean ABI (±standard deviation)	0,49±0,114	0,51±0,096	1,0
Hypertension	31 (89%)	32 (91%)	0,671
Hypercholesterolemia	14 (40%)	20 (57%)	0,396
Smoking	17 (49%)	22 (63%)	0,393
Chronic renal failure	13 (37%)	8 (23%)	0,196
Diabetes	13 (37%)	6 (17%)	0,538
Coronary artery disease	28 (80%)	28 (80%)	1,0

Table 3

Limb ischemia categories in patients and characteristics of arterial lesions

Limb ischemia category (Rutherford)	Group 1 (n=35)	Group 2 (n=35)	p-value
3	29 (83%)	25 (71%)	0,32
4	4 (11%)	7 (20%)	0,41
5	1 (3%)	3 (9%)	0,61
6	1 (3%)	0	1
Characteristics of arterial lesions			
Stenosis/occlusion	12/23	10/25	p=0,741
Arterial lesion length (±standard deviation)	22,92±5,62 (cm)	21,2±5,42 (cm)	p=1
Mean artery diameter	5±0,81 (mm)	4,73±0,76 (mm)	p=0,15
Outflow vessel (Rutherford)	6,32±1,71	6,04±2,43	p=0,79

Table 4

Number of stents implanted

Number of stents implanted	Group 1 (n=35)	Group 2 (n=35)	p-value
1	24 (69%)	25 (71%)	1
2	11 (31%)	10 (29%)	1

Table 5

Dynamics of ABI change (±standard deviation) in control points

Follow-up periods	Group 1 (n=35)	Group 2 (n=35)	p-value
Before the intervention	0,49±0,12	0,52±0,1	1
Before discharge	0,9±0,06	0,9±0,1	1
3 months	0,84±0,14	0,83±0,15	1
6 months	0,76±0,15	0,78±0,17	1
12 months	0,7±0,2	0,77±0,16	1

Table 6

Predictors of restenosis and reocclusion of the operated segment (logistic regression)

Predictor	Odds ratio [95% CI]	p-value
Hypertension	0,69 [0,1; 4,8]	0,7
Hypercholesterolemia	0,44 [-1,98; 0,34]	0,16
Smoking	0,84 [0,23; 3,13]	0,79
Chronic renal failure	0,74 [-1,5; 0,93]	0,62
Diabetes	0,18 [0,04; 0,81]	0,02
Coronary artery disease	1,1 [0,26; 4,58]	0,89
Treatment method	3,78 [1,1; 12,5]	0,026

Table 7

Predictors of restenosis and reocclusion of the operated segment (odds ratio)

Predictor	Odds ratio [95% CI]	p-value
Hypertension	1,32 [0,31; 5,6]	0,71
Hypercholesterolemia	1,52 [0,66; 3,47]	0,32
Smoking	0,99 [0,44; 2,21]	0,98
Chronic renal failure	1,07 [0,46; 2,5]	0,87
Diabetes	2,5 [1,1; 5,65]	0,02
Coronary artery disease	0,98 [0,37; 2,62]	0,97
Treatment method	0,47 [0,2; 1,09]	0,08

groups did not differ significantly at all follow-up periods (Table 5).

To assess the effect of comorbidities on restnosis/reocclusion, a multivariate analysis was performed, according to which the type 2 diabetes (T2D) significantly affected the long-term outcome. To clarify the influence of each factor, a logistic regression and odds ratio calculation was carried out.

The presence of T2D was a predictor of restenosis/reocclusion. The logistic regression also showed superiority in patients underwent experimental procedure, although odds ratios did not significantly differ between the groups (Tables 6, 7).

The Spearman correlation analysis showed that the smaller the diameter of the operated segment, the higher the risk of restenosis/reocclusion (Figure 2).

According of Spearman's correlation analysis, the ischemia category did not affect the primary patency during the follow-up period (Figure 3).

Primary patency at control points for group 1 was as follows: 3 months — 72%, 6 months — 60%, 12 months — 36%. For group 2, the primary patency was as follows: 3 months — 80%, 6 months — 76%, 12 months — 72% (Figure 4). By 12 months, the restenosis/reocclusion ratio in group 1 was 3/13, and in group 2 — 4/3 (Figure 4).

During the follow-up period, all patients took medication as prescribed.

There were no reinterventions during the follow-up period in both groups. In patients with significant restenosis/reocclusion of the operated segment, acute ischemia did not occur in any case. There was a return

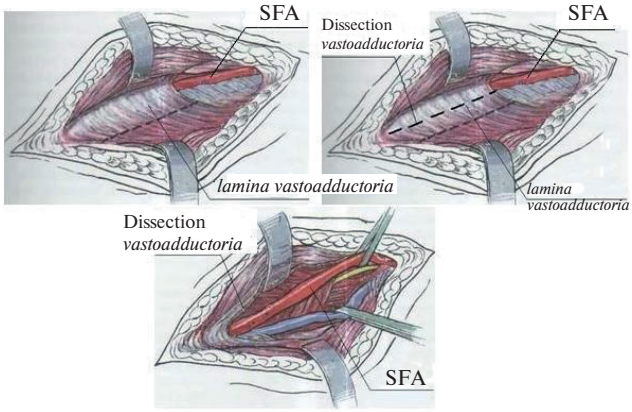

Figure 1. Dissection stages of *l. vastoadductoria*.
Note: SFA — superficial femoral artery.

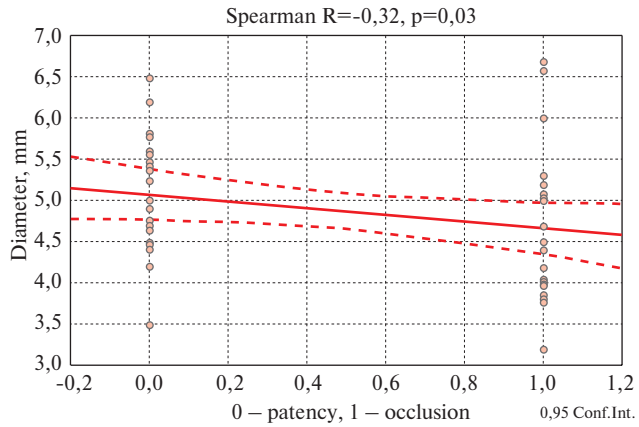

Figure 2. Correlation of the primary patency of the operated segment on the SFA diameter.

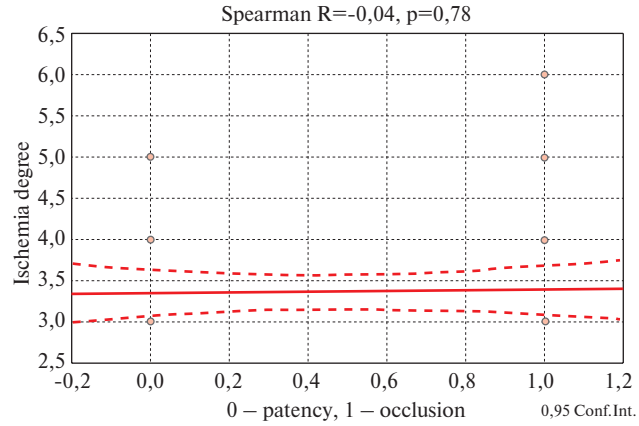

Figure 3. Correlation of the primary patency of the operated segment on the limb ischemia degree.

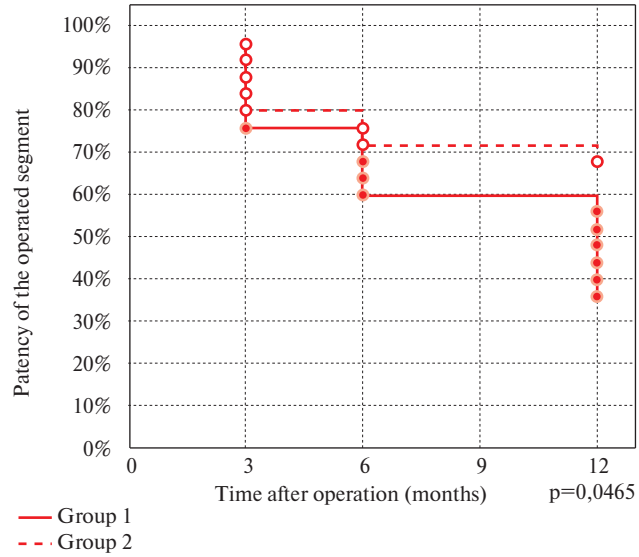

Figure 4. Primary patency of the operated segment (Kaplan-Meier).

of chronic limb ischemia to the initial level. In patients with Rutherford category 4-6 ischemia, a decrease to category 3 was noted. Limb-sparing rate was 100%.

Discussion

Trends in reconstructive arterial interventions are aimed at increasing the proportion of endovascular procedures, which is quite important for age category of patients with a large number of comorbidities. In the treatment of TASC II type A, B SFA lesions, endovascular techniques have shown an advantage.

Stenting technology in the treatment of short and long SFA lesions has shown an advantage over balloon angioplasty. In turn, drug-eluting balloons and stents reduces the intensity of neointimal hyperplasia [11].

If in the treatment of type A and B SFA lesions, endovascular surgery is the first-line strategy, then with regard to long type C and D lesions, discussions continue. Despite the high percentage of technical intraoperative success, long-term outcomes remain unsatisfactory [7, 8].

In primary patency, stenting is better in the short-term period in comparison with balloon angioplasty. With an increase in the length of stented segment, the risk of stent fracture increases [8]. To a certain extent, this is due to the unique SFA biomechanics, which are not found in other vascular systems [14].

To reduce the risk of stent fracture and improve the long-term outcomes of stenting of long SFA lesions, braided nitinol stents and methods for improving the technical characteristics of bare metal stents have been developed. But currently, the rate of restenosis with braided stents is 30% to 40% within a year (RAPID study — Legflow® Paclitaxel Eluting Balloon (LPEB) with stentplacement versus standard percutaneous transluminal angioplasty with stentplacement for the treatment of occlusive disease of the superficial femoral artery).

Our results for primary patency within one year in patients with fascia dissection were 72%, which is slightly higher than in retrospective studies such as DURABILITY-200 (Physician Initiated Trial Investigating the Efficacy of the Implant of EverFlex 200 mm Long Nitinol Stents in TASC C&D

Femoropopliteal Lesions) (64,8%), STELLA (Long Superficial Femoral Artery Stenting With SuperA Interwoven Nitinol Stents) (66%), SUPERStudy (Randomized Trial of the SMART Stent versus Balloon Angioplasty in Long Superficial Femoral Artery Lesions) (45,9%). In comparison with the control group, the primary patency is significantly higher (36% vs 72%). At the same time, the length of the affected segment in the presented study is comparable between the groups — 22,92±5,62 cm and 21,2±5,42 cm, as well as in other studies: 24,2 cm (DURABILITY-200) and 22 cm (STELLA) [12].

According to logistic regression, diabetes and the treatment method were the predictors that significantly influenced the long-term outcome.

The work had certain limitations, since it was a single-center, pilot study. There were no complications in the surgical approach areas in both groups.

The *lamina vastoadductoria* dissection after stenting of type C and D SFA showed good primary patency within 1 year. There was also an improvement in ABI score and clinical scores at control points, such as the category of limb ischemia.

Considering the significant effect of impaired carbohydrate metabolism and microvascular changes on long-term patency [15], it is probably worth excluding patients with total lesions and diabetes from further research.

Conclusion

Lamina vastoadductoria dissection is safe and does not lead to limb functional limitations. Biomechanical changes in the distal SFA segment contribute to the improvement of primary patency after stenting of SFA long lesions. Preliminary results of the single-center pilot study demonstrate the safety and efficacy of SFA stenting with *lamina vastoadductoria* dissection, emphasizing the need for further larger studies to compare it with conventional stenting and to assess the effectiveness during the long-term follow-up.

Relationships and Activities: none.

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Changes in pattern of complications in acute myocardial infarction over a ten-year follow-up: gender specificities

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Aim. To compare changes in pattern of complications in acute myocardial infarction (MI) among Tomsk population at the age of >20 years over a ten-year follow-up period (2008-2017).
Material and methods. The study was carried out on the basis of the World Health Organization Acute Myocardial Infarction Registry. In 2008, 800 MI cases were recorded (62,4% — men; 37,6% — women (p<0,001)). In 2017, acute MI was restarted in 906 patients (58,1% — men; 41,9% — women (p<0,05)). According to age pattern in 2008, there were 62,1% of patients >60 years of age (among men — 49,1%; among women — 83,7% (p<0,0001)), which after 10 years were 74,5% (p<0,001).
Results. In 2008, a complicated course of MI was observed in 49,9% of patients, in 2017, much more often — in 80,4% of patients (p<0,001). Over the analyzed period, incidence of acute aneurysm, myocardial rupture, and recurrent MI decreased. At the same time, the number of patients with post-MI heart failure (HF) significantly increased. In 2008, there were no significant differences in the incidence of MI complications in men and women. The most common complication in both men and women was arrhythmias and conduction disorders. After 10 years, the statistics remained virtually unchanged, with the exception of pulmonary embolism, which was significantly more common in women. Noteworthy is a significant increase in the number of HF patients (among men and women).
Conclusion. Over a ten-year follow-up period, significant changes in patterns of MI complications in Tomsk were not revealed. It should be noted that MI became more severe and was more often accompanied by complications, the most common of which was HF. This is due to an increase in the age pattern of elderly and senile patients.
Key words: acute myocardial infarction, complications.

Relationships and Activities: none.

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Introduction

Despite recent advances in the Russian healthcare system in treating cardiovascular diseases, they remain the leading cause of death. Cardiovascular diseases (CVD), and, above all, acute myocardial infarction (MI), still occupy a leading position in the patterns of death and disability in the population of most developed countries, including the Russian Federation (RF) [1].

The prognosis of complications and outcomes of MI has been one of the urgent problems in cardiology for many years. With a wide range of drugs and interventional techniques used in the treatment of acute coronary disorders, the most important task is to identify groups of patients who have a high risk of complications such as cardiogenic shock, recurrent MI, left ventricular failure, ventricular fibrillation, early postinfarction angina, etc. [2-4]. With the development of medical research and improvement of diagnosis and treatment strategies of AMI, some factors, the influence of which was beyond doubt, are ruled out and replaced by others. Consequently, studies aimed at investigating the course of MI, will be of certain interest both for research and for practical health care.

It should be also noted that the increased attention to the course of MI is caused by two important reasons. At present, the general trend, along with a decrease in the birth rate and an increase in average life expectancy, is a steady increase in the proportion of older age persons. According to the World Health Organization (WHO), the number of people aged >60 is growing rapidly, while the number of those aged 15 to 59 is also rapidly declining. It is predicted that by 2050, 80% of elderly people will live in Europe and North America, and in the RF by this time the number of them will increase significantly and will amount to >35 million people [5]. The population ageing leads to an increase in the age structure of elderly and senile patients with MI.

For a long time, it was believed that the main cause of death for women is endometrial, ovarian, and breast cancers, while men die mainly from CVD. However, in recent years, it has become obvious that CVD, including MI, are in the first place in the mortality structure among men and women [6, 7]. In this regard, the issue of sex characteristics of MI course and outcomes is relevant. This is due, firstly, to a downward trend in MI incidence in young men and increase in older women, and, secondly, to a decrease in mortality due to MI in men, but not in women [6-9].

The aim was to compare changes in pattern of complications in MI among Tomsk population at the

age of >20 years over a ten-year follow-up period (2008-2017).

Material and methods

The study was carried out on the basis of the WHO Acute Myocardial Infarction Registry. The study was performed according to the standard diagnostic (clinical, electrocardiographic, biochemical, pathomorphological) criteria [10]. The MI was established according to the WHO diagnostic criteria at the time of registry creation, as well as taking into account modern clinical guidelines [11]. Statistical processing was carried out using Statistica 9.0 and 10.0 software. To assess the significance of qualitative differences, a nonparametric chi-squared test was used for paired values. The result was interpreted using Bonferroni correction for multiple comparisons. Differences were considered significant at p<0,05.

In 2008, 800 cases of MI were registered (men, 62,4%; women, 37,6%; p<0,001). In 2017, MI developed in 906 patients (men, 58,1%; women, 41,9%; p<0,05). In 2008, the proportion of persons >60 years old was 62,1% (men, 49,1%; women, 83,7%; p<0,0001); after 10 years — 74,5% (p<0,001). Ageing of patients was due to men — 65% (p<0,05). Among women, the increase in the proportion of elderly and senile people was not so significant — 87,6%.

Results

In 2008, a complicated course of MI was observed in 49,9% of patients; in 2017, much more often — 80,4% (p<0,001). Comparison of the structure and frequency of complications are shown in Table 1. According to the presented data, the frequency of cardiogenic shock, left ventricular failure, arrhythmias, pulmonary embolism (PE) did not change significantly over 10 years. Acute aneurysm, myocardial rupture, as well as a recurrent course of disease are recorded much less frequently.

At the same time, the proportion of patients with MI complicated by chronic heart failure (CHF) has significantly increased. Among all types of complications, arrhythmias predominated most often, both in the first and second years of the study. Noteworthy is the fact that in the structure of arrhythmias, the proportion of atrioventricular (AV) block has significantly decreased — from 30,4 to 15% (p<0,05), moreover, due to second- and third-degree AV blocks. Differences in other cardiac arrhythmias were insignificant. Sex differences in the frequency and structure of MI complications in these years

Table 1

Prevalence and patterns of complications in MI among patients in Tomsk in 2008 and 2017

Complication	2008		2017		p
	n	%	n	%	
Total number of patients	399	49,9	728	80,4	<0,001
Cardiogenic shock	89	22,3	135	18,5	>0,05
Left ventricular failure (Killip III)	98	24,6	191	26,2	>0,05
CHF (NYHA class II-IV)	113	28,3	486	66,8	<0,001
Cardiac arrhythmias	148	37,1	280	38,5	>0,05
PE	19	4,8	22	3,0	>0,05
Myocardial rupture	24	6,0	24	3,3	<0,05
Aneurysm	45	11,3	25	3,4	<0,001
Recurrence	58	14,5	51	7,0	<0,001

Note: NYHA — New-York Heart Association, CHF — chronic heart failure, PE — pulmonary embolism.

Table 2

Prevalence and patterns of complications in MI in men and women in Tomsk in 2008 and 2017

Complication	2008					2017				
	Men		Women		p	Men		Women		p
	n	%	n	%		n	%	n	%	
Total number of patients	216	43,3	183	60,8	<0,001	396	75,3	332	87,4	<0,001
Cardiogenic shock	48	22,2	41	22,4	>0,05	70	17,7	65	19,8	>0,05
Left ventricular failure (Killip III)	49	22,7	49	26,8	>0,05	95	24,0	96	28,9	>0,05
CHF (NYHA class II-IV)	53	24,5	60	32,8	>0,05	271	68,4	215	64,8	>0,05
Cardiac arrhythmias	87	40,3	61	33,3	>0,05	141	35,6	139	41,9	>0,05
PE	7	3,2	12	6,6	>0,05	7	1,8	15	4,5	<0,05
Myocardial rupture	7	3,2	17	9,3	<0,05	6	1,5	18	5,4	<0,05
Aneurysm	22	10,2	23	12,6	>0,05	15	3,8	10	3,0	>0,05
Recurrence	27	12,5	31	16,9	>0,05	32	8,1	19	5,7	>0,05

Note: NYHA — New-York Heart Association, CHF — chronic heart failure, PE — pulmonary embolism.

are presented in Table 2. In 2008, no significant differences in the frequency of MI complications in men and women, with the exception of myocardial rupture, were found. The most frequent complication in both men and women was arrhythmias. In its structure, premature beats were significantly more frequent in women than in men — 78,7 and 52,9%, respectively (p<0,002).

After 10 years, the situation practically did not change, with the exception of PE, which was diagnosed much more often in women. Attention is drawn to a significant increase in the number of patients among men and women with CHF, which exceeded those with arrhythmias.

It was also revealed that the number of male patients with CHF significantly increased from 24,5 to 68,4% (p<0,001) and with aneurysm decreased from 10,2 to 3,8% (p<0,05). The number of female patients with CHF also increased from 32,8 to 64,8% (p<0,001), while the number of those with aneurysm decreased from 12,6 to 3% (p<0,002) and with recurrent course of the disease — from 16,9 to 5,7% (p<0,01). It should also be noted that over the 10-year period, mortality among patients with complicated MI decreased from 59,9% to 44,1% (p<0,05).

Conclusion

Over a ten-year follow-up period, significant changes in patterns of MI complications in Tomsk were not revealed. It should be noted that MI became more severe and was more often accompanied by complications, the most common of which was CHF. This is due to an increase in the age pattern of elderly and senile patients, which is consistent with the literature data [12]. In turn, this fact is a natural reflection of the demographic situation in Tomsk, which is characterized by a tendency towards population ageing [13]. The decrease in the incidence of recurrent MI, acute aneurysm and myocardial rupture is possibly associated with the use of highly effective drugs, as well as with the widespread use of modern interventional techniques. Another factor with a positive effect on the complication rate was the improvement of timely hospitalization of MI patients. Thus, during the analyzed period, the number of patients hospitalized in the first 6 hours from the disease onset increased from 69,1 to 73,8% (p<0,05). Probably, the above factors contributed to the reduction in mortality among patients with complicated MI.

Relationships and Activities: none.

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Prevalence of hypotension in populations of the Russian Federation and the United States of America according to 30-year follow-up

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Aim. To study the prevalence of hypotension according to several criteria in the Russia and the USA.

Material and methods. We used data of Russian population studies performed in 1975-1982 and ESSE-RF study performed in 2012-2014 at the National Medical Research Center for Therapy and Preventive Medicine. A comparison was made with the data of cross-sectional studies of the US population — National Health and Nutrition Examination Survey (NHANES): NHANES II (1976-1980) and Continuous NHANES (2007-2012). We analyzed age, sex, and systolic and diastolic blood pressure. The prevalence of individuals with hypotension was calculated in men and women of five age groups using four different criteria for hypertension.

Results. The prevalence of hypotension in studies of different years according to different criteria was as follows: in the Russia — 0,3-9,0% in men and 2-15% in women; in the USA — 5-30% in men and 8-45% in women. In age group >30 years, the prevalence of hypotension in Russia, by most criteria, decreased approximately by 50% in men and did not change in women. In the United States, according to all criteria, the prevalence in men and women has increased 2-3 times.

Conclusion. The prevalence of hypotension in the adult population ranges from decimal percentages to 45% and varies many times depending on the selected criterion.

Key words: hypotension, prevalence, population, Russia, USA, epidemiological study.

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Introduction

Clinical description of hypotension (HoTN) appeared in the late 19th and early 20th centuries. The Italian scientist Andrea Ferranini is considered to be the founder of HoTN study [1]. The main manifestation of HoTN is an excessive decrease in blood pressure (BP) >20% of the norm.

HoTN is called a forgotten illness [2]. This is due to the fact that with the accumulation of information about the role of hypertension (HTN) as the most important risk factor for cardiovascular diseases and one of the leading causes of death and disability in developed countries, HTN has attracted more and more attention of researchers and health professionals. Therefore, HoTN is in the shadow of HTN [3].

According to the International Classification of Diseases, Tenth Revision (ICD-10), there are following diseases: idiopathic hypotension (I95.0); orthostatic hypotension (I95.1); Hypotension due to drugs (I95.2); other hypotension (I95.8); unspecified hypotension (I95.9). Obviously, in the part of the listed disorders, HoTN is secondary, and represents a symptom of other diseases. As already mentioned, much less attention is paid to the problem of HoTN in comparison with HTN. There is an opinion that low BP is not associated with increased cardiovascular mortality. Therefore, HoTN is regarded as a nondisease [4]. However, according to some population-based prospective studies, the dependence of mortality on BP is not linear, but J-shaped — with an excessively low BP, mortality is higher in comparison with its optimal level. Although the severity of this effect is significantly lower than the increase in mortality due to HTN [5]. In a Russian cohort study of persons ⩾55 years old adjusted for risk factors, an association of cardiovascular mortality with both high BP and systolic BP (SBP) <120 mm Hg was found [6].

There is no single approach to the diagnosis of HoTN. Some researchers took into account only

Table 1

Prevalence of HoTN according to the HoTN-1 criterion

Sex and age (years)	Population											
	RF-80			NHANES2			ESSE-RF			C.NHANES		
	A/n	ER	P0÷P1	A/n	ER	P0÷P1	A/n	ER	P0÷P1	A/n	ER	P0÷P1
						Men						
18-24	1/312	0,3	0÷1,5	65/843	7,7	6,3÷9,4						
25-34	4/715	0,6	0,2÷1,3	52/901	5,8	4,6÷7,2	50/2049	2,4	1,9÷3,1	74/475	15,6	12,9÷18,6
35-44	14/2885	0,5	0,3÷0,8	14/651	2,2	1,3÷3,3	18/1686	1,1	0,7÷1,6	37/486	7,6	5,7÷9,9
45-54	15/5246	0,3	0,2÷0,4	9/617	1,5	0,8÷2,5	20/2049	1,0	0,7÷1,4	41/514	8,0	6,1÷10,2
>54	4/1974	0,2	0,1÷0,5	55/2126	2,6	2,1÷3,2	17/2091	0,8	0,5÷1,2	46/470	9,8	7,6÷12,3
Total	38/11132	0,3	0,2÷0,5	195/5138	3,8	3,4÷4,3	105/7875	1,3	1,1÷1,6	198/1945	10,2	9,1÷11,4
						Women						
18-24	23/144	16,0	11,2÷21,9	182/890	20,4	18,2÷22,8						
25-34	72/932	7,7	6,3÷9,3	157/994	15,8	13,9÷17,8	201/2330	8,6	7,7÷9,6	121/473	25,6	22,3÷29,1
35-44	32/1431	2,2	1,6÷3,0	56/721	7,8	6,2÷9,6	84/2507	3,4	2,8÷4,0	105/556	18,9	16,2÷21,8
45-54	6/1390	0,4	0,2÷0,9	25/644	3,9	2,7÷5,4	80/3837	2,1	1,7÷2,5	64/529	12,1	9,8÷14,7
>54	5/1847	0,3	0,1÷0,6	83/2411	3,4	2,9÷4,1	58/4467	1,3	1,0÷1,6	70/469	14,9	12,3÷17,9
Total	138/5744	2,4	2,1÷2,8	503/5660	8,9	8,3÷9,5	423/13141	3,2	3,0÷3,5	360/2027	17,8	16,4÷19,2

Note: RF-80 — Russian population studies conducted in 1975-1982; ESSE-RF — study conducted in 2012-2014; A — number of persons with HoTN; C.NHANES — Continuous NHANES study conducted in 2007-2012; ER — proportion of persons with HoTN; NHANES2 — NHANES II study conducted in 1976-1980; n — total number of subjects in the group; P0÷P1 — prevalence confidence interval for p=0,95.

the BP level, but a more common point of view is that, in addition to BP, it is necessary to distinguish physiological and pathological HoTN and take into account clinical manifestations of insufficient blood supply to organs [1].

The diagnostically significant BP values proposed by different researchers differ. For example, according to numerous researchers (meta-analysis for 1914-1955), the limits of hypotension for SBP varied from 120 to 90 mm Hg and for diastolic BP (DBP) from 70 to 40 mm Hg [1]. Some authors recommend the distribution of BP values based on a specific sample [7].

The aim was to study the prevalence of HoTN according to several criteria in the Russia and the USA.

Material and methods

The work used data from Russian population-based studies performed in 1975-1982 and ESSE-RF study performed in 2012-2014 at the National Medical Research Center for Therapy and Preventive Medicine [8, 9]. The study was approved by the ethics committee of the National Medical Research Center for Preventive Medicine. All patient signed informed consent.

A comparison was made with the data of cross-sectional studies of the US population — National Health and Nutrition Examination Survey (NHANES): NHANES II (1976-1980) and Continuous NHANES (2007-2012). The design of these is described in the original documents [10]. The studies included only white people.

The age, sex, SBP and DBP values measured on the brachial artery were analyzed. The Russian studies took into account the data on the history of HTN and the use of antihypertensive agents.

The prevalence of HoTN was calculated in men and women in the following age groups: 18-24, 25-34, 35-44, 45-54, ⩾55 years. Due to the absence of a generally accepted criterion for HoTN, the prevalence of HoTN was studied according to several criteria:

- HoTN-1 — single criterion for men and women, regardless of age, with a SBP/DBP level of ⩽90/60 mm Hg [11];
- HoTN-2 — persons ⩽25 years old — SBP <100 or DBP <60 mm Hg; persons >25 years — SBP <105 or DBP <60 mm Hg, regardless of sex [1];
- HoTN-3 — persons ⩽35 years old — SBP ⩽100 or DBP ⩽60 mm Hg; persons 36-54 years old — SBP ⩽110 or DBP ⩽70 mm Hg; persons ⩾55 years old — SBP ⩽120 or DBP ⩽70 mm Hg, regardless of sex [12];
- HoTN-4 — criteria for men — SBP <110 or DBP <60 mm Hg; for women — SBP <100 or DBP <60 mm Hg, regardless of age [13].

Data on the prevalence of HoTN in age and sex groups for each of the listed criteria are shown in Tables 1-4.

For statistical analysis, standard statistical procedures were used. The proportion of persons with HoTN was calculated according to the corresponding criterion and its confidence interval (P0÷P1) [14], which allows to estimate the HoTN prevalence in the general population with a confidence coefficient of 0,95 and compare it in different samples.

Results and discussion

According to the HoTN-1 criterion [11], the prevalence of HoTN in the modern Russian population (2012-2014ESSE-RF) is 1,3% in men and 3,2% in women, and in the US population (2007-2012 Continuous NHANES) — 10,2% and 17,8%, respectively. In both populations, in men 25-34 years old, the frequency of HoTN is significantly higher than in older age groups. In women, the prevalence of HoTN naturally decreases with an increase in age from 25 to 54 years (Table 1).

Table 2

Prevalence of HoTN according to the HoTN-2 criterion

Sex and age (years)	Population											
	RF-80			NHANES2			ESSE-RF			C.NHACNES		
	A/n	ER	P0÷P1	A/n	ER	P0÷P1	A/n	ER	P0÷P1	A/n	ER	P0÷P1
Men												
18-24	2/312	0,6	0,1÷2,0	45/843	5,3	4,1÷6,8						
25-34	31/715	4,3	3,2÷5,8	85/901	9,4	7,9÷11,2	62/2049	3,0	2,4÷3,7	85/475	17,9	15,1÷21,0
35-44	131/2885	4,5	3,9÷5,2	38/651	5,8	4,4÷7,6	32/1686	1,9	1,4÷2,5	60/486	12,3	10,0÷15,1
45-54	142/5246	2,7	2,4÷3,1	30/617	4,9	3,5÷6,5	35/2049	1,7	1,3÷2,3	74/514	14,4	11,9÷17,2
>54	36/1974	1,8	1,4÷2,4	64/2126	3,0	2,4÷3,7	23/2091	1,1	0,8÷1,6	68/470	14,5	11,9÷17,4
Total	342/11132	3,1	2,8÷3,4	262/5138	5,1	4,6÷5,6	152/7875	1,9	1,7÷2,2	287/1945	14,8	13,5÷16,1
Women												
18-24	29/144	20,1	14,8÷26,4	175/890	19,7	17,5÷22,0						
25-34	166/932	17,8	15,8÷20,0	283/994	28,5	26,1÷30,9	393/2330	16,9	15,6÷18,2	207/473	43,8	39,9÷47,7
35-44	119/1431	8,3	7,1÷9,6	133/721	18,4	16,1÷21,0	272/2507	10,9	9,8÷11,9	184/556	33,1	29,8÷36,5
45-54	53/1390	3,8	3,0÷4,8	60/644	9,3	7,5÷11,4	184/3837	4,8	4,2÷5,4	117/529	22,1	19,2÷25,3
>54	16/1847	0,9	0,5÷1,3	96/2411	4,0	3,4÷4,7	87/4467	1,9	1,6÷2,3	90/469	19,2	16,2÷22,4
Total	383/5744	6,7	6,1÷7,2	747/5660	13,2	12,5÷14,0	936/13141	7,1	6,8÷7,5	598/2027	29,5	27,8÷31,2

Note: RF-80 — Russian population studies conducted in 1975-1982; ESSE-RF — study conducted in 2012-2014; A — number of persons with HoTN; C.NHANES — Continuous NHANES study conducted in 2007-2012; ER — proportion of persons with HoTN; NHANES2 — NHANES II study conducted in 1976-1980; n — total number of subjects in the group; P0÷P1 — prevalence confidence interval for p=0,95.

According to this criterion, in the 1980s, the frequency of HoTn in Russian men was ~4 times lower in comparison with ESSE-RF and did not significantly depend on age. In comparison with modern data, the prevalence of HoTN in Russian women was on average slightly lower (significant for age ⩾45 years).

In the US population in the late 1980s, in comparison with the Continuous NHANES study, the incidence of HoTN was significantly lower in all age groups of men and women. In the United States, the prevalence of HoTN has on average increased 3 times in men and 2 times in women over 30 years (Table 1).

Thus, when using the HoTN-1 criterion not taking into account sex and age, a number of regularities were revealed:

• Prevalence of HoTN in women is higher than in men;

• In comparable periods of follow-up, the prevalence of HoTN was higher in the United States compared to the Russian Federation in both men and women (in the 2010s, 5-7 times; in the 1980s, 3-12 times);

• The prevalence of HoTN for 30 years has increased in men and women, both in the Russian Federation and in the United States.

The BP level rises with age, which the basis of the approach of the researchers who proposed the criteria for HoTN adjusted for age [1, 12, 15]. Such criteria can be relatively simple, using fixed BP values in several age ranges [1, 12], or more complex, when the cut-off values are calculated as 102+ age multiplied by 0,6 for SBP; and as 63+ age multiplied by 0,4 for DBP [15].

The prevalence of HoTN was studied according to the N. S. Molchanov criterion. The scientific school founded by him occupied a leading position in HoTN issue in Russia [1]. According to this criterion, HoTN includes persons ⩽25 years old with SBP <100 or DBP <60 mm Hg, and persons >25 years old with SBP <105 or DBP <60 mm Hg, regardless of sex (HoTN-2 criterion). The data on the prevalence of HoTN according to this criterion are presented in Table 2. The results obtained demonstrated a higher incidence of HoTN, which is most likely associated with a greater contribution of SBP. The patterns described above are confirmed, with the exception of the 30-year HoTN prevalence in the Russian Federation: the prevalence of HoTN-2 in men has decreased, and in women, the increase in HoTN prevalence is not as demonstrative as when using the HoTN-1 criterion.

It should be noted that in modern populations of both the Russian Federation and the United States, persons aged 25 and over were examined. Therefore, the N. S. Molchanov criterion is almost independent of age. In the RF-1980 and NHANES II studies, the prevalence of HoTN in persons aged 18-24 was lower than expected, since in young people a higher prevalence was expected. It can be assumed that, as applied to population data, age is not taken into account correctly in the HoTN-2 criterion.

The HoTN-3 criterion, differentiated for three age ranges, was described by J. Yu. Chefranova (2008) [12]. The prevalence of HoTN according to this criterion are presented in Table 3. The higher prevalence of HoTN in women compared with men was revealed. The

Table 3

Prevalence of HoTN according to the HoTN-3 criterion

Sex and age (years)	Population											
	RF-80			NHANES2			ESSE-RF			C.NHANES		
	A/n	ER	P0÷P1	A/n	ER	P0÷P1	A/n	ER	P0÷P1	A/n	ER	P0÷P1
						Men						
18-24	2/312	0,6	0,1÷2,0	45/843	5,3	4,1÷6,8						
25-34	14/715	2,0	1,2÷3,0	30/901	3,3	2,4÷4,5	34/2049	1,7	1,2÷2,2	64/475	13,5	11,0÷16,3
35-44	322/2885	11,2	10,2÷12,2	72/651	11,1	9,1÷13,3	124/1686	7,4	6,3÷8,5	144/486	29,6	26,2÷33,2
45-54	366/5246	7,0	6,4÷7,6	54/617	8,8	7,0÷10,9	113/2049	5,5	4,7÷6,4	156/514	30,4	27,0÷33,9
>54	285/1974	14,4	13,2÷15,8	315/2126	14,8	13,6÷16,1	230/2091	11,0	9,9÷12,2	210/470	44,7	40,8÷48,6
Total	989/11132	8,9	8,4÷9,3	516/5138	10,0	9,4÷10,8	501/7875	6,4	5,9÷6,8	574/1945	29,5	27,8÷31,3
						Women						
18-24	29/144	20,1	14,8÷26,4	175/890	19,7	17,5÷22,0						
25-34	102/932	10,9	9,3÷12,8	147/994	14,8	13,0÷16,8	217/2330	9,3	8,3÷10,4	133/473	28,1	24,7÷31,7
35-44	280/1431	19,6	17,9÷21,4	177/721	24,5	21,9÷27,3	553/2507	22,1	20,7÷23,5	284/556	51,1	47,5÷54,7
45-54	159/1390	11,4	10,1÷12,9	113/644	17,5	15,1÷20,2	518/3837	13,5	12,6÷14,4	243/529	45,9	42,3÷49,6
>54	130/1847	7,0	6,1÷8,1	383/2411	15,9	14,7÷17,2	659/4467	14,8	13,9÷15,7	248/469	52,9	49,0÷56,8
Total	700/5744	12,2	11,5÷12,9	995/5660	17,6	16,8÷18,4	1947/13141	14,8	14,3÷15,3	908/2027	44,8	43,0÷46,6

Note: RF-80 — Russian population studies conducted in 1975-1982; ESSE-RF — study conducted in 2012-2014; A — number of persons with HoTN; C.NHANES — Continuous NHANES study conducted in 2007-2012; ER — proportion of persons with HoTN; NHANES2 — NHANES II study conducted in 1976-1980; n — total number of subjects in the group; P0÷P1 — prevalence confidence interval for p=0,95.

Table 4

Prevalence of HoTN according to the HoTN-4 criterion

Sex and age (years)	Population											
	RF-80			NHANES2			ESSE-RF			C.NHANES		
	A/n	ER	P0÷P1	A/n	ER	P0÷P1	A/n	ER	P0÷P1	A/n	ER	P0÷P1
						Men						
18-24	34/312	10,9	8,1÷14,2	132/843	15,7	13,6÷17,9						
25-34	77/715	10,8	8,9÷12,9	124/901	13,8	11,9÷15,8	129/2049	6,3	5,4÷7,3	118/475	24,8	21,6÷28,3
35-44	289/2885	10,0	9,1÷11,0	60/651	9,2	7,4÷11,3	70/1686	4,2	3,4÷5,0	100/486	20,6	17,6÷23,8
45-54	329/5246	6,3	5,7÷6,9	45/617	7,3	5,7÷9,3	63/2049	3,1	2,5÷3,8	109/514	21,2	18,3÷24,4
>54	82/1974	4,2	3,4÷5,0	88/2126	4,1	3,5÷4,9	42/2091	2,0	1,5÷2,6	88/470	18,7	15,8÷21,9
Total	811/11132	7,3	6,9÷7,7	449/5138	8,7	8,1÷9,4	304/7875	3,9	3,5÷4,2	415/1945	21,3	19,8÷22,9
						Women						
18-24	29/144	20,1	14,8÷26,4	175/890	19,7	17,5÷22,0						
25-34	102/932	10,9	9,3÷12,8	147/994	14,8	13,0÷16,8	217/2330	9,3	8,3÷10,4	133/473	28,1	24,7÷31,7
35-44	56/1431	3,9	3,1÷4,9	54/721	7,5	5,9÷9,3	121/2507	4,8	4,1÷5,6	117/556	21,0	18,2÷24,1
45-54	24/1390	1,7	1,2÷2,4	21/644	3,3	2,2÷4,7	85/3837	2,2	1,8÷2,7	74/529	14,0	11,6÷16,7
>54	9/1847	0,5	0,3÷0,9	43/2411	1,8	1,4÷2,3	46/4467	1,0	0,8÷1,3	75/469	16,0	13,3÷19,0
Total	220/5744	3,8	3,4÷4,3	440/5660	7,8	7,2÷8,4	469/13141	3,6	3,3÷3,9	399/2027	19,7	18,2÷21,2

Note: RF-80 — Russian population studies conducted in 1975-1982; ESSE-RF — study conducted in 2012-2014; A — number of persons with HoTN; C.NHANES — Continuous NHANES study conducted in 2007-2012; ER — proportion of persons with HoTN; NHANES2 — NHANES II study conducted in 1976-1980; n — total number of subjects in the group; P0÷P1 — prevalence confidence interval for p=0,95.

prevalence of HoTN over a 30-year period in Russian men decreased instead of growth according to the HoTN-1 criterion.

Many researchers have described a higher prevalence of HoTN in women [1] and some have recommended sex-differentiated criteria for HoTN. An example is the HoTN-4 criterion [13]. Data on the prevalence of HoTN-4 are presented in Table 4. The ratio of HoNT in men and women changed as expected. The prevalence of HoTN in the Russian population decreased during 30-year period in men in all age groups, while there were changes in women. In the Russian and American populations in the 1980s, the prevalence of HoTN in age groups of men did not differ. Other data are described in Table 1.

It can be assumed that when only BP values are used for HoTN diagnosis, some hypertensive patients receiving antihypertensive drugs may fall

into normotensive and even hypotensive groups. The influence of this factor was studied in Russian studies. The prevalence of HoTN was calculated according HoTN-4 criterion, in which all persons who answered positively to the question of whether they had HTN or taking antihypertensive agents were excluded from HoTN group. There were no differences in the prevalence of HoTN according to HoTN-4 criterion.

As already noted, the prevalence of HoTN has changed significantly over a 30-year period. In the United States, it has increased significantly. The differences are significant according to all the studied criteria in all age groups, both in men and women. In Russian populations, the differences are not so unambiguous. According to the HoTN-1 criterion, the prevalence of HoTN increased in most age groups, while according to other criteria, a decrease was more typical for men, and for women the changes was less pronounced. A large number of factors are known that affect the normal BP, including ambient temperature, atmospheric pressure, and many others. Some of these factors in this study can be ignored, since samples from the population of one country were studied.

Particular attention is drawn to such a factor as mental strain at the population level. In 1931, the role of autonomic nervous system changes under the social influence in HoTN pathogenesis was noted [1]. This is consistent with the well-known pronounced increase in the frequency of HoTN during significant socio-economic disruptions: for example, after the Second World War, the number of hypertensive patients in Germany, compared with the pre-war period, increased by 60%, and the number of people with HoTN — by 120% [1]. In this context, the data on the prevalence of HoTN in the Russian Federation, including the 30-year dynamics, look more favorable in comparison with the USA.

It was shown above how several HoTN criteria work on population material, in which fixed BP values are used, including those differentiated depending on sex and age. It should be noted that such criteria were developed on clinical material and selective samples [1, 12]. Another approach is known based on the assessment of the threshold BP levels by their distribution in the surveyed group [7]. It is impractical to study the prevalence of HoTN according to such criteria, since it will be due to the selected cutoff point.

Conclusion

The prevalence of HoTN in the adult population is at least a few percent. This is a common condition, which explains the practical importance of study, control and prevention of HoTN.

The prevalence of HoTN significantly depends on the selected criterion. This makes relevant the development of a pathophysiologically reasonable criterion. Most of the described criteria do not have such a substantiation. An exception is the HoTN-1 criterion (BP $\leqslant$90/60 mm Hg), which corresponds to a mean BP <70 mm Hg, ie, the threshold BP for maintaining autoregulation of cerebral blood flow [11].

By analogy with the history of hypertension study, it can be assumed that criterion should be associated with the long-term prognosis at the population level.

To compare the prevalence of HoTN in different populations, one of the known criteria can be used, while preference should be given to the simplest ones undifferentiated by age and sex.

The results of this analysis are consistent with data of a number studies with pronounced changes in the prevalence of HoTN in different historical periods. The interpretation of these observations is still difficult.

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Associations of NT-proBNP and hepcidin levels with clinical and laboratory parameters in patients with heart failure with various severity of left ventricular systolic dysfunction

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Data on hepcidin levels in patients with heart failure (HF) are contradictory and do not make clear its contribution to the progression of multiple organ failure. There remain a number of issues about the prognostic significance of the N-terminal pro-brain natriuretic peptide (NT-proBNP) in HF with preserved ejection fraction (EF). The authors suggested the relationships between these markers in decompensated HF, as well as their associations with other clinical and laboratory parameters.

Aim. To identify the association of NT-proBNP and hepcidin levels with clinical and laboratory parameters in patients with HF with various severity of left ventricular (LV) systolic dysfunction.

Material and methods. The study included 68 patients (29 women, 39 men; mean age — 72,3±11,7 years) hospitalized due to decompensated HF. Patients were divided into three groups: reduced (HFrEF) (n=20), mid-range (HFmrEF) (n=23), and preserved EF (HFpEF) (n=24). Upon admission, along with standard diagnostic tests, all patients were examined for NT-proBNP and hepcidin levels by enzyme-linked immunosorbent assay. Statistical processing was carried out using the software package Statistica 8.0.

Results. NT-proBNP levels in the entire sample was 315,9 [129,9; 576,1] pg/ml. Significantly higher concentrations of NT-proBNP were found in patients with lower EF: 433,05 [346,8-892,6] pg/ml for HFrEF, 289,97 [185,9-345,3] pg/ml for HFmrEF pg/ml and 214,98 [207,37-562,31] pg/ml for HFpEF ($p<0,05$). At the same time, hepcidin levels in the HFrEF group (31,63 ng/ml [22,0; 71,6]) was significantly higher than in the HFmrEF (23,89 ng/ml [21,1; 27,9]) ($p<0,05$) and HFpEF (26,91 ng/ml [18,6; 31,1]) ($p<0,05$). In HFpEF patients, there was a correlation of hepcidin level with body mass index ($r=0,47$, $p<0,05$) and chronic obstructive airway diseases ($r=0,44$, $p<0,05$). A correlation of hepcidin level with cardiac arrhythmias ($r=0,61$, $p<0,05$) was revealed in the HFmrEF group. In the HFrEF group, there were correlations of a significantly increased level of NT-proBNP (median — 433,05; 95% confidence interval: 346,8-892,6) with indicators of disease severity and multiple organ dysfunction: decrease in systolic blood pressure, cardiorenal syndrome, decrease in hemoglobin level and mean corpuscular hemoglobin concentration, characteristic of iron-deficiency anemia.

Conclusion. Patients with lower EF showed higher NT-proBNP values and a trend towards higher hepcidin levels. Relationships of hepcidin and NT-proBNP levels with following clinical parameters were found: body mass index, presence of obstructive airway diseases, cardiac arrhythmias, as well as low cardiac output syndrome, cardiorenal syndrome and anemia.

Key words: heart failure, hepcidin, NT-proBNP, clinical and laboratory associations.

Relationships and Activities: none.

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The prevalence of heart failure (HF), despite the improved treatment and prevention strategy, is steadily growing, reaching the scale of a non-infectious pandemic [1]. According to the Russian population-based study EPOCHA-CHF, today no more than 8,5% of the population of the European Russia suffer from HF [2]. Its prevalence specifies the need to search for new methods and markers for assessing the patients' condition in order to form clinical phenotypes of HF and determine a personalized strategy.

The role of brain natriuretic peptide and N-terminal pro-brain natriuretic peptide (NT-proBNP) in the pathogenesis of HF has been well known since the beginning of 2000s, while the serum determination of these biomarkers is currently the gold standard of laboratory diagnosis of HF [1, 3-4]. However, the issue of the prognostic significance of an increase in these markers remains poorly understood, especially in patients with preserved left ventricular ejection fraction (LVEF) [5-6]. The study of the predictor significance of NT-proBNP decrease in patients hospitalized with decompensated HF continues, as well as the search for effective therapy aimed at reducing the level of this biomarker [7].

The value of hepcidin, a regulator of systemic iron homeostasis, has been well studied in patients with HF and anemia [8-10]. Currently, its diagnostic and prognostic role is studied as a new marker of liver damage in HF [9]. Despite the fact that it is produced by many body cells, including adipocytes, macrophages, pancreatic β-cells, cardiomyocytes, the main synthesis site is the liver, which expresses 15-1500 times more of

hepcidin than other cells of the body [9-13]. The main mechanism for controlling iron metabolism by hepcidin is its binding to the ferroportin, a transmembrane transporter of iron located on the surface of enterocytes, macrophages and hepatocytes, and its inactivation. This leads to a decrease in iron absorption in the small intestine and release from macrophages, resulting in iron deficiency and anemia. With a lack of hepcidin, there is an uncontrolled absorption of iron and accumulation in tissues, primarily in the liver, where it has a cytotoxic effect through oxidative stress [10].

Previous research on hepcidin role in the anemia in HF patients did not give an unambiguous answer about the change in hepcidin levels with the disease progression, while the place of this marker in the continuum of cardio-renal-hepatic anemia syndrome in decompensated HF in patients with different systolic dysfunction is also not identified [3, 9-13].

The aim was to identify the association of NT-proBNP and hepcidin levels with clinical and laboratory parameters in HF patients with LV systolic dysfunction of different severity.

Material and methods

This non-randomized uncontrolled study included 68 patients (29 women, 39 men) with coronary artery disease and/or hypertension hospitalized due to decompensated HF. All patients signed informed consent. This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The medical ethics committee approved this study. There were following inclusion criteria: age >18 years, presence of class II-IV HF at least 6 months, NT-proBNP of 125 pg/ml upon admission to the hospital. The exclusion criteria were primary liver (viral, toxic, etc.) and biliary tract disorders, cancer, dialysis-requiring renal failure.

Along with the standard diagnostic tests, all patients were studied for NT-proBNP using Biomedica BI-20852W kit (BNP-fragment (Austria)) and serum hepcidin-25 using CEB979Hu 96 Tests Enzyme-linked Immunosorbent Assay Kit For Hepcidin (Hepcidin ELISA) (Cloud-Clone Corp, USA). According to echocardiography, the patients were divided into 3 groups: with preserved LVEF (>50%) — 25 patients, mid-range LVEF (40-50%) — 23 patients, and reduced LVEF (<40%) — 20 patients.

Statistical evaluation was carried out using the SPSS and Statistica 8.0 software. The distribution normality was assessed using the Shapiro-Wilk test. In normal distribution, differences between groups were analyzed using the parametric Student's t-test. In non-normal distribution, the nonparametric Mann-Whitney U-test or the nonparametric Jonckheere-Terpstra test was used. To study a correlation between the variables, we used the linear Pearson's correlation coefficient with a normal distribution and Spearman's correlation coefficient with a non-normal distribution. To compare the frequency, the Chi-squared test and Fisher's exact test were used. Differences were considered significant at $p<0,05$.

Results

The mean age of the examined patients was 72,3±11,7 years (LVEF — 46,3±11,3%). All patients had clinical manifestations of NYHA class III-IV HF. The most common cause of HF in patients with mid-range and reduced LVEF was old myocardial infarction. The general clinical characteristics of patients are presented in Table 1.

The NT-proBNP level in all patients included in the study exceeded the threshold value of 125 pg/ml [1] and amounted to 315,9 [129,9; 576,1] pg/ml. Moreover, in patients with LVEF <40%, the NT-proBNP and hepcidin levels were higher than in patients with preserved and mid-range EF (Table 2).

Correlation analysis in the general sample of patients with HF showed the negative correlations of NT-proBNP level with LVEF ($r=-0,3$, $p<0,05$) and body mass index (BMI) ($r=-0,4$, $p<0,05$), as well as its positive correlations with laboratory parameters reflecting the severity of multiple organ dysfunction in patients with HF (Table 3).

The revealed correlations between the NT-proBNP and total bilirubin levels ($r=0,3$, $p<0,05$), as well as the international normalized ratio (INR) allow to consider an increased NT-proBNP concentration as a marker of cardiohepatic syndrome. At the same time, the relationship between NT-proBNP and urea nitrogen

Table 1

Clinical characteristics of patients

Parameter, n (%)	HFpEF (n=25)	HFmrEF (n=23)	HFrEF (n=20)
Gender, M/F	10/15 (40%/60%)	17/6 (74%/26%)	14/6 (70%/30%)
Age, years	75,88±11,45	72,13±12,05	68,15±11,19
NYHA class III-IV HF	23 (92%)	19 (79,1%)	20 (100%)
Type 2 diabetes	10 (40%)	11 (45,8%)	4 (20%)
Old myocardial infarction	9 (36%)	15 (62,5%)	13 (65%)
Anemia	3 (12%)	9 (37,5%)	6 (30%)
Pneumonia	12 (48%)	15 (62,5%)	10 (50%)
CKD G3-4 (CKD-EPI GFR <60 ml/min/1,73 m^2)	15 (60%)	11 (45,8%)	12 (60%)

Note: M/F — males/females.

Table 2

NT-proBNP and hepcidin levels in patients with HFpEF, HFmrEF and HFrEF

Parameter	HFpEF (n=25)	HFmrEF (n=23)	HFrEF (n=20)	HFpEF (n=25)	p_{2-3}	p_{1-3}
NT-proBNP, pg/ml (median, [Q1; Q3])	214,98 (207,37-562,31)	289,97 (185,9-345,3)	NA	433,05 (346,8-892,6)	0,01	0,006
Hepcidin, ng/ml (median, 95% CI)	26,9 (20,8-28,9)	23,9 (21,7-27,0)	NA	31,6 (22,2-69,6)	NA	NA

Table 3

Correlation coefficients between the NT-proBNP level and parameters reflecting the severity of the condition and multiple organ dysfunction in the general sample of HF patients

Parameter	Patients with HF (n=68)
	NT-proBNP level
Systolic blood pressure, mm Hg	-0,18
Urea nitrogen, mmol/l	0,29*
Creatinine, μmol/l	-0,02
Total bilirubin, μmol/l	0,3*
Albumin, mmol/l	-0,335
INR	0,29*
Platelets, $x10^9$/l	0,29*
Hemoglobin, g/l	-0,22
Mean corpuscular hemoglobin, pg	-0,21
BMI, kg/m^2	-0,38*
LVEF, %	-0,27*

Note: * — significant (p<0,05) Spearman's correlation coefficients.

Table 4

Correlation coefficients between the NT-proBNP level and parameters reflecting the severity of the condition and multiple organ dysfunction in patients with HFrEF

Parameter	Patients with HFrEF (n=20)
	NT-proBNP level
Systolic blood pressure, mm Hg	-0,34*
Urea nitrogen, mmol/l	0,55*
Creatinine, μmol/l	-0,015
Total bilirubin, μmol/l	0,026
Albumin, mmol/l	-0,5
INR	0,19
Platelets, $x10^9$/l	0,32
Hemoglobin, g/l	-0,65*
Mean corpuscular hemoglobin, pg	-0,44*

Note: * — significant (p<0,05) Spearman's correlation coefficients.

(r=0,3, p<0,05) serve as markers of the cardiorenal syndrome.

Taking into account that 95% CI for the median hepcidin in the group of HF with mid-range EF (HFmrEF) (40-50%) fits into the 95% CI for the median hepcidin in the group of HF with preserved EF (HFpEF) (>50%), it can be assumed that in itself a LVEF decrease with hypoperfusion of the liver and kidneys stimulates its synthesis. At the same time, a large scatter of hepcidin levels within one group, as well as the absence of significant differences between groups with different HF phenotypes (p=0,131), may indicate the predominance of different regulation mechanisms in patients with different severity of systolic dysfunction.

Therefore, we analyzed the relationship of NT-proBNP and hepcidin levels with clinical and laboratory parameters within each of the groups.

In patients with HFpEF, differences in hepcidin level in the presence of chronic obstructive lung diseases were revealed — 50,34 ng/ml [46,66; 54,02] and, in their absence — 25,99 ng/ml [17,93; 28,89] (p<0,05), as well as its positive correlation with BMI. At the same time, a negative correlation was found between BMI and NT-proBNP (r=-0,48, p<0,05).

In the HFmrEF group, the hepcidin level in patients with cardiac arrhythmias (atrial fibrillation and high-grade ventricular premature contractions) was 26,55 ng/ml [23,03; 43,91], while in patients without arrhythmias — 21,06 ng/ml [18,56; 21,4], (p<0,05). NT-proBNP values in these subgroups were 343,78 pg/ml [151,21; 504,20] and 381,41 pg/ml [217,89; 711,82] (p=0,181), respectively. Correlations of the NT-proBNP level with INR (r=0,6, p<0,05) can be considered as an indicator of cardiohepatic syndrome even with mid-range EF.

In the group of patients with HF with reduced EF (HFrEF) (<40%), there was a relationship between a significantly increased NT-proBNP (median, 433,05; 95% CI, 346,8-892,6 pg/ml) and severe clinical condition and multiple organ dysfunction (Table 4).

Discussion

Recently, not only an active study of new CF markers, but also an assessment of their influence on remodeling of internal organs and the development of multiple organ dysfunction is being carried out.

The diagnostic and predictive role of an increased NT-proBNP level has been well studied in patients with HFrEF. However, there are still questions about the significance of NT-proBNP in HFpEF [6-7]. High NT-proBNP values in patients with reduced LVEF are an independent marker of the HF phenotype, characterized by an unfavorable prognosis, and is combined with other unfavorable prognostic factors, such as hypotension and weight loss, as well as anemia, cardiorenal and cardiohepatic syndromes.

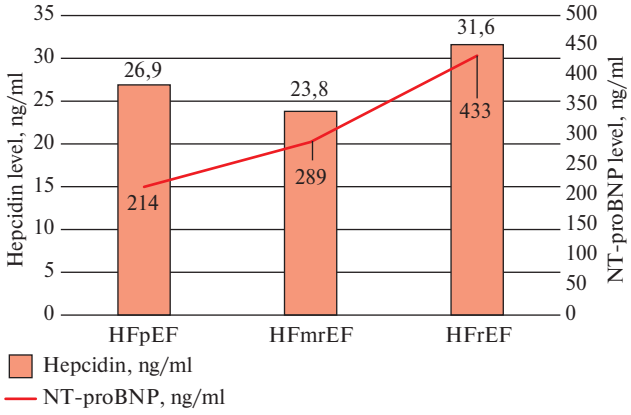

Figure 1. NT-proBNP and hepcidin levels in patients with different HF phenotypes.

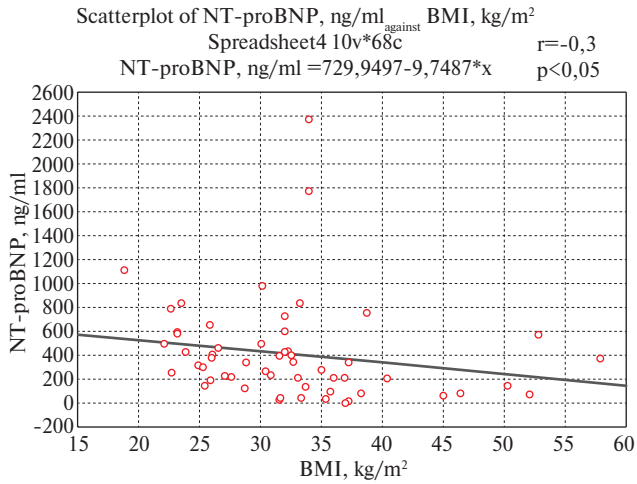

Figure 2. Correlation of NT-proBNP level and BMI in patients with HF.

The change in the hepcidin levels in patients with HF is due to many regulatory mechanisms. According to previous studies, the main mechanisms for regulating the hepcidin level are iron-deficiency, which suppresses its synthesis by negative feedback, and inflammation, which induces its formation in the liver and in immunocompetent cells [6, 10]. In patients with HF, along with the indicated mechanisms, there are a number of other factors that can have a significant effect on the hepcidin synthesis: hypoxia, impaired synthetic liver function, diabetes, obesity, chronic kidney disease (CKD) [6-9].

In the present study, despite the absence of a linear correlation between NT-proBNP and hepcidin, both in the general sample and in the groups of patients with different LV systolic dysfunction ($r<-0,14$, $p>0,05$), a tendency towards higher hepcidin values in patients with HFrEF was revealed, accompanied by a significant increase in NT-proBNP (Figure 1).

The revealed effect of obstructive lung diseases on the hepcidin level is due to two key factors: on the one hand, this group of diseases is accompanied by an inflammatory reaction, and on the other, it makes an additional contribution to the progression of right ventricular failure, increasing venous stasis in the systemic circulation [14-16].

With an increase in BMI, the proportion of adipose hormonally active tissue increases, which not only contributes to the maintenance of a high level of proinflammatory cytokines that enhance hepcidin production, but also directly synthesizes it by itself [10, 17]. At the same time, it is known that an increase in BMI in patients with severe HF is considered by some researchers as a factor of a favorable prognosis, described as the obesity paradox [18]. However, in recent years, controversy has resumed regarding the considering obesity as an adaptive mechanism [19]. Inverse correlation between BMI and NT-proBNP in the general sample, which is especially significant in patients with HFrEF, confirms the presence of this phenomenon (Figure 2).

It is known that the presence of severe arrhythmias further worsens organ perfusion in HF, aggravating hypoxia. *In vitro* experiments have shown that hypoxia inhibits the synthesis of hepcidin [3, 6], and therefore more expected was a negative relationship between its level and arrhythmias. The increase in hepcidin in patients with cardiac arrhythmias made it possible to consider other factors as a probable cause of this, including those leading to an increase in pro-inflammatory cytokines, which, as shown by previous studies, have a stimulating effect on hepcidin synthesis [5, 7, 20].

To confirm this hypothesis, a more detailed analysis of the clinical characteristics of this group was carried out, in which it was revealed that 15 (62,5%) patients had a history of acute myocardial infarction, 11 (45,8%) suffered from type 2 diabetes. All patients had signs of congestion in both circulations, with a decrease in exercise tolerance (NYHA class III-IV HF) in 19 (79,1%) patients, of which 15 (62,5%) had clinical, instrumental and laboratory signs of pneumonia, while 4 subjects had clinical and instrumental signs of ascites. Also, 11 (45,8%) patients had CKD with a decrease in the glomerular filtration rate (GFR) >60 ml/min/1,73 m^2, while 9 (37,5%) patients suffered from anemia.

In patients with LVEF <40%, along with an increase in NT-proBNP level, there was an increase in low cardiac output syndrome, manifested by a decrease in systolic blood pressure, cardiorenal and anemic syndromes.

It is known that hepcidin plays an important role in the development of anemia in HF, the median level of which in patients with HFrEF was higher than in other groups — 31,6 ng/ml (95% CI, 22,2-69,6). At the same time, there were no significant correlations between the level of hepcidin and other clinical parameters, including with the levels of creatinine, urea and GFR, which allows to consider a hepcidin increase in patients with LVEF <40% as one of the markers of multiple

organ dysfunction in HF and an additional factor of unforable prognosis.

Conclusion

In the examined patients with different HF phenotypes, selected depending on severity of LV systolic dysfunction, various associations were revealed between the NT-proBNP and hepcidin levels and clinical and laboratory parameters. In patients with HFrEF, a high level of NT-proBNP correlated with low body weight, cardiorenal and cardiohepatic syndromes, as well as anemia.

The revealed tendency to a hepcidin increase in HFrEF without correlations of its level with other clinical and laboratory parameters does not allow one to determine its independent role in HF progression, since the regulation of hepcidin levels in HF patients largely depends on various metabolic parameters and comorbid conditions, which complicates its assessment as a diagnostic and prognostic marker. Being an acute-phase protein, hepcidin also reflects the different severity of systemic inflammation characteristic of HF, which also complicates the interpretation. The results of this study coincide with the study by Jankowska EA, et al. with 321 HF patients, which did not demonstrate the association of hepcidin levels with either anemia or inflammation [12]. On the contrary, in the study of Solomakhina NI, et al., in patients with HF and anemia, a high level of hepcidin positively correlated with high values of proinflammatory cytokines, and negatively — with hemoglobin, which allowed the authors to consider inflammation as the cause of hepcidin increase in elderly and senile patients [13].

Relationships and Activities: none.

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Bleeding risk scales in patients with acute coronary syndrome: place of the ORACUL scale

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Aim. To compare the diagnostic value of different bleeding risk scales in patients with acute coronary syndrome (ACS).

Material and methods. The study included 1502 patients with ACS from the observational, open-label, multicenter trial ORACUL II. The mean age was 65,7±12,9 years. At follow-up visits (hospital discharge, 25, 90, 180 and 360 days from the index event), all cases of bleeding were recorded with a description of bleeding characteristics, source, severity, treatment, and classification according to the BARC, TIMI, and ISTH scales.

Results. During the follow-up period, bleeding was recorded in only 170 (11,3%) patients: within the index hospitalization — in 39 (26%), within a year after the index hospitalization — in 131 (8,6%). In 19 (1,2%) patients, recurrent bleeding at several visits was recorded. In comparison with such scores as CRUSADE, ACTION-ICU, ACUITY, PARIS, the ORACUL scale had the highest predictive value in relation to the in-hospital bleeding risk. The only scale with comparable diagnostic value was the BleeMACS score. It should be noted that the ORBIT and HASBLED scores had a lower predictive value for the in-hospital bleeding risk. In general, all scores were better at predicting major bleeding and slightly worse for clinically relevant ones.

Conclusion. The ORACUL scale seems to be the most acceptable tool for assessing the bleeding risk in patients after ACS in actual clinical practice in Russia.

Key words: acute coronary syndrome, bleeding, mortality, risk score.

Relationships and Activities. The study was investigator-initiated and was conducted under the guidance of the Department of Therapy, Cardiology and Functional Diagnostics of the Central State Medical Academy (Moscow, Russia). No external funding was used.

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In the management of patients with acute coronary syndrome (ACS), more and more attention is paid to the prevention of bleeding, which significantly affects the prognosis of patients after ischemic events [1]. The increasing incidence of complications is associated with the need for active antithrombotic therapy (ATT) [2]. Bleeding avoidance strategies is gradually being introduced into practice, aimed at preventing bleeding events. One of the key parts of this strategies is the development of individualized ATT based on the bleeding risk assessment, for which a large number of scales have been developed [3]. At the same time, their diagnostic value in different groups of patients can vary significantly. The developed ORACUL bleeding risk scale, based on observational study, showed good diagnostic value [4]. It should be noted that not all bleeding affects the prognosis. According to BARC (Bleeding Academic Research Consortium) classification [5], an increase in the risk of recurrent ischemic events in patients with ACS is characteristic of type 2 bleeding and higher, while type 1 does not significantly affect the risk of adverse outcomes [6]. The prognostic value of type 3b bleeding was comparable to the recurrent myocardial infarction (MI), and after type 3 c bleeding, the mortality rate was significantly higher than after MI [7]. To assess the severity of bleeding, other classifications are used — TIMI (Thrombolysis In Myocardial Infarction), ISTH (International Society on Thrombosis and Haemostasis) [8, 9], etc.

The aim was to compare the diagnostic value of different bleeding risk scales in patients with acute coronary syndrome (ACS).

Material and methods

The study included patients from the observational, open-label, multicenter study ORACUL II. The inclusion criteria were the ACS and an indication for percutaneous coronary intervention (PCI) in the current hospitalization, regardless of whether or not PCI was performed. Inclusion in the study was carried out from 2014 to 2017. The inclusion criteria are described in detail in previous publications [10].

The presented analysis included data on 1502 patients who had at least 1 follow-up visit after enrollment in the study. The exclusion criteria were the absence of signed informed consent or the impossibility to contact with the patient after discharge.

All patients received standard therapy based on current guidelines. Of 1502 patients, 560 (34,7%) were included in the study due to ST-segment elevation ACS and 942 (64,3%) due to non-ST-segment elevation ACS. The mean age of the patients was 65,7±12,9 years. The surveyed group included 894 (59,5%) men and 608 (40,5%) women. A total of 1132 (74,7%) patients had a history of coronary artery disease, 466 (31,5%) patients — prior MI, 1320 (87,9%) — history of hypertension (HTN), 769 (51,2%) — heart failure (HF), 216 (14,3%) — gastric and duodenal ulcer, 131 (8,7%) — history of cancer.

At follow-up visits (hospital discharge, 25, 90, 180 and 360 days after the index event), all cases of bleeding were recorded with a description of its characteristics, source, severity, treatment, and classification according to the BARC, TIMI, and ISTH scores.

For a reference assessment of the bleeding risk in this study, the ORACUL scale previously developed by the authors was used [4]. The calculation of the bleeding risk was carried out using factors such as age, hemoglobin level upon admission, glomerular filtration rate, heart failure upon an index event, history of peptic ulcer disease, PCI during index hospitalization, and taking oral anticoagulants (Table 1).

For comparison, risk scales were selected to assess the risk of short-term bleeding in ACS and PCI: Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) [11], Acute Coronary Treatment and Intervention Outcomes Network — Intensive Care Unit (ACTION-ICU) [12], ACUITY — Acute Catheterization and Urgent Intervention Triage Strategy and Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS) [13], as well as out-of-hospital bleeding: Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome (BleeMACS) [14], Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients (PARIS) [15]. In addition, some scales for thrombosis risk assessment were tested for the predictive value of bleeding risk — Global Registry of Acute Coronary Events (GRACE) [16] and TIMI [17]. The prognostic value of the Outcomes Registry for Better Informed Treatment (ORBIT) and Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly (HASBLED) scores, designed to assess the bleeding risk during anticoagulation, were also studied. It should be noted that some of the considered risk factors are common in different scores (Table 2). The use of different scales for bleeding risk assessment in patients after ACS was previously used in other studies [18, 19].

Table 1

ORACUL scale

Parameters	
Age:	
⩽55 years	0 points
56-65 years	8 points
66-75 years	16 points
>75 years	24 points
Hemoglobin at admission:	
>125 g/l	0 points
100-125 g/l	48 points
<100 g/l	96 points
Killip class at admission:	
Class 1	0 points
Class 2-4	17 points
Creatinine clearance:	
>90 ml/min	0 points
60-89 ml/min	6 points
<60 ml/min	12 points
History of gastric or duodenal ulcer	20 points
Anticoagulation in combination with antiplatelet agents after ACS (dual or triple therapy)	36 points
PCI during index hospitalization	38 points

Statistical data processing was carried out using the SPSS 23.0 and MedCalc 18.5 software. For continuous traits, the distribution and normality were analyzed, as well as the mean and standard deviations (M±SD) were calculated. With normal distribution, the Student's t-test was used. With non-normal distribution, nonparametric calculation methods were used. Discrete values were compared using Pearson's chi-squared test.

The analysis of diagnostic accuracy was carried out by creating the receiver operator characteristic curves (ROC curves) for each diagnostic criterion and calculating the area under these curves (AUC). Also, for each tested diagnostic criterion, the sensitivity and specificity were calculated.

The tested diagnostic criterion was assessed as effective if the lower limit of AUC confidence interval was >0,5 and $p<0,05$. The AUC interval from 0,9 to 1,0 corresponded to excellent quality of the diagnostic test, from 0,8 to 0,9 — very good, from 0,7 to 0,8 — good, and from 0,6 to 0,7 — satisfactory. If the AUC was <0,6, the diagnostic test was considered unsatisfactory.

Comparison of the predictive accuracy of different scales was carried out by comparing the AUC using the DeLong's method.

Results

Bleeding in the ORACUL study. During the follow-up period, bleeding was recorded in 170 (11,3%) patients, during the index hospitalization — in 39 (2,6%), and within a year after the index hospitalization — in 131 (8,6%). Nineteen (1,2%) patients had recurrent bleeding. Table 3 shows the characteristics of the incidence and severity of bleeding, assessed on different scales. It should be noted that the severity of bleeding on different scores varied as follows: on the TIMI score, the incidence of major and clinically significant bleeding was less than on the BARC and ISTH scores.

Comparison of the predictive value of the ORACUL scale with other models

The ORACUL scale had the highest predictive value for in-hospital bleeding risk, surpassing in importance such scores as CRUSADE, ACTION-ICU, ACUITY, and PARIS. The only scale with comparable

Table 2

Bleeding and ischemic risk scores used in the study

Score	Parameters	Disease	Predicted outcome	Characteristics of the prototype study		
				Number of patients	Age	Area under the ROC curve
ACTION [12]	Age, creatinine, SBP, HR, hemoglobin, weight, sex, warfarin, diabetes mellitus, HF, peripheral arterial disease	ACS	Hospital major bleeding (decrease in hemoglobin by 4 g/dL, intracranial, retroperitoneal bleeding, blood transfusion)	72131	64	0,73
CRUSADE [11]	Hematocrit, creatinine clearance (Cockcroft-Gault), HR, SBP, peripheral arterial disease, diabetes, HF, sex	ACS	Hospital bleeding (intracranial, retroperitoneal bleeding, hematocrit decrease ⩾12%, any blood transfusion)	71277	67	0,71
ACUITY-HORIZONS [13]	Age, sex, creatinine, WBC count, anemia, ST depression, ATT	ACS	Major bleeding (TIMI0 within 30 days)	17421	62	0,74
PARIS [15]	Age, BMI, smoking, anemia, creatinine clearance, triple ATT	PCI	Major bleeding (BARC type 3-5) within 24 months	4190	65	0,73
BleeMACS [14]	Age, hypertension, peripheral arterial disease, history of bleeding, cancer, creatinine, hemoglobin	ACS+PCI	Significant bleeding (TIMI type II-III) within 12 months	10750	63,6	0,71
ORBIT [18]	Age, decreased hemoglobin, hematocrit, anemia, decreased GFR, history of bleeding, antiplatelet therapy	Atrial fibrillation	Major bleeding (ISTH) within 1 year	10132	75	0,67
HAS-BLED [19]	Age, hypertension, impaired renal function, alcohol, prior stroke, prior bleeding, antiplatelet therapy	Atrial fibrillation	Major bleeding (ISTH) within 1 year	3456	66,8	0,72
GRACE [16]	Age, SBP, HR, creatinine, HF, prior myocardial infarction, ST changes, PCI, dynamics of myocardial damage markers	ACS	Death within 6 months	15007	65	0,81 death 0,61 major bleeding
TIMI [17]	Age, SBP, heart rate, ST changes, history of risk factors, ASA intake	ACS	Death and ischemic events within 14 days	3910	65	0,65

Note: ASA — acetylsalicylic acid, SBP — systolic blood pressure, GFR — glomerular filtration rate, BMI — body mass index.

diagnostic value was the BleeMACS score. It should be noted that the ORBIT and HASBLED scores had a lower predictive value for in-hospital bleeding risk. In general, all scores were better at predicting major bleeding and slightly worse for clinically significant ones. The diagnostic value for out-of-hospital bleeding was lower in all scores than for in-hospital ones. The ORACUL scale had a good diagnostic value for out-of-hospital bleeding and the AUC was the highest among all scores (Tables 4-6).

Discussion

Bleeding events in patients with ACS can be one of the most important unfavorable prognostic factors that often precede recurrent ischemic events [20]. Currently, in clinical practice, several scores are used to assess the bleeding risk. The most common scores are presented in Table 2. It should be noted that the factors used in bleeding risk scores are often at the same time risk factors for ischemic events. These factors are the blood pressure (BP), heart rate (HR), age, renal function, comorbidities (hypertension, diabetes, peripheral arterial disease, etc.). In a number of studies, to assess bleeding risk, risk assessment scores for ischemic events (such as GRACE and TIMI) are used. In the presented work, the diagnostic value of these scores was compared with the model developed by the authors for assessing the bleeding risk.

In clinical practice, the GRACE score is used to assess the risk of coronary events in patients with non-ST-segment elevation ACS. The calculation is of fundamental importance in choosing the management strategy, therefore, it is used in most patients. An attempt was made to assess whether it can be used to assess the bleeding risk. The GRACE score had a good predictive value for the risk of major and minor bleeding and insufficient for BARC type 3-5 bleeding. Previously, it was shown that the GRACE score may have even greater diagnostic value than the CRUSADE score [21]. In the meta-analysis of 9 studies that included >13700 patients with ACS, the GRACE score was comparable to the ACTION, CRUSADE, and ACUITY scores in relation to the bleeding risk [22].

TIMI score is used to stratify the risk of ACS complications in the first 14 days after the hospitalization. It correlates not only with the risk of coronary events, but also with the bleeding risk. On the TIMI score, high-risk patients have the bleeding risk >4 times higher than in low-risk patients [23]. The TIMI area under the receiver-operating characteristics curve (AUROC) for major bleeding was 0,71 [24]. In the present study, it was slightly less — 0,61.

Table 3

The incidence and severity of bleeding in the ORACUL II study

Score	Hospital bleeding during index hospitalization	All bleeding in 1-year follow-up
	BARC	
5 (fatal)	1 (0,06%)	5 (0,3%)
4 (related to CABG)		2 (0,1%)
3 (Major)	8 (0,5%)	16 (1,06%)
2 (minor)	19 (1,3%)	43 (2,9%)
1 (minor, not requiring medical attention)	11 (0,7%)	104 (6,9%)
	TIMI	
III (major)	5 (0,3%)	13 (0,8%)
II (minor)	24 (1,6%)	49 (3,3%)
I (minimal)	10 (0,67%)	108 (7,2%)
	ISTH	
Major	10 (0,6%)	33 (2,2%)
Clinically significant minor	24 (1,6%)	58 (3,9%)
Not significant	5 (0,3%)	79 (5,2%)

Note: CABG — coronary artery bypass grafting.

To predict the risk of major bleeding after discharge from the hospital, the scores originally developed for assessing the in-hospital bleeding risk (CRUSADE, ACTION, and ACUITY-HORIZONS) were also used. These scores have been repeatedly validated in cohorts of ACS patients. So, according to the Italian registry of ACS patients, the AUROC for the CRUSADE score was 0,69, and for ACUITY-HORIZONS — 0,73 [3]. In the Chinese registry of patients after ACS, the AUROC for major bleeding risk after discharge was 0,579 and 0,591, respectively [25]. The CRUSADE score better predicts the risk of major bleeding within 1 month after PCI in ACS patients than VerifyNow platelet function assay (AUROC: 0,81 and 0,61, respectively) [26].

CRUSADE is one of the most accurate bleeding risk scores, the sensitivity and specificity of which is 80% and 73%, respectively [27]. The ORACUL score was comparable to CRUSADE in specificity, but inferior in sensitivity. The diagnostic value of the CRUSADE score in this study was slightly lower in relation to major bleeding within the year. In patients with ACS and comorbidities, the value of the

Table 4

Predictive value of bleeding risk assessment scores (in- and out-of-hospital) in clinical practice (ORACUL study) using various bleeding criteria

Score	BARC 2-5		BARC 3-5		TIMI III		TIMI II-III		ISTH major		ISTH major+significant	
	AUC 95% CI	p*	AUC 95% CI	p	AUC 95% CI	p*	AUC 95% CI	p*	AUC 95% CI	p*	AUC 95% CI	p*
ORACUL	0,762 [0,727-0,795]		0,794 [0,761-0,825]		0,739 [0,712-0,764]		0,699 [0,658-0,737]		0,642 [0,600-0,682]		0,696 [0,655-0,734]	
CRUSADE	0,702 [0,665 -0,737]	0,185	0,643 [0,604-0,680]	**0,04**	0,651 [0,616-0,684]	0,11	0,652 [0,609-0,690]	0,41	0,652 [0,611-0,692]	0,80	0,628 [0,586-0,669]	0,144
ACTION-ICU	0,524 [0,491-0,557]	**0,002**	0,605 [0,572-0,637]	**0,01**	0,502 [0,471-0,534]	**0,049**	0,565 [0,522-0,607]	**0,03**	0,512 [0,469-0,555]	**0,05**	0,555 [0,512-0,597]	**0,004**
ACUITY-HORIZONS	0,647 [0,617-0,675]	0,117	0,630 [0,600-0,659]	**0,03**	0,633 [0,607-0,659]	**0,05**	0,592 [0,558-0,624]	**0,05**	0,592 [0,550-0,634]	0,57	0,581 [0,548-0,613]	0,07
BleeMACS	0,642 [0,613-0,670]	**0,032**	0,693 [0,665-0,720]	0,32	0,661 [0,635-0,685]	0,47	0,624 [0,591-0,656]	0,13	0,711 [0,670-0,749]	0,34	0,594 [0,561-0,626]	0,17
PARIS	0,657 [0,628- 0,684]	**0,05**	0,601 [0,572-0,630]	**0,04**	0,669 [0,643-0,695]	0,29	0,644 [0,611-0,675]	0,38	0,625 [0,583-0,666]	0,55	0,642 [0,600-0,683]	0,24
ORBIT	0,675 [0,630-0,718]	0,09	0,661 [0,616-0,705]	0,20	0,532 [0,485-0,579]	**0,03**	0,626 [0,580-0,671]	0,17	0,598 [0,551-0,644]	0,31	0,587 [0,540-0,633]	**0,03**
HASBLED	0,512 [0,465-0,559]	**0,003**	0,525 [0,478-0,572]	**0,012**	0,514 [0,467-0,561]	**0,02**	0,515 [0,467-0,562]	**0,037**	0,533 [0,486-0,580]	0,26	0,516 [0,469-0,563]	**0,02**
GRACE	0,609 [0,577-0,641]	**0,003**	0,561 [0,491-0,613]	**0,004**	0,507 [0,476-0,538]	**0,01**	0,586 [0,552-0,619]	**0,02**	0,610 [0,558-0,643]	0,52	0,571 [0,538-0,604]	**0,03**
TIMI	0,611 [0,580-0,641]	**0,003**	0,618 [0,587-0,649]	**0,01**	0,677 [0,649-0,704]	0,97	0,585 [0,551-0,617]	**0,04**	0,601 [0,559-0,643]	0,41	0,617 [0,574-0,658]	0,13

Note: p* — compared with the AUC for ORACUL scale. CI — confidence interval.

Predictive value

Excellent and very good | Good | Satisfactory | Low | No value | Not calculable

Table 5

Predictive value of in-hospital bleeding risk scores

Score	BARC 2-5		BARC 3-5		TIMI III		TIMI II-III		ISTH major		ISTH major+significant	
	AUC 95% CI	p*	AUC 95% CI	p	AUC 95% CI	p*	AUC 95% CI	p*	AUC 95% CI	p*	AUC 95% CI	p*
ORACUL	0,777 [0,739-0,812]		0,951 [0,929-0,967]		0,586 [0,543-0,628]		0,713 [0,673-0,751]		0,620 [0,578-0,662]		0,658 [0,616-0,698]	
CRUSADE	0,746 [0,707-0,782]	0,75	0,688 [0,647-0,727]	**0,0003**	0,519 [0,476-0,562]	0,77	0,688 [0,647-0,727]	0,78	0,728 [0,688-0,765]	0,34	0,669 0,628-0,709	0,87
ACTION-ICU	0,676 [0,635-0,716]	0,67	0,802 [0,766-0,835]	**0,001**	0,599 [0,556-0,641]	0,94	0,595 [0,552-0,637]	0,26	0,649 [0,607-0,690]	0,91	0,545 [0,502-0,588]	0,08
ACUITY-HORIZONS	0,750 [0,711-0,786]	0,77	0,604 [0,561-0,646]	**0,0001**	0,561 [0,518-0,604]	0,92	0,645 [0,602-0,685]	0,71	0,617 [0,574-0,658]	0,75	0,585 [0,542-0,627]	0,12
BleeMACS	0,817 [0,782-0,849]	0,34	0,996 [0,987-1,000]	0,99	0,817 [0,782-0,849]	0,50	0,769 [0,731-0,804]	0,32	0784 [0,747-0,818]	0,82	0,693 [0,653-0,732]	0,34
PARIS	0,717 [0,677-0,755]	0,54	0,610 [0,567-0,652]	**0,001**	0,550 [0,507-0,593]	0,84	0,675 [0,633-0,714]	0,31	0,650 [0,609-0,691]	0,42	0,647 [0,605-0,688]	0,78
ORBIT	0,662 [0,616-0,706]	**0,017**			0,585 [0,538-0,631]	0,8	0,660 [0,614-0,703]	0,20	0,511 [0,464-0,558]	**0,048**	0,661 [0,615-0,704]	0,82
HASBLED	0,575 [0,528-0,621]	**0,009**			0,549 [0,502-0,596]	0,69	0,514 [0,467-0,561]	**0,005**	0,594 [0,548-0,640]	0,95	0,505 [0,458-0,552]	**0,005**
GRACE	0,678 [0,646-0,726]	0,42	0,694 [0,653-0,733]	**0,0003**	0,567 [0,524-0,610]	0,92	0,646 [0,604-0,686]	0,41	0,701 [0,660-0,740]	0,54	0,614 [0,571-0,655]	0,45
TIMI	0,798 [0,762-0,831]	0,081	0,626 [0,584-0,667]	**0,003**	0,718 [0,678-0,755]	0,23	0,678 [0,637-0,718]	0,82	0,718 [0,678-0,756]	0,99	0,636 [0,593-0,676]	0,66

Note: p* — compared with the AUC for ORACUL scale. CI — confidence interval.

Predictive value

Excellent and very good | Good | Satisfactory | Low | No value | Not calculable

Table 6

Predictive value of bleeding risk scores within 1 year after index hospitalization

Score	BARC 2-5		BARC 3-5		TIMI III		TIMI II-III		ISTH major		ISTH major+significant	
	AUC 95% CI	p*	AUC 95% CI	p	AUC 95% CI	p*	AUC 95% CI	p*	AUC 95% CI	p*	AUC 95% CI	p*
ORACUL	0,748 [0,692-0,798]		0,769 [0,714-0,817]		0,722 [0,687-0,755]		0,693 [0,652-0,731]		0,633 [0,596-0,668]		0,674 [0,633-0,713]	
CRUSADE	0,665 [0,606-0,720]	0,26	0,609 [0,549-0,667]	0,14	0,729 [0,690-0,766]	0,91	0,613 [0,570-0,654]	0,24	0,604 [0,562-0,645]	0,63	0,587 [0,545-0,629]	0.11
ACTION-ICU	0,542 [0,481-0,601]	**0,01**	0,503 [0,443-0,564]	**0,03**	0,638 [0,596-0,678]	0,06	0,516 [0,473-0,559]	**0,02**	0,531 [0,488-0,573]	0,28	0,530 [0,488-0,573]	**0,01**
ACUITY-HORIZONS	0,687 [0,629-0,741]	0,47	0,676 [0,617-0,730]	0,40	0,755 [0,717-0,790]	0,62	0,611 [0,568-0,652]	0,31	0,582 [0,540-0,624]	0,49	0,605 [0,563-0,647]	0,27
BleeMACS	0,546 [0,509-0,583]	**0,05**	0,643 [0,597-0,669]	0,37	0,546 [0,527-0,601]	**0,05**	0,509 [0,472-0,546]	0,02	0,575 [0,549-0,602]	0,06	0,549 [0,523-0,576]	0,06
PARIS	0,615 [0,578-0,651]	0,43	0,633 [0,596-0,669]	0,38	0,643 [0,607-0,678]	0,40	0,551 [0,513-0,588]	0,59	0,595 [0,558-0,632]	0,43	0,525 [0,488-0,562]	**0,012**
ORBIT	0,607 [0,570-0,643]	0,30	0,647 [0,611-0,683]	0,40	0,654 [0,617-0,689]	0,39	0,530 [0,493-0,568]	0,03	0,613 [0,576-0,649]	0,77	0,523 [0,485-0,560]	0,10
HASBLED	0,517 [0,475-0,559]	**0,008**	0,555 [0,513-0,597]		0,508 [0,466-0,551]	**0,02**	0,548 [0,506-0,590]	0,10	0,566 [0,524-0,608]	0,06	0,540 [0,497-0,582]	0,08
GRACE	0,552 [0,515-0,589]	**0,04**	0,579 [0,541-0,615]	**0,012**	0,512 [0,475-0,550]	**0,05**	0,555 [0,518-0,592]	0,64	0,526 [0,489-0,563]	0,024	0,500 [0,463-0,538]	**0,03**
TIMI	0,508 [0,470-0,545]	**0,01**	0,591 [0,553-0,627]	0,25	0,550 [0,513-0,588]	0,07	0,544 [0,507-0,582]	0,58	0,521 [0,483-0,558]	0,21	0,500 [0,463-0,537]	**0,05**

Note: p* — compared with the AUC for ORACUL scale. CI — confidence interval.

Predictive value

Excellent and very good | Good | Satisfactory | Low | No value | Not calculable

scores may decrease. If for all patients with ACS the AUROC is 0,71, then in patients with chronic kidney disease it is lower — 0,65 [28]. In patients >75 years of age, the CRUSADE score loses its predictive value (AUROC, 0,51), although the GRACE score retains a sufficient predictive value in relation to death and MI risks [29].

The PARIS score in the original study showed a high predictive value for major bleeding (AUROC, 0,71) [30]. In the presented study, the PARIS score allowed to assess the risk of both major and minor bleeding. Although its diagnostic value was lower than the developed scale.

One of the novel risk scores created to assess the risk of bleeding in patients with ACS is the BleeMACS score, developed on the basis of same-name registry, which included 15401 ACS patients observed in 15 hospitals in 10 countries in America, Europe and Asia. All patients underwent PCI. The mean age of patients was 63,6 years, which is close to the age of patients in the current registry. The incidence of major bleeding according to BARC in the 1st year after discharge from the hospital was 3,6 per 100 patient years (in this registry, there were lower number of such patients — 1,3%). The BleeMACS score includes factors such as age, creatinine level, history of bleeding and cancer, hemoglobin level, history of hypertension and vascular disease. External validation of the score was carried out on a cohort of ACS patients from Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies Registry (SWEDEHEART), which included 96239 patients with ACS after PCI and 93150 patients who did not undergo PCI. In the original study, the AUROC was 0,71, while in the SWEDEHEART cohort — 0,63 and 0,61 for patients with and without PCI, respectively, which demonstrates good predictive value and goodness of fit (p>0,2 according to the Hosmer-Lemeshow test) [14]. In the present study, the diagnostic value of the BleeMACS score was 0,691 for major bleeding and was the only score comparable with ORACUL. For major and minor bleeding, the diagnostic value of BleeMACS was significantly lower.

Conclusion

The ORACUL scale seems to be the most acceptable tool for assessing the bleeding risk in patients after ACS in actual clinical practice in Russia.

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Stress echocardiography vs coronary computed tomography angiography for the detection of obstructive coronary artery disease in patients aged ⩾70 years with suspected stable coronary artery disease

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Aim. To compare stress echocardiography and coronary computed tomography angiography (CTA) in the diagnosis of stable coronary artery disease (CAD) in patients aged ⩾70 years.

Material and methods. The study included 390 patients aged ⩾70 years with suspected stable CAD, which underwent elective coronary artery angiography (CAG). Initially, patients for whom stress echocardiography and CTA is appropriate was determined. After that diagnostic accuracy of both methods in the detection of obstructive CAD was evaluated in patients with atypical angina and non-anginal chest pain.

Results. Among 111 patients with atypical angina and non-anginal pain which underwent stress echocardiography and had unequivocal results, 69 (62%) patients had obstructive CAD. Stress echocardiography has sensitivity of 89%, specificity of 95%, positive likelihood ratio (LR+) of 17,8, and negative likelihood ratio (LR-) of 0,1. Positive result increased probability of obstructive CAD from 62% to 95%, while negative result reduced probability to 16%. Among 82 patients with atypical angina and non-anginal pain which underwent CTA, 48 (59%) patients had obstructive CAD. CTA has sensitivity of 100%, specificity of 88%, LR+ of 8,3, and LR- of 0,3. Positive result increased post-test probability of obstructive CAD from 59% to 86%, while negative result reduced post-test probability to 0%.

Conclusion. Stress echocardiography and CCTA has comparable diagnostic accuracy in the detection of obstructive CAD in patients aged ⩾70 years with atypical angina and non-anginal pain. Stress echocardiography has a greater diagnostic value of positive result; CTA has a greater diagnostic value of negative result.

Key words: older adults, coronary computed tomography angiography, stress echocardiography, stable coronary artery disease.

Relationships and Activities: none.

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The algorithm for diagnosing stable coronary artery disease (CAD) at the first stage involves a clinical assessment of pretest probability, which is most often carried out taking into account age, sex and characteristics of chest pain [1, 2]. Determining the pretest probability is a key moment in deciding on further actions. According to the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes [3], in the case of an equal opportunity to carry out stress imaging or computed tomography angiography (CTA), both methods are considered as the first-line. Of the imaging stress techniques, stress echocardiography with exercise is the most appropriate method for diagnosing obstructive CAD in older patients. Exercise stress echocardiography is more accurate than exercise ECG [4]. Older patients often have ECG changes that requires preventing stress tests. Unlike myocardial perfusion scintigraphy, patients are not exposed to radiation. There are few studies on the accuracy of exercise stress echocardiography and CTA in the diagnosis of stable CAD in patients of older age. There is no data on the question of how great is the difference between exercise stress echocardiography and CTA in the diagnosis of obstructive CAD in such patients. The aim of this study was to compare stress echocardiography and coronary computed tomography angiography (CCTA) in the diagnosis of stable CAD in patients aged ⩾70 years.

Material and methods

The study protocol was approved by the local ethics committee. All patients signed informed consent.

This prospective, non-randomized, comparative study included 390 patients ⩾70 years of age who were hospitalized with suspected stable CAD and who underwent an elective coronary angiography (CAG). The study did not include patients with suspected myocardial infarction or unstable angina, a history of myocardial infarction or myocardial revascularization, hypertrophic and dilated cardiomyopathy, atrial fibrillation or atrial flutter, frequent (>5 per minute) premature beats, pulmonary embolism, severe valvular heart disease, congestive heart disease.

Among men, 81 (47%) patients had typical angina, 65 (37%) patients — atypical angina pectoris; 28 (16%) patients had nonanginal pain or exercise dyspnea, which was regarded as equivalent to angina. Among women, 52 (24%) patients had typical angina pectoris, 113 (52%) — atypical angina pectoris,

51 (24%) — nonanginal pain. The quantitative assessment of CAD was carried out visually and using the Xcelera software (Philips, Netherlands). A decrease in the diameter of left coronary artery and/or one of the main coronary arteries by ⩾50% was considered hemodynamically significant [5].

At the first stage, the frequency of obstructive CAD detection was assessed depending on sex and the nature of chest pain, as well as the contingent of patients in whom stress echocardiography and CTA for the diagnosis of stable CAD was inappropriate was determined. Such a contingent included patients in whom the obstructive CAD detection rate exceeded 85%. At the second stage, the diagnostic accuracy of stress echocardiography and CTA was assessed in detecting obstructive CAD in patients with a detection rate of ⩽85%. The sensitivity was calculated = TPR/(TPR+FNR), where TPR is a true positive rate, FNR — a false negative rate; specificity = TNR/(TNR+FPR), where TNR is a true negative rate, FPR — a false positive rate; positive predictive value (PV+) = TPR/(TPR+FPR); negative predictive value (PV-) = TNR/(NR+FNR); predictive accuracy (PA) = TPR+TNR/(TPR+FPR+TNR+FNR); positive likelihood ratio (LR+) = sensitivity/(1-specificity); negative likelihood ratio (NLR-) = (1-sensitivity)/specificity. The posttest probability was calculated as follows:

$$\text{posttest probability} = \frac{\text{(pretest probability/[1 – pretest probability]) × PV}}{\text{pretest probability/[1 – pretest probability]) × PV + 1}}$$ [6].

Exercise stress echocardiography on a semi-reclining ergometer (Ergoline, Germany) was performed in 179 patients. Echocardiography was performed on an ultrasound system Philips iE33. The patient had a continuous stepwise increasing load, starting from 25 W. The increase at each load stage with a duration of 3 min was 25 W. Echocardiography was recorded at rest, during exercise and at the 3rd, 6th, 12th minutes of the recovery [7]. Echocardiographic images were recorded in 5 heart sections: parasternal long axis view, short axis papillary muscle view, in the apical 4-, 3- and 2-chamber views. Local left ventricular (LV) contractility was analyzed by studying clips at rest and at the load peak. Local contractility was studied using 16-segment model [8]. The contractility of each of the segments was assessed using a 4-point scale, where 1 — hypokinesis, 2 — hypokinesis, 3 — akinesis, 4 — dyskinesis. The index of impaired local LV contractility was calculated as the ratio of the sum of asynergy points to the number of assessed segments. The criteria for a positive test were the appearance of transient local contractility disorders, such as a decreased amplitude of wall motion, a decreased systolic thickening in ⩾2 segments, a decreased contractility of initially hypokinetic myocardium, decreased global LV contractility, no increase in ejection fraction, LV dilatation, even without clinical and ECG criteria for myocardial ischemia. Without LV contractility deterioration in the scar area at the load peak, the test results were considered negative. There were following criteria for stopping test: angina attack; ischemic ECG abnormalities; a patient's refusal to continue the exercise; submaximal age-related heart rate (HR); severe arrhythmias; pronounced blood pressure increase. The submaximal age-related HR was 85% of the maximum age-related heart rate, which was calculated using the formula: 208-(0,7×age) [9].

CTA was performed on an Aquilion 64 CT scanner (Toshiba, Japan) with ECG gating. The study did not include patients with an adverse reaction to iodine-based contrast agents, blood creatinine levels >1,5 mg/dL and/or glomerular filtration rate <40 ml/min, weight >100 kg. Patients with a heart rate >70 bpm received beta-blockers to achieve a heart rate of <70 bpm. The CTA protocol included native and arterial phases: phase 1 (native) was performed before contrast agent administration; phase 2 (arterial) was performed in a spiral mode, providing 64 slices 0,5 mm thick in 400 ms with continuous movement of the table with the patient. The current and voltage across the tube were 400 mA and 120 kV, respectively. A contrast agent (optiray-350 or omnipaque-350) at a dose of 100-150 ml (1,5 ml per kg of body weight) was injected intravenously 5 ml/s with an automatic syringe. The assessment of coronary arteries permeability was carried out by analyzing the heart images on transverse tomographic sections. For a detailed assessment of the coronary system state, a multi-plane and three-dimensional image reconstructions with a semi-automatic calculation of stenosis degree were performed. Coronary arteries were assessed according to the American Heart Association [10]. The degree of coronary stenosis was determined according to the following parameters: a patent coronary artery — no stenosis or stenosis <50%; hemodynamically significant stenosis — stenosis >50%; coronary artery occlusion. Image quality was assessed according to the following parameters: excellent — image without artifacts; good — minor artifacts due to coronary artery motion, step artifacts or moderate calcification; poor — pronounced artifacts due to coronary artery motion, step artifacts and/or calcification, preventing the assessment of artery lumen. Arteries <2 mm in diameter were not included in the study. Only excellent and good quality images were used to evaluate the diagnostic CTA.

The data obtained were processed using the Statistica 6.0 program. Quantitative data are presented as mean±standard deviation. To test statistical hypotheses on distribution, the Shapiro-Wilk W-test was used. For a comparative analysis of both groups, nonparametric statistics were used: Fisher's exact test and Yates's chi-squared test — for comparison of qualitative traits; Mann-Whitney U-test — for comparison of quantitative traits. The differences were considered significant at $p<0,05$. The risk of bias was assessed according to the QUADAS tool [11].

Results

According to CAG data, obstructive CAD was detected in 81 (100%) men and 46 (88%) of 52 women with typical angina and in 44 (68%) of 65 men and 48 (42%) of 113 women with atypical angina. It was also revealed in 4 (14%) of 28 men and 11 (22%) of 51 women with nonanginal pain. Due to the fact that, with a high (>85%) detection rate of obstructive CAD, its non-invasive diagnosis is inexpedient [1], the analysis of diagnostic significance of stress echocardiography and CTA in patients with typical angina was not carried out. The probability of obstructive CAD detection in men and women with atypical angina and nonanginal pain was 42% (95% confidence interval (CI), 36-48%).

Stress echocardiography was performed in 134 patients with atypical angina and nonanginal pain. The test did not achieve the diagnostic criteria in 23 (17%)

Table 1

Patient characteristics

	Stress echocardiography (n=111)	CTA (n=82)
Age, years	75±5	75±5
Men/women	58 (51%)/53 (49%)	32 (39%)/50 (61%)
Hypertension	111 (100%)	82 (100%)
Dyslipidemia	111 (100%)	82 (100%)
Diabetes	20 (18%)	22 (27%)
Smoking	26 (23%)	23 (28%)
Positive family history	22 (20%)	21 (26%)
Without MCA lesion	42 (38%)	34 (41%)
With MCA lesion	69 (62%)	48 (59%)
Single-vessel lesion	36 (32%)	15 (31%)
Two-vessel lesion	38 (34%)	16 (33%)
Three-vessel lesion	37 (33%)	17 (35%)
LMCA	5 (5%)	3 (6%)

Note: LMCA — left main coronary artery, MCA — main coronary artery; p>0,05 for all.

patients. Nighty two patients with atypical angina and nonanginal pain were referred for CTA. The study was impossible in 10 (11%) patients due to severe coronary calcification (Agatston score >400). Patients in whom stress echocardiography achieved the diagnostic criteria did not differ in characteristics from patients who underwent CTA (Table 1).

Among 111 patients in whom stress echocardiography achieved the diagnostic criteria, 69 (62%) patients had obstructive CAD (p>0,05 compared with patients with atypical angina and nonanginal pain who underwent CAG). In 62 patients, the test was positive, in 7 patients — negative. The sensitivity in obstructive CAD diagnosis was 89% (95% CI, 80-95). Of 111 patients, 42 (38%) patients did not have obstructive CAD. In 40 patients, the test was negative; in 2 patients — positive. The specificity was 95% (95% CI, 83-99). PV+ was 97% (95% CI, 89-99), PV- — 85% (95% CI, 71-93), PA — 92% (95% CI, 87-95%), LR+ — 17,8 (95% CI, 4.8-42), LR- — 0,1 (95% CI, 0,01-0,2). A positive result increased the likelihood of obstructive CAD from 62% to 95%, while a negative result reduced it to 16%.

Among 82 patients who underwent CTA, 48 (59%) patients had obstructive CAD. The sensitivity of CTA in the diagnosis of obstructive CAD was 100%. In 30 (88%) of 34 patients without obstructive CAD, the CTA indicated the absence of disease, in 4 (12%) patients — the presence. The specificity of CTA in the diagnosis of obstructive CAD was 88% (95% CI, 80-92). PV+ was 92% (95% CI, 89-99), PV- — 100%, PA — 95% (95% CI, 78-99), LR+ — 8,3 (95% CI, 3,9-12,5), LR- — 0. A positive CTA increased the probability of obstructive CAD from 59% to 86%, while a negative result reduced it to 0%. In comparison with CTA, stress echocardiography is less sensitive and has a lower PV- in the diagnosis of obstructive CAD in patients with atypical angina and nonanginal pain (Table 2). The difference was revealed in the values of LR+ and LR- of both diagnostic methods. The risk of bias, according to the QUADAS tool, was 9, which is a low value.

Discussion

According to the results, in men and women ⩾70 years old with typical angina, the detection rate of obstructive CAD is high (>85%) — 100% and 88%, respectively. With this detection rate, non-invasive diagnostic examination is not indicated. In this regard, the analysis of diagnostic accuracy of stress echocardiography and CTA in identifying obstructive CAD in patients with typical angina has not been performed. The high pretest probability of obstructive CAD in men ⩾70 years old with typical angina is stated in the ESC guidelines [1]. According to these guidelines, the probability of obstructive CAD in women 70-79 years old with typical angina is 68%, which is less than in the present study. In the UK guidelines, women of similar age with typical angina have a pretest probability of >90% [12], which is consistent with the present study.

According to the study results, the sensitivity and specificity of CTA in the diagnosis of obstructive CAD in patients ⩾70 years of age with atypical angina and nonanginal pain is 100% and 88%, respectively. Similar values were obtained in studies that included patients with an intermediate pretest probability regardless of age. In a study by Meijboom WB, et al. (2007), the sensitivity and specificity of CTA were 100% and 84%, respectively [13]. According to a meta-analysis of 18 studies, the sensitivity and specificity of CTA in the diagnosis of obstructive CAD is 98% (95% CI, 97-99%) and 82% (95% CI, 79-84%), respectively [14]. According to this study, the sensitivity and specificity of stress echocardiography in the diagnosis of obstructive CAD in patients ⩾70 years of age with atypical angina and nonanginal pain is 89% and 95%, respectively. These values are slightly higher than in meta-analyzes,

Table 2

Diagnostic accuracy of stress echocardiography and CTA in obstructive CAD detection

	Sensitivity	Specificity	PV+	PV-	PA	LR+	LR-
CTA	100%	88%	92%	100%	95%	8,3	0
Stress echocardiography	89%	95%	97%	85%	92%	17,8	0,1
p	0,0007	0,12	0,21	0,0003	0,4	0,02	0,004

which included patients regardless of age. According to these meta-analyzes, the sensitivity of exercise stress echocardiography was 83-85%, while the specificity — 82-84% [15, 16]. According to this study, exercise stress echocardiography is a less sensitive test in the diagnosis of obstructive CAD than CTA. Both samples have comparable specificity, which is consistent with the results of the above studies.

According to the present study, the PV+ and PV- of CTA in the diagnosis of obstructive CAD is 92% and 100%, respectively; the PV+ and PV- of exercise stress echocardiography — 97% and 85%, respectively. PV+ and PV- depends on the incidence of the diagnosed disease among the examined patients. This pattern makes it impossible to compare these indicators in studies with different incidence of the disease. In the present study, the frequency of obstructive CAD detection among patients who underwent CTA and stress echocardiography did not differ, which made it possible to compare the indicators.

To assess how the test result changes the initial data on the probability of disease, it is most appropriate to use LR+ and LR- [17]. LR+ indicates the ratio of TP and FP results, while LR- — the ratio of FN and TN results. According to the LR values, it is possible to estimate how significant the increase or decrease in the posttest probability is (Table 3) [18]. According to the results of this study, the LR+ and LR- of CTA were 8,3 and 0, respectively. This LR+ value indicates moderate differences between the pretest and posttest probability of obstructive CAD, while the LR- value — pronounced differences. Comparable values of these parameters were obtained in studies that included patients with intermediate pretest probability regardless of age. In the study by Meijboom WB, et al. (2007) [13], the LR+ and LR- of the CTA result were 6,38 and 0, respectively; in the ACCURACY trial [19] — 5,56 and 0,06, respectively. According to the results of this study, the LR+ and LR- of stress echocardiography were 17,8 and 0,1, respectively. This LR+ value indicates a pronounced difference between the pretest and posttest probability of obstructive CAD, while the LR- value — moderate difference. LR+ (11,34) and LR- (0,17) of exercise stress echocardiography in the study by Banerjee A, et al. (2012) [4] are close to the values obtained in the presented study.

Table 3

Differences between pretest and posttest probability

Difference	LR+	LR-
Not significant	<2	<0,5
Low	2-5	0,5-0,2
Moderate	5-10	0,1-0,2
High	>10	<0,1

According to the results of this study, a positive CTA increases the likelihood of obstructive CAD from 59% to 86%, while a negative result reduces the likelihood to 0%. A positive stress echocardiography increases the likelihood from 62% to 95%, while a negative result reduces the likelihood to 16%. In the first case, the changes in the posttest probability are so pronounced that they allow changing the initial intermediate probability to a high (>85%) or low (<15%). Such an increase in the likelihood with a positive CTA result allows to establish obstructive CAD, while a decrease in the probability with a negative result allows to conclude that there is no obstructive CAD. Similar results have been demonstrated by Meijboom WB, et al. (2007) [13]. A positive CTA increased the likelihood of obstructive CAD to 88%, while a negative result reduced the likelihood to 0%. An increase in the probability with a positive result of stress echocardiography also allows to ascertain the obstructive CAD, and a decrease in the probability with a negative result gives strong grounds to rule out it. Changes in the obstructive CAD likelihood depending on stress echocardiography result in the present study are consistent with the changes in likelihood that are reported in the meta-analysis [4]. A positive result of exercise stress echocardiography increases the likelihood of obstructive CAD from 49% to 92%, while a negative result reduces the likelihood to 16%.

Conclusion

Stress echocardiography and CTA has comparable diagnostic accuracy in the detection of obstructive CAD in patients aged ⩾70 years with atypical angina and non-anginal pain. Stress echocardiography has a greater diagnostic value of positive result; CTA has a greater diagnostic value of negative result.

Relationships and Activities: none.

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Features of in-hospital clinical course of pulmonary embolism in patients of different age groups

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Aim. To study the clinical course and management of patients with pulmonary embolism (PE) of various age groups hospitalized in a cardiology hospital.

Material and methods. This prospective single-center study in the period from 2016 to 2018 included 154 patients with PE verified by computed tomography. Statistical processing was conducted using the MedCalcVersion 16.2.1 software package (Softwa, Belgium).

Results. In all groups, female patients dominated, but the highest number of women (70,7%) belonged to the group of senile patients, while in the group <60 years, only half of patients with PE were women. Comorbid cardiovascular disease and deep vein thrombosis was diagnosed in eldest patients significantly more often than in those <60 years of age. The highest prevalence of cancer and recurrent PE were identified in the group of elderly patients. Thrombolytic therapy was performed most often in patients 60-75 years old, since these patients had a high risk of 30-day mortality according to Pulmonary Embolism Severity Index, but did not have severe comorbidities, as patients older than 75 years. An increase of right atrium size was found in the group of elderly and senile patients in comparison with patients <60 years. The highest pulmonary artery systolic and diastolic pressure was observed in the patients older than 75 years.

Conclusion. In the Kemerovo Oblast, PE most often develops in patients aged 60-75 years and is characterized by a more severe clinical course compared with patients younger than 60 years. Patients over the 60 years of age have severe cardiovascular comorbidity status, atrial fibrillation/flutter and recurrent PE. Surgical treatment for senile patients is limited due to the high risk of postoperative complications, which specifies high mortality. Patients <60 years of age are a third of all patients hospitalized with PE. They have a low risk of mortality, but have an unfavorable course of the hospital period.

Key words: pulmonary embolism, age, deep vein thrombosis, risk factors, cardiovascular comorbidity.

Relationships and Activities: none.

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Introduction

Modern medicine has achieved success in the diagnosis and treatment of pulmonary embolism (PE), despite this, hospital mortality remains high both in Russia and abroad [1]. It is the study of risk factors and management strategy during in-hospital period that the overwhelming majority of modern studies on PE are devoted to [2]. A number of modern papers focuses on young patients, as the most common group of patients with venous thromboembolism [3]. However, most studies show the highest hospitalization rates for PE among elderly patients >60 years of age. Thus, in a general hospital in Astrakhan, PE was diagnosed at the age of <30 years in 8%, 30-40 years — in 11%, 40-50 years — in 21%, 50-60 years — 23%, >60 years — 38% of patients [4]. The results of the prospective Framingham study also revealed a relationship of PE with old age, obesity, and cancer [5]. In the RIETE (Registro Informatizado Enfermedad TromboEmbolica) registry, the risk of unfavorable outcome was also associated with elderly and senile age [6]. The unfavorable course of PE in elderly patients with severe comorbidities has been confirmed in other works [7-9]. Recently, however, cases of hospitalization among young people diagnosed with PE are increasingly common. It is of interest to study the age characteristics of patients with PE and risk factors associated with a certain age group.

Thus, the aim was to determine the risk factors for development and unfavorable course of PE in different age categories of patients hospitalized in a cardiology hospital.

Material and methods

This prospective, single-center registry conducted from 2016 to 2018 included 154 patients who were hospitalized in Kuzbass Cardiology Center due to PE established by multislice computed tomography pulmonary angiography.

We collected medical history and complaints, assessed the objective status, and determined the 30-day mortality by calculating Pulmonary Embolism Severity Index (PESI). Subsequently, 16-lead electrocardiography was conducted. Laboratory parameters (complete blood count, biochemical blood test, D-dimer level, coagulation test) were determined. Echocardiography was performed to determine the right ventricular (RV) size and pulmonary artery pressure (PAP). Duplex ultrasound of lower limb veins was performed. This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The medical ethics committee approved this study. All patients signed informed consent. The baseline clinical characteristics of patients are presented in Table 1.

Of the 154 patients with established PE, 61,6% were women (men age, 66 years). More than half of the patients had hypertension (HTN), heart failure (HF), deep vein thrombosis (DVT). Such comorbidities as coronary artery disease (CAD) were observed in 22,1% of cases, type 2 diabetes (T2D) — in 13,6%, cancer — in 10,3%. A prior PE was observed in 18,2% of patients, while only 4% of patients previously took regular anticoagulant therapy. In 7,1% of patients, the use of hormonal therapy was a risk factor for PE, in 5,8% — trauma and immobilization; in the overwhelming number of cases PE was idiopathic.

The most common symptom of PE was shortness of breath (75,9%) and chest pain (31,2%), while loss of consciousness and hemoptysis was observed in 16,8% and 9,1%, respectively. Examination of patients revealed an increase in D-dimer level to an average of 3230 ng/ml. It is noteworthy that echocardiography revealed a pulmonary hypertension and increase in RV size. The mean PESI score was 89 (intermediate risk). The management tactics for patients with PE was different. The vast majority of patients (80,5%) received conventional anticoagulant therapy, while 16,8% of patients underwent thrombolytic therapy (TLT). Pulmonary thrombectomy was performed in 4 (2,5%) patients. Among all patients with an established PE, hospital mortality was 4,6% (n=7).

Statistical processing was carried out using the MedCalcVersion 16.2.1 software package (Softwa, Belgium). Qualitative traits are presented as frequencies and percentages. Quantitative indicators are presented as median with a quartile range (25^{th} and 75^{th} percentiles). Comparison in three groups was performed using the Kruskal-Wallis test with Bonferroni correction; in two groups — using the Mann-Whitney test for quantitative data. Qualitative data were compared using 3x2 and 2x2 contingency tables with Pearson's test and Fisher's exact test when the number of observations in the group was <5. The differences were considered significant at $p<0,05$.

Table 1

Clinical characteristics of patients with PE

Parameter	Patients with PE, n=154
Age, years	66 (56; 77)
HTN, n (%)	88 (57,1)
Female sex, n (%)	95 (61,6)
T2D, n (%)	21 (13,6)
CAD, n (%)	34 (22,1)
HF	81 (52,6)
DVT, n (%)	80 (51,9)
Cancer, n (%)	16 (10,3)
Prior pulmonary embolism, n (%)	28 (18,2)
Post-traumatic pulmonary embolism, n (%)	9 (5,8)
Prior anticoagulation therapy, n (%)	6 (3,9)
Prior hormonal therapy, n (%)	11 (7,1)
PESI score	89,0 (72,5; 112,5)
Chest pain, n (%)	48 (31,2)
Loss of consciousness, n (%)	26 (16,8)
Shortness of breath, n (%)	117 (75,9)
Hemoptysis, n (%)	14 (9,1)
SpO_2 (%)	93 (89; 96)
D-dimer, ng/ml	3230,0 (3230,0; 4946,2)
RV size, cm	2,6 (2,0; 2,8)
Pulmonary arterial pressure, mm Hg	49,0 (38,0; 59,7)

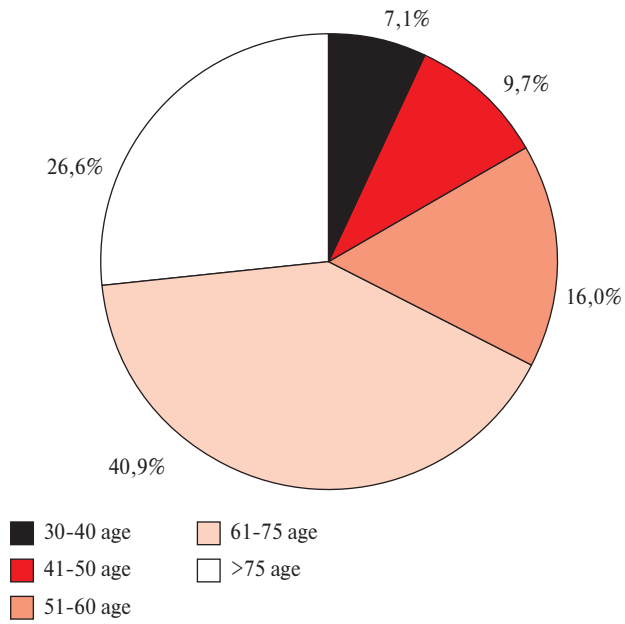

Figure 1. Age categories of patients with PE.

Results

Among the studied patients with PE, persons of elderly age groups prevailed (40,9%). Senile patients were hospitalized in 26,6%, while about a third of all patients were young and middle-aged (Figure 1).

All 154 patients were divided into 3 groups depending on age: 1 — patients <60 years old (n=50; 32,2%), 2 — elderly patients 60-75 years old (n=63; 40,9%) and 3 — senile patients >75 years old (n=41; 26,6%). Subsequently, these groups were compared with each other (Table 2).

In all groups, female patients predominated, however, the largest number of women (70,7%) belonged to the senile age group, while in the group <60 years old, only half of the PE patients were women (p=0,04). At the same time, in the group of senile patients, a significant prevalence of comorbid cardiovascular pathology (HTN, T2D, CAD, HF, non-

Table 2

Clinical factors in groups of PE patients of different ages

Parameter	<60 years of age, n=50	60-75 years of age, n=63	>75 years of age, n=41	p
	1	2	3	
Female sex, n (%)	25 (50,0)	40 (63,5)	29 (70,7)	0,040 1-2=0,211 1-3=0,043 2-3=0,581
HTN, n (%)	22 (44,0)	32 (50,7)	24 (58,5)	0,01 1-2=0,091 1-3=0,041 2-3=0,751
T2D, n (%)	3 (6,0)	10 (15,8)	8 (19,5)	0,038 1-2=0,105 1-3=0,074 2-3=0,967
CAD, n (%)	4 (8,0)	13 (20,6)	17 (41,5)	<0,0001 1-2=0,049 1-3=0,0001 2-3=0,034
HF, n (%)	14 (28,0)	22 (34,9)	19 (46,3)	0,017 1-2=0,236 1-3=0,036 2-3=0,396
AF/AFL, n (%)	4 (8,0)	12 (19,0)	12 (29,3)	0,004 1-2=0,110 1-3=0,012 2-3=0,484
Cancer, n (%)	2 (4,0)	10 (15,8)	4 (9,8)	0,119
DVT, n (%)	3 (6,0)	7 (11,2)	10 (24,9)	0,0007 1-2=0,508 1-3=0,016 2-3=0,128
Prior pulmonary embolism, n (%)	10 (20,0)	17 (26,9)	3 (7,3)	0,001 1-2=0,520 1-3=0,131 2-3=0,021
Post-traumatic pulmonary embolism, n (%)	2 (4,0)	7 (11,2)	5 (12,2)	0,207
Symptoms and clinical course				
PESI score	72,5 (65,0; 90,0)	105 (95,0; 127,0)	118 (99,5; 140,0)	<0,0001 1-2<0,0001 1-3<0,0001 2-3=0,073
SpO_2 (%)	99 (93,4; 100)	93 (89,5; 96,5)	90 (87,2; 93,7)	0,134
Shortness of breath, n (%)	33 (66,0)	37 (58,7)	25 (48,7)	0,359
Chest pain, n (%)	14 (28,0)	14 (22,2)	6 (14,6)	0,157
Heart rate, bpm	90 (81; 98)	96 (83; 110)	99 (80; 118)	0,748
RR, bpm	18 (16; 20)	18 (17; 22)	20 (16; 23)	0,491
D-dimer, ng/ml	2800 (1792; 4791)	3250 (2144; 5000)	4584 (3000; 5000)	0,184
Positive troponin test, n (%)	12 (24,0)	11 (17,5)	7 (17,0)	0,616
Treatment strategy				
In-hospital TLT, n (%)	13 (26,0)	27 (42,8)	14 (34,1)	0,542
Surgery, n (%)	5 (10,0)	1 (1,6)	0	-

Notes: AFL — atrial flutter, AF — atrial fibrillation, RR — respiratory rate.

sinus rhythm) was revealed, compared with the group of patients <60 years old. At the same time, the highest incidence of cancer and a recurrent PE were found in the group of elderly patients (60-75 years old). The PESI score increased significantly from the first to the third group, and was the highest in the group of senile patients.

It should be noted that the patients did not differ in symptoms and clinical manifestations. Most often TLT was performed in the age group 60-75 years old,

Table 3

Echocardiographic parameters in groups of PE patients of different ages

Parameter	<60 years of age, n=50	60-75 years of age, n=63	>75 years of age, n=41	p
	1	2	3	
RV size, cm	2,5 (2,0; 2,8)	2,65 (2,2; 3,0)	2,65 (2,1; 2,9)	0,318
RVEF, %	48,5 (40,0; 51,5)	54,0 (35,0; 55,0)	49,0 (43,0; 50,0)	0,607
TAPSE	1,9 (1,7; 1,9)	1,8 (1,6; 1,9)	1,7 (1,3; 2,3)	0,709
LA diameter, cm	2,9 (2,6; 3,0)	2,5 (2,3; 3,2)	2,7 (2,5; 2,9)	0,936
RA Vmax, ml	56,0 (44,0; 66,0)	63,5 (38,0; 97,0)	65,0 (48,0; 103,0)	0,697
RA length, cm	4,9 (4,5; 5,1)	5,4 (5,1; 5,8)	5,6 (5,3; 6,1)	0,030 p_{1-2}=0,061 p_{1-3}=0,024 p_{2-3}=0,393
RA width, cm	4,4 (4,0; 4,6)	4,6 (3,9; 5,5)	4,2 (3,9; 5,0)	0,838
Pulmonary artery diastolic pressure, mm Hg	15 (9; 18,5)	19 (15; 23)	23 (18,7; 25)	0,048 p_{1-2}=0,063 p_{1-3}=0,04 p_{2-3}=0,343
Pulmonary artery diastolic pressure, mm Hg	41 (30; 44)	44 (40; 58)	57 (52; 62)	0,014 p_{1-2}=0,105 p_{1-3}=0,004 p_{2-3}=0,219

Notes: RVEF — right ventricular ejection fraction, RA Vmax — maximum RA volume, TAPSE — Tricuspid annular plane systolic excursion.

since these patients were characterized by a high PESI risk of 30-day mortality, but at the same time did not have severe comorbidities, as patients >75 years old. Pulmonary embolectomy underwent 10% of patients <60 years and one elderly patient; in all cases there was a favorable outcome. Figure 2 shows an in-hospital mortality. Noteworthy is the same mortality rate in the group of patients <60 years and >75 years old (~7%), while the lowest death rate was noted in elderly patients. Lethal outcome was associated with positive markers for myocardial damage (p=0,02), the embolism of pulmonary trunk (p=0,02), HTN (p=0,01), and respiratory failure (p=0,01) in the general sample of patients.

Table 3 shows echocardiographic data of patients with PE.

There was an increase in the right atrial (RA) size in the group of elderly and senile patients in comparison with patients <60 years old, while the maximum RA volume in the groups did not differ. The most unfavorable values of systolic and diastolic pulmonary pressure were observed in senile patients.

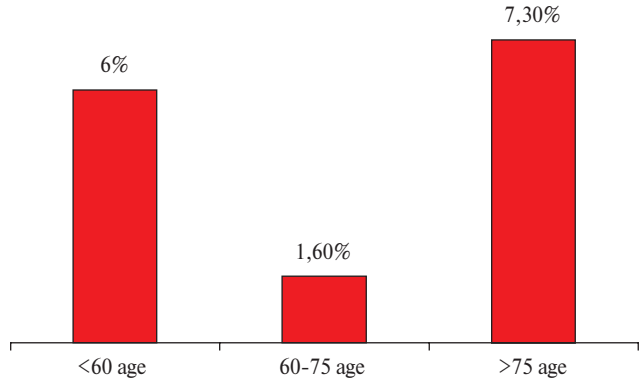

Figure 2. In-hospital mortality rate in PE patients of different ages.

Discussion

The distribution of PE by age groups in this study is comparable to the study carried out in a general hospital in Astrakhan, where PE was diagnosed at the age of <30 years in 8%, 30-40 years — in 11%, 40-50 years — in 21%, 50-60 years — in 23%, >60 years — in 38% of patients [4]. According to the study performed in B.A. Korolev clinical hospital, 138 elderly and senile patients with PE underwent surgical treatment [10]. A 2017 study found that 65% of patients with PE are ⩾60 years old with a mean age of 62 years, while the number of patients >80 years old is eight times more than patients <50 years old. In addition, this study showed that women predominate in the group of young patients, and after 50 years, the prevalence of PE in both sexes is the same [11], while in the present study, it was found that the older the patients, the more women were observed in the group.

The Korean study showed a predominance of women with an average age of 64,8 years [12]. Another study found that patients aged >76 years had a higher percentage of submassive PE (91,1%; p=0,0006), RV dysfunction (91,1%; p=0,0001), increased systolic pulmonary pressure (42,64±16,70 mm Hg, p=0,00004) and an increased level of cardiac troponin I (0,22±0,40 ng/ml, p=0,004) compared with patients <76 years

old. Similar data were obtained in the present study: patients >75 years old have signs of an unfavorable disease course, as well as a high prevalence of comorbid cardiovascular disease, which worsens the prognosis in this category of patients [13].

The current results are consistent with the study by O. Ya. Vasiltseva (2013), where the mean age of patients with PE was 59 years, while at the age of 60-69 years, PE was detected in 37% of patients; there was a predominance of women with a prior PE [14]. The present study also showed that PE is more common in elderly patients (60-75 years old) compared to other age groups and more common in women in groups over 60 years old, which may be associated with a significant predominance of the female population in the Siberian region [15].

Recent studies disprove age as an independent risk factor for PE, explaining the increase in morbidity by an increase in the number of comorbidities [16]. Indeed, the study also found a higher prevalence of multimorbidity in patients of an older age group. The SWIVTER (2012) registry of patients with venous thromboembolism showed that 52% of patients were >65 years old, while they were more likely to have a massive PE; hospital mortality was 6,6% vs 3,2% (p=0,033) [17]. According to the study by O. Ya. Vasiltseva (2017), in the group of patients >70 years old, massive PE and blood clots in the large pulmonary artery branches increased the death risk (odds ratio (OR), 9,73; 95% confidence interval (CI), 5,65-16,76 (p<0,001); OR, 7,58; 95% CI, 4,37-13,15 (p<0,001)). The recurrent embolism and thrombophlebitis also increased the risk of death due to PE (OR, 2,60; 95% CI, 1,59-4,27 (p<0,001); OR, 3,62; 95% CI, 1,26-10,47 (p<0,001).

Diagnosis of PE in older age groups is extremely difficult due to non-pronounced clinical symptoms, concomitant cardiovascular disease, high prevalence of recurrent thrombosis associated with high mortality. According to the PIOPED study, among patients >65 years of age who died in hospital from PE, the diagnosis was made in only 21% [18]. As a cause of death in outpatients, PE is diagnosed at autopsy in 90% [19]. The unfavorable course of PE in elderly patients with severe comorbidities has been repeatedly confirmed in other papers [7-9]. In the present study, it was also determined that patients >75 years old had a high mortality rate, which is explained by severe comorbidities. However, the high mortality rate in a group of patients <60 years old requires detailed study. The unconditional benefit of TLT is shown in a sample of patients aged 60-75 years; this category of patients underwent TLT in a high percentage of cases and had the lowest in-hospital mortality.

The issue of a high incidence of PE and an increased risk of its unfavorable course in women was raised earlier by the authors [20]. In the study by N. G. Vardugina (2017), among women with PE, a high frequency of obesity (63,6%) and HTN (52,6%) was revealed, while the DVT was detected in 68%. Among women, bilateral PE was also more common (63%) with a predominant lesion of large pulmonary vessels [21].

Conclusion

In the Kemerovo and Kemerovo Oblast, PE most often develops in patients aged 60-75 years and is characterized by a more severe clinical course compared with patients younger than 60 years. Patients over the 60 years of age have severe cardiovascular comorbidity status, atrial fibrillation/flutter and recurrent PE. Surgical treatment for senile patients is limited due to the high risk of postoperative complications, which specifies high mortality. Patients <60 years of age are a third of all patients hospitalized with PE. They have a low risk of mortality, but have an unfavorable course of the hospital period along with patients >75 years old.

Relationships and Activities: none.

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Role of epicardial adipose tissue in the development of atrial fibrillation in hypertensive patients

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Obesity is a progressing epidemic, the prevalence of which has doubled over the past 30 years. The distribution of adipose tissue is an important factor in predicting the risk of cardiovascular events. The most significant inflammatory activity is characteristic of epicardial adipose tissue (EAT), the role of which in the development of atrial fibrillation (AF) remains a subject of discussion.

Aim. To study the effect of EAT size on the development of AF in hypertensive (HTN) patients.

Material and methods. The study included 95 patients with HTN aged 38-72 years (mean age, 61,5±1,8 years), including 45 patients with paroxysmal AF (group I) and 50 patients in the comparison group (group II). In order to assess the severity of visceral obesity, all patients underwent a general examination and echocardiography. To determine the EAT volume, cardiac multislice computed tomography was performed.

Results. Echocardiography revealed that the EAT thickness was significantly greater in hypertensive patients with paroxysmal AF than in the comparison group: 11,6±0,8 and 8,6±0,4 mm, respectively (p<0,001). According to cardiac multislice computed tomography, a significant increase in EAT volume was revealed in patients of group I (4,6±0,4 ml) compared with group II (3,5±0,25 ml) (p=0,019). In hypertensive patients with paroxysmal AF, a positive moderate relationship between the EAT volume and left atrial volume was revealed (r=0,7, p=0,022). Multivariate analysis showed that in hypertensive patients, EAT thickness >10 mm and volume >6 ml can serve as integral markers of the onset of paroxysmal AF.

Conclusion. Integral markers of AF in hypertensive patients are an increase in the EAT thickness >10 mm (odds ratio, 4,1; 95% confidence interval, 1,1-5,6) and volume >6 ml (odds ratio 3,7; 95%, confidence interval 1,0-4,2).

Key words: obesity, atrial fibrillation, epicardial adipose tissue, predictors.

Relationships and Activities: none.

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Obesity is a growing epidemic, the overall prevalence of which has doubled over the past 30 years. In Russia, more than 24% of the population is overweight [1]. The modern lifestyle provokes changes in the work and rest schedule, nutrition, and physical activity, therefore obesity and overweight can be considered problems of modern times [2].

It has been proven that obesity is an independent risk factor for the development of hypertension (HTN), diabetes, coronary artery disease (CAD), and heart failure (HF). The role of obesity in the development of atrial fibrillation (AF) is discussed [3]. Several influence mechanisms of excess body weight on the development of arrhythmias are described in modern studies: activation of sympathoadrenal system, renin-angiotensin-aldosterone system hyperactivity, development of HTN, insulin resistance, lipid metabolism disorders, and systemic inflammation [4, 5].

Concomitant cardiovascular disease in obese patients increases the likelihood of the development and progression of cardiac arrhythmias. The first place among the causes of AF is held by hypertension, which is diagnosed in 30% of patients with various arrhythmias. The mechanisms leading to the AF associated with HTN include the occurrence of atrial triggered activity, structural and electrical atrial remodeling, and systemic inflammation.

The distribution of adipose tissue is an important factor in predicting the risk of cardiovascular events. In contrast to subcutaneous fat, which accounts for up to 75% of the total-body adipose tissue, visceral fat is considered as a hormone-producing tissue [6]. The most significant inflammatory activity is observed in epicardial adipose tissue (EAT), which surrounds the myocardium, is located between the epicardium and the visceral pericardial layer, and is close to the myocardium. The functions of EAT include lipid accumulation, thermoregulation, and protection of the autonomic cardiac ganglia.

One of the largest studies that examined the effect of visceral adipose tissue on the development of

arrhythmias was the meta-analysis by Shamloo AS, et al. [7]. The authors have shown that the prevalence of visceral obesity is higher in patients with AF compared to patients without arrhythmias [7]. Similar results were obtained in the study by Zhu YM, et al. [8]. EAT secretes some biologically active substances that contribute to an increase in fatty infiltration of atrial myocardium and an increase in fibrotic activity.

At the same time, there are data not only on the damaging, but also on the cardioprotective function of EAT, which was demonstrated in the study [9]. The authors showed that in EAT and visceral fat, as compared to subcutaneous fat, the expression of three genes encoding enzymes of arachidonic acid metabolism is increased: the *PTDS* gene encoding prostaglandin D2, which has vasodilator and anticoagulant effects and is involved in the plaque stabilization, as well as *NMB* and *ACL1* genes, responsible for the incorporation of arachidonic acid within membrane phospholipids and its turnover [9].

Thus, the role of EAT in AF development remains a matter in dispute. In the modern medical literature, there are practically no works devoted to the EAT role in AF development in patients with HTN.

The aim was to study the effect of EAT size on the development of AF in hypertensive patients.

Material and methods

The study included 95 patients with HTN aged 38-72 years (mean age, 61,5±1,8 years), including 45 patients with paroxysmal AF (group I) and 50 patients of the comparison group (group II). The clinical characteristics of the patients are presented in Table 1.

The inclusion criterion in group I (n=45) was the documented paroxysmal AF in HTN patients, confirmed by electrocardiography (ECG) or 24-hpur Holter monitoring. The comparison group consisted of 50 hypertensive patients without cardiac arrhythmias.

Table 1

Clinical characteristics of patients in groups I and II

	Group I	Group II	p
Number of patients, n	45	50	ns
Mean age, years	60,0±1,8	54,91±2,5	ns
Females, n (%)	22 (49%)	24 (48%)	ns
Males, n (%)	23 (51%)	26 (52%)	ns
HTN, n (%)	45 (100%)	50 (100%)	ns
Grade I, n (%)	8 (17,8%)	13 (26%)	ns
Grade II, n (%)	7 (15,6%)	10 (20%)	ns
Grade III, n (%)	30 (66,6%)	27 (54%)	ns
Duration of hypertension, years	16,5±1,4	12,6±1,4	ns
Obesity, n (%)	45 (100%)	50 (100%)	ns
Class I, n (%)	21 (46,7%)	25 (50%)	ns
Class II, n (%)	15 (33,3%)	15 (30%)	ns
Class III, n (%)	9 (20%)	10 (20%)	ns

Note: ns — not significant.

There were following exclusion criteria: secondary HTN; class I-IV angina of effort; prior myocardial infarction or cerebral stroke; acute coronary syndrome; class III-IV HF; inflammatory heart disease; heart defects; severe disease of kidneys, liver, lungs; anemia; cancer; pregnancy; mental illness.

All patients signed informed consent. The study was approved by the local ethics committee (protocol № 10-19 dated July 17, 2019).

The studied groups were comparable in sex, age, prevalence of obesity, and HTN duration. The duration of AF in patients of group I was 5,9±1,1 years. The incidence of AF episodes was 2,4±0,9 episodes per month.

One of the most important prognosis indicators in patients with AF is the risk assessment of stroke and thromboembolic events using the CHA_2DS_2VASc score (Congestive Heart failure, Hypertension, Age (2 ball), Diabetes mellitus, Stroke (2 ball), Vascular disease, Age, Sex category) and bleeding using the HAS-BLED score (Hypertension, Abnormal renal-liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (65 years), Drugs or alcohol concomitantly). In patients with paroxysmal AF and HTN, the mean CHA_2DS_2VASc and HAS-BLED scores were 2,2±0,4 and 1,6±0,3, respectively.

In order to assess the severity of visceral obesity, all patients underwent a general clinical examination with an anthropometric assessment: body mass index (BMI), waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR), sagittal abdominal diameter (SAD).

The structural and functional myocardial state was assessed by echocardiography using a Siemens ultrasound system (Germany). EAT thickness was assessed in the parasternal long axis view.

To determine the volume of EAT, cardiac multislice computed tomography (MSCT) was performed using a Toshiba Aquillion 640 scanner (Japan). We received 5 slices with a thickness of 0,5 cm and radio signal range from -150 to -70 Hounsfield units (HU), starting from the base of the heart at tracheal bifurcation level and ending with the apex of the heart above the diaphragm. After calculating the volume of each of the five slices, the values were summed up. The obtained images were processed on a Toshiba Aquillion 640 workstation.

Statistical processing was carried out using the SPSS 23.0 program. The results were described using the arithmetic mean (M) and standard deviation (σ). Statistical analysis was performed using the nonparametric Mann-Whitney test. Correlation analysis was carried out using Pearson's correlation test. The influence of quantitative traits on AF development was assessed by the Cox linear regression. The differences were considered significant at $p<0,05$.

Results

There were no significant differences in BMI and SAD between hypertensive patients with paroxysmal AF and those without cardiac arrhythmias. The mean BMI was 31,97±1,67 and 34,43±1,2 kg/m^2, respectively. Significant differences were found in WC and WHtR: in the group of obese patients with AF, the WC was 118,9±3,3 cm, while in patients without arrhythmias —

Table 2

Anthropometric parameters in patients of groups I and II

Parameters	Group I	Group II	p
BMI, kg/m^2	34,43±1,2	31,97±1,67	ns
WC, cm	118,9±3,3	110,2±1,4	0,038
WHR	1,05±0,04	1,09±0,09	ns
WHtR	0,7±0,02	0,6±0,02	0,001
SAD, cm	29,5±0,82	27,4±1,09	ns

Note: ns — not significant.

Table 3

Echocardiographic parameters of groups I and II

Parameters	Group I	Group II	p
LVEF, %	55,0±2,18	59,1±1,1	ns
LV posterior wall thickness, mm	9,9±0,3	9,5±0,2	ns
Interventricular septal thickness, mm	10,05±0,9	11,1±0,5	ns
LV EDV, ml	111,4±12,9	108,5±3,2	ns
LV ESV, ml	54,9±12,5	42,4±1,9	ns
LV mass, g	182,4±15,9	188,0±9,5	ns
LA volume, ml	72,4±1,5	63,2±2,6	0,007
E/A	0,7±0,02	0,8±0,05	ns
EAT thickness, mm	11,6±0,8	8,6±0,4	<0,001

Note: LVEF — LV ejection fraction, EDV — end-diastolic volume, ESV — end-systolic volume, E/A — ratio of peak velocity blood flow in early diastole to peak velocity flow in late diastole.

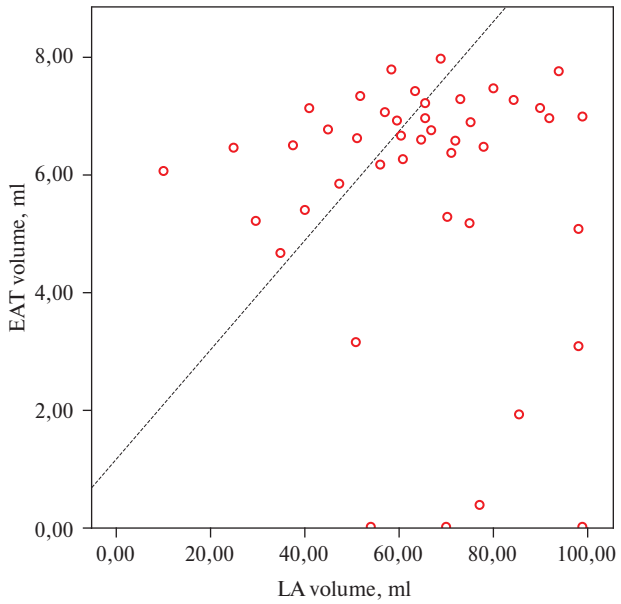

Figure 1. Correlation between EAT volume and LA volume in patients of group I.

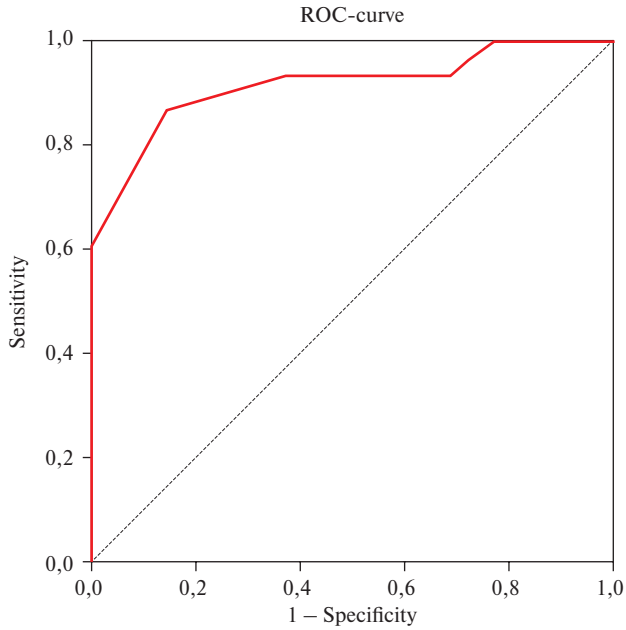

Figure 2. ROC-curve of the EAT thickness.

110,2±1,4 cm (p=0,038); the WHtR in patients with obesity and AF was 0,7±0,02, while in patients without arrhythmias — 0,6±0,02 (p=0,001) (Table 2).

According to echocardiography, there were no significant differences between the study groups in either LV systolic or diastolic function (Table 3). The EAT thickness was significantly higher in patients with HTN and paroxysmal AF than in the comparison group: 11,6±0,8 and 8,6±0,4 mm, respectively (p<0,001).

Significantly higher EAT volume was revealed in patients of group I (4,6±0,4 ml) compared with patients in group II (3,5±0,25 ml) (p=0,019).

In patients with hypertension and paroxysmal AF, a positive moderate relationship was found between the volumes of EAT and left atrial (LA) (r=0,7, p=0,022) (Figure 1).

In the group of hypertensive patients with paroxysmal AF, the contribution of anthropometric parameters, echocardiography, and EAT sizes in AF was assessed. The selected parameters were included in the Cox regression model for predictive value analysis.

Multivariate analysis revealed a significant effect of EAT thickness (odds ratio, 4,1; 95% confidence interval (CI), 1,1-5,6) assessed by echocardiography and EAT volume (OR, 3,7; 95% CI, 1,0-4,2) assessed by cardiac MSCT on AF likelihood in HTN patients.

To determine the threshold values for EAT thickness and volume, a ROC analysis was performed (Figure 2). In hypertensive patients, an EAT thickness >10 mm with a sensitivity of 81,6% and a specificity of 79,8% indicates the paroxysmal AF (area under the curve (AUC), 0,915).

EAT volume ⩾6 ml also had a high diagnostic value with a sensitivity of 83,2% and specificity of 80,7% (Figure 3) for paroxysmal AF in HTN patients (AUC, 0,891).

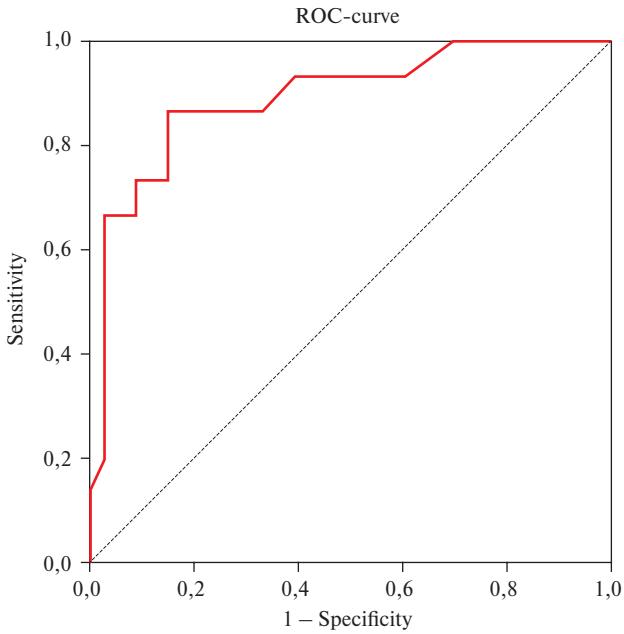

Figure 3. ROC-curve of the EAT volume.

Thus, increased thickness and volume of EAT can serve as markers of AF in hypertensive patients.

Discussion

The overwhelming majority of patients had a "secondary" AF, which develops due to cardiac or noncardiac diseases, which lead to electrophysiological and structural atrial remodeling. Along with the already studied reasons, such as HTN, HF, CAD, obesity can also be considered. It is visceral obesity, according to most authors, is one of the most significant predictors of adverse cardiovascular events.

In the present study, it was found that in patients with HTN and paroxysmal AF, the detection rate of visceral obesity was significantly higher than in patients without cardiac arrhythmias. At the same time, the BMI in the studied groups were comparable, and significant differences were observed only in the mean WC and WHtR values. Similar results were obtained in the Framingham study, which included 3217 participants [10].

Echocardiography reveled a significantly higher EAT thickness in group I compared with group II. In hypertensive patients with paroxysmal AF, a relationship was established between the EAT thickness and the LA size. This relationship characterizes the negative effect of EAT increase on the LA structural remodeling, which increases the risk of AF. The most accurate method for EAT assessment is to determine its volume using cardiac MSCT. In our study, the volume of EAT was significantly greater in hypertensive patients with AF than in patients without cardiac arrhythmias. Multivariate analysis revealed that an increase in the EAT thickness >10 mm and volume >6 ml are reliable markers of AF in HTN patients.

The role of visceral obesity in AF development is probably mediated by its effect on the structural and electrical atrial remodeling. Haemers P, et al. proved that subepicardial fatty infiltration significantly increases the risk of AF [11]. The study by Venteclef N, et al. [12] showed that humoral factors produced by EAT lead to active atrial fibrosis in rats. EAT can have following effects: release of adipokines that can initiate the development of fibrosis; expression of pro-inflammatory cytokines involved in the atrial remodeling; promotion of fatty infiltration of atrial cardiomyocytes. It also contains ganglionated plexuses that play an important role in the development of a proarrhythmogenic substrate in the myocardium [13-16].

Thus, an increase in the thickness and volume of EAT are integral markers of arrhythmias in hypertensive patients. Multivariate analysis, for the first time, revealed the threshold values of thickness and volume of EAT, which can help in diagnosis of AF in hypertensive patients.

Conclusion

1. In hypertensive patients with paroxysmal AF, when compared with those without cardiac arrhythmias, significantly higher thickness and volume of EAT were revealed.

2. In hypertensive patients with paroxysmal AF, the EAT thickness is positively associated with an increase in the LA volume (r=0,77).

3. The integral markers of AF in hypertensive patients are EAT thickness >10 mm and volume >6 ml.

Relationships and Activities: none.

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Secondary prevention in patients with coronary artery disease in Russia and Europe: results from the Russian part of the EUROASPIRE V survey

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Aim. To assess the secondary prevention in Russian patients with coronary artery disease in the long-term period after acute myocardial infarction, acute coronary syndrome (ACS), percutaneous coronary intervention and/or coronary artery bypass grafting, obtained in the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE V) survey in comparison with the general population of the study.

Material and methods. EUROASPIRE V is a cross-sectional study with 27 countries, including Russia, which involved patients with ACS or indications for myocardial revascularization. At participating centers, patients admitted to hospital due to ACS or for percutaneous coronary intervention or coronary artery bypass grafting were identified. After 6 months and <2 years after discharge, patients were examined.

Results. In total, 699 patients were identified in Russia, 399 of which visit an interview (women, 27,1%; mean age, 62,8±8,7 years). In the general population of the study, 16,208 patients were identified, 8,261 of which were interviewed (women, 25,8%; mean age, 63,6±9,6 years). At the time of the interview, 18,5% of Russian patients continued to smoke (16,8% in the general study population), the prevalence of overweight or obesity — 85,4 and 81,7%, abdominal obesity — 60,4 and 58,5%, diabetes — 21,9 and 29,3% of patients, respectively. In 19,7 and 16,4% of patients, respectively, diabetes was first diagnosed with a glucose tolerance test in the study. The target glycated hemoglobin was achieved in 47,1 and 54,4%, blood pressure — in 64,0 and 53,7%, low-density lipoprotein cholesterol — in 27,6 and 29,0% of patients, respectively.

Conclusion. There were significant differences between the Russian cohort and the general study population. Some key secondary prevention parameters were more favorable in the Russian cohort, and some parameters — in the general group. In both compared populations, significant reserves are retained for further optimization.

Key words: coronary artery disease, secondary prevention, risk factors, target levels.

Relationships and Activities: none.

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In recent years, undoubted advances have been achieved in the prevention and treatment of cardiovascular diseases (CVD) and, in particular, coronary artery disease (CAD), which makes the greatest contribution to cardiovascular mortality pattern, but even in countries with the most favorable the CVD situation, this problem cannot be considered completely solved [1-3]. Control of cardiovascular risk factors (RF), which are key indicators of the effectiveness of secondary disease prevention, is critically important for reducing the risk of cardiovascular complications and unfavorable outcomes in patients with CAD. The assessment of the adequacy of measures to correct CVD RFs within secondary prevention of CAD is carried out at various levels. International programs of this kind are of particular interest, since they provide an opportunity to globally assess the secondary prevention of CAD, compare it

across regions and countries, and also allow determining priority optimization goals.

One of the most famous international programs is the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE), which has been conducted since 1994 by the European Society of Cardiology (ESC) every few years to assess the effectiveness of the practical implementation of current European guidelines for CVD prevention. Currently, five studies of EUROASPIRE have been carried out: in 1995-1996 (EUROASPIRE I) — with the participation of 9 European countries and 3569 patients with CAD [4], in 2000-2001 (EUROASPIRE II) — with the participation of 15 European countries and 5556 patients with CAD [5], in 2006-2007 (EUROASPIRE III) — with the participation of 22 European countries and 13593 patients with CAD [6], in 2013 (EUROASPIRE IV) — with the participation of 24 European countries and 13586 patients with CAD [7] and, finally, in 2016-2017 (EUROASPIRE V) — with the participation 27 European countries and 16208 patients with CAD [8].

Russian centers took part in the hospital parts of the last three studies (EUROASPIRE III, IV and V), which made it possible to conduct not only a comparative analysis with the European population as a whole and for individual countries, but also to analyze the changes over the past period in Russian cohorts. The EUROASPIRE V studies are of particular interest compared to earlier studies due to their wider geography and the fact that at the time of its implementation, modern approaches to the treatment of patients with CAD in Russia were already fully implemented [9, 10].

The aim was to assess the secondary prevention in Russian patients with coronary artery disease in the long-term period after acute myocardial infarction (MI), acute coronary syndrome (ACS), percutaneous coronary intervention (PCI) and/or coronary artery bypass grafting (CABG), obtained in the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE V) survey in comparison with the general population of the study.

Material and methods

EUROASPIRE V [8] is a cross-sectional study involving 27 European countries: Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Egypt, Finland, Germany, Greece, Ireland, Italy, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, the Netherlands, Poland, Portugal, Romania, Russian Federation, Serbia, Slovenia, Spain, Sweden, India, Ukraine, Great Britain. In each country, one or more geographical areas were selected, in which inpatient cardiology centers were identified, among which one or more facilities were selected so that all patients with acute CAD or indications for myocardial revascularization using PCI or CABG had a chance of being admitted to the institution. At the participating centers, on the basis of discharge summaries (or registers), all admitted patients (aged 18-80 years) were identified without exception, hospitalized due to ST-segment elevation MI (STEMI), non-STEMI or ACS or for the purpose of elective/emergency PCI or CABG. The period from the moment of patient identification to the interview was ⩾6 months and <2 years. Each of the participating countries was recommended to include in the study at least 400 patients. The exclusion criteria were severe acute conditions, chronic decompensated diseases, severe mental disorders, drug or alcohol dependence, refusal to participate in the study. All patients with documented CAD were invited to interview in order to assess the long-term results of treatment, clinical, psychological status and life quality, the presence and achievement of target RF levels, as well as to assess the adequacy of non-pharmacological and medication recommendations provided to patients. Each patient signed an informed consent.

When analyzing medical records, the authors took into account socio-demographic characteristics of patients, medical history, availability of information on RF (smoking, obesity, hypertension (HTN), dyslipidemia, hyperglycemia), therapy prescribed during hospitalization and after discharge (with the drug names and daily doses), as well as non-drug recommendations for changing lifestyle provided to patients.

During the interview, using a structured individual report form and validated questionnaires, a detailed survey of patients was carried out on the main aspects of lifestyle (smoking, diet, physical activity, psychosocial factors), drug intake and adherence to non-pharmacological recommendations.

The following anthropometric data were recorded: height, body weight, and waist circumference (WC). Overweight was determined in body mass index (BMI) ⩾25 and <30 kg/m^2; obesity — ⩾30 kg/m^2; abdominal overweight — WC ⩾80 and <88 cm in women and ⩾94 and <102 cm in men; abdominal obesity — WC ⩾88 cm in women and ⩾102 cm in men.

Blood pressure (BP) was measured twice after 5-minute rest on the right hand at 5-minute intervals in the sitting position using an automatic BP monitor (Omron M6). Smoking was objectively assessed by the concentration of carbon monoxide in expired air using a Smokerlyser device (Bedfont Scientific, Micro+).

The level of physical activity was assessed by the question: "Do you exercise regularly for at least 30 minutes on average 5 times a week?" and the question of conducting any physical exercise.

All of these data were entered into a patient report form, as well as into an electronic patient form in database of the EURObservational Research Program.

During the interview, fasting venous blood was taken to determine the levels of total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglycerides, low density lipoprotein cholesterol (LDL-C), as well as blood glucose and glycated hemoglobin (HbA_{1c}). All patients without diabetes and with a fasting glucose level <11,1 mmol/L underwent an oral glucose tolerance test. Blood glucose concentration was determined using a portable system (Glucose 201RT, HemoCue®, Ängelholm, Sweden). Blood for tests of TC, LDL-C, HDL-C was taken into clot activator tube to determine the level of HbA_{1c} — EDTA (Venosafe). The blood was centrifuged (2000 rpm) at room temperature for 10 min, after which the plasma was placed in coded tubes, frozen at -70° C and sent from all countries participating in the study to

Table 1

Proportion of medical records of patients with CAD, where data on CVD RFs was recorded upon admission to the hospital, in Russian and general population of the EUROASPIRE V study

	Patients of Russian centers	General EUROASPIRE V population
History of diabetes, %	98	85,8
Smoking status, %	88,2	81,4
Body mass, %	68,7	64,9
WC, %	26,3	13,9
Systolic BP, %	83,7	85,8
Total cholesterol, %	80,7	68,7
LDL-C, %	51,6	58,2
Blood glucose, %	83,5	75,1
HbA_{1c}, %	2,8	17,8
OGTT, %	3,3	1,6

the central laboratory (Laboratory in the National Institute for Health and Welfare, Helsinki, Finland), where the appropriate parameters were measured on a clinical chemistry analyzer (Architect c8000; Abbott Laboratories, Abbott Park, Illinois, USA).

Statistical analysis was carried out at the Department of Public Health of the Ghent University (Belgium) using SAS 9.4 (Statistical Analysis System, SAS Institute Inc., USA) software package.

In Russia, the following 4 centers participated in the EUROASPIRE V study: National Medical Research Center for Preventive Medicine (Moscow), City Clinical Hospital № 36 (Moscow), Moscow Regional Cardiology Center (Zhukovsky), and Regional Clinical Hospital (Barnaul). The Russian part of the EUROASPIRE V study was conducted under the auspices of the National Medical Society of Preventive Cardiology. The Russian part of the EUROASPIRE V study by the Independent Ethics Committee of the National Medical Research Center for Preventive Medicine. All patients signed informed consent.

Results and discussion

In total, 699 patients with CAD were identified and included in the study in Russian centers, the mean age of which at the time of hospitalization was 61,7±8,7 years (women, 27,1). In Europe as a whole, there were 16208 patients with the mean age of 62,4±9,6 years (women, 25,8%). At the same time, 9,8% of patients included in Russia at the time of hospitalization were <50 years old, 30,6% — 50-59 years, 43,6% — 60-69 years old, and 16% — ⩾70 years old.

According to the current ESC for CVD prevention [11], in hospitalized patients with CAD who have undergone acute conditions or interventions for myocardial revascularization, it is critically important to start adequate measures for secondary prevention even before discharge from the hospital. From this point of view, an important indicator is the data on the main CVD RFs in the medical records of patients with CAD (Table 1).

In Russian patients and in the general population of the study, there is significant heterogeneity of information on CVD RFs. In the overwhelming majority of cases, upon admission of patients, information about the systolic BP, the diabetes presence and smoking status was noted, while the level LDL-C was recorded only in about half of the cases, while WC levels and key characteristics of carbohydrate metabolism — in a minority of patients. In general, the frequency of RF registration in the medical records of Russian patients was either comparable to that in the general study population, or slightly exceeded it. In particular, in Russian patients, body weight was indicated in 68,7% of cases, WC — in 26,3%, diabetes — in 98%, smoking status — in 88,2%, systolic BP — in 83,7%. In the total sample, these parameters were 64,9, 13,9, 85,8, 81,4 and 85,8%. In Russian centers, information on LDL-C values was recorded in every second patient (51,6%), on TC — in 80,7%. In the general population of the study, information on LDL-C was recorded more often (58,2%) and about the TC level — less often (68,7%). The results of blood plasma glucose and oral glucose tolerance test (OGTT) were more fully reflected in Russian patients (Table 1). The only exception was HbA_{1c}, which appeared much less frequently in Russian medical records (2,8% versus 17,8% in the general population), which is apparently due to the availability of this analysis.

A similar performance was observed in discharge reports of patients — information on RFs was more often indicated in Russian centers than in the EUROASPIRE V study as a whole. In the discharge reports of Russian patients, the smoking status was recorded in 89,0%, the presence of overweight or obesity — in 88,7%, the presence of hypertension — in 98,7%. Lipid metabolism was reflected in 96,5% of cases, carbohydrate metabolism — in 99,5%, kidney function — in 97,0%. In the general population of the study, these parameters were described in 78,3,

71,5, 89,6, 80,5, 76,7 and 84,5% of discharge reports, respectively.

In the Russian cohort, the interview was on average 0,92 (0,67-1,45) years after the initial hospitalization for AMI, ACS, PCI or CABG, while in the general population — after 1,12 (0,82- 1,56) years. Excluding deceased patients and those who could not attend the interview for other objective reasons (significant health deterioration or moving), the response was 67,4% of patients in the Russian cohort and 56,3% in the general sample. Among the Russian participants, there were 27,1% women (25,8% in the general sample). The mean age of Russian patients who came for a interview was 62,8±8,7 years (7,3% — <50 years, 29,8% — 50-59 years, 42,4% — 60-69 years, 20, 6% — ⩾70 years), while in the general population — 63,6±9,6 years (18,4, 20,8, 26,0 and 32,4% in age groups <50 years, 50-59 years, 60-69 years and ⩾70 years, respectively). The overwhelming majority of Russian participants (92,2%) had a history of one or another intervention for myocardial revascularization, mainly PCI (89,2%), while 9,8% of patients had previously undergone CABG. In the general study population, the frequency of previous myocardial revascularization was 88,9%, while the proportion of patients with a CABG history was significantly higher than in the Russian cohort (18,6%); 80,2% of general sample patients underwent PCI. The proportion of patients with involvement of other vascular systems was small both in Russian centers and in the general sample: a history of strokes was noted in 3,3 and 4,1%, and hospitalizations for peripheral arterial disease — in 2,3 and 2,7% of patients, respectively. Hospitalizations due to heart failure were also rare (3,5% and 6,3% of patients, respectively).

As in the earlier EUROASPIRE studies [12, 13], the educational level of the Russian cohort was generally higher than in the general study population: 40,8% of Russian patients had a higher education, 38,5% — specialized secondary education, 20,8% — secondary education (in all EUROASPIRE V countries — 27,2, 15,7 and 42,1%, respectively).

Follow-up of Russian patients after the index clinical event was most often performed by cardiologists (88,7 vs 77,9% in the general study population). About 41,4% of Russian patients were also followed up by a general practitioner (64,8% in the general sample).

In the considered sample with a very high cardiovascular risk, long-term smoking after AMI, ACS and/or myocardial revascularization was reported by 18,5% of Russian patients, while in general sample the proportion of smoking patients was slightly lower (16,8%). At the same time, as in the previous EUROASPIRE IV study [12], smoking prevalence in Russia consisted of a higher smoking frequency in men (23,7%) and a lower one in women (4,6%). Identifying carbon monoxide in the expired air (>10 ppm), carried out in this study, did not reveal a significant change in the proportion of smoking patients (Figure 1).

Although smoking cessation is one of the most effective secondary prevention measures [14, 15], the likelihood of smoking cessation in patients who smoked for a month before the initial hospitalization was low: in the Russian cohort, about two-thirds of the patients who initially smoked continued to smoke; in the general population — slightly more than half. The rate of successful smoking cessation was especially low in Russian women (only 16,7%). It should be noted that at the time of interview, about half (54,1% in total, 53,6% of men and 60% of women) of Russian patients who continued to smoke wanted to quit smoking in the next six months. In the general population of the study, the proportion of patients motivated to quit smoking was even slightly less — 46,6% (47,2% of men and 43,8% of women).

In addition to patients who successfully quit smoking (33,7%), among Russian patients who smoked at the time of index hospitalization, 61,7% reduced the number of cigarettes smoked (49,0 and 37,6%, respectively). This happened despite the extremely low frequency of any medical assistance for smoking cessation: among Russian patients, only 3,1% participated in specialized programs, and pharmacological support was limited only to nicotine replacement therapy (NRT) in 4,1% of patients. Nobody took varenicline or bupropion, which is not available in Russia. In the general sample of the study, these parameters were slightly higher, although the coverage of care for smoking cessation was insufficient: 5,2% of patients were observed in specialized clinics or programs; NRT was received by 7,1%, bupropion — 1,4%, varenicline — 2,4% of patients. Therapy of nicotine addiction had quite pronounced regional differences and in some countries these drugs were prescribed much more often than the European average. For example, in Sweden, NRT was given to 35,4% of smokers with CAD, varenicline — 10,4%, bupropion — 6,2% of patients, while in Ireland, NRT was prescribed to 37,5% of smokers, varenicline — 3,4%, and bupropion was not used at all. Finally, it should be noted that in the centers participating in the EUROASPIRE V study, hospital-based physicians were not involved at all in smoking cessation care. Thus, in the general population of the study, varenicline or bupropion were not recommended for any of the patients at discharge, and only 0,5% of discharge reports included NRT.

Overweight and obesity are another RFs, the importance of which has been emphasized all over the world in recent years [16]. The EUROASPIRE V study assessed both BMI and the degree of visceral adipose tissue according to the WC data. The mean BMI in the Russian cohort was 29,9±4,9 kg/m^2 (men, 29,4±4,8 kg/m^2; women, 31,3±4,8 kg/m^2), while in the general population of the study — 29,2±5,0 kg/m^2 (men, 28,9±4,6 kg/m^2; women, 30,0±5,8 kg/m^2).

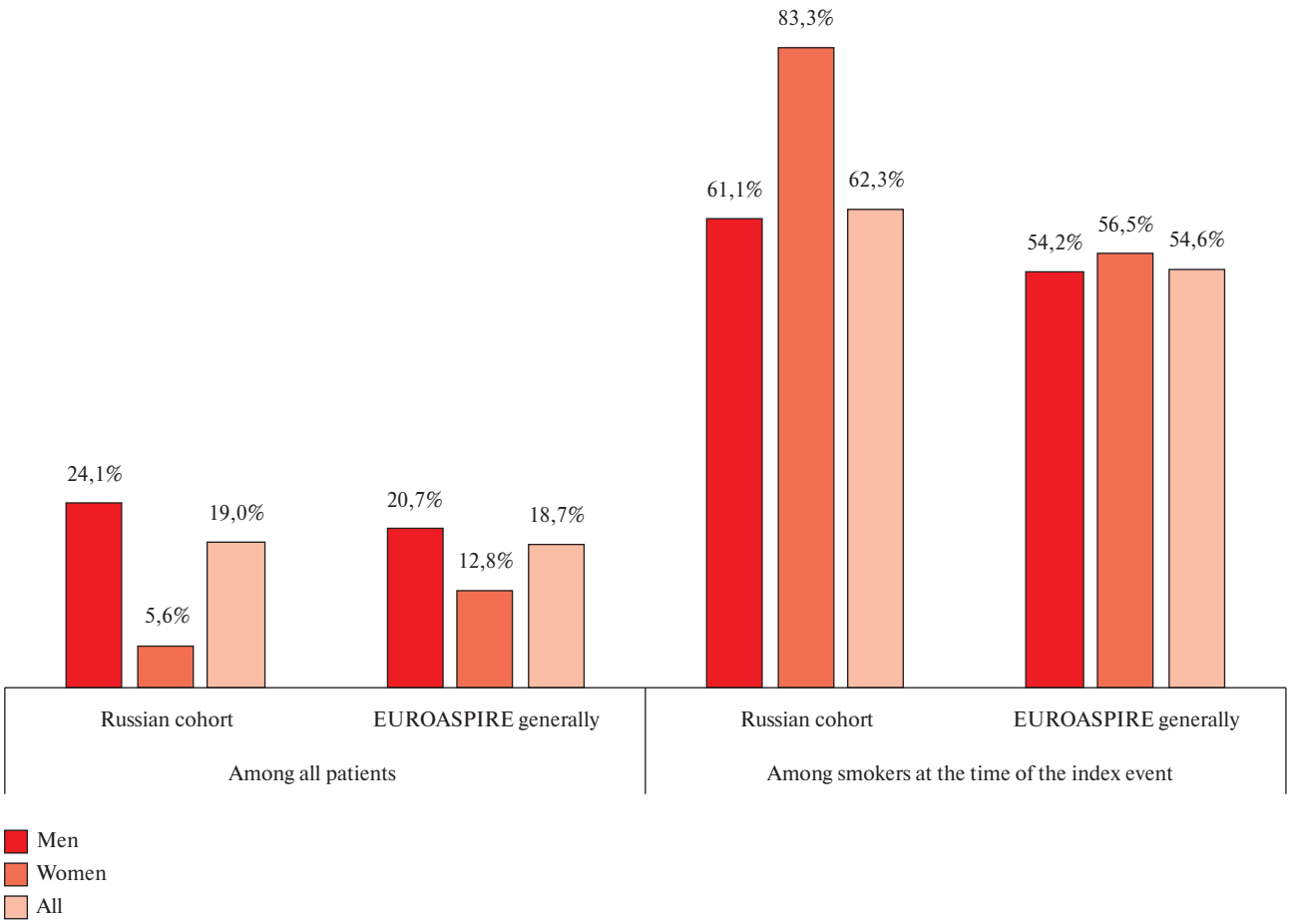

Figure 1. Prevalence of smoking in Russian and general population of the EUROASPIRE V study among all participants and smokers at the month preceding the index event.

Note: Patients were classified as smokers based on survey and/or detection of carbon monoxide in expired air >10 ppm.

An extremely high incidence of overweight and obesity among Russian patients with CAD has been established. Only 14,6% of Russian patients had normal body weight, while in Europe as a whole, there were slightly more such patients (18,3%). At the same time, if the proportion of men with overweight or obesity in Russia was comparable to the general population data, then the situation in Russian women was clearly worse than in the study as a whole (Figure 2). This parameter significantly differed in various countries of EUROASPIRE V, but even in the countries with the best performance, only about a quarter of patients had adequate body weight. Prevalence of obesity (BMI $\geqslant$30 kg/m^2) among Russian patients with CAD was the highest — 47,0%.

Given that abdominal obesity has a higher predictive value than BMI-estimated obesity [17],

the analysis of WC data is also important. These indicators in the Russian cohort practically did not differ from the general population of the study — 103,1±12,1 cm in men and 97,7±12,1 cm in women vs 102,6±12,8 and 98,2±14,2 cm, respectively. The excessive WC (WC $\geqslant$94 cm in men and $\geqslant$80 cm in women) was recorded in 84,4% of our patients, which is slightly more than in the general study population (81,3%). The proportions of patients with central obesity (WC $\geqslant$102 cm in men or $\geqslant$88 cm in women) in the Russian cohort and in the general study population did not differ practically (60,4 and 58,5%, respectively). It should also be noted that in Russia and in other European countries, abdominal obesity was more typical for women (Figure 3).

The overwhelming majority of Russian obese patients (88,2%) were informed by medical workers about this problem (in the general sample — 75,0%). Moreover, in Russia, 44,4% of patients with CAD and obesity during the month preceding the interview tried to reduce body weight (in the general sample — 48,1%). In addition, Russian patients were very motivated in future: 73,3% of patients planned actions to reduce body weight in the next six months, which is almost 1,5 times more than in the general sample (55,2%). It should also be noted that most patients with CAD, received fairly detailed recommendations in this area. Thus, 82,8% of Russian patients received recommendations for diet, 86,1% — for regular exercise (in the general population — 51,7 and 55,0%). Moreover, about two-

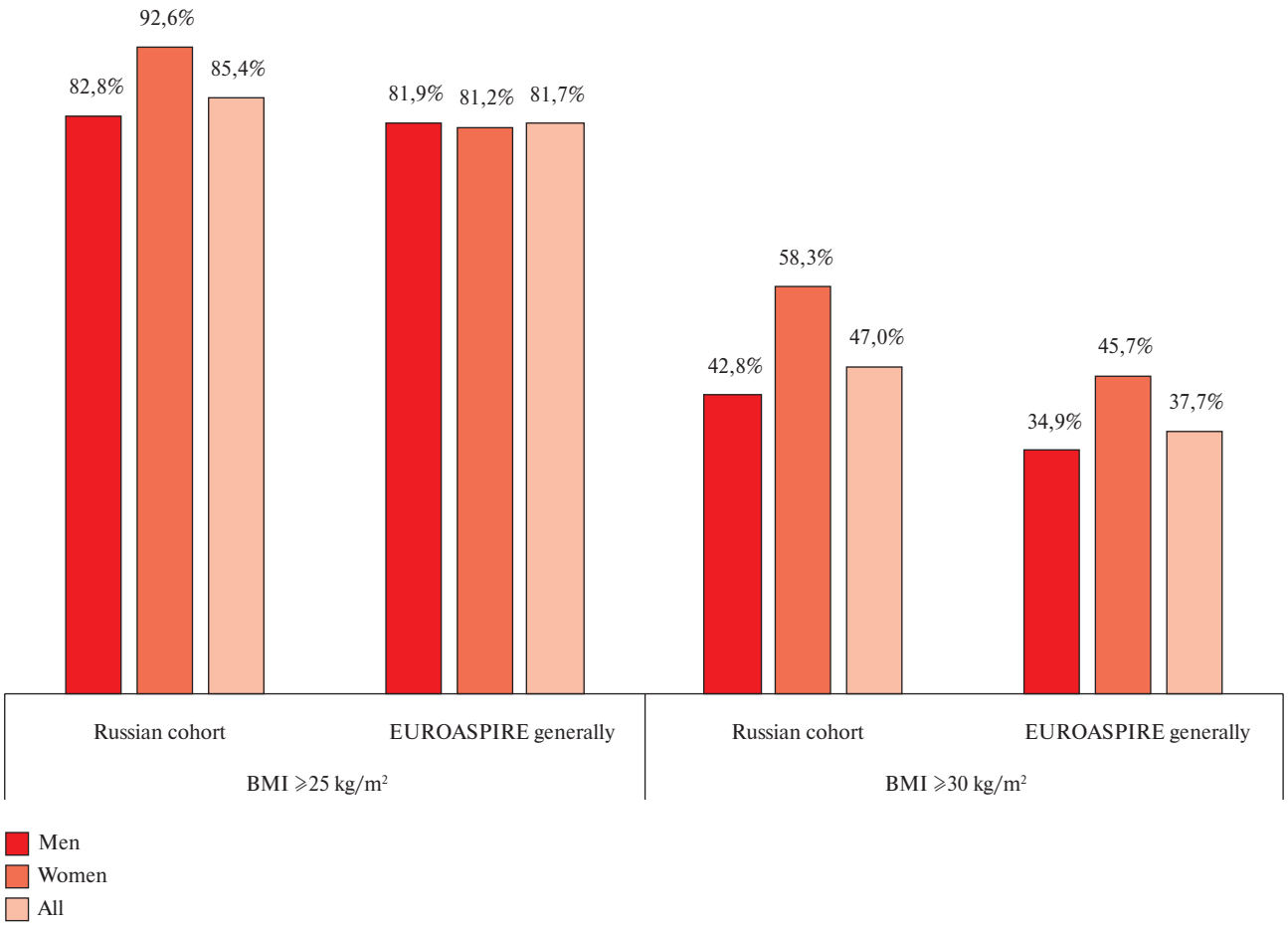

Figure 2. Prevalence of excess body weight and obesity (according to BMI) at the interview in Russian and general population of the EUROASPIRE V study.

thirds of patients from Russian centers (and ~40% of general sample) believed that they were following these advices. The dietary recommendations provided to patients were quite detailed: 93,7% of Russian participants recalled the advice to reduce fat intake, 87,6% — to change the fats consumed, 87,5% — to reduce the daily calorie intake, 92,1% — to increase vegetable and fruit consumption, 90,8% — to eat more fish, 85,0% — to reduce the sugar consumption. These parameters in the general group were slightly lower — 77,3, 68,3, 64,5, 73,2, 66,5 and 67,0%, respectively. Drug therapy for obesity was recommended very rarely — in 3,8 and 8,0% of cases, respectively. Thus, both in Russia and in other EUROASPIRE V countries, there is a combination of a high prevalence of fat metabolism disorders with low efficiency of a routine approach to counseling these patients on healthy diet and body weight management, despite the rather high motivation of the participants. This may be based on, on the one hand, the low availability of nutritional counseling, and on the other, the objective difficulties in correcting body weight in obesity [18, 19].

Diabetes is generally recognized as a significant RF of CVD, moreover, in many cases associated with overweight and obesity [20]. Every fifth patient with CAD who came for an interview to Russian centers had a previously diagnosed diabetes (21,9%; men, 18,3%; women, 31,5%). This is slightly less than in Europe as a whole, where 29,3% of patients had diabetes at baseline (men, 28,0%; women, 33,1%). About 14,9% of Russian patients with previously diagnosed diabetes had diabetic retinopathy, 11,5% — nephropathy, 23,0% — neuropathy. In the general study population, the incidence of retinopathy was slightly higher (16,2%), while the incidence of nephropathy and neuropathy was lower (8,3 and 16,6%, respectively).

In the Russian cohort, measures to manage diabetes were represented by diet and/or other lifestyle changes in 47,1% of participants; 72,4% of patients took oral hypoglycemic drugs and 14,9% received insulin. In the general population, there were 2 times more patients using insulin (31,7%); 56,7% of patients adhered to diet and other non-drug measures and 73,7% of patients received oral hypoglycemic drugs. Regular self-monitoring of blood sugar levels was reported by 87,4% of Russian patients with CAD and diabetes, and among women, such responses were the overwhelming majority — 97,1% versus 81,1% in men. In the study as a

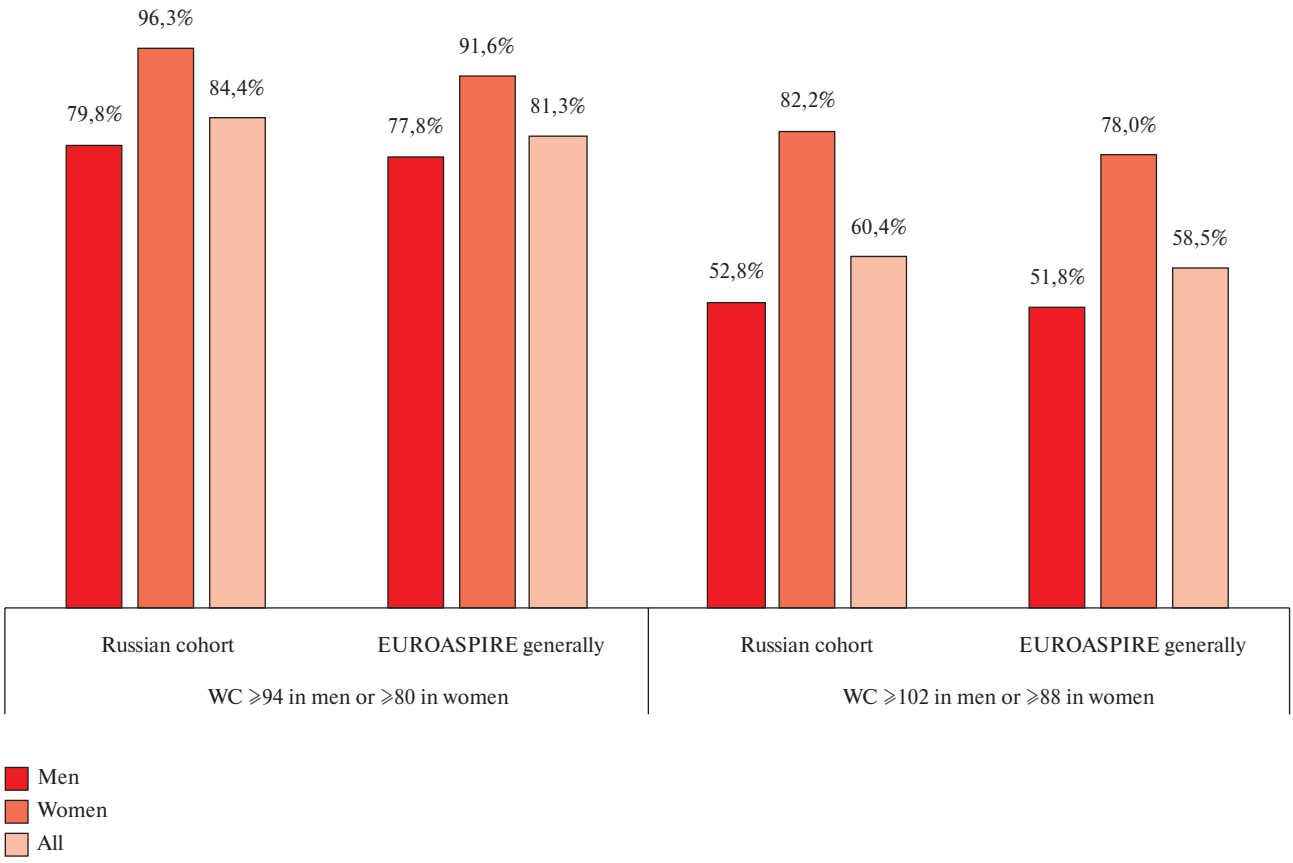

Figure 3. Prevalence of excess WC values and abdominal obesity at the interview in Russian and general population of the EUROASPIRE V study.

whole, self-management of glycemia was carried out by 71,8% of patients with diabetes without significant sex differences.

Nevertheless, despite the self-management, according to patients, the parameters of diabetes management in the Russian cohort were slightly worse than the average for EUROASPIRE V countries, which could be explained by both the lower treatment efficiency and the choice of different target HbA_{1c} levels. In particular, the average fasting glycemic level in diabetes in the Russian cohort was 9,07±3,28 mmol/L (8,75±3,10 mmol/L in men and 9,56±3,54 mmol/L in women), while in the general study population — 8,71±3,01 mmol/L (8,58±2,87 mmol/L in men and 9,03±3,30 mmol/L in women). The average HbA_{1c} level in Russian patients with diabetes was 7,50±1,79% (7,34±1,61% in men and 7,76±2,04% in women), while in general sample — 7,24±1,68% (7,12±1,59% in men and 7,53±1,88% in women). The proportion of patients who achieved an HbA_{1c} <7% in Russian centers (Figure 4) was slightly lower than in the general study population, both in men and women.

Given the high incidence of undiagnosed diabetes, especially in older age groups [21], one of the key features of the EUROASPIRE V study was screening participants for carbohydrate metabolism disorders using OGTT, which was performed in patients without a history of diabetes and with fasting glucose <11,1 mmol/L. As can be seen in Table 2, the test results were fully normative in 38,7% of Russian patients with CAD (,6% in the general group). At the same time, with OGTT, diabetes was first diagnosed in 19,7% of Russian patients with CAD (16,4% in the general study population).

The diagnostic HbA_{1c} level for diabetes (⩾6,5%) was established in 4,5% of Russian patients without a previously established diabetes (men, 5,5; women, 1,4%), while in general sample, a similar data was observed — 4,7% (men, 4,7%; women 4,8%). Even the initial fasting blood glucose level gave reason to suspect diabetes in every tenth Russian patient with CAD. These data and the detection of previously undiagnosed diabetes using OGTT in every fifth patient with CAD in Russia specifies the need for more careful attention to the carbohydrate metabolism parameters at the outpatient stage of care.

BP management is one of the key components of the secondary prevention of CAD. The mean systolic BP in Russian patients with CAD was 129,4±17,8 mm Hg (men, 129,1±17,1; women, 130,3±19,7 mm Hg), while diastolic BP — 78,6±10,9 mm Hg (men, 79,6±10,8 mm Hg; women, 75,8±10,7 mm Hg). In the general population of the study, these parameters were slightly higher: systolic BP — 134,5±18,6

mm Hg (men, 134,3±18,2; women, 134,9±19,7 mm Hg), diastolic BP — 80,7±10,9 mm Hg (men, 81,0±10,7; women, 79,8±11,5 mm Hg). Figure 5 shows the proportion of patients with uncontrolled hypertension at the time of the interview, which among the Russian participants was lower than in the general population of the EUROASPIRE V study — 36,0 vs 46,3% (34,9% vs 46,0% in men and 38,9% vs 47,1% in women, respectively). Antihypertensive therapy was received by 97,2% of Russian patients (men, 96,6%; women, 99,1%) and 95,0% (men, 94,7%; women, 95,8%) in the general population. Medication adherence was rather high: 89,3% of Russian patients and 77,6% of general sample participants reported that they regularly these medications within 2 weeks before the interview. With regard to undiagnosed hypertension, the situation in Russian centers was quite favorable. Among patients without hypertension, a history of blood pressure ⩾140/90 mm Hg (or ⩾140/80 mm Hg in the presence of diabetes) was found only in 12,2% (men, 11,4%; women, 20,0%), while in the general study population this feature was characteristic of more than 2 times more patients — 28,3% (men, 29,8%; women, 21,8%).

The blood lipid levels in the Russian cohort were generally comparable to the general study population: the mean TC in Russian centers was 4,25±1,15 mmol/L (4,19±1,17 mmol/L in men and 4,43±1,08 mmol/L in women) vs 4,28±1,21 mmol/L (4,16±1,15 mmol/L in men and 4,64±1,31 mmol/L in women), LDL-C — 2,38±0,98 mmol/L (2,36±0,99 mmol/L in men and 2,42±0,96 mmol/L in women) vs 2,41±0,99 (2,33±0,94 mmol/L in men and 2,63±1,09 mmol/L in women), HDL-C — 1,14±0,27 mmol/L (1,10±0,26 mmol/L in men and 1,16±0,33 mmol/L in women) vs 1,14±0,30 mmol/L (1,10±0,28 mmol/L in men and 1,25±0,34 mmol/L in women), triglycerides — 1,62±0,97 mmol/L (1,61±1,04 mmol/L in men and 1,65±0,76 mmol/L in women) vs 1,64±1,12 mmol/l (1,63±1,15 mmol/l in men and 1,66±1,05 mmol/l in women).

LDL-C exceeded the target level for patients with CAD in approximately three quarters of the participants both in Russia and in all EUROASPIRE V countries (Figure 6): LDL-C ⩾1,8 mmol/L was recorded in 72,4% of Russian patients (71,5% in men and 74,5% in women) and 71,0% of general sample patients (68,6% in men and 77,9% in women).

In Russian cohort, 88,7% of patients (87,3% of men and 92,6% of women) received lipid-lowering drugs, which was even slightly higher than in the general study — 84,2% (85,7% of men and 80,1% of women). The frequency of achieved LDL-C target level among patients with CAD undergoing lipid-lowering therapy was low both in Russia (30,2%; 31,7% in men and 26,5% in women) and in the general population of the study (32,0; 34,1 and 25,7% respectively), which

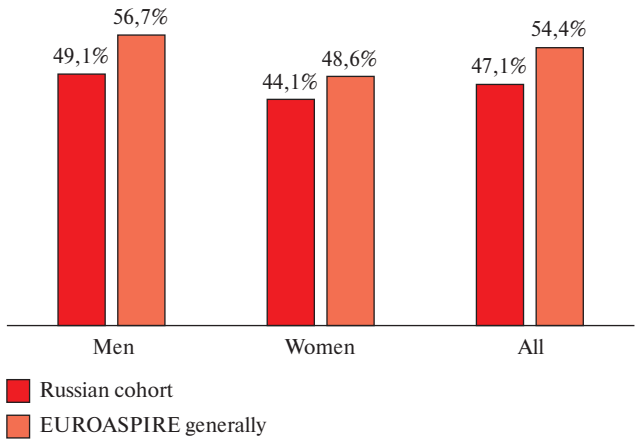

Figure 4. Prevalence of HbA_{1c} <7% at the interview among persons with previously diagnosed diabetes in Russian and general population of the EUROASPIRE V study.

indicates the use of insufficiently effective drugs, insufficient doses and the rare appointment of combined lipid-lowering therapy.

According to patients with CAD, the physical activity recommended by the World Health Organization (>30 min ⩾5 times a week) was followed by 52,0% of Russian patients (55,1% of men and 44,2% of women), which is noticeably higher than in the general sample — 34,4% (36,8% of men and 27,5% of women). In Russian cohort, 52,9% of patients reported that they made some effort to increase physical activity after the initial hospitalization (47,3% in the general study population). About one third of participants purposefully focused in various types of exercise: 30,9% in the Russian cohort and 34,8% in the general group. Also, 33,2% of Russian participants reported that they did not have such exercise at the moment, but intend to increase activity in future (23,8% in the general population). Another 35,8% of Russian patients indicated that they do not plan any sports activities in the future (41,5% in the general cohort).

In Russian cohort, 64,0% of patients (46,2% in the general study population) was recommended to take part in the cardiac rehabilitation program after the initial hospitalization, but only 39,4% were able to complete such a program even by half, which was significantly lower than in the general study group (68,9%).

It should be noted that the EUROASPIRE V study has limitations in that the results obtained for the participating countries cannot be considered completely representative of all CAD patients in the region. Obtaining fully representative national data is practically impossible due to the number of participating countries and the lack of target funding. Moreover, the EUROASPIRE studies mainly included high-quality healthcare facilities, which can skew the overall results for the better. Partly to overcome this limitation is the interval between the initial hospitalization and the interview, during which patients are observed within

Table 2

Proportion of patients with undiagnosed carbohydrate metabolism disorders before the interview in Russian and general population of the EUROASPIRE V study

	Patients of Russian centers	General EUROASPIRE V population
According to fasting blood glucose level at the interview		
Impaired fasting glucose (blood glucose ⩾6 and <7 mmol/L), %	17,4	18,1
Diabetic glycemia (blood glucose ⩾7 mmol/L), %	10,4	8,2
According to HbA_{1c}		
HbA_{1c} ⩾6,5%, %	4,5	4,7
According to OGTT		
Impaired fasting glycemia (fasting glycemia ⩾6,1 and <7 mmol/L, glycemia after 2 hours <7,8 mmol/L),%	9,3	13,3
Impaired glucose tolerance (fasting glycemia <7 mmol/L, glycemia after 2 hours ⩾7,8 and <11,1 mmol/L),%	32,3	24,7
Newly diagnosed diabetes (fasting glycemia ⩾7 mmol/L or glycemia after 2 hours ⩾11,1 mmol/L),%	19,7	16,4

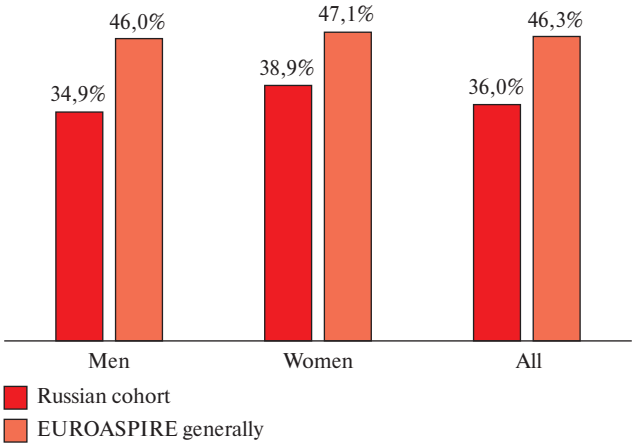

Figure 5. Prevalence of patients with uncontrolled blood pressure (systolic blood pressure ⩾140 mm Hg and/or diastolic blood pressure ⩾90 mm Hg in the absence of diabetes or ⩾80 mm Hg in the presence of diabetes) at the interview in Russian and general population of the EUROASPIRE V study.

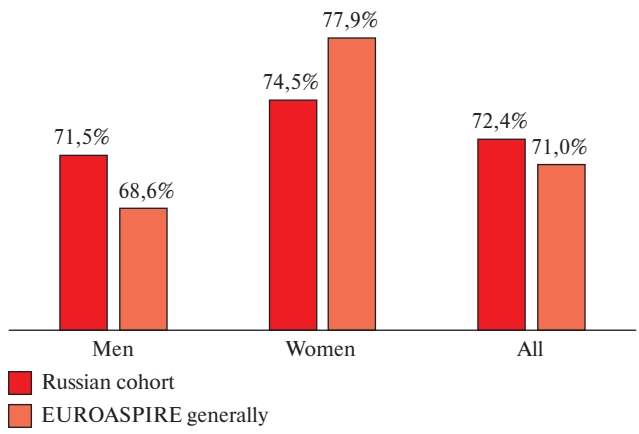

Figure 6. Prevalence of LDL-C ⩾1,8 mmol/L at the interview in Russian and general population of the EUROASPIRE V study.

routine clinical practice in primary care. In addition, in the EUROASPIRE V study, the geography of the project was significantly expanded in each of the participating countries by increasing the number of medical institutions and including facilities from several regions [8].

Conclusion

The assessment of key indicators of secondary prevention of CAD in patients after AMI, ACS, PCI, and CABG, carried out within the EUROASPIRE V study, revealed significant differences between the Russian cohort and the general study population. At the same time, for some RFs, in particular, for hypertension management, Russian patients with CAD achieved better results, while with regard to smoking, overweight and obesity, and diabetes, a less favorable situation was noted. The study results indicate significant reserves for further optimization and the need to further improve measures for the secondary prevention of CAD in patients after AMI, ACS, PCI, and CABG in order to achieve optimal treatment results and reduce the risk of recurrent cardiovascular events and improve the quality of life of patients.

Relationships and Activities: none.

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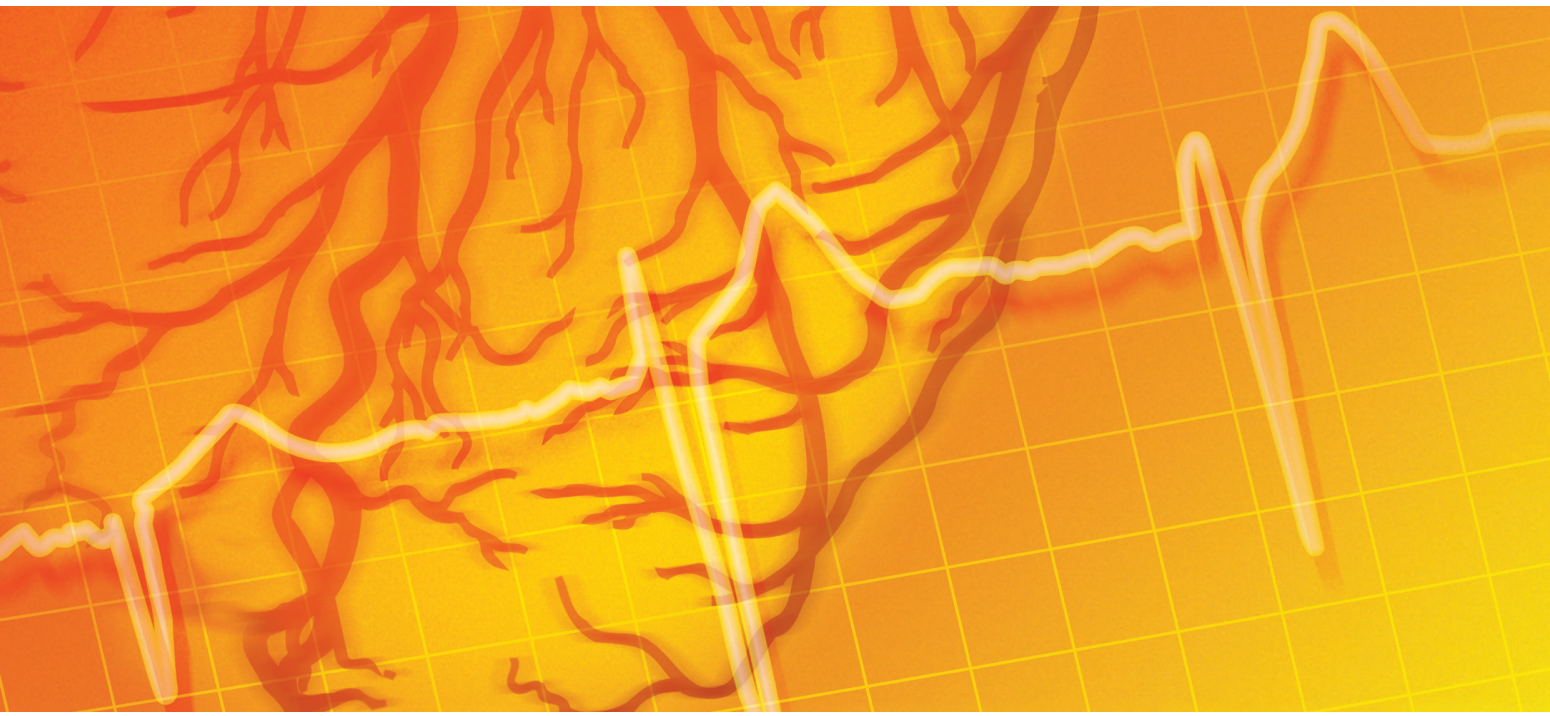

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