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BEST PRACTICES FOR ORGANIZATION OF CARDIAC CARE IN THE CONSTITUENT ENTITIES OF THE RUSSIAN FEDERATION

ORIGINAL ARTICLES

Dear colleagues,

Nowadays, a steady reduction in cardiovascular mortality is one of the highest priority goals, the achievement of which is impossible, on the one hand, without the active participation of each specialist and the entire cardiology community, and on the other, without the implementation of regional and national programs aimed at developing the healthcare system, improving the quality of care and accessibility of most modern and effective methods of treatment.

Currently, the Russian Federation implements large-scale set of measures against cardiovascular diseases. An important part of them is the changing a role of leading medical institutions of the country, the National Medical Research Centers, and giving them authority to coordinate activities against cardiovascular diseases with the largest regional institutions.

Close interaction with regional institutions and in-depth analysis of the current situation allows the National Medical Research Centers to identify unique, best practices related to prevention, control of cardiovascular risk factors, screening, models of care organization, benefit drug provision, coordination and integration of cardiac care in the regions.

Practical experience in implementing effective measures to im prove care for cardiac patients is invaluable and is the best guide to action. Since 2020, the Russian Journal of Cardiology plans a new series of publications on the best practices successfully implemented in different regions of Russia.

Detailed descriptions of successful projects and analysis of their results, confirming effectiveness, identified barriers to implementation and experience in overcoming them are the best things that need to be presented for discussion, implementation and widespread use, further improvement, and development. From our point of view, a broad overview of best practices is the most important task of the professional community and a key step towards providing the best cardiac care in all regions of the country and achieving the most ambitious goals to reduce mortality.

Editor-in-chief
President of the Russian Society of Cardiology
E. V. Shlyakhto, Academician of the Russian Academy of Science

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Implemented models and elements for heart failure care in the regions of the Russian Federation: prospects for transformation into regional cardiovascular risk management systems

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The high and growing incidence and mortality of patients with heart failure (HF) should receive priority attention when developing an action plan to reduce cardiovascular mortality in the Russian Federation. The article provides an analysis of the implemented elements of HF care in 40 Russian regions (Northwestern, North Caucasian, Volga, Southern Federal districts), some of the best practices, as well as prospects for implementation of the cardiovascular risk management system.

Key words: heart failure, health care models, transitional care.

Relationships and Activities: not.

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Heart failure is a targeted group for programs aimed at reducing cardiovascular mortality

The implantation of effective methods for treating cardiovascular diseases (CVD) contributed to an increase in the life expectancy of patients, but also specified the rapid increase in the prevalence of heart failure (HF). The global demographic transition towards an aging population [1] and poor control of cardiovascular risk factors [2] also contribute to an increase in HF prevalence [3]. In the Russian Federation (RF), the number of HF patients doubled between 1998 and 2014, mainly at the expense of class III-IV cases, and the HF prevalence reached 8,8% [4]. At the same time, despite the availability of effective pharmaceutic and hardware treatment methods, the prognosis of HF patients remains unfavorable. An increase in age and comorbidity in HF, health-seeking behavior of these patients, the risk of recurrent events and death make HF patients "super heavy users" for the healthcare system, who requires expensive medical care. Social and economic losses emphasize the need for priority attention to the HF problem when developing an action plan to reduce the global burden of CVDs around the world [5].

The main directions and necessary elements to improve the quality of HF health care

Despite the high validity and positive effect on hard endpoints demonstrated in a number of cases, the effectiveness of introducing certain healthcare elements for HF remains controversial. Most of them cannot be translated into routine clinical practice, and its isolated use may not lead to the expected result.

Of crucial significance is the providing a "seamless" system of care for HF patients [6] — with information exchange between institutions, ensuring timely medical examination after discharge, widespread use of rehabilitation and palliative care. Interdisciplinary programs for comorbid patients have been validated, since all-cause rehospitalizations may constitute a significant proportion [7]. A recent analysis demonstrated the cost-effectiveness of using transitional care services (disease management clinics, nurse home visits, and nurse case management) for HF patients over 75 years of age compared with the standard approach [8]. These data emphasize that transitional care should be the standard to improve outcomes after discharge, especially for older patients with HF.

The results of a three-year follow-up of patients included in the Russian Hospital Heart Failure Registry (RUS-HFR) [9] demonstrated that the management of patients in multidisciplinary centers with specialized departments of HF and further follow-up by HF specialists is characterized by a higher frequency of prescribing optimal drug therapy and the use of high-tech treatments that are associated with improved outcomes.

The need for timely diagnosing the impairment to prevent hospitalizations due to decompensated HF makes telemedicine useful for remote monitoring of patients. The effect of telemetry on mortality and rehospitalizations due to HF was not demonstrated in all observational and randomized trials and their meta-analyzes [10]. Improving compliance and monitoring effectiveness can be achieved using a mobile application [11]. Optimization of HF therapy based on measuring pulmonary artery pressure by the CardioMems led to a reduction of HF hospitalizations and mortality, with a low rates of complications and device defects [12]. However, the high cost and invasiveness significantly limit its use in widespread practice. An increase in the number of telemedicine consultations between primary care physicians and specialists can significantly improve the quality of healthcare for complicated and non-standard cases of HF and become the basis for a "team" approach in the treatment of this patient cohort.

The multidisciplinary approach necessary for the effective control of HF morbidity and mortality can be implemented as part of cardiovascular risk management system (Figure 1) [13]. Cardiovascular risk management system is a constantly changing, adapting and improving list of rules and measures for identifying, assessing and responding to risks, as well as monitoring and controlling their level in each region and across the country as a whole.

Implemented regional models and elements of HF healthcare system

An analysis of HF healthcare systems in 40 federal subjects of Russia (Northwestern, North Caucasian, Volga, Southern Federal Districts) showed that approaches of improving care for HF patients and reducing associated risk vary significantly between regions (Figure 2). The most widely used specialized strategies for HF are 'patient schools'. We present the best practices of organizing care for HF patients in federal subjects of Russia.

Providing secondary care to HF patients in the Nizhny Novgorod Oblast. On March 04, 2016, the City Center for HF Treatment was formed in Nizhny Novgorod on the basis of City Clinical

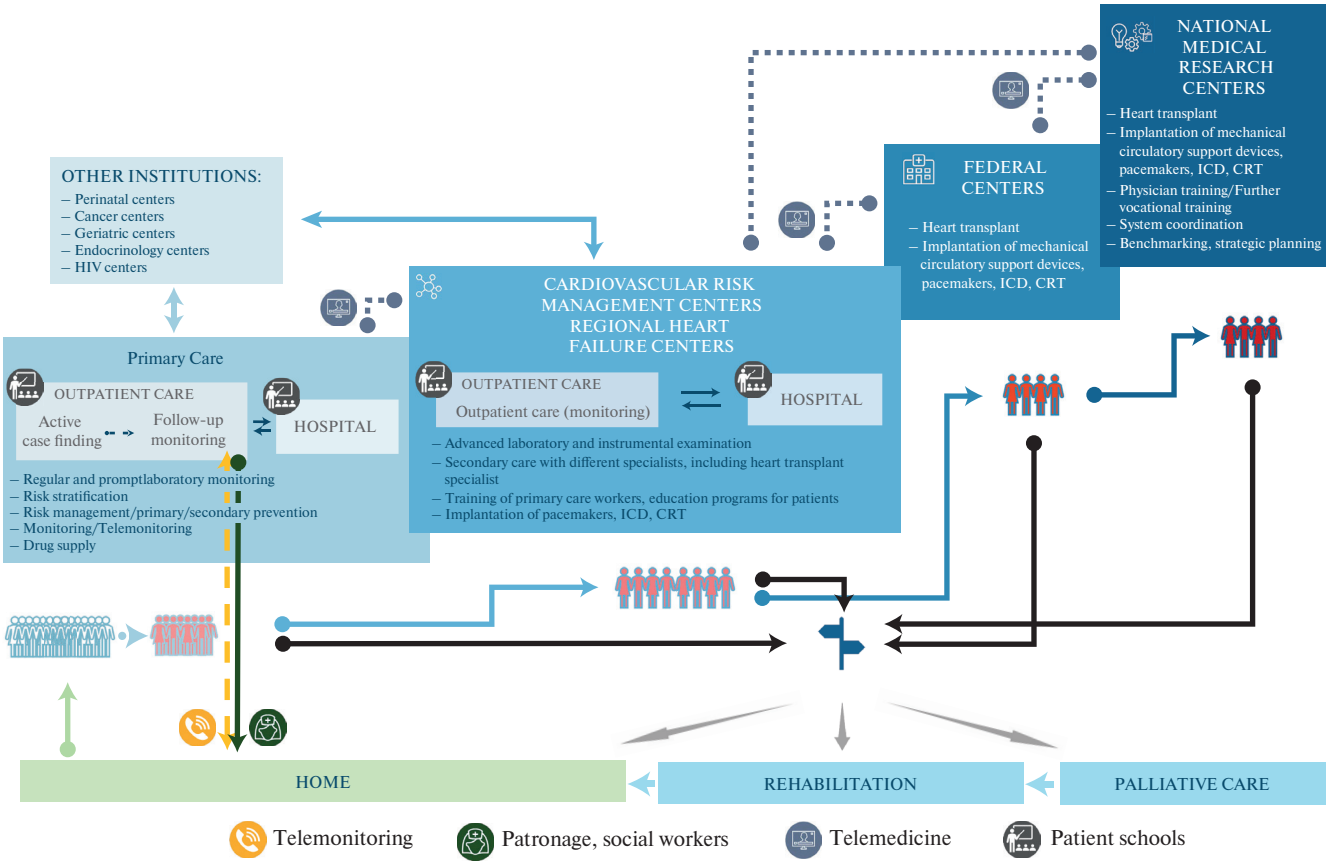

Figure 1. Cardiovascular risk management system for a population of patients with heart failure.
Abbreviations: ICD — implantable cardioverter-defibrillator, CRT — cardiac resynchronization therapy.

Hospital №38. Patients with acute decompensated HF (ADHF) are daily admitted with hemodynamic instability and the need for intravenous loop diuretics. Hospitalization of patients is carried out by ambulance teams or after outpatient visit to City Center for HF Treatment. The hospital includes a cardiology department (30 beds), an intensive care unit (6 beds), a consultation room for HF patients, designed for 400 outpatient visits per month (Figure 3).

The principle of "seamless" outpatient care for HF patients after discharge is implemented in the City Center for HF Treatment. In the hospital, diuretic therapy, drug titration, an education program for HF patients, and physical rehabilitation are performed. Patients master self-monitoring diaries of weight, urine output, blood pressure, pulse, and nutrition. At discharge, patients are recommended to continue monitoring in consultation room for drug titration, treatment of comorbidities, rehabilitation, receiving information and education. Patients who did not agree to follow-up at City Center for HF Treatment are monitored in local health facilities. Re-examination is carried out 1-2 weeks after discharge, depending on the severity, then according to an individual plan once every 1-3 months. Outpatient consultations with a cardiologist are completed by nursing monitoring (phone calls once a month) and interventions (change of lifestyle and adherence to treatment, adjustment of vitamin K antagonist and loop diuretics doses). A registry of patients hospitalized with ADHF was created.

Already after 6 months of follow-up, all-cause mortality was higher in the group of patients monitored in local health facilities compared with those monitored in City Center for HF Treatment: 13,7% versus 1,2%, odds ratio (OR) 12,6, 95% confidence interval (CI) 3,5-45,0; p<0,001 [14].

The high prevalence of atrial fibrillation in HF patients has led to a need for a monitoring of anticoagulant therapy by specialists of consultation room. It was shown that the actual effectiveness of warfarin use in HF patients was 12,6%, which is significantly lower than the values calculated by SAMe-TT_2R_2 score, and the outcomes were worse in patients without anticoagulant therapy. All-

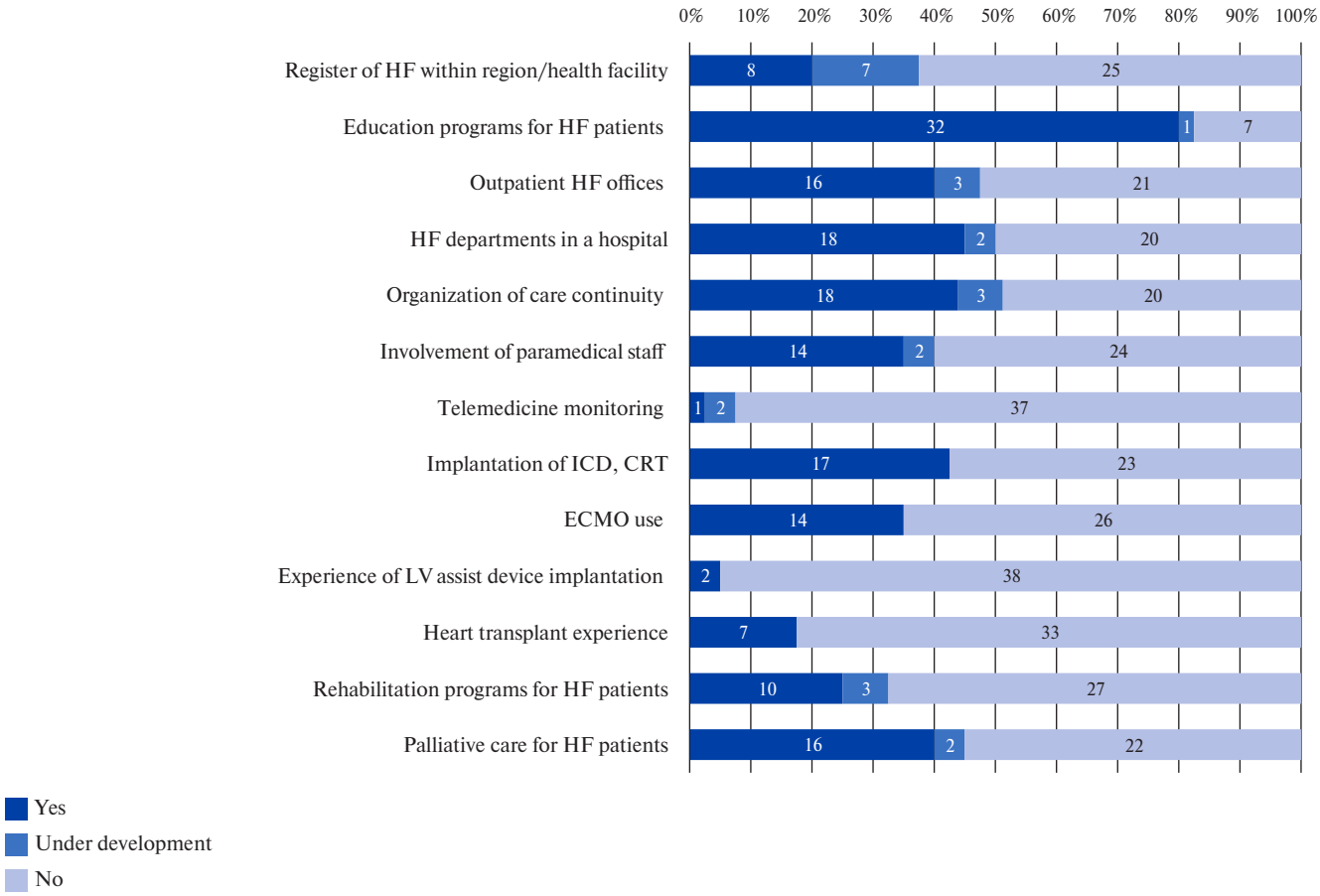

Figure 2. Implemented and expected elements of heart failure care in 40 subjects of the Russian Federation.
Abbreviations: HF — heart failure, CRT — cardiac resynchronization therapy, ICD — implantable cardioverter defibrillator, ECMO — extracorporeal membrane oxygenation, LV — left ventricle.

cause mortality in patients without anticoagulant therapy was higher in comparison with patients receiving anticoagulants (OR 2,4, 95% CI 1,0-5,7; p=0,03) [15].

After 1 year, 38,6% of patients monitored in City Center for HF Treatment stopped visiting, on the contrary, 11,3% of patients monitored in local health facilities started regular visiting the consultation room during the second year of follow-up. The entire sample of patients (n=942) was divided into 4 groups: group 1 (n=313) — patients who were constantly monitored in City Center for HF Treatment for two years (at least 4 consultations per year); group 2 (n=383) — patients who never monitored in City Center for HF Treatment after discharge, group 3 (n=197) — patients who were monitored in City Center for HF Treatment only during the first year, group 4 (n=49) — patients who refused to be monitored after discharge, but changed the decision at the second year. All-cause mortality over 2 years of follow-up was higher in group 2 compared with group 1 (32,4% versus 11,2%, OR 3,8, 95% CI 2,5-5,7; p<0,001), as well as compared with groups 3 and 4. The survival curves depending on the adherence to monitoring are shown in Figure 4 [16].

Thus, patients who were constantly monitored in City Center for HF Treatment were characterized by a lower risk of all-cause mortality compared with patients monitored in local health facilities. These data indicate the high efficiency of the selected monitoring model for HF patients after hospitalization with ADHF in actual clinical practice.

In 2019, based on the data obtained in the Nizhny Novgorod Oblast, a regional program Combating Cardiovascular Diseases was developed, and on December 31, 2019, an order was issued by the Ministry of Health of the Nizhny Novgorod Oblast On opening interdistrict cardiology offices with the function of HF care center

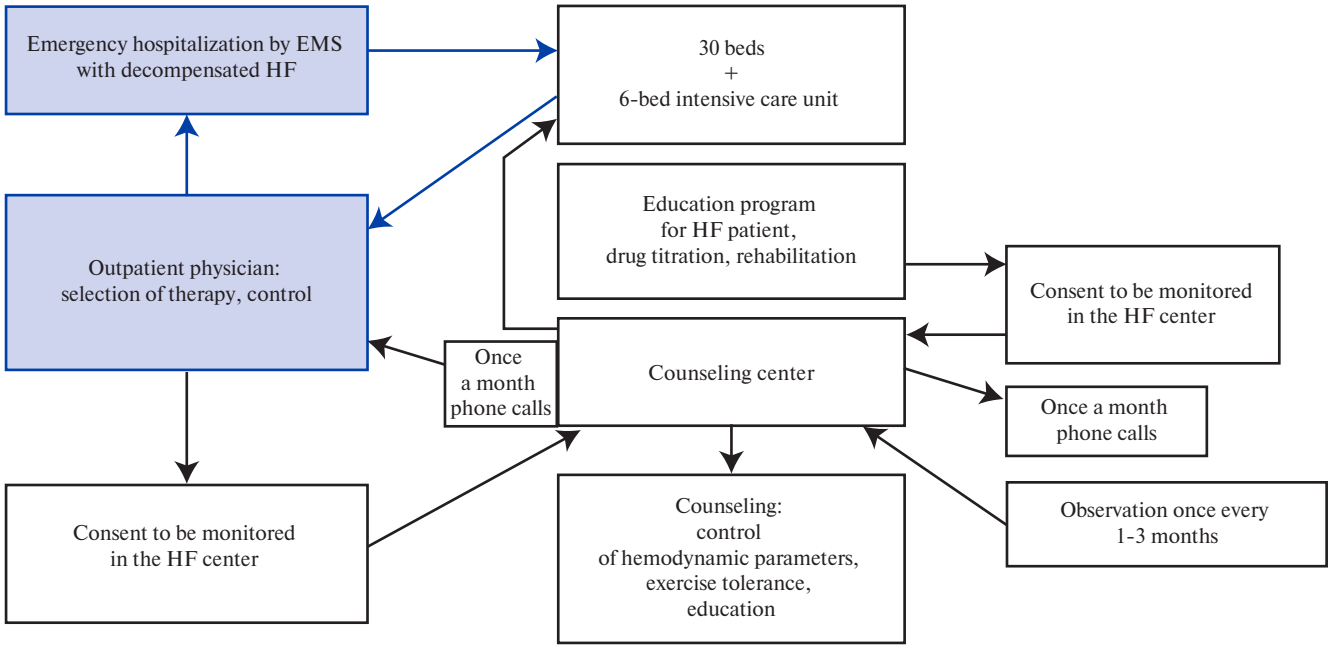

Figure 3. The structure of the City Center for HF Treatment in Nizhny Novgorod.

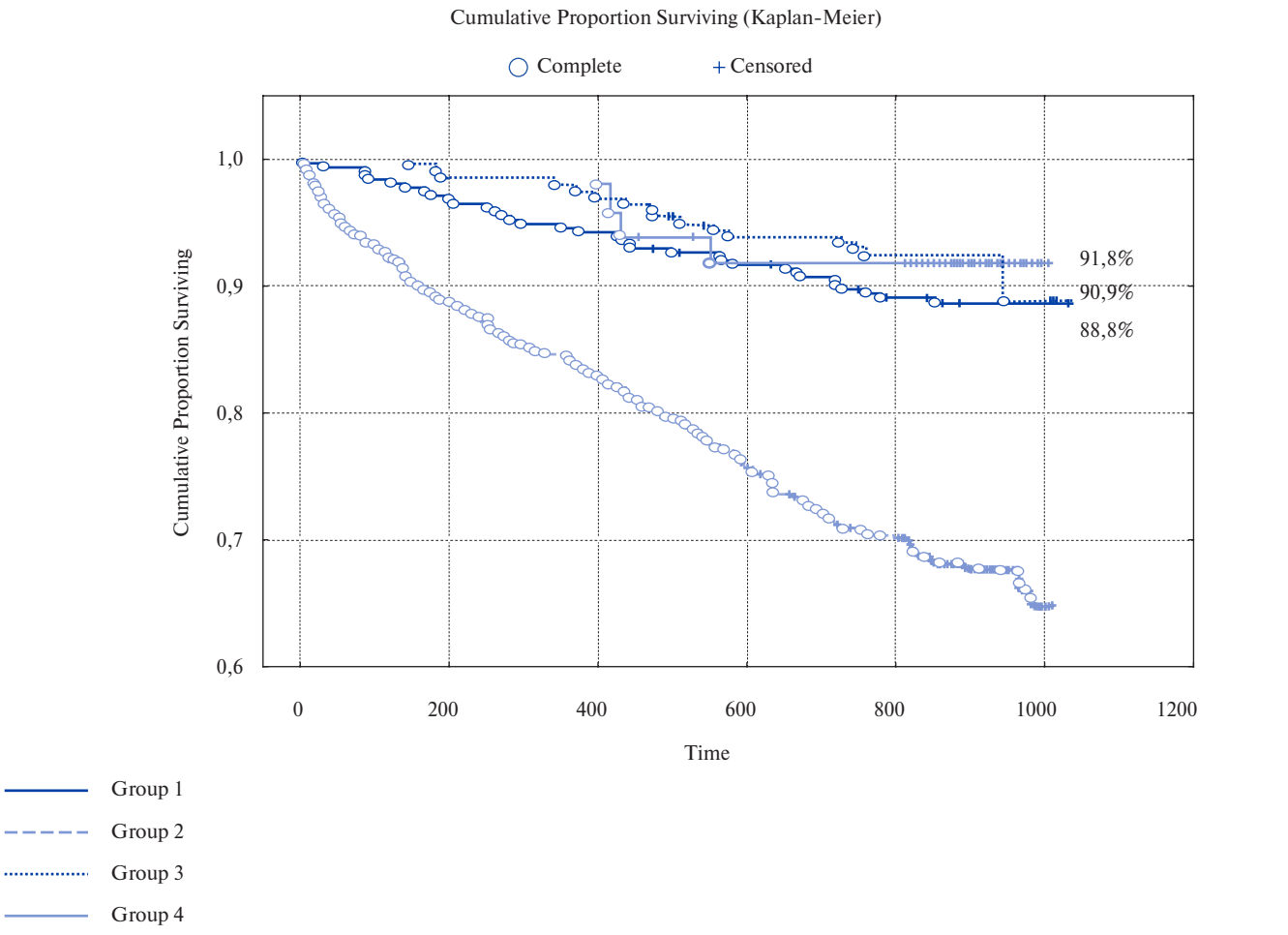

Figure 4. Kaplan-Mayer survival curves depending on patient adherence to monitoring in City Center for HF Treatment.

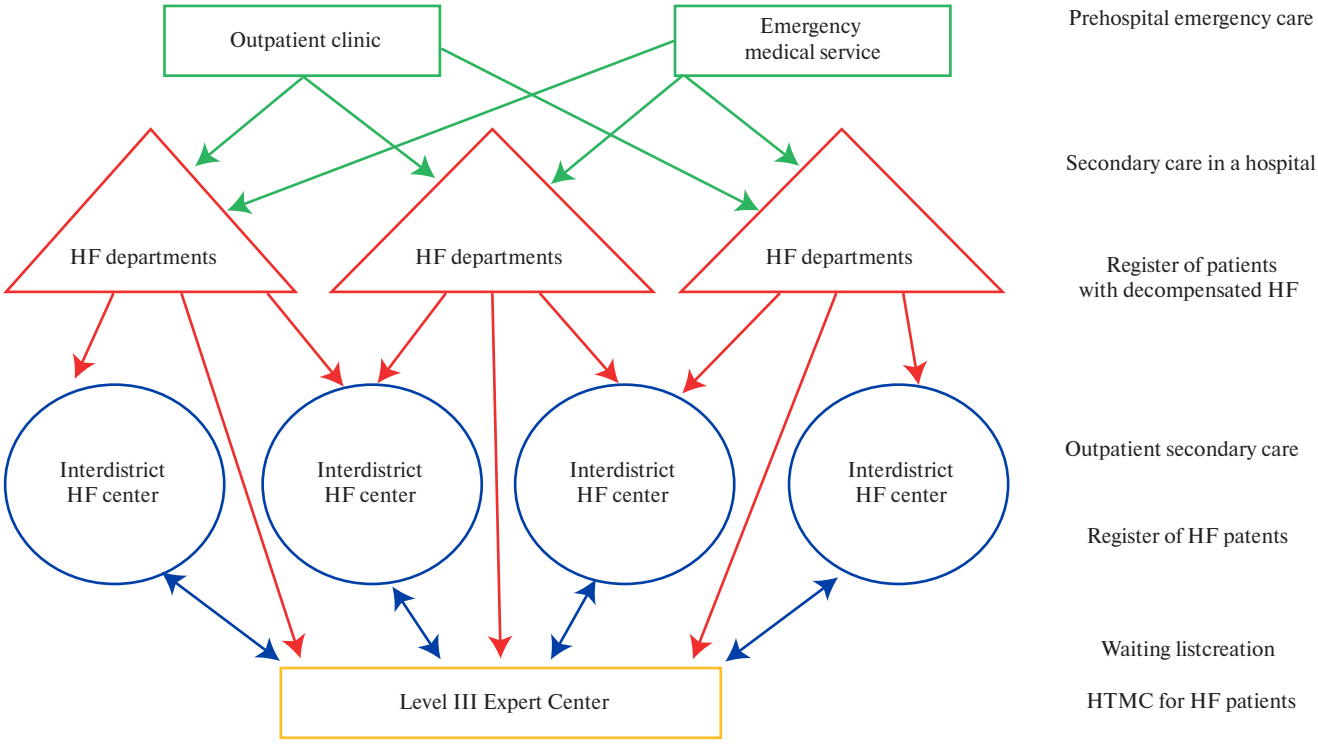

Figure 5. The structure of secondary care for HF patients in the Nizhny Novgorod Oblast.

and level I anticoagulant office. At the moment, there are 3 such cardiology offices. The structure of secondary care for HF patients in the Nizhny Novgorod Oblast is presented in Figure 5.

Heart Failure Center in Pskov Oblast

In 2017, on the basis of the Pskov City Hospital, HF Center was created, which includes a Cardiologist office for HF patients, a "Heart Sufficiency School" office, a nursing service for HF patients, and cardiology department with an intensive care unit (10-12 beds).

The functions of cardiologist office are the follow-up of NYHA class IV and III (in case of hemodynamic instability) HF patients, selection and referral of them to hospitalization in the cardiology department, as well as to provide high-tech healthcare (cardiac resynchronization therapy, heart transplant). Referral of HF patients to the office is carried out by cardiology department specialists at the discharge or by physicians of other medical organizations in Pskov. If a cardiologist in office decide to include a patient in the monitoring group, the relevant information is transmitted to the referring medical organization; therapy and future visits are planned by an office cardiologist. If a patient is not included in the monitoring group, a consultation summary report with recommendations is given.

"**Heart Sufficiency School**" operates both in the consultative and diagnostic department (for patients receiving primary care), and in the cardiology department with an intensive care unit. By agreement, it is possible to conduct classes in other medical organizations of Pskov. The main functions of this education program are conducting classes with HF patients and their relatives caring for patients, providing reading materials (guidelines, memos, patient diaries), increasing adherence to the treatment, and teaching self-care skills. The selection criteria for referral are established by the physician (patients with class I-III HF, having questions for doctors, those with low adherence to treatment, etc.).

The Nursing Service was created to monitor the condition of HF patients. Monitoring is carried out by telephone in a timely manner (in the first month after discharge — weekly; then, in case of stable condition — once a month). During telephone conversation, using the standardized questionnaire, the patient condition is assessed. When symptoms of state deterioration appear, a nurse informs physician for a decision making. There are following solution options: invitation of a patient for therapy change; release of information to the local health facilities for a visit by a physician; calling an ambulance for emergency hospitalization.

To provide **secondary care** in the cardiology department with the intensive care unit, 10-12 beds for the treatment of HF patients are provided.

Indications for hospitalization are:

— decompensated HF of ischemic and non-ischemic nature with an ejection fraction <35% or class III-IV HF in patients receiving angiotensin converting enzyme inhibitors, beta-blockers, mineralocorticoid receptor antagonists, loop diuretics;

— decompensated HF in patients with low adherence to treatment;

— class III-IV HF in patients first hospitalized with this diagnosis;

— acute non-ischemic HF (cardiac asthma, pulmonary edema, cardiovascular collapse). Acute ischemic HF (pulmonary edema, cardiogenic shock with acute coronary syndrome) is an indication for hospitalization in a regional cardiovascular center.

A patient is referred for emergency hospitalization directly by a health professional who has established the indications (ambulance paramedic or doctor, outpatient clinic paramedic, general practitioner, cardiologist of a medical organization).

Currently, about 400 patients are included in the monitoring program.

Pilot project: Improving care for heart failure patients in Saint Petersburg

Since 2017, a HF project has been implemented in St. Petersburg on the basis of value-based medicine, which involves the creation and implementation of new approaches to managing the disease using the methodology of clinical pathways, patient routing optimization, training doctors, organizing patient education programs, and implementing a systematic data collection to monitor the effectiveness.

At the initiation phase, 3 hospitals of St. Petersburg and nearby outpatient facilities took part in the project. At the project preparation, the current data on hospitalization structure, the quality of in- and outpatient care for HF patients were assessed [17]. To assess the continuity, the database of the territorial compulsory medical insurance fund was analyzed (information on rehospitalizations, outpatient visits and emergency calls after the hospital discharge). Inpatient care was characterized by the absence of necessary diagnostics (36%), non-administration or insufficient titration of recommended drugs (23%), insufficient description of recommendations on the continuation of outpatient care (34%). After discharge from the hospital, delayed help-seeking (<30% of patients visit outpatient facilities within 10 days after discharge), insufficient continuity of in- and outpatient facilities regarding the therapy retention, non-continuation drug titration, low awareness of patients about early signs of decompensation symptoms for daily monitoring.

The next step was the development and implementation of a monitoring system for HF patients, covering all stages of care and ensuring continuity between them. Quality-of-care criteria were developed. Management templates for HF patients have been introduced in health information systems (HIS). Experts of the Almazov National Medical Research Center has developed a special discharge summary and outpatient medical certificate for HF patients, the data of which are stored in HIS and transferred in the regional integrated electronic health record. At the same time, a specialist operating in HIS fills in the standard documentation, into which the results of diagnostic tests are automatically added. Based on the data obtained from the health records, a HF registry was created. It allows to unload data on patients with a certain diagnosis in real time, quickly monitor the implementation of the project and evaluate the quality of care.

An important aim of the project is also to compare the effectiveness of different outpatient monitoring models for HF patients. The results can be the basis for changes in ambulatory care of HF patients.

In order to train specialists working in accordance with a particular model, additional educational measures were conducted to raise the awareness about modern approaches and recommendations for management of HF. In 2018-2019, 7 education programs and 26 grand rounds for specialists of medical organizations participating in the project were conducted on the basis of Almazov National Medical Research Center. An algorithm for HF diagnosis has been developed. Education programs for HF patients have been introduced into the daily practice of in- and outpatient facilities. Patients brochures “Diary of a patient with heart failure”, “5 rules of a patient with heart failure” have been developed.

One of the project directions is the introduction of a remote monitoring system for HF patients with creation of a service for analyzing its effectiveness. Currently, work is in progress to increase the number of St. Petersburg medical organizations involved in the project.

Conclusion

The absence or insufficient implementation of elements for HF care can prevent the achieve-

ment of the necessary rate of cardiovascular mortality reduction, established by the Federal project. It is necessary to recognize the socio-economic importance of HF, create a register of HF patients, timely identify such patients and use a multidisciplinary approach for their management. The creation of a cardiovascular risk management system ensuring the continuity of care, timely referral of patients to a specialized facility, the availability of high-tech treatments, rehabilitation and palliative care programs should become the basis for the progressive development of regional healthcare systems to decline the burden of HF and CVD in general.

Relationships and Activities: not.

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Risk factors for acute decompensated heart failure in type 2 diabetes patients

Koziolova N. A., Veclich A. S., Karavaev P. G.

Aim. To identify risk factors for acute decompensated heart failure (ADHF) in patients with type 2 diabetes (T2D).
Materials and methods. In the cardiology department, 129 patients with ADHF were registered within 8 months, 59 (45,7%) of them had T2D. The study included 117 ADHF patients who were divided into two groups depending on the presence of T2D: group 1 (n=49; 41,9%) — patients with T2D, group 2 (n=67; 55,9%) without T2D. The ADHF was verified by rapid progress of hypoperfusion and congestion, which required emergency hospitalization and inotropic and/or intravenous diuretic therapy. In the first 48 hours of hospitalization, echocardiography was performed, levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and creatinine were determined; the glomerular filtration rate was estimated.
Results. The incidence of T2D among patients with ADHF was 45,7%. There were following risk factors for ADHF in T2D patients: diabetic ketoacidosis (p=0,002), hypertensive crisis (p=0,017), history of acute coronary syndrome (p=0,048), atrial fibrillation (p=0,030), chronic kidney disease (p=0,003), pneumonia (p=0,035), progression of anemia (p=0,049), low prevalence of beta-blockers use (p=0,001), use of inappropriate antidiabetic drugs for HF patients (sulfonylureas, insulin). ADHF, assessed by NT-proBNP level, was significantly more severe in T2D patients (p=0,001) with pronounced congestion symptoms (p=0,001), which led to an increase in the need for diuretic therapy (p=0,002). Cardiac remodeling in T2D patients with ADHF is characterized mainly by the preserved left ventricular ejection fraction (LVEF), severe LV diastolic dysfunction (LVDD) and LV hypertrophy (LVH).
Conclusion. The development of ADHF in T2D patients is associated with various risk factors and is characterized by severe congestion symptoms, high need for diuretic therapy, mainly preserved LVEF in combination with severe LVDD and LVH.

Key words: acute decompensated heart failure, diabetes.

Relationships and Activities: not.

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The prevalence of type 2 diabetes (T2D) among patients hospitalized with heart failure (HF) is 44%, among patients with a preserved left ventricle ejection fraction (LVEF) — 46% [1]. In patients with acute decompensated HF (ADHF), the prevalence of T2D reaches 34%, prediabetes — 17% [2].

According to the meta-analysis of randomized clinical trials (RCT) and registers, T2D increases the risk of cardiovascular mortality in patients with acute HF by 32%, and re-hospitalizations — by 16% [3]. The mortality risk among patients with T2D and ADHF increases by 1,7 times during hospitalization, 1,4 times after 18 months, 1,3 times after 5 years [4].

Target glucose levels for patients with T2D and ADHF are not defined. According to a study by Shirakable A, et al., glucose levels >22,2 mmol/L increases the death risk in patients after ADHF during the year by 2,3 times, while levels <5,6 mmol/L — by 3,25 times [5].

There are conflicting data on risk factors, clinical features of ADHF, types of cardiac and target organ remodeling, the need and duration of parenteral diuretic therapy, the need for inotropic agents and modification of background HF therapy, the choice of antidiabetic therapy at the time of event and after it [1-3].

The solution to these issues will allow timely prevention of ADHF hospitalizations, which can significantly improve the prognosis and quality of life of T2D patients.

The aim of this study was to identify risk factors for ADHF in T2D patients.

Material and methods

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The local medical ethics committee approved this study. All patients signed informed consent.

In the cardiology department of the multidisciplinary clinic, 129 patients with ADHF were registered in 8 months, of which 59 (45,7%) patients had T2D.

ADHF was verified following a rapid increase in symptoms and signs of hypoperfusion (low pulse pressure, cold extremities, fatigue, oliguria) and scongestion (orthopnea, jugular vein distention, lower extremity edema, ascites, hepatomegaly), which required emergency hospitalization, use of inotropic agents and/or intravenous diuretic therapy.

T2D was verified under the World Health Organization criteria (1999-2013).

The inclusion criterion was the presence of ADHF. There were following exclusion criteria: cardiogenic shock, pulmonary edema, acute thromboembolism, type 1 diabetes, prediabetes, acute coronary syndrome (ACS) and/or stroke less than a month before, aortic dissection, acute heart valve disorders (chordae tendinae rupture, etc.), major surgery less than a month before, heart injuries, infectious endocarditis, acute hepatitis and cirrhosis, end-stage renal disease, alcohol abuse, non-cardiac edema, cancer, dementia and mental illness.

A total of 117 patients with ADHF were examined, which were divided into 2 groups depending on the presence of T2D. The first group consisted of 49 (41,9%) patients with T2D, the second — 67 (55,9%) non-diabetic patients.

The congestion was assessed by congestion score of the European Society of Cardiology, endorsed by the European Society of Intensive Care Medicine (2010).

Depending on symptoms and signs of congestion and hypoperfusion, ADHF phenotypes were identified by hemodynamic profile based on the Forrester JS and Stevenson LW classification.

Echocardiography was performed in the first 48 hours of hospitalization using the VIVID 7 ultrasound system (GE Healthcare, USA) according to European Association of Cardiovascular Imaging and American Society of Echocardiography guidelines.

The concentration of serum N-terminal pro-brain natriuretic peptide (NT-proBNP) was determined by enzyme-linked immunosorbent assay using Vector-Best (Russia) reagent kit and Expert Plus Microplate Reader (Biochrom, UK). ADHF was diagnosed at NT-proBNP >300 pg/ml.

Renal function was assessed by serum creatinine concentration and glomerular filtration rate (GFR), calculated by CKD-EPI equation.

Statistical processing was performed using the STATISTICA 12.0 software package. The normality was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Quantitative traits were presented as mean and standard deviation (M±SD) or median and quartiles (Me [Q1; Q3]). For qualitative traits, the absolute frequency and the frequency in percent (%) were calculated. In non-normal distribution, statistical processing was carried out using Mann-Whitney test for quantitative traits and chi-squared test or Fisher's test ($n \leqslant 5$) for qualitative traits. The relationship between traits was studied using Spearman's rank correlation coefficient. The differences were considered significant at $p<0,05$.

Results

The prevalence of T2D among patients with ADHF amounted to 45,7%.

Table 1 presents anamnestic data before and during hospitalization for groups of subjects. Table 1 shows compared with the second group, in the first group ADHF were significantly more likely to be

Table 1

Comparison of anamnestic data of ADHF patients with/without T2D (n=117)

Parameter	Group 1 (ADHF+T2D, n=49)	Group 2 (ADHF, n=68)	p
Age, years	66,0±6,8	70,0±9,2	0,008
Sex, m/f, abs./%	18/31 (37/63)	41/27 (60/40)	0,012/0,012
Smoking, abs./%	17/34,7	29/42,6	0,755
Duration of HF, years	5,8 [2,1;7,2]	5,2 [2,6;6,9]	0,237
Mean HF class before hospitalization	3,2 [2,5;3,8]	3,0 [2,4;3,6]	0,261
Duration of T2D, years	9,1 [3,8;17,5]	-	
DKA, abs./%	7/14,3	0/0	0,002
Hypertension, abs./%	47/95,9	62/91,2	0,317
Hypertensive crisis at admission, abs./%	4/8,2	0/0	0,017
CAD, abs./%	33/67,3	38/55,9	0,211
History of ACS, abs./%	24/49,0	21/30,9	0,048
History of CABG, abs./%	11/22,4	6/8,8	0,040
History of PCI, abs./%	12/24,5	13/19,1	0,485
History of AF, abs./%	10/20,4	9/13,2	0,300
AF with HR >110 bpm at admission, abs./%	8/16,3	3/4,4	0,030
History of PE, abs./%	2/4,1	0/0	0,093
Ventricular rhythm disturbances, abs./%	25/51,0	38/55,9	0,603
TIA, history of stroke, abs./%	12/24,5	7/10,3	0,182
Stage 3-4 CKD, abs./%	23/46,9	14/20,6	0,003
Pneumonia, abs./%	5/10,2	1/1,5	0,035
History of COPD, abs./%	7/14,3	9/13,2	0,871
Exacerbation of COPD, abs./%	4/4,1	1/1,5	0,078
Acute inflammatory diseases, abs./%	2/4,1	2/3,0	0,738
Progression of chronic anemia, abs./%	6/12,2	2/3,0	0,049

Abbreviations: ADHF — acute decompensated heart failure, T2D — type 2 diabetes, HF — heart failure, DKA — diabetic ketoacidosis, CAD — coronary artery disease, ACS — acute coronary syndrome, CABG — coronary artery bypass grafting, PCI — percutaneous coronary intervention, AF — atrial fibrillation, HR — heart rate, PE — pulmonary embolism, TIA — transient ischemic attack, CKD — chronic kidney disease, COPD — chronic obstructive pulmonary disease.

caused by diabetic ketoacidosis (DKA), hypertensive crisis, ACS history, atrial fibrillation (AF) with heart rate (HR) >110 bpm, CKD, pneumonia, anemia aggravation.

Comparison of laboratory parameters between groups are presented in Table 2.

Significant differences in laboratory parameters between groups confirm differences in the prevalence of comorbidities. ADHF, assessed by the NT-proBNP level, was significantly more severe in T2D patients.

Correlation analysis of patients with ADHF and T2D revealed a direct moderate and strong significant relationship of plasma glucose (r=0,41; p=0,035), systolic blood pressure (r=0,38; p=0,011), HR >110 bpm (r=0,69; p=0,002), C-reactive protein (r=0,58; p=0,005) and inverse strong dependence of GFR (CKD -EPI) (r=-0,55; p=0,023) and hemoglobin (r=-0,56; p=0,018) with a NT-proBNP concentration.

Table 3 shows a comparison of symptoms in ADHF patients between groups.

Patients with ADHF and T2D had a higher frequency and severity of congestion symptoms, the wet+warm phenotype was more often recorded.

Correlation analysis of patients with ADHF and T2D revealed a direct moderate significant relationship between glycated hemoglobin (HbA_{1c}) and the average congestion score (r=0,44; p=0,026).

Characteristics of therapy for HF and T2D patients before and after hospitalization is presented in Table 4.

In both groups, before hospitalization, there was a low frequency of recommended drug use, which required its more intensive intake during hospitaliza-

Table 2

Comparison of laboratory data of ADHF patients with/without T2D (n=117)

Parameter	Group 1 (ADHF+T2D, n=49)	Group 2 (ADHF, n=68)	p
Hemoglobin, g/L	121,5 [98,6;139,0]	130,7 [112,4;140,8]	0,011
Hematocrit, %	40,5 [34,5;44,1]	41,2 [36,8;45,0]	0,267
Fasting plasma glucose, mmol/L	9,1 [4,3;22,8]	5,5 [3,6;8,0]	<0,001
Persistent hyperglycemia >10 mmol/L, abs./%	12/24,5	0/0	0,001
HbA_{1c}, %	9,8 [6,7;12,5]	5,3 [4,5;5,9]	<0,001
Total cholesterol, mmol/L	5,2 [3,4;6,1]	5,7 [3,5;6,6]	0,672
Total protein	62,8 [61,3;69,5]	66,5 [62,2;71,6]	0,348
Albumin	36,8 [33,4;39,8]	38,1 [33,5;39,0]	0,389
Plasma sodium, mmol/L	144,3±6,1	142,8±6,4	0,078
Plasma potassium, mmol/L	4,8 [4,2;5,1]	4,2 [3,6;4,6]	<0,001
Total bilirubin, μmol/L	18,3 [12,5;20,0]	19,4 [13,2;22,4]	0,189
ALT, U/L	22,8 [18,9;38,6]	25,0 [19,2;36,7]	0,672
AST, U/L	34,6 [22,3;45,1]	32,9 [21,7;43,0]	0,785
Serum creatinine, μmol/L	111,6 [86,2;143,1]	99,8 [78,4;132,9]	<0,001
Urea	8,0 [5,7;10,8]	7,8 [5,7;9,2]	0,763
GFR (CKD-EPI), ml/min/1,73 m^2	61,3 [44,8;72,7]	68,7 [49,1;77,5]	0,005
ESR, mm/h	23,8 [15,3;47,3]	18,7 [12,3;27,9]	0,008
C-reactive protein, mg/L	14,5 [4,1;26,2]	8,2 [3,3;12,4]	<0,001
NT-proBNP, pg/ml	987,9 [563,0;1676,7]	846,6 [453,3;1156,8)	<0,001

Abbreviations: ADHF — acute decompensated heart failure, T2D — type 2 diabetes, HbA_{1c} — glycated hemoglobin, ALT — alanine aminotransferase, AST — aspartate aminotransferase, GFR — glomerular filtration rate, ESR — erythrocyte sedimentation rate, NTproBNP — N-terminal pro-brain natriuretic peptide.

Table 3

Comparison of clinical data of ADHF patients with/without T2D (n=117)

Parameter	Group 1 (ADHF+T2D, n=49)	Group 2 (ADHF, n=68)	p
Congestion score	4,5 [2,5;6,5]	3,0 [2,0;4,0]	<0,001
Frequency of congestion, abs./%	41/83,7	45/66,2	0,035
Resting HR per minute	91,3±22,6	88,8±20,9	0,444
Resting RR per minute	22,6±3,8	21,9±4,0	0,143
SBP, mm Hg	138,7±25,5	134,9±23,2	0,373
DBP, mm Hg	88,7±12,7	86,1±10,8	0,329
PP, mm Hg	52,5±17,4	49,7±15,6	0,315
Wet-warm phenotype, abs./%	42/85,7	47/69,1	0,038
Wet-cold phenotype, abs./%	2/4,1	7/10,3	0,214
Dry-warm phenotype, abs./%	4/8,2	10/14,7	0,283
Dry-cold phenotype, abs./%	1/2,0	5/7,4	0,199
SpO_2, %	94,5±3,4	95,1±3,8	0,078

Abbreviations: ADHF — acute decompensated heart failure, T2D — type 2 diabetes, HR — heart rate, RR — respiratory rate, SBP — systolic blood pressure, DBP — diastolic blood pressure, PP — pulse pressure, SpO_2 — arterial blood oxygenation.

tion. Patients with ADHF and T2D took beta-blockers significantly less prior to hospitalization. The frequency of use of glucose-lowering drugs not recommended for HF was high.

Table 5 shows characteristics of in-hospital treatment of patients with ADHF by groups. The need for diuretic therapy in the first group was significantly higher than in the second.

Table 4

Comparison of therapy data of ADHF patients with/without T2D (n=117)

Drugs before/after admission to the hospital, abs./% (p)	Group 1 (ADHF+T2D, n=49)	Group 2 (ADHF, n=68)	p_{1-2}
ACE inhibitors	22/44,4 38/77,6 p*<0,001	33/48,5 55/80,9 p*<0,001	0,698 0,660
ARB	10/20,4 11/22,4 p*=0,806	12/17,6 13/19,1 p=0,825	0,707 0,660
Beta blockers	12/24,5 44/89,8 p*<0,001	36/52,3 66/97,1 p*<0,001	0,003 0,103
MCRA	5/10,2 40/81,6 p*<0,001	7/10,3 56/82,4 p*<0,001	0,988 0,921
Oral loop diuretics	18/36,7 42/85,7 p*<0,001	23/33,8 61/89,7 p*<0,001	0,745 0,512
Digoxin	9/18,4 12/24,5 p*=0,461	8/11,8 12/17,6 p*=0,333	0,318 0,366
Anticoagulants	5/10,2 15/30,6 p*=0,013	4/5,9 21/30,9 p*<0,001	0,387 0,976
Sulfonylureas	23/46,9 18/36,7 p*=0,306	-	-
Metformin	29/59,2 12/24,5 p*<0,001	-	-
Insulin therapy	10/20,4 27/55,1 p*<0,001	-	-
SGLT2 inhibitors	2/4,1 2/4,1 p*=0,999	-	-
Combination of glucose-lowering drugs	35/71,4 16/32,7 p*<0,001	-	-

Note: p* — before and after admission to the hospital.

Abbreviations: ADHF — acute decompensated heart failure, T2D — type 2 diabetes, ACE inhibitors — angiotensin converting enzyme inhibitors, ARB — angiotensin II receptor blockers, MCRA — mineralocorticoid receptor antagonists, SGLT2 — sodium/glucose cotransporter 2.

Parameters of cardiac structure and function by groups according to echocardiography are presented in Table 6.

LVEF and the prevalence of HF with preserved EF (HFpEF), the severity of left ventricular diastolic dysfunction (LVDD), the left ventricular myocardial mass index (LVMI) were significantly higher in patients with ADHF and T2D.

Correlation analysis of patients with ADHF and T2D revealed a direct moderate and strong significant relationship between LVEF (r=0,32; p=0,018), E/e' (r=0,49; p=0,002), LVMI (r=0,65; p<0,001) and HbA_{1c}.

There are following study limitations: a small sample of patients with T2D and ADHF; to determine the predictor value of newly revealed risk factors for ADHF in T2D patients, contingency tables should be created and the odds ratio and relative risk should be calculated, indicating sensitivity and specificity for each factor.

Discussion

In our study, the prevalence of T2D among patients with ADHF was 45,7%. In single studies, such data are presented. Similar value was obtained in a study by Khoo K, et al. with 1191 patients, where it amounted to 49% [2].

Table 5

Comparison of ADHF therapy in patients with/without T2D (n=117)

Parameter	Group 1 (ADHF+T2D, n=49)	Group 2 (ADHF, n=68)	p
Intravenous furosemide			
Starting dose on the first day, mg	60 [40;100]	60 [60;80]	0,435
Total dose during hospitalization, mg	640 [480;960]	480 [320;800]	0,002
Duration of treatment, days	7,2 [6,1;9,8]	5,2 [3,0;6,3]	<0,001
Oral loop diuretics			
Daily dose of furosemide, mg	40,0 [40,0;80,0]	40,0 [40,0;80,0]	0,873
Daily dose of torasemide, mg	20,5 [5,9;18,5]	15,1 [5,0;12,6]	0,014
Intravenous nitroglycerin, abs./%	25/51,0	30/44,1	0,461
Inotropic support/Vasopressors, abs./%	4/8,2; 4/8,2	2/2,9; 2/2,9	0,207 0,207

Note: ADHF — acute decompensated heart failure, T2D — type 2 diabetes.

Table 6

Comparison of ADHF therapy in patients with/without T2D (n=117)

Parameter	Group 1 (ADHF+T2D, n=49)	Group 2 (ADHF, n=68)	p
LVEF, %	52,2±12,7	45,3±13,1	0,004
LVEF >50%, abs./%	34/69,4	25/38,8	<0,001
LVEF of 40-49%, abs./%	9/18,4	29/42,6	0,006
LVEF <40%, abs./%	6/12,2	14/20,6	0,237
E/e´ mean	11,4 [4,7;17,0]	14,5 [9,7;18,3]	<0,001
E/e´ mean >14, abs./%	28/57,1	29/42,6	0,122
LVMI, g/m^2	112,2 [89,6;131,9]	101,4 [76,5;123,]	<0,001
LAV/BSA, ml/m^2	38, 2 [33,1;44,2]	35,1 [25,41;44,03]	0,143
LAV/BSA >34 ml/m^2	40/81,6	49/72,1	0,232
RAD/BSA, cm/m^2	2,9 [1,8;3,3]	2,6 [1,6;3,1]	0,076
RAD/BSA >2,5 cm/m^2, abs./%	37/75,5	40/58,8	0,061
PASP, mm Hg	41,7 [30,2;56,4]	37,4 [32,0;49,7]	0,035
Pulmonary hypertension, abs./%	38/77,6	47/69,1	0,313
IVC diameter, mm	0,24 [0,20;0,25]	0,20 [0,20;0,23]	0,018
IVC extension, abs./%	23/46,9	22/32,4	0,110
No IVC collapse, abs./%	22/44,9	19/27,9	0,058

Abbreviations: ADHF — acute decompensated heart failure, T2D — type 2 diabetes, LVEF — left ventricular ejection fraction, E — early ventricular filling velocity, e' mean — mean early diastolic mitral annular velocity, LVMI — left venricular mass index, LAV — left atrial volume, BSA — body surface area, RAD — right atrial diameter, PASP — pulmonary arterial systolic pressure, IVC — inferior vena cava.

Clinicians are well aware that DKA can cause ADHF, especially in elderly patients. In our study, DKA was recorded in 14,3% of patients with ODS. However, the literature data do not describe pathogenesis of this relationship. DKA is considered mainly from the perspective of respiratory failure; there are no guidelines on rehydration and diuretic therapy in ODS due to DKA [6].

A number of authors agree that in patients with T2D, the risk of ADHF is associated, as shown in our study, with atherosclerosis-related diseases, a history of arrhythmias, CKD, and a low beta-blocker use [7]. Many researchers have also demonstrated that pneumonia and inflammatory diseases can cause rehospitalizations with HF, already within 30 days in T2D patients [8].

Rubin DJ, et al. proposed a special calculator for risk of rehospitalizations in T2D patients — DERRI (Diabetes Early Readmission Risk Indicator), which included the same laboratory parame-

ters that are presented in our study as risk factors for ADHF [9].

In our study, 46,9% of patients with T2D and HF took sulfonylureas prior to hospitalization. Recently, more and more data has been collecting that these glucose-lowering drugs not only increases the risk of HF, but also related hospitalizations. According to the study by Heaton PC, et al., sulfonylureas were found to increase the risk of hospitalization with HF by 29% [10].

Endocrinologists regulate that insulin therapy should be used only with persistent hyperglycemia >10 mmol/L, regardless of the time it was determined [11]. In our study, only 24,5% of T2D patients had persistent hyperglycemia >10 mmol/L on the first day of hospitalization, however, the frequency of insulin therapy during hospitalization was significantly increased from 20,4% to 55,1% (p<0,001). According to the post-hoc analysis of EVEREST study (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan), insulin therapy in patients with ADHF increases the risk of cardiovascular mortality and hospitalization with HF by 25% [12].

In a meta-analysis of 11 observational studies, it was determined that the use of metformin reduces the risk of all-cause mortality by 22% in HF patients [13]. In our study, the frequency of metformin use prior to hospitalization was 59,2%; during hospitalization it was significantly reduced to 24,5%. The unreasonable withdrawal of metformin in ADHF is probably associated with a risk of lactic acidosis. According to Chang CH, et al., the frequency of lactic acidosis in the metformin group is not higher than when using other antidiabetic therapy [14]. Moreover, data have been obtained that the metformin use for T2D patients in acute heart failure reduces the death risk by 67% (p<0,001) [15].

Khoo K, et al., confirmed our results in relation to cardiac structural and functional features in T2D patients, characterized by the predominance of preserved LVEF, severe LVDD and LV concentric hypertrophy [2].

Conclusion

The incidence of T2D among patients with ADHF was 45,7%. There were following risk factors for ADHF in T2D patients: DKA, hypertensive crisis, history of ACS, AF with HR >110 bpm, CKD, pneumonia, progression of anemia, low beta-blockers use, use of inappropriate antidiabetic drugs for HF patients (sulfonylureas, insulin). ADHF, assessed by NT-proBNP level, was significantly more severe in T2D patients with severe congestion symptoms, which led to an increase in the need for diuretic therapy with a group without T2D. Cardiac remodeling in T2D patients with ADHF is characterized mainly by the preserved LVEF, severe LVDD and LV hypertrophy.

Relationships and Activities: not.

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Insulin resistance contribution to pathogenesis of cardiac remodeling in patients with hypertension in combination with obesity and type 2 diabetes

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Aim. To evaluate the insulin resistance contribution to pathogenesis of left ventricular (LV) remodeling in patients with hypertension (HTN) in combination with obesity and type 2 diabetes (T2D).

Material and methods. The study included 320 patients with stage II-III HTN and stages 1-3B chronic kidney disease (CKD) aged 45-70 years: group 1 (n=102) — HTN patients only, group 2 (n=90) — patients with HTN and obesity, group 3 (n=96) — patients with HTN, obesity and T2D, group 4 (n=32) — patients with HTN and T2D. The groups were comparable in main clinical and demographic parameters. We performed a clinical examination, assessed cardiac structure, insulin levels and insulin resistance indices. We used nonparametric statistics, multiple regression, stepwise linear discriminant and canonical analyzes. Data are presented as Me [Q25; Q75], where Me is the median, Q25 and Q75-25 and 75 percentiles, respectively.

Results. LV mass index was significantly higher in the group of HTN, obesity and T2D compared with HTN patients only (107,5 [9,5; 125,6] vs 96,0 [85,1; 106,1] g/m^2, respectively). The percentage of patients with LV hypertrophy was significantly higher in groups 2, 3 and 4 compared with group 1, and also in group 3 compared with groups 2 and 4. A stepwise discriminant analysis revealed that BMI increase in HTN±T2D patients was accompanied by an increase in values of metabolic index, triglyceride-to-high-density-lipoprotein-cholesterol ratio. Canonical analysis showed that an increase in the median values of Insulin Resistance function in all groups was associated with a deterioration in the median values of Cardio function.

Conclusion. The data obtained specifies the LV geometry characteristics, as well as the insulin resistance contribution to pathogenesis of LV remodeling in HTN patients with/without obesity and/or T2D.

Key words: hypertension, visceral obesity, diabetes, insulin resistance.

Relationships and Activities: not.

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Epidemiological studies showed that the risk of left ventricular (LV) remodeling and dysfunction doubled in patients with obesity and insulin resistance compared to healthy people — this tendency continued with an increase in body mass index (BMI) [1]. It was reported that insulin resistance was induced even in patients with cardiovascular disease who did not have concomitant diabetes, and that it made patients prone to diabetes [2]. Therefore, there may be a close relationship between insulin resistance caused by obesity or type 2 diabetes (T2D) and impaired cardiac structure. The pathogenesis of LV remodeling is complex: in obese patients, the secretion of inflammatory cytokines and insulin resistance increases [3]. Then, insulin resistance further contributes to insulin secretion. Insulin overproduction, as well as increased fatty acid oxidation and decreased glucose absorption leads to disruption of the intracellular transduction of the insulin signal in various tissues, including myocardium. It should be noted that activation of the sympathetic nervous system, renin-angiotensin-aldosterone system and related sodium retention and increase in plasma volume occur after an insulin resistance increase. These changes cause LV hypertrophy (LVH) and interstitial fibrosis.

When hypertension (HTN) and obesity are combined by T2D, there is a further progression of structural and functional cardiac disorders. LVH is a characteristic morphological manifestation of diabetic cardiomyopathy, usually representing a later stage of the disease, and is a common disorder in T2D patients, even in those without coronary heart disease (CAD) or HTN. Although LVH is often associated with increased afterload in patients with T2D and HTN, it can also occur regardless of pressure overload.

To date, characteristics of LV geometry in HTN patients with obesity and/or T2D have not been fully determined. Contribution of insulin resistance to myocardial remodeling in patients only with HTN, with HTN and obesity, with HTN and T2D, as well as with HTN, obesity and T2D is also unclear.

Objective: to assess the pathogenetic contribution of insulin resistance to the development of LV myocardial remodeling in patients with hypertension in combination with obesity, type 2 diabetes.

The aim of the study was to evaluate the insulin resistance contribution to pathogenesis of LV remodeling in patients with HTN in combination with obesity and T2D.

Material and methods

The open-label comparative prospective study included 320 patients with stage II-III HTN (not reached target blood pressure (BP) levels) and stages 1-3B chronic kidney disease (CKD) aged 45-70 years: group 1 (n=102) — HTN patients only, group 2 (n=90) — patients with HTN and obesity, group 3 (n=96) — patients with HTN, obesity and T2D, group 4 (n=32) — patients with HTN and T2D (Table 1). The groups were comparable in age, sex, prevalence of smoking, duration of hypertension, level of office systolic BP (SBP) and heart rate (HR). Patients of groups 3 and 4 were also comparable in T2D duration and dosage of glucose-lowering drugs. Groups 1 and 4 were considered as control groups. The exclusion criteria were as follows: uncontrolled malignant HTN; acute coronary syndrome and acute cerebrovascular accidents in the last 6 months; hemodynamically significant heart defects and rhythm disturbances; type 1 diabetes; class III obesity; severe liver failure; CKD stage >3B; alcoholism; any other diseases that could affect the results of the study.

We identified and assessed complaints, medical history, risk factors for HTN, general condition, office BP, heart rate, and anthropometric parameters (height, weight, BMI, percent of subcutaneous and visceral fat by bioelectrical impedance analysis (BIA) using an Omron BF-508, waist (WC) and thigh circumference (TC)). Abdominal obesity was identified by waist-to-thigh ratio (WTR) (WTR >0,9 in men and WTR >0,85 in women), as well as by WC value (WC ⩾102 cm in men and WC ⩾88 cm in women). Visceral obesity was diagnosed with visceral fat ⩾9% according to BIA [4]. The structural cardiac parameters were analyzed by echocardiography followed by an assessment of LV geometry — the LV mass was calculated according to American Society of Echocardiography (ASE) guidelines [5].

To determine insulin resistance, basal insulin concentration was measured (by enzyme-linked immunosorbent assay using DRG kits (USA) and clinical chemistry analyzer Uniplan (Russia)), and special indices characterizing tissue sensitivity to insulin were used [6]. The HOMA-IR index, triglyceride-to-high-density-lipoprotein-cholesterol ratio (TG/HDL-C) and metabolic index (MI) were used using parameters of carbohydrate and lipid metabolism. Based on the results obtained, insulin resistance was determined with values of HOMA-IR >2, TG/HDL-C >1,37 and MI ⩾7 [6].

Statistical processing was carried out using the statistical software package Microsoft Excel 2010 and Statistica 10.0. The normality of distributions was evaluated using the Shapiro-Wilk test. Data are presented as Me [Q25; Q75], where Me is the median, Q25 and Q75 are 25th and 75th percentiles, respectively. For qualitative traits, the incidence (%) was identified. Multiple comparisons of the characteristics of independent samples were performed using the Kruskal-Wallis test. Differences were considered significant at $p<0,05$. If there were significant diffe-

Table 1

Clinical and demographic parameters of patients (Me [25%;75%])

Parameter	Group 1 HTN without obesity and T2D	Group 2 HTN+obesity	Group 3 HTN+obesity+T2D	Group 4 HTN+T2D
Number of patients, n	102	90	96	32
Men/women, (%)	34,4/65,6	37,8/62,2	32,3/67,7	34,4/65,6
Age, years	62,0 [55,0; 66,0]	62,0 [55,3; 65,8]	62,0 [58,0; 65,0]	63,0 [60,0; 66,0]
BMI, kg/m^2	26,7*,† [25,4; 28,7]	32,9†† [31,1; 36,0]	34,7§§ [32,5; 37,5]	27,2 [25,9; 28,5]
WC, cm	94,0*,† [83,0; 100,0]	105,0†† [99,3; 111,8]	107,0§§ [102,0; 116,0]	93,5 [88,3; 99,3]
TC, cm	102,0*,† [99,0; 105,0]	115,0†† [110,0; 125,0]	116,0§§ [108,0; 122,0]	103,5 [98,0; 105,3]
WTR	0,91 [0,82; 0,96]	0,91 [0,85; 0,99]	0,94 [0,88; 1,00]	0,91 [0,87; 0,96]
Proportion of patients with abdominal obesity estimated by WTR, %	51,2*,†,§	73,7**	86,3	71,9
Proportion of patients with abdominal obesity estimated by WC, %	61,0*,†,§	100,0††	100,0§§	90,6
Subcutaneous fat, %	30,7*,† [26,0; 39,2]	45,1†† [39,3; 49,4]	44,7§§ [38,1; 50,0]	35,2 [27,0; 40,1]
Visceral fat, %	10,5*,† [8,0; 13,0]	14,0†† [11,0; 16,0]	14,0§§ [13,0; 17,0]	9,5 [8,0; 11,0]
Proportion of patients with visceral obesity, %	57,5*,†	100,0††	100,0§§	50,0
Smokers, %	21,6	21,1	20,8	21,9
Proportion of patients with CKD, %	100,0	100,0	100,0	100,0
Duration of hypertension, years	12,0 [8,0; 19,0]	12,0 [7,0; 20,0]	15,0 [9,5; 20,0]	12,0 [7,0; 20,0]
Duration of diabetes, years	0†,§	0**,††	7,0 [3,0; 10,0]	7,0 [4,5; 10,0]
Office SBP, mm Hg	160 [150; 170]	160 [150; 170]	159 [150; 170]	160 [150; 164]
Office DBP, mm Hg	100†,§ [91; 103]	100**,†† [94; 108]	93 [90; 100]	90 [83; 100]
Office PP, mm Hg	60†,§ [50; 70]	60 [55; 70]	62 [60; 77]	70 [60; 75]
HR, bpm	70 [65; 75]	73 [64; 78]	70 [64; 76]	70 [65; 80]

Note: * — significance of differences between groups 1 and 2, † — significance of differences between groups 1 and e, § — significance of differences between groups 1 and 4, ** — significance of differences between groups 2 and 3, †† — significance of differences between groups 2 and 4, §§ — significance of differences between groups 3 and 4.

Abbreviations: DBP — diastolic blood pressure, BMI — body mass index, TC — thigh circumference, WC — waist circumference, WTR — waist-to-thigh ratio, PP — pulse pressure, SBP — systolic blood pressure, CKD — chronic kidney disease, HR — heart rate.

rences according to the Kruskal-Wallis test, Bonferroni-Dunn test was used. In the case of dichotomous traits, the statistical significance was estimated using the Fisher's exact test. Spearman's correlation analysis was performed to evaluate associations. To determine the dependence of one trait on several other independent traits, multiple regression analysis was used. Obtained regression model was analyzed using the coefficient of multiple determination (R^2) and the level of statistical significance. When studying the pathogenesis of HTN in patients with obesity and T2D, linear discriminant analysis and canonical analysis were used.

This study was performed in accordance with the Helsinki declaration, Good Clinical Practice standards and legislation of the Russian Federation. The regional medical ethics committee approved this study. All patients signed informed consent.

Results

Significant BMI differences between groups 1 and 2, 1 and 3, 2 and 4, 3 and 4 were revealed: BMI was higher in groups 2 and 3 ($p<0,0001$).

WC and TC were also significantly higher in groups of patients with HTN+obesity and HTN+obesity+T2D than in patients with HTN and HTN+T2D ($p<0,0001$). Higher values of WTR were noted among patients with HTN+obesity+T2D, but the differences were not significant.

Noteworthy is the high incidence of abdominal obesity in all studied groups estimated by WTR, WC, and also by visceral fat. Moreover, the percentage of patients with abdominal obesity estimated by WTR was significantly lower in group 1 compared with groups 2, 3, and 4. Using the WC values for assessing the abdominal obesity, significant differences were noted between groups 1 and 2, 1 and 3 (Table 1).

Table 2

Structural cardiac parameters of patients (Me [25%;75%])

Parameter	Group 1 HTN without obesity and T2D	Group 2 HTN+obesity	Group 3 HTN+obesity+T2D	Group 4 HTN+T2D
LVPWd, cm	1,00 [1,00; 1,05]	1,10†† [1,00; 1,20]	1,10§§ [1,00; 1,15]	1,00 [1,00; 1,10]
IVST, cm	1,0† [1,0; 1,05]	1,05 [1,00; 1,20]	1,10 [1,00; 1,20]	1,0 [1,0; 1,20]
ESD, cm	3,3 [3,0; 3,6]	3,3 [3,0; 3,6]	3,4 [3,0; 3,7]	3,3 [3,0; 3,7]
EDD, cm	4,9† [4,6; 5,1]	5,0 [4,8; 5,3]	5,1 [4,8; 5,3]	4,9 [4,6; 5,4]
LVMI, g/m^2	96,0† [85,1; 106,1]	98,6 [82,5; 118,5]	107,5 [92,5; 125,6]	101,4 [80,8; 122,5]
RWT, %	0,42 [0,39; 0,45]	0,44 [0,40; 0,46]	0,43 [0,41; 0,46]	0,40 [0,38; 0,46]
LVH, %	21,5*,†,§	53,3**	86,5§§	52,0

Note: * — significance of differences between groups 1 and 2, † — significance of differences between groups 1 and e, § — significance of differences between groups 1 and 4, ** — significance of differences between groups 2 and 3, †† — significance of differences between groups 2 and 4, §§ — significance of differences between groups 3 and 4.

Abbreviations: LVH — left ventricular hypertrophy, LVMI — left ventricular mass index, EDD — end diastolic dimension, ESD — end systolic dimension, IVST — interventricular septal thickness, RWT — relative wall thickness, LVPWd — LV posterior wall dimension.

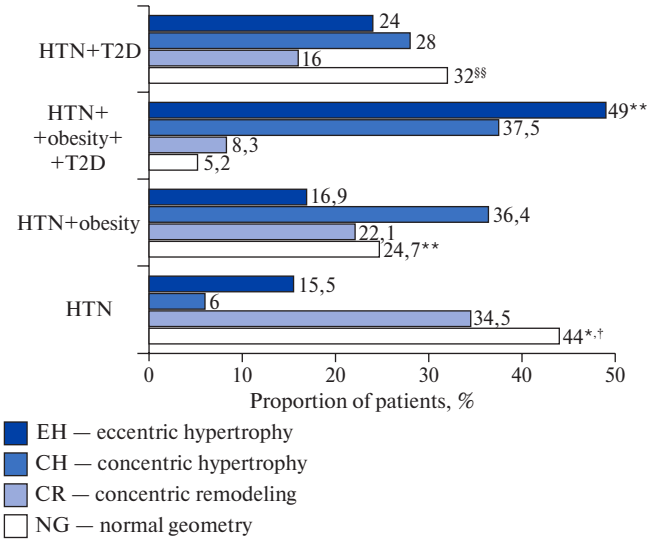

Figure 1. Types of LV remodeling in the studied groups.
Notes: * — significance of differences between groups 1 and 2, † — significance of differences between groups 1 and 3, ** — significance of differences between groups 2 and 3, §§ — significance of differences between groups 3 and 4.
Abbreviations: CH — concentric hypertrophy, CR — concentric remodeling, HTN — hypertension, NG — normal geometry, EH — eccentric hypertrophy, T2D — type 2 diabetes.

Subcutaneous and visceral fat values were significantly lower in groups 1 and 4 compared with groups 2 and 3 (p<0,0001 for both parameters). At the same time, at least half of the patients in all groups had visceral obesity, although there was no BMI obesity in groups 1 and 4: 57,5 vs 100,0 vs 100,0 vs 50,0% in groups 1, 2, 3, and 4, respectively (p<0,0001).

There were significant differences between groups 1 and 2 in comparison with groups 3 and 4 in terms of office diastolic BP (DBP) (p<0,0001). Lower DBP values are typical for patients with T2D. In this regard, higher office pulse pressure (PP) was detected in individuals of groups 3 and 4 compared with groups 1 and 2 (p=0,0009 in both comparisons).

There were correlations between WC and visceral fat extent (r=0,73, p<0,05), office SBP (r=0,13, p<0,05), office PP (r=0,19 , p<0,05), levels of serum glucose (r=0,44, p<0,05), insulin (r=0.32, p<0,05), insulin resistance indices (HOMA-IR (r=0,41, p<0,05), TG/HDL-C (r=0,28, p<0,05), MI (r=0,40, p<0,05)), structural cardiac parameters (LV posterior wall dimension — LVPWd (r=0,44, p<0,05), interventricular septum thickness — IVST (r=0,39, p<0,05), end-systolic dimension — ESD (r=0,34, p<0,05), end-diastolic dimension — EDD (r=0,36, p<0,05), LV mass index — LVMI (r=0,35, p<0,05)).

Assessment of structural cardiac parameters (Table 2) revealed that LVPWd was significantly higher in the group of HTN+obesity+T2D compared with HTN+T2D patients (1,10 [1,00; 1,15] vs 1,00 [1,00; 1,10] cm, respectively). IVST and EDD were higher in group 3 compared with group 1 (1,10 [1,00; 1,20] vs 1,0 [1.0; 1,05] cm (p=0,024) and 5,1 [4,8; 5,3] vs 4,9 [4,6; 5,1] cm (p=0,015), respectively). LVMI increased with the combination of HTN with obesity and T2D and was significantly higher in the group of HTN+obesity+T2D compared with the group of HTN (107,5 [92,5; 125,6] vs 96,0 [85,1; 106,1] g/m^2, respectively). We determined correlations between LVMI and WC (r=0,56) in group 1, as well as between LVMI and WC (r=0,50), visceral fat extent (r=0,57) and glucose level (r=0,57) in group 5.

The results of a regression analysis regarding HTN+obesity patients revealed an association between LVMI and WC (LVMI=-35,4+1,2*WC;

Table 3

Parameters of insulin resistance of patients (Me [25%; 75%])

Parameters	Group 1 HTN without obesity and T2D	Group 2 HTN+obesity	Group 3 HTN+obesity+T2D	Group 4 HTN+T2D
Insulin, μIU/ml	9,8*,† [6,0; 12,5]	16,6 [12,6; 24,2]	16,8 [13,0; 24,0]	12,7 [8,6; 18,6]
HOMA-IR	2,28*,†,§ [1,49; 3,14]	4,58 [2,80; 6,40]	5,30 [4,22; 7,47]	3,97 [2,45; 5,40]
TG/HDL-C	1,17*,† [0,75; 1,62]	1,50 [1,20; 1,91]	1,57 [1,32; 2,16]	1,30 [0,90; 1,78]
MI	8,72*,† [6,34; 9,97]	10,50†† [7,91; 13,52]	13,59§§ [10,36; 18,43]	9,24 [7,16; 13,85]

Note: * — significance of differences between groups 1 and 2, † — significance of differences between groups 1 and e, § — significance of differences between groups 1 and 4, ** — significance of differences between groups 2 and 3, †† — significance of differences between groups 2 and 4, §§ — significance of differences between groups 3 and 4.

Abbreviations: MI — metabolic index, TG/HDL-C — triglyceride-to-high-density-lipoprotein-cholesterol ratio.

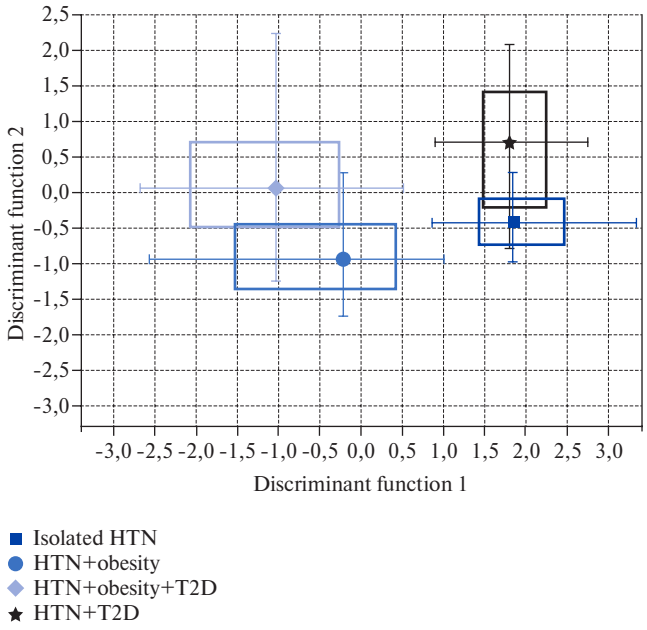

Figure 2. Distribution of the patients depending on the values of discriminant functions.

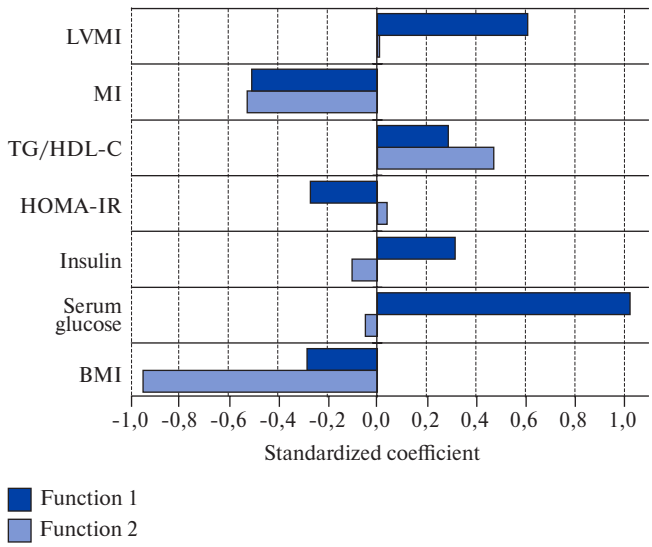

Figure 3. Distribution of the patients depending on the values of standardized coefficients.

Abbreviations: LVMI — left ventricular mass index, BMI — body mass index, MI — metabolic index, TG/HDL-C cholesterol — triglyceride-to-high-density-lipoprotein-cholesterol ratio.

adjusted R^2=0,33, p<0,001); in the group of HTN+obesity+T2D — between LVMI and the obesity extent (LVMI=77,3-7,2*BMI+2,2*WC; adjusted R^2=0,77, p=0,041; LVMI=114+1,78*visceral obesity+0,22*BMI; adjusted R^2=0,76, p=0,047); in the group of HTN+T2D — between LVMI and parameters of carbohydrate and lipid metabolism (LVMI=57,5+11,5*fasting glucose-9,75*HDL-C+18,4*VLDL-C; adjusted R^2=0,30, p<0,01).

The percentage of people with LVH was significantly higher in groups 2, 3, and 4 compared with group 1 (Table 2), as well as in group 3 compared with groups 2 and 4. The distribution of groups by types of LV remodeling is shown in Figure 1.

Insulin levels were significantly lower in patients with HTN compared with HTN+obesity and HTN+obesity+T2D participants (9,8 [6,0; 12,5] vs 16,6 [12,6; 24,2] and 16,8 [13,0; 24,0] μIU/ml, respectively) (Table 3).

HOMA-IR and TG/HDL-C ratio were significantly lower in patients with HTN compared with persons of groups 2, 3 and 4 (2,28 [1,49; 3,14] vs 4,58 [2,80; 6,40], 5,30 [4,22; 7,47] and 3,97 [2,45; 5,40] and 1,17 [0,75; 1,62] vs 1,50 [1,20; 1,91] и 1,57 [1,32; 2,16], respectively) (Table 3).

The MI value increased with the combination of HTN with obesity and/or T2D, reaching significant differences between groups 1 and 2, 1 and 3, 2 and 3, 3 and 4 (Table 3).

To identify the pathogenesis of HTN in commination obesity and T2D, a stepwise discriminant analysis was performed. Figure 2 shows that the shift of groups with HTN+obesity±T2D to negative values for 1 function is associated not only

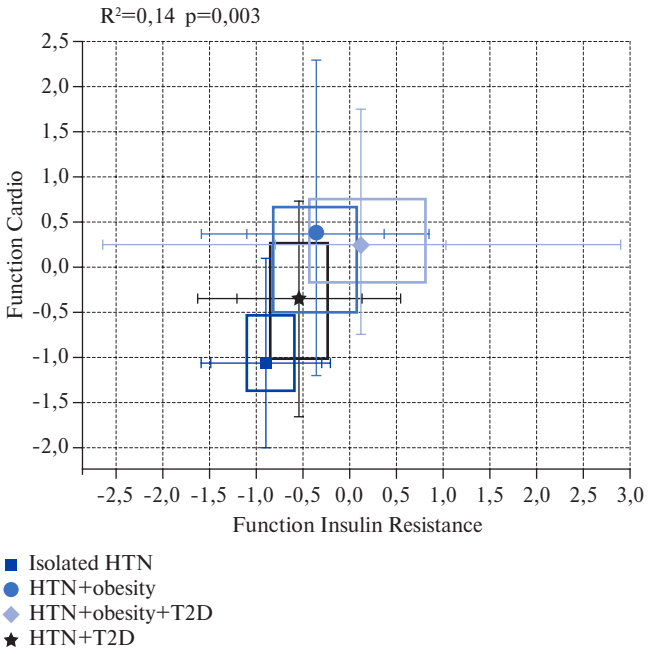

Figure 4. Distribution of the patients depending on the values of the canonical functions Insulin Resistance and Cardio.

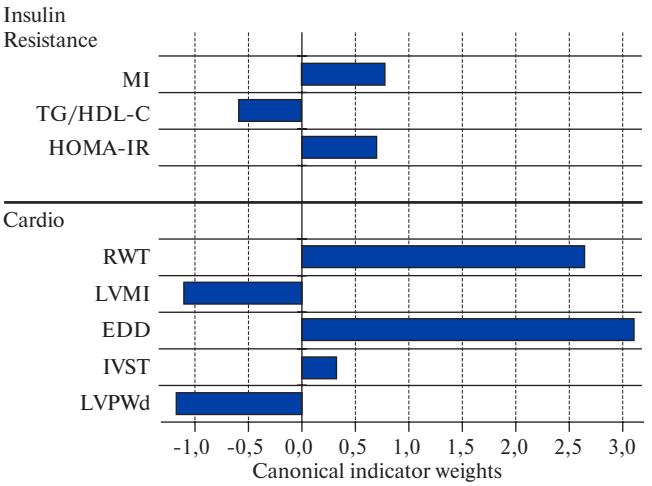

Figure 5. Relative contribution of parameters of insulin resistance and cardiac structure in the patients.
Abbreviations: LVMI — left ventricular mass index, EDD — end diastolic dimension, ESD — end systolic dimension, IVST — interventricular septal thickness, MI — metabolic index, RWT — relative wall thickness, LVPWd — LV posterior wall dimension, TG/HDL-C cholesterol — triglyceride-to-high-density-lipoprotein-cholesterol ratio.

with BMI increase, but also with an increase of insulin resistance severity. Thus, it was shown that the BMI increase in patients with HTN±T2D was accompanied by an increase in MI and TG/HDL-C ratio.

Combination of HTN with T2D, regardless of the obesity presence/absence, the maximum discriminant contribution is made by fasting serum glucose and LVMI; MI, insulin level, and TG/HDL-C ratio are somewhat less important (Figure 3). Thus, glycemia increase is associated with raised insulin resistance and is characterized by LVMI increase. In the space of two discriminant functions, the groups were located in different areas (Figure 2).

The data obtained suggest that the differences were most pronounced regarding not only metabolic parameters, but also the structural cardiac parameters. The analysis in this system is rather difficult, therefore, at the next stage, the contribution of insulin resistance to cardiac remodeling in groups of patients with HTN, HTN+obesity, HTN+obesity+ +T2D, HTN+T2D was studied.

When assessing the distribution of patients in the function space of Insulin Resistance and Cardio, a set of canonical functions with R^2=0,14 was obtained (p=0,003) (Figure 4).

According to the structure of Insulin Resistance function, its shift towards higher values is associated with an increase in MI and HOMA-IR (Figure 5).

According to the structure of Cardio function, the greatest contribution to LV remodeling is made by the EDD, LV relative wall thickness (RWT), as well as LVPWd and LVMI (Figure 5).

An analysis of the distribution of patients in the function space of Insulin Resistance and Cardio (Figure 4) shows that an increase in the median values of Insulin Resistance function in all groups is associated with a deterioration in the median Cardio function values. Moreover, patients with HTN+obesity+T2D were the most heterogeneous sample with a wide scatter in extreme values, which is probably due to the individual course of comorbidities and a worsening prognosis in this category of patients.

Discussion

Significant differences in BMI between groups 1 and 2, 1 and 3, 2 and 4, 3 and 4 are due to the design of the study. With an increase in BMI, the percentage of subcutaneous and visceral fat and WTR increased.

The practical significance of identifying a high percentage of patients with abdominal obesity in patients only with HTN and HTN in combination with T2D in groups of people with normal and excess BMI is the need to assess not only BMI for obesity diagnosis, but also WC, WTR, as well as visceral fat content.

Significantly higher values of office PP are characteristic of patients with a combination of HN and T2D due to a decrease of office DBP, which is a sign of increased arterial stiffness and subclinical target organ damage [7].

Significant correlations between BMI, WC, TC, WTR, subcutaneous and visceral fat levels and structural cardiac parameters obtained in the study confirms the pathogenetic role of obesity in the progression of target organ damage. It should be noted that in addition to the general trend of correlation analysis, the relationship features in each of the studied groups were revealed, which indicates a different significance level of pathogenesis components with the combination of HTN with obesity and T2D.

A significantly higher percentage of LVH among people with HTN and/or obesity and T2D (21,5% in patients only with HTN; 53,3% — with a combination of HTN and obesity; 52% — with a combination of HTN and T2D; 86,5% — with a combination of HTN, obesity and T2D) is associated with LV remodeling due to the negative contribution of both obesity and T2D, which is most pronounced in their combination [8]. The results of the study are consistent with data of Mancusi C, et al. (2017), where a multivariate logistic analysis with 8815 HTN patients, divided by BMI, revealed that obesity is associated with a higher prevalence of LVH by 6,9 times (95% confidence interval 5,84-8,17, p=0,0001), regardless of significant associations with the female gender, age, diabetes, office SBP, antihypertensive and antiplatelet therapy [9]. According to the review by Sakamoto M, et al. (2018), the basis of structural and functional cardiac impairment in patients with HTN in combination with obesity and/or T2D are the following mechanisms: chronic inflammation, oxidative stress in the heart and blood vessels, which in turn leads to vascular endothelial damage, LVH and interstitial fibrosis [10]. The prevalence of LV concentric hypertrophy in our study was significantly higher already with combination of HTN with obesity or T2D and is comparable to the group with HTN, obesity and T2D. The results are consistent with data of Orhan AL, et al. (2010), which showed that among obese individuals, concentric hypertrophy is more common than eccentric [11].

Perhaps this is due to chronic overload of the left atrium due to an increase in plasma volume caused by obesity and LV diastolic dysfunction [11]. However, in the group of HTN patients with obesity and T2D, patients with LV eccentric hypertrophy were significantly more frequent, which indicates the most unfavorable type of LV remodeling and is associated with overload not only by pressure but also by volume [12].

Thus, among patients with HTN, obesity, and T2D, compared with patients with HTN and without obesity and/or T2D, the most unfavorable types of LV remodeling significantly more often occurred: concentric and eccentric LVH.

Intracellular metabolic disorders and increased oxidative stress due to hyperglycemia, insulin resistance and chronic inflammation are pathogenetic mechanisms involved in the development of LV remodeling caused by T2D [10, 13]. These mechanisms lead to structural cardiac changes, such as LVH and interstitial fibrosis, as a result of which HF subsequently develops.

Results of regression analysis confirm the contribution of these pathogenetic components to LV remodeling.

In combination of HTN with obesity and/or T2D, insulin levels significantly increased in comparison with individuals only with “HTN in parallel with insulin resistance indices. The results are consistent with data of Seravalle G, et al. (2016) [14].

Thus, insulin resistance leads to a number of negative pathophysiological processes that can initiate destabilization of cells and tissues, including the heart, causing structural and functional disorders and increasing the risk of cardiovascular events [15].

The canonical analysis revealed the contribution of insulin resistance to the progression of structural cardiac changes in groups of individuals only with hypertension, with HTN in combination with obesity and/or T2D. It was noted that the Insulin Resistance function plays the greatest role in the group of T2D patients. Moreover, among participants with HTN, obesity and T2D compared with patients with HTN and T2D, the decrease in Cardio function was more significant, which indicates the additional contribution of obesity to the pathogenesis of cardiovascular damage. The heterogeneity of the sample of patients with HTN, obesity, and T2D with a wide scatter in extreme values probably due to the individual course of comorbidities and a worsening prognosis in this category of patients.

Conclusion

The data obtained specifies the LV geometry characteristics, as well as the insulin resistance contribution to pathogenesis of LV remodeling in HTN patients with/without obesity and/or T2D.

Relationships and Activities: not.

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Outcomes in patients with hypertension and type 2 diabetes receiving a stent for angina

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Aim. To study the outcomes in hypertensive (HTN) patients receiving a stent for class III angina, depending on concomitant type 2 diabetes (T2D).

Material and methods. The study included 295 patients aged 45 to 75 years. All patients underwent coronary angiography followed by elective stenting. Clinical outcomes were evaluated after outpatient follow-up (average 44 months). Patients were divided into two groups: group 1 — 214 patients with coronary artery disease (CAD) in combination with HTN; group 2 — 81 patients with CAD in combination with HTN and T2D.

Results. In the group of patients without T2D, during the follow-up period, class III angina was observed in 92 patients (43%). The decrease in systolic blood pressure (BP) (SBP) and diastolic BP (DBP) in this subgroup was 18 and 14 mm Hg, respectively (p<0,001); 35 patients (38%) had myocardial infarction (MI). In the group of patients with T2D, class III angina was recorded in 60 patients (74,1%). The decrease in SBP and DBP in this subgroup was 19 and 12 mm Hg, respectively (p<0,001). There were 58 cases of MI in this subgroup (96,7%).

Conclusion. After stent insertion, patients with CAD, HTN and T2D still reporting class III angina were more likely to have MI than patients without T2D. This indicates a greater contribution of T2D to MI development, despite an equal decrease of SBP in patients with/without T2D.

Key words: hypertension, myocardial infarction, diabetes, systolic blood pressure, angina of effort.

Relationships and Activities: not.

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It is known that the combination of coronary artery disease (CAD) with hypertension (HTN) significantly worsens the prognosis of patients [1]. Cardiovascular diseases remain the main cause of morbidity and mortality in patients with type 2 diabetes (T2D) [2]. The combination of CAD with T2D significantly worsens the prognosis of patients. In this regard, patients with T2D and concomitant cardiovascular diseases are at a very high risk [3].

Severe angina requires measures to improve the quality of life by reducing myocardial ischemia. In this regard, along with pharmacotherapy, coronary artery revascularization is effectively used. However, the presence of angina pectoris after coronary stenting is observed in 20-40% of patients [4]. There is very little data on angina in T2D patients with HTN after coronary stenting and on outcomes in the long-term follow-up [5].

The aim was to study the outcomes in HTN patients receiving a stent for class III angina, depending on concomitant T2D.

Material and methods

The study included 295 patients aged 45 to 75 years (mean age 61,35±8,2 years). All patients signed informed consent. There were following inclusion criteria: age <75 years, CCS class III angina, HTN with BP ⩽180/110 mm Hg, sinus rhythm, signed informed consent. The exclusion criteria were: age >75 years, not signed informed consent, stage ⩾2 heart failure, a history of cerebrovascular accident, severe kidney (creatinine >160 μmol/L) and liver failure (transaminase levels ⩾3 times the normal range), any heart rhythm disorders requiring treatment, second- and third-degree atrioventricular block, bradycardia (⩽50 bpm), sinoatrial block, respiratory failure (⩾II degree), ineffective contraception in women of reproductive age, pregnancy and lactation, alcoholism and drug addiction, history of cancer.

We assessed the following parameters in all patients: a complete blood count; lipid profile; levels of creatinine, glucose, and blood potassium. Electrocardiography, echocardiography, and coronary angiography (CA) were performed. All patients underwent coronary stenting followed by dual antiplatelet and statin therapy. Conventional antihypertensive therapy was chosen taking into account the individual response of patients and was continued after hospitalization.

All patients were divided into two groups: group 1 (n=214) — patients with CAD and HTN; group 2 (n=81) — patients with CAD in combination with HTN and T2D.

The clinical course of angina was evaluated by questioning of patients. Assessment of BP parameters was based on data of patient self-monitoring. The dynamics of angina and HTN severity were evaluated on average 44 months after discharge from the hospital by telephone survey.

Statistical processing was carried out using the Statistica 6.0 software package (StatSoft Inc., USA). Normality of distribution was determined using the Shapiro-Wilk test. To describe normally distributed quantitative traits, the arithmetic mean (M) and the standard deviation (σ) were considered as M±σ. To describe the sampling distribution of non-normally distributed quantitative traits, we used the median (Me), lower (25%) and upper (75%) quartiles (Q_1 and Q_3) as Me [Q_1; Q_3]. The statistical significance of quantitative trait differences was evaluated by the nonparametric Mann-Whitney U test, and qualitative traits — by the Pearson's chi-squared test. Relative frequencies and their 95% confidence intervals (CI) were estimated to describe the qualitative traits. To identify the association between laboratory and instrumental parameters, nonparametric Spearman's correlation analysis was used. To assess the significance of differences between groups, the nonparametric Wilcoxon test was used.

Results

Data on laboratory parameters are shown in Table 1. Significant differences in laboratory parameters were revealed regarding the levels of high-density lipoprotein cholesterol (which were higher by 1,9% in the group without T2D patients) and plasma creatinine (which were higher by 6,9% in the group without T2D patients).

In the group of patients without T2D, during the follow-up, class III angina persisted in 92 patients (43%). The decrease in systolic (SBP) and diastolic BP (DBP) in this subgroup was 18 and 14 mm Hg, respectively (p<0.001), while 35 patients (38%) had MI (Table 2). In the group of patients with T2D, class III angina persisted in 60 patients (74,1%). The decrease in SBP and DBP in this subgroup was 19 and 12 mm Hg, respectively (p<0,001). There were 58 (96,7%) cases of MI in this subgroup (Table 3).

In 122 patients without T2D (57%), angina progression from class III to IV was observed. The decrease in SBP and DBP in this subgroup was 10 and 18 mm Hg, respectively. During the follow-up period, 110 cases of MI (90,2%) and 10 cases of acute cerebrovascular accident (CVA) were recorded (Table 2). In 21 patients with T2D (26%), angina progression from class III to IV was observed. The decrease in SBP and DBP in this subgroup was 18 and 7 mm Hg, respectively (p<0,001 and p=0,05); during the follow-up period, 17 cases of MI (80,9%) and 4 cases of acute CVA were recorded (Table 3).

Table 1

Comparison of laboratory parameters

Parameter	Group I, n=214	Group II, n=81	P
	Me [Q_1;Q_3]	Me [Q_1;Q_3]	
Age, years	61,00 [56,00;68,00]	62,00 [57,00;66,00]	0,36
Plasma potassium, mmol/L	4,70 [4,30;5,00]	4,70 [4,40;5,00]	0,73
TC, mmol/L	5,32 [4,32;6,21]	5,38 [4,64;6,12]	0,70
HDL-C, mmol/L	1,04 [0,89;1,25]	1,02 [0,84;1,16]	0,047
LDL-C, mmol/L	3,20 [2,47;4,10]	3,15 [2,50;4,04]	0,94
Creatinine, μmol/L	98,00 [87,10;109,00]	91,20 [83,30;107,90]	0,026
Blood glucose level, mmol/L	5,51 [5,20;5,97]	7,89 [6,55;10,09]	<0,001
Leukocyte count, $x10^9$/L	6,50 [5,65;7,60]	6,79 [5,70;8,35]	0,15

Abbreviations: TC — total cholesterol, HDL-C — high density lipoprotein cholesterol, LDL-C — low density lipoprotein cholesterol.

Table 2

Changes in angina classes and BP levels in patients without T2D at the beginning and end of the study

Classes of angina and complications	Number of patients	Δ SBP, mm Hg	Δ DBP, mm Hg
Class III angina → Class III angina	92	18*	14
MI	35		
CVA	0		
Class III angina → Class IV angina	122	10*	18
MI	110		
CVA	10		

Notes: * — p<0,05, Δ — the difference between the pressure at the beginning and at the end of the study.
Abbreviations: DBP — diastolic blood pressure, MI — myocardial infarction, CA — coronary angiography, CVA — acute cerebrovascular accident, SBP — systolic blood pressure.

Table 3

Changes in angina classes and BP levels in patients with T2D at the beginning and end of the study

Classes of angina and complications	Number of patients	Δ SBP, mm Hg	Δ DBP, mm Hg
Class III angina → Class III angina	60	19*	12*
MI	58		
CVA	0		
Class III angina → Class IV angina	21	18*	7
MI	17		
CVA	4		

Notes: * — p<0,05, Δ — the difference between the pressure at the beginning and at the end of the study.
Abbreviations: DBP — diastolic blood pressure, MI — myocardial infarction, CA — coronary angiography, CVA — acute cerebrovascular accident, SBP — systolic blood pressure.

Discussion

Epidemiological data suggest that HTN and T2D are often combined. Pathophysiology of T2D and HTN has much in common, leading to a mutual increase in the risk of cardiovascular events, despite adequate glycemic and BP control. One of the large studies with 99,720 HTN patients and 12,7-year follow-up, including 7480 patients with T2D and 244,816 normotensive patients was conducted. During the follow-up period, 14,050 deaths were recorded, while the mortality among T2D patients was higher than among hypertensive patients without T2D: all-cause mortality — 14,05% vs 7,43%, cardiovascular mortality — 1,28% vs 0,7%, respectively [6].

Another adverse combination is T2D and CAD. The data obtained by a coronary computed tomographic angiography showed that T2D patients have a greater severity of coronary artery lesions both in relation to the extent and prevalence of atherosclerosis [7].

There are several suggestions regarding the mechanisms of atherosclerosis progression in patients with T2D. Different phases of coronary artery atherosclerosis are regulated by various mechanisms, and T2D accelerates the occurrence of cardiovascular events due to accelerated progression of atherosclerosis, since many glucose-induced signaling mechanisms are mediated by active lipids. Activation of the receptors of advanced glycation end products is considered as a mediator of atherogenesis. Inflammation is also important, in which both high glucose levels and modified lipoproteins or saturated fatty acids take part [8].

The importance of coronary stenting with optimal pharmacotherapy in reducing the angina symptoms remains controversial [9]. In the widely discussed ORBITA study [10], the benefits of coronary stenting compared with placebo remained unknown, but this study is criticized because of its methodological limitations [11]. According to the researchers, one of the possible mechanisms for angina persistence after stenting is microvascular angina [10], which is also present in T2D. Stent placement can cause or exacerbate coronary microvascular dysfunction, increasing the tendency to coronary epicardial vasospasm. According to the authors, combination of these mechanisms can be the causes of angina after stenting in almost half of patients [4].

Clinical outcomes and severity of angina 1, 6 and 12 months after stenting were presented in the US registry, which included 10 medical centers [5]. Among 1080 patients, 34% had T2D. The severity of angina was the same among patients with/without T2D. T2D patients received calcium channel blockers and long-acting nitrates in addition to beta blockers. A multivariate analysis revealed that after 1 year the risk of angina was the same in patients with/without T2D (relative risk 1,04; 0,80-1,36). The authors concluded that patients with CAD and T2D had the same severity of angina as patients without T2. The authors concluded that patients with CAD and T2D had the same severity of angina as patients without T2D. These data contradict the generally accepted opinion that in patients with T2D, the manifestations of angina are less pronounced due to the silent myocardial ischemia.

Study limitations: a small sample, especially among patients with T2D; using a telephone survey.

Conclusion

In patients with CAD, HTN and T2D, despite the persistence of class III angina after coronary stenting, a greater number of MI cases occurred during the follow-up period than in the group of patients without T2D. This indicates a greater contribution of T2D to MI development, despite an equal decrease of SBP in patients with/without T2D.

Relationships and Activities: not.

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Barriers to effective outpatient hypertension treatment: a view of physicians and patients

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Aim. To study the opinion of primary care physicians and hypertensive (HTN) outpatients with different compliance rate on factors preventing effective antihypertensive therapy (AHT).

Material and methods. Primary care physicians and HTN outpatients were questioned. Questionnaires for physicians and patients included informative and survey parts, with a list of possible factors aggravated adherence to treatment. The assessment was carried out using visual analogue scale. The patient questionnaire also included questions about AHT and the eight-item Morisky Medication Adherence Scale (MMAS-8). The calculation was carried out with a 95% confidence interval (CI).

Results. The survey involved 298 physicians and 517 patients. Among patients, about 1% had a high compliance rate, 34% — moderate, 65% — low. In all groups, AHT did not significantly differ and was characterized by a low frequency of prescribing fixed-dose combinations (27,1%). According to physicians, the most significant and equivalent are the economic aspects of treatment — 7,9±2,1 (95% CI: 7,51-8,38), the need for lifestyle change — 7,9±2,4 (95% CI: 7,37-8,38) and, to a slightly lesser extent, psychological aspects 6,8±2,2 (95% CI: 5,43-6,43). The economic aspects of treatment and need for lifestyle change were also most significant factors according to patients with high (8,8±1,8 (95% CI: 7,23-10,37) and 8,4±1,7 (95% CI: 6,93-9,87), respectively) and low (95% CI: 6,4±3,0 (5,65-7,07) and 6,2±2,8 (95% CI: 5,5-6,82) respectively) compliance rates. For patients with moderate compliance rate, the most significant and almost equivalent factors were the need for lifestyle change — 5,6±3,3 (95% CI: 4,53-6,71), the need for regular visits — 5,6±3,1 (95% CI: 4,53-6,58) and the need for self-management — 5,6±2,8 (95% CI: 4,63-6,48).

Conclusion. The results obtained make it possible to forecast the compliance rate of patients with HTN, and, therefore, direct more efforts to those with a low rate, thereby increasing the effectiveness of AHT.

Key words: hypertension, antihypertensive therapy, adherence to treatment, questionnaire, economic aspects of therapy.

Relationships and Activities: not.

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Achieving a target level of blood pressure (BP) is critical to reducing the risk of cardiovascular events (CVE) and improving the prognosis in patients for hypertension (HTN) [1]. However, in actual clinical practice, only about a third of patients receiving antihypertensive therapy (AHT) reach BP <140/90 mm Hg and a little more than 10% — <130/80 mm Hg. [2]. Inadequate control of BP may be due to medical influence (irrational AHT, insufficient dosing, low frequency of using fixed-dose combinations (FDC), etc.), as well as factors related to patients. First of all, this regards to a low adherence to treatment, expressed in non-compliance or incomplete compliance with prescribed AHT, which, in turn, is influenced by various aspects of pharmacotherapy and personal characteristics of patients [3]. The present work is devoted to the study and evaluation of these factors.

The aim was to study the opinion of primary care physicians and HTN outpatients with different compliance rate on factors preventing effective AHT.

Material and methods

The multicenter (18 ambulatory clinics of Volgograd and Volzhsky) open-label observational study was performed. A voluntary, anonymous survey of primary care physicians, cardiologists and HTN outpatients was conducted. Doctors completed the questionnaire independently. Questioning of patients was carried out by doctors in the same health facilities after completing the informed consent. The questionnaires were based on questions similar to those used in the previous studies [4]. The questionnaire for medical practitioners consisted of two sections. The first was informational in nature and consisted of questions about demographics (sex and age) and work experience. In the second section, a list of possible factors lowing patient compliance with the prescribed treatment was proposed. Respondents were asked to determine the level of significance of each of them. Evaluation of these factors was carried out using visual analogue scale (VAS), where 0 was considered as the minimum and 10 as the maximum value. The content of this section corresponded to the same section in the patient questionnaire. The questionnaire for patients with HTN consisted of three sections. The first included questions about socio-demographic data (sex, age, education, marital status, social status, financial standing, presence/absence of disability, and questions on the AHT). These questions were clarified, if necessary, by the questioning doctors. The second section included the eight-item Morisky Medication Adherence Scale [5, 6], which is necessary for assessing medication adherence. The results of this test were evaluated as follows: 1 point was awarded for each negative answer, except for the question of taking all drugs yesterday — 1 point was given for a positive answer to this question. In the question, how often do you have difficulty remembering to take all your medications, 1 point was awarded only for the answer "never". Patients who scored 8 points had high adherence, those with 6-7 points — medium adherence, and those with 5 or less points — low adherence. In the third section of the questionnaire, it was proposed to evaluate the significance of factors that, in the opinion of patients, prevent medication compliance. The assessment was carried out using VAS, in which 0 was taken as the minimum, and 10 as the maximum value. This section for patients corresponded in content to the second section for doctors and was intended to assess the agreement between the opinions of practitioners and patients regarding the main issues of HTN treatment. The inclusion criteria were as follows: signed informed consent; age >18 years; verified HTN and taking AHT. There were following exclusion criteria: not signed informed consent; age <18 years; hospitalization due to cardiovascular disease over the past 3 months (including revascularization), severe clinical course and/or severe decompensated heart failure (HF), chronic kidney disease, liver failure, cognitive impairment, symptomatic hyperuricemia/gout, pregnancy, lactation. The data of patients as a whole and in subgroups with different medication adherence rates were analyzed. For data assessing, descriptive statistics were used: proportions (%), mean (M), standard deviation (σ). The calculation was carried out with a 95% confidence interval (CI). Assessment of the normality of the distribution was carried out using the Kolmogorov-Smirnov test. For the normally distributed traits, independent-samples Student's t-test was used to assess the statistical significance of differences. For the non-normally distributed traits, the nonparametric Mann-Whitney U-test was used. To assess the statistical significance of differences in qualitative traits, the Pearson's chi-squared test was used. Statistical processing was performed using the software package BIOSTAT and SPSS 16.0.

Results

The survey involved 298 primary care physicians (112 men and 186 women) with mean age 45,6±11,6 years (95% CI: 43,28-47,87) and mean work experience 21,5±11,9 years (95% CI: 19,13-23,89). The study also included data of 517 patients (176 men and 341 women) who met the inclusion criteria. The mean age of the patients was 61,8±12,3 (95% CI: 59,53-64,15) years. Table 1 presents data for the studied population of HTN patients as a whole and in groups with different medication compliance rate. Groups were comparable with respect to age and sex (p>0,05). The results of a survey using MMAS-8 are

Table 1

Data of patients in general study population and in subgroups with different medication adherence rate

Parameter	General study population	Subgroups with different medication adherence rate according to MMAS-8*		
		High, 8 points	Medium, 6-7 points	Low, 0-5 points
Proportion, % (n)	100 (517)	1 (5)	34 (181)	65 (331)
Demographic information				
Male/Female, % (n)	34/66 (176/341)	40/60 (2/3)	27,6/72,4 (50/131)	36,0/64,0 (119/221)
Age, years (M±σ)	61,8±12,3	60,4±11,3	63,4±13,4	61,1±11,8
Social information				
Higher education, % (n)	39,8 (206)	40 (2)	38,9 (70)	1,5 (5)
Intermediate vocational education, % (n)	59,2 (306)	60 (3)	61,1 (111)	58,2 (193)
Basic general education, % (n)	0,97 (5)	-	-	40,3 (133)
Marital status				
Married, % (n)	67,0 (346)	100 (5)	69,4 (126)	65,8 (218)
Divorced, % (n)	9,7 (50)	-	5,6 (10)	10,4 (34)
Widowed, % (n)	8,7 (45)	-	19,4 (35)	11,9 (39)
Single, % (n)	14,6 (76)	-	5,6 (10)	11,9 (39)
Social status				
Working, % (n)	32 (165)	40 (2)	30,6 (55)	32,8 (109)
Unemployed pensioner, % (n)	47,6 (246)	40 (2)	52,8 (96)	44,8 (148)
Employed pensioner, % (n)	20,4 (106)	20 (1)	16,6 (30)	22,4 (74)
Disability				
Disability, % (n)	17,4 (90)	-	11,1 (20)	21,2 (70)
Disability category, % (n)	I / II / III	I / II / III	I / II / III	I / II / III
	- / 14,5 (75) / 2,9 (15)	- / - / -	/ 100 (20) /	/ 78,6 (55) / 21,4 (15)
Financial standing **				
Above the average, % (n)	0,97 (5)	-	2,8 (5)	-
Average, % (n)	84,5 (437)	100 (5)	91,7 (166)	80,6 (267)
Below the average, % (n)	14,6 (75)	-	5,6 (10)	19,3 (64)
Numbers of antihypertensive agents				
Average (M±σ)	2,9±1,1	2,0±1,4	2,6±0,9	2,6±1,0
One agent, % (n)	9,7 (50)	0	8,3 (15)	10,6 (35)
Two agents, % (n)	38,1 (197)	60 (3)	36,0 (65)	38,0 (126)
Three agents, % (n)	35,0 (181)	40 (2)	39,2 (71)	31,7 (105)
Four or more agents, % (n)	17,2 (89)	0	16,7 (30)	19,6 (65)
Prevalence of fixed-dosed combinations				
Number of administrations, % (n)	27,1 (140)	40 (2)	28,7 (52)	26,0 (86)

Note: * — MMAS-8 — 8-item Morisky Medication Adherence Scale, ** — subjective patient's opinion about his material well-being.

presented in Table 2; an analysis of the data obtained is shown in Table 3. It was found that the proportion of patients with a high medication adherence was about 1% (n=5). Medium adherence was noted in 34% (n=176) of patients. The remaining 65% (n=336) of patients had a low medication adherence. Most patients had an intermediate vocational training. In the group with a low adherence, the proportion of patients with higher education was 1,5% (n=5), which is significantly lower compared to other groups

Table 2

Eight-item Morisky Medication Adherence Scale (MMAS-8). Patient survey results

Questions that suggest discrete answers		
Questions	Answers, %	
	Yes	No
Do you sometimes forget to take your antihypertensive medications?	31,1	68,9
Thinking over the past two weeks, were there any days when you forget to take your antihypertensive medications?	33	67
Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?	37,9	62,1
When you travel or leave home, do you sometimes forget to bring along your medication?	36,9	63,1
Did you take your medicine yesterday?	93,2	6,8
When you feel like your blood pressure is under control, do you sometimes stop taking your medicine?	46,6	53,4
Do you ever feel hassled about sticking to your antihypertensive treatment plan?	44,7	55,3
A question that involves choosing one of the options		
How often do you have difficulty remembering to take all your antihypertensive medications?		
Never	49,5	
Once in a while	26,2	
Sometimes	18,4	
Usually	3,9	
All the time	1,9	

Table 3

Assessment of adherence rate according to 8-item Morisky Medication Adherence Scale (MMAS-8)

Score, adherence rate	Proportion of patients, % (n)
8 points, high	1 (5)
7 points, medium	4,3 (22)
6 points, medium	29,8 (154)
5 points, low	17,8 (92)
4 points, low	17,9 (93)
3 points, low	11,8 (61)
2 points, low	13,3 (69)
1 point, low	3,9 (20)
0 point, low	0,2 (1)

($p<0,01$), while the proportion of basic general education was significantly greater (40,3%; n=133) than in other groups ($p<0,01$). All groups were dominated by married persons. In the studied population, unemployed pensioners prevailed — 47,6% (n=246). There were no significant differences in relation to this parameter between groups. There were 17,4% of patients with disabilities, and their largest proportion (21,2%; n=70) was noted in the low adherence group ($p<0,05$). None of the groups revealed individuals with category I disability. There were no disabled patients in high adherence group. Majority of respondents rated their financial standing as average (84,5%), however, in the low adherence group, the percentage of people who rated their financial situation as lower than average was significantly higher — 19,3% (n=64) than in other groups ($p<0,05$). To assess the possible effect on the opinion of patients, characteristics of AHT was studied, which did not have significant differences in the groups. Dual and triple AHT was most frequently prescribed — 38,1% (n=197) and 35,0% (n=181), respectively. The prevalence of FDC was extremely low in all groups. These drugs have been used in less than a third of patients. Assessment of factors affecting AHT, according to physicians and patients, is presented in Table 4. According to physicians, the most significant and equivalent are the economic aspects of treatment — 7,9±2,1 (95% CI: 7,51-8,38), the need for lifestyle change — 7,9±2,4 (95% CI: 7,37-8,38) and, to a slightly lesser extent, psychological aspects 6,8±2,2 (95% CI: 5,43-6,43). The lowest meaning had insufficient knowledge of patients about their disease — 5,5±2,3 points (95% CI: 5.05-6.01). The economic aspects of treatment and need for lifestyle change were also most significant factors according to patients with high (8,8±1,8 (95% CI: 7,23-10,37) and 8,4±1,7 (95% CI: 6,93-9,87), respectively) and low (95% CI: 6,4±3,0 (5,65-7,07) and 6,2±2,8 (95% CI: 5,5-6,82) respectively) compliance rates. For patients with moderate compliance rate, the most significant and almost equivalent factors were the need for life-

Table 4

Assessment of factors affecting antihypertensive therapy according to physicians and patients

Factors	Physicians		Patients							
	Score, M±σ (95% CI)	Factor rank	General study population		Subgroups with different medication adherence rate					
			Score, M±σ (95% CI)	Factor rank	High rate		Medium rate		Low rate	
					M±σ (95% CI)	Factor rank	M±σ (95% CI)	Factor rank	M±σ (95% CI)	Factor rank
Insufficient patient knowledge about the disease	5,5±2,3 (5,05-6,01)	8	4,7±3,3 (4,07-5,33)	7	5,8±4 (2,33-9,27)	6	5,1±3,3 (3,91-6,04)	7	4,5±3,4 (3,67-5,28)	7
Inadequate patient awareness about possible complications	5,9±2,4 (5,43-6,43)	6	4,9±3,2 (4,31-5,54)	6	7,6±2,5 (5,4-9,8)	3	5,2±3,2 (4,16-6,23)	6	4,6±3,3 (3,8-5,36)	6
Need for regular office visits	5,9±2,4 (6,37-5,37)	7	5,6±3,1 (5-6,15)	3	5,6±3,8 (2,29-8,91)	7	5,6±3,1 (4,53-6,58)	2	5,6±3,0 (4,86-6,31)	3
Need for self-management	6,3±2,4 (5,79-6,79)	4	5,4±2,9 (4,85-5,93)	5	7,6±2,6 (5,31-9,89)	4	5,6±2,8 (4,63-6,48)	3	5,1±2,8 (4,45-5,82)	5
Need for regular drug taking	6,2±2,7 (5,62-6,74)	5	5,5±3,1 (4,89-6,06)	4	7,4±2,6 (5,11-9,69)	5	5,3±3,3 (4,21-6,34)	5	5,4±3,1 (4,7-6,17)	4
Need for lifestyle change	7,9±2,4 (7,37-8,38)	2	6,1±3,3 (5,53-6,64)	2	8,4±1,7 (6,93-9,87)	2	5,6±3,3 (4,53-6,7)	1	6,2±2,8 (5,5-6,82)	2
Psychological problems	6,8±2,2 (6,35-7,25)	3	4,7±3,4 (4,13-5,26)	8	5,8±3 (3,14-8,46)	8	5,0±3,1 (4-6)	8	4,4±2,9 (3,74-5,15)	8
Economic aspects of treatment	7,9±2,1 (7,51-8,38)	1	6,2±3,2 (5,56-6,77)	1	8,8±1,8 (7,23-10,37)	1	5,4±3,6 (4,27-6,61)	4	6,4±3 (5,65-7,07)	1

Abbreviations: M — mean, σ — standard deviation, CI — confidence interval.

style change — 5,6±3,3 (95% CI: 4,53-6,71), the need for regular visits — 5,6±3,1 (95% CI: 4,53-6,58) and the need for self-management — 5,6±2,8 (95% CI: 4,63-6,48). Lower meaning had economic aspects of treatment — 5,4±3,6 points (95% CI: 4,27-6,61). Patients of all groups rated the insufficient knowledge about their disease and psychological aspects as the least significant factors. Groups with low and medium medication adherence had significant difference regarding the value of need for lifestyle change (χ^2=11,012; d.f.=9; p<0,05). No significant intergroup differences with respect to other factors were found.

Discussion

The practitioners participated in this study mainly had a long-term work experience, which gives reason to consider the information obtained as objective. The demographics of patients in subgroups with different adherence rates did not significantly differ. In all compared groups of patients, AHT did not have significant differences. Dual and triple AHT were prescribed most frequently, at the same time, the prevalence of using FDC was extremely low. Noteworthy is the quantitative disproportion of groups with high and low medication adherence (1% and 65%, respectively). This is probably due to the fact that the majority of HTN participants had features that did not allow them to achieve a high adherence. This may be due to low level of education, which can lead to a misunderstanding of the need to comply with medical recommendations, reassessment of one's own knowledge in medicine, and, consequently, propensity to self-medication. Perhaps these factors explain the unexpected low number of patients with high adherence and the significant socio-economic differences in low adherence group (lower level of education, lower financial standing, higher number of disabled patients). The dependence of adherence rate on the level of education (the higher the level of education, the higher the medication adherence rate) was demonstrated in earlier studies [7]. According to physicians, the most significant factors preventing effective therapy were the economic aspects of treatment and, equally, the need for lifestyle change, as well as the mental problems. According to patients, economic aspects of treatment and, equally, the need for lifestyle change were the most significant factors. The value of these factors in the subgroups had

some differences. For patients with medium medication adherence, the most significant were the need for lifestyle change and for self-monitoring during treatment and, to a lesser extent, the need for regular physician office visit. The economic aspects of treatment were in fourth place. In patients with low adherence, economic aspects of treatment were the most important, followed by the need for lifestyle change and for regular physician office visit. Perhaps it is precisely the socio-economic vulnerability of these patients that affected the results of the study. In contrast to the physicians' opinion regarding the importance of psychological aspects, patients themselves, regardless of the adherence rate, rated this factor as the least significant. The influence of psychological factors on medication adherence was noted in other studies [8]. Both among practitioners and patients, insufficient knowledge about the disease had a low value. In previous studies [4], dissociation was revealed regarding the importance of economic aspects, which physicians considered the most significant, and patients put them only in the 5th place. In our study, both physicians and most patients rated this factor as the most significant, as well as the need for lifestyle changes. Thus, at present, the opinion of doctors and patients on AHT have become more consolidated.

Conclusion

According to most physicians and patients, the economic aspects of treatment and the need for lifestyle change are the most significant factors preventing effective AHT. Most patients had a low medication adherence rate. Among them, the smallest proportion of people with higher education was noted; one fifth of these patients rated their financial standing below the average level and the same proportion were disabled. In addition, psychological problems were considered by physicians as one of the most significant factors of ineffective treatment. However, patients rated this factor as the least significant. The results obtained make it possible to form a preliminary judgment on the expected level of adherence of patients with AH, and, therefore, direct more efforts to work with patients with a low level of adherence, thereby increasing the effectiveness of AHT.

Relationships and Activities: not.

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