The aim: To determine the independent predictors of adverse cardiovascular events in patients with CHF.

Materials and methods: The study enrolled 88 patients (men - 52% (n=46); women - 48% (n=42)) with CHF of ischemic origin, stage II AB, II-IV FC according to NYHA, in which 58 - patients with reduced left ventricle ejection fraction (LV EF <40%,) and 30 - with preserved LV EF (>55%). Patients with different phenotypes of CHF were comparable in age, sex, height, weight, body surface area. Cumulative endpoints considered death, myocardial infarction and progressive angina pectoris, stroke and progressive heart failure.

Results. Analysis of the frequency of endpoints depending on the phenotype of CHF didn’t reveal a significant difference between the study groups of 18.97% (11/58) vs. 10% (3/30); log-rank test (p= 0.378). According to univariate models of analysis of proportional hazards of Cox, the relative risk of adverse cardiovascular events in patients with CHF increased in 1.44 times (HR 1.44, 95% CI 1.0142 - 1.9942; p= 0.044) in the presence of pulmonary hypertension. At the same time, the presence of inspiratory IVC collapse more than 50% reduced the relative risk of adverse cardiovascular events in patients with CHF by 59% (HR 0.41; 95% CI 0.1796 - 0.9497; p= 0.038). Adverse cardiovascular events were not associated with individual anthropometric parameters of patients; structural and geometric, functional parameters of the heart; parameters of filtration and concentration function of the kidneys, plasma potassium concentration; tubulo- interstitial injury. The multivariate model (p= 0.0014), included factors such as age over 66 years (HR 1.13; 95% CI 1.0230 – 1.2555; p= 0.0172), body weight over 82 kg (HR 1.065; 95% CI 1.0043 – 1.1301; p= 0.036), index TEI LV over 0.52 c.u. (HR 30.69; 95% CI 1.3241 – 711.5572; p= 0.033), peak mitral valve pressure gradient over 1.9 mmHg. (HR 1.22, 95% CI 1.0210 - 1.4470; p= 0.029), the maximum flow velocity in the aorta over 98 cm/sec (HR 1.008; 95% CI 1.0009 - 1.0155; p= 0.0014), was associated with a increase in the relative risk of adverse cardiovascular events in patients with CHF of ischemic origin, regardless of sex, glomerular filtration rate and tubular interstitial injury.

Conclusion: Independent risk factors for adverse cardiovascular events in patients with CHF should be considered: age and body weight, index TEI LV, peak gradient pressure MK and the maximum flow velocity (Vao) in the aorta. Dependent risk factors for adverse cardiovascular events in patients with CHF are baseline sonographic parameters of E/A and mean pressure gradient MK, plasma sodium concentration, the presence of pulmonary hypertension. Inspiratory IVC collapse of more than 50% is associated with a reduction in the relative risk of adverse cardiovascular events in patients with CHF.

Key words: Chronic heart failure, index TEI, adverse cardiovascular events, outcomes.
Introduction.

Chronic heart failure (CHF) remains a major burden on the health care system due to low quality of life, high morbidity, and mortality [1].

Every year, nearly 50% of deaths in Europe are caused by cardiovascular diseases, 42% of men and 51% among women [2].

The incidence of heart failure (HF) is gradually increasing due to our aging population. Obesity contributes to a steep rise in the prevalence of HF, which is projected to increase by almost 50% from 2012 to 2030 [3].

An important aspect in the management of heart failure is to provide clinicians and patients with CHF necessary knowledge and resources to make better decisions about their treatment tactics. Prognostic model - is one of these resources, which is the formal combination of several predictors on which we can calculate the risks specific outcome for individual patients [1].

Therefore, finding out independent predictors of adverse course of heart failure is an important task of internal medicine and cardiology.

The aim: To determine the independent predictors of adverse cardiovascular events in patients with CHF.

Materials and methods: The study was performed on the clinical basis of the Department of Propaedeutics of Internal Medicine, Radiation Diagnostics and Radiation Therapy ZSMU in the cardiology department of the City Hospital №6, Zaporizhzhya, in accordance with the standards of good clinical practice and principles of good clinical practice. The study protocol was approved by the Ethics Committee of Zaporizhzhia State Medical University.

After signing the informed consent, the study enrolled 88 patients (men - 52% (n=46); women - 48% (n=42)) with CHF of ischemic origin, stage II AB, II-IV FC according to NYHA, in which 58 - patients with reduced left ventricle ejection fraction (LV EF <40%,) and 30 - with preserved LV EF (> 55%). Patients with different phenotypes of CHF were comparable in age, sex, height, weight, body surface area. The diagnosis of CHF of ischemic origin was established in accordance with the Recommendations for the diagnosis and treatment of chronic heart failure (2017) of the Association of Cardiologists of Ukraine and the Ukrainian Association of Heart Failure [4]. Cumulative endpoints considered death, myocardial infarction and progressive angina pectoris, stroke and progressive heart failure.

Statistical processing of the material was performed using the software package Statistica 13.0 (StatSoft, USA), license number JPZ8041382130RCN10-J and MedCalc 10.2.0.0. The normality of the distribution of quantitative traits was analyzed using the Shapiro – Wilk test. The parameters that had a normal distribution are given as the arithmetic mean and standard deviation (M ± SD). For indicators that had a distribution that differed from normal, descriptive statistics are given as the median and lower and upper quartiles - Me (Q25; Q75).

Quantitative indicators in the groups were compared using the criteria of Student (for the normal distribution of traits), Mann-Whitney (for the distribution of traits other than normal).

Using regression analysis of proportional hazards of Cox, univariate and multivariate prognostic models were constructed. The ROC analysis was performed to find out the cut-off values of the parameters. The Kaplan – Meier multiple estimation method was used to estimate the survival function. Gehan's Wilcoxon Test, Cox-Mantel Test, Log-rank-test were used to compare cumulative endpoints in groups. The difference at p <0.05 was considered statistically significant. All tests were bilateral.

Results. During the follow-up period (median 396 days [53-1302]), 14 endpoints were registered, which accounted for 15.91% of events: deaths 7 cases (8%), strokes 2 cases (2.3%), myocardial infarction 1 case (1.15%), progressive angina 1 case (1.15%), progressive heart failure 3 cases (3.4%). Analysis of the frequency of endpoints depending on the phenotype of CHF didn’t reveal a significant difference between the study groups of 18.97% (11/58) vs. 10% (3/30); log-rank test (p= 0.378).

Since, there were no statistically difference in the number of cumulative endpoints between groups of patients with CHF with reduced and preserved LV EF found, in order to determine the predictors of adverse events in this cohort of patients, a single database was created, which combined all patients with CHF regardless of LV EF (n = 88).

According to the results of univariate regression analysis of analysis of proportional hazards of Cox, four covariates (E/A ratio (E/A), peak mitral valve pressure gradient (GE MK), plasma sodium concentration, pulmonary hypertension) were identified, which were associated with an increasing and one (Inspiratory inferior vena cava (IVC) collapse of more than 50%) with a decreasing the relative risk of adverse cardiovascular events in patients with CHF. From these five factors, pulmonary hypertension and inspiratory IVC collapse were categorical and the rest - quantitative. The following cut-off values were set for quantitative indicators using ROC analysis: E/A > 0.99 c.u. (area under the curve 0.709; 95% CI 0.602-0.801; p= 0.011); GE MK > 1.9 mm Hg (area under the curve 0.676; 95% CI 0.568-0.772; p= 0.0367); plasma sodium concentration <= 142.5 mmol/l (area under the curve 0.461; 95% CI 0.355-0.571; p= 0.6525).

According to univariate models of analysis of proportional hazards of Cox, the relative risk of adverse cardiovascular events in patients with CHF increased in 1.44 times (HR 1.44, 95% CI 1.0142 - 2.0323; p= 0.042) in case of excess of baseline the E/A 0.99 c.u.; in 1.71 (HR 1.71, 95% CI 1.1032 - 2.6642; p= 0.017) times in cases where the GE MK exceeds 1.9 mm Hg; in 1.22 times (HR 1.22, 95% CI 1.0210 - 1.4470; p= 0.029) at a plasma sodium concentration <= 142.5 mmol/l; and in 2.16 times (HR 2.16, 95% CI 1.0230 - 4.5799; p= 0.044) in the presence of pulmonary hypertension. At the same time, the presence of inspiratory IVC collapse more than 50% reduced the
relative risk of adverse cardiovascular events in patients with CHF by 59% (HR 0.41; 95% CI 0.1796 - 0.9497; p= 0.038).

Adverse cardiovascular events were not associated with individual anthropometric parameters of patients: age (p= 0.1905), height (p= 0.7635), weight (p= 0.6070), body surface area (p= 0.4637), sex (p= 0.5464). Also, there was no effect on the prognosis of the initial structural and geometric parameters of the heart: left atrium diameter (LAD) (p= 0.4854), LV end-diastolic volume (LV EDV) (p= 0.9683), LVDs (p= 0.9573), PW (p= 0.2307), IVS (p= 0.6972), LV mass index (LVMI) by Penn g/m² (p= 0.4076), LVMi by ASE g/m² (p= 0.3676), diameter of right ventricle (RV) (p= 0.7343); functional parameters of the heart: LV EF (p= 0.9691), dp/dt (p= 0.4110), index TEI left ventricle (TEI LV) (p= 0.3757), TEI RV (p= 0.2907), s' medial (p= 0.3313), E/e' lateral (p= 0.07936), E/e' medial (p= 0.1073), E'/e' medial (p= 0.1223), e' lateral (p= 0.4058), e' medial (p= 0.3901), pulmonary artery systolic pressure (PASP) (p= 0.1029), mean pulmonary artery pressure (p= 0.1371), right atrium pressure (RAP) (p= 0.8291); parameters of filtration and concentration function of the kidneys, plasma potassium concentration: CKD-EPI (p= 0.6374), MDRD (p= 0.8986), Cockcroft-Gold (p= 0.6801), plasma potassium concentration (p= 0.9386), KIM-1, pg/ml (p= 0.3248), NAG, ng/ml (p= 0.2532), NGAL, ng/ml (p= 0.7468).

In the vast majority of cases, there is a simultaneous effect of several factors. Therefore, it is important to build multifactor models to determine the independent factors and relative risks of probable adverse events.

The multivariate model (p= 0.0014) included five parameters: age, body weight, index TEI LV, GE MK, and maximum Vao. In the obtained multivariate model, only the GE MK demonstrated its predictor properties in the univariate model. The remaining indicators showed prognostic ability only in the multifactor model. According to the results of ROC analysis, the TEI LV index ≥ 0.52 (p= 0.935) increased the risk of adverse cardiovascular events in patients with CHF by 30.7 times (HR 30.69; 95% CI 1.3241 - 711.5572; p= 0.033), the age of patients over 66 years increased the risk of adverse cardiovascular events by 13% (HR 1.13; 95% CI 1.0230 - 1.2555; p= 0.0172), body weight patient at the enrollment in the study of more than 82 kg increased the risk of adverse cardiovascular events by 7% (HR 1.065; 95% CI 1.0043 – 1.1301; p= 0.036), the Vao over 98 cm/sec increased the risk of adverse cardiovascular events in patients with CHF, but only by 0.8% (HR 1.008; 95% CI 1.0009 - 1.0155; p= 0.0014).

The inclusion in the multivariate model parameters of tubulo-interstitial dysfunction (in parentheses indicates the reliability of the models after the inclusion of markers of tubulo-interstitial injury) didn’t affect its power (NGAL, p= 0.0160), (NAG, p= 0.0101), (KIM-1, p= 0.0152). The obtained multivariate model also was independent from the glomerular filtration rate (p= 0.0080) and sex (p= 0.0076).

Thus, a combination of factors such as age over 66 years, body weight over 82 kg, index TEI LV over 0.52 c.u., peak mitral valve pressure gradient over 1.9 mmHg., the maximum flow velocity in the aorta over 98 cm/sec was associated with an increase in the relative risk of adverse cardiovascular events in patients with CHF of ischemic origin, regardless of sex, glomerular filtration rate and tubular interstitial injury.

**Discussion:** According to the results of the univariate regression analysis of the analysis of proportional hazards of Cox, out of more than 100 studied parameters, only five factors were identified, which were associated with adverse cardiovascular events in patients with CHF. Among these factors, four covariates (E/A, GE MK, plasma sodium concentration, pulmonary hypertension) increased the relative risk of adverse events. That are dependent risk factors can be considered diastolic LV dysfunction, pulmonary hypertension and hyponatremia.

The results obtained in our research is fully consistent with the results of the study [5]. According to research Baldasseroni S. et al. (2011) mild to moderate hyponatremia was an independent cause of annual mortality. Although the relationship between sodium concentration and mortality was not linear, a 1 mmol/l decrease in lower than 142.9 mmol/l increased the mortality rate by 10% (HR 1.10; 95% CI 1.07-1.12; p <0.0001) [5].

In our research, hyponatremia ≤ 142.5 mmol/l was associated with an increase in the relative risk of the cumulative end-points by 22% (HR 1.22; p= 0.029).

In the study Su Y. et al. (2020) in a regression analysis of proportional hazards of Cox proved that hyponatremia was an independent predictor of three adverse effects (mortality from all causes: HR 1.54, 95% CI 1.07-2.91, p= 0.034; rehospitalization about HF: HR 1.28, 95% CI 1.16 - 2.47, p= 0.013, stroke: HR 1.78, 95% CI = 1.04-2.89, p= 0.016) . In China, in a cohort of CHF patients with preserved LV EF, hyponatremia on admission to the hospital was significantly associated with all-cause mortality, rehospitalization, and stroke within 24 months. [6]

However, in clinical practice there is no single action of risk factor, but a number of factors, a combination of which determines the prognosis. Many functional scales have been created and are used to unify the prediction of CHF. The choice of (Seattle Heart Failure Model), [1] and MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) [7] is determined by the volume and characteristics of the explorations, the availability of validation, experience.

The most validated scale for outpatients with CHF is SHFM, which was developed on a representative sample of 1125 outpatients with severe HF (III-IV class NYHA, EF ≤30%) without severe comorbidity. The SHFM scale includes age, sex, ischemic etiology, NYHA class, EF, systolic blood pressure (BP), diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), statins. The scale predicts the survival of patients with HF using available simple clinical features. The scale provides an accurate assessment of 1-, 2- and 3-year
The MAGGIC scale was created by an international team of researchers based on an analysis of the database, which includes a large number of registers and studies (39372 patients, 30 studies, 15851 deaths), and allows to estimate annual and three-year mortality of patients with CHF. The scale is the result of analysis of the phenotypes of CHF and LV dysfunction which are predictors of overall mortality in patients with CHF with both reduced and preserved LV EF. The scale includes 13 predictors: age, sex, body mass index, LV EF, NYHA functional class, plasma creatinine levels, diabetes, beta-blockers, ACE inhibitors or ARBs, blood pressure, smoking, chronic obstructive pulmonary disease (COPD). The disadvantages of the MAGGIC scale are the lack of external validation and natriuretic peptide [7].

It should be noted that these scales include such indicators as age, body mass index of the patient, ischemic etiology of CHF, LV systolic function. Similar indicators revealed independent predictor power in our prognostic model. We obtained a multivariate model of Cox's proportional risks (p=0.0014), which included five indicators: age, weight, index TEI LV, peak mitral valve pressure gradient (GE MK) and maximum flow velocity (Vao) in aorta.

A number of studies confirmed the viability of our prognostic model for the influence of the TEI index on the risk of adverse cardiovascular events in patients with CHF. In a research by Sasao H. et al. (2004) concluded that a TEI index greater than 0.70 correlated with the development of episodes of heart failure (BP 14,139 95% CI 1.269–157,553). Souza L.P. et al. (2011) found that LV EF ≤45% was associated with an increased chance of heart failure progression, but only among patients ≥ 60 years of age with a TEI index ≥ 0.57. Biering Sorensen T. et al. (2013) reported that TEI index values greater than (0.59 ± 0.16 vs. 0.52 ± 0.13, P <0.001) was associated with major adverse events, including congestive heart failure, myocardial infarction, and mortality[11].

At the same time, Rahman N. and co-authors (2009) showed that the TEI index value > 0.40 had better sensitivity (86% vs. 65%), specificity (82% vs. 50%) and accuracy (83% vs. 58%) compared with LV EF <40% to predict cardiac complications, including cardiogenic shock, revascularization, rehospitalization, congestive heart failure, and atrioventricular block [11].

The next parameter that has proven its prognostic properties in our multivariate model is the flow velocity in the aorta over 98 cm/sec. It was associated with a probable increase in the risk of adverse cardiovascular events in patients with CHF, but only by 0.8% (HR 1.008; 95% CI 1.009 - 1.0155; p= 0.0014). Although the effect is quite small (less than 1%), but a high
degree of probability suggests that the deterioration of the damping properties of blood vessels, which cause an increase in blood flow in the aorta, in patients with CHF of ischemic origin has a significant impact on the disease.

Our data were confirmed by a study by Strange G et al. (2019), which proved in the Australian population that with increased flow velocity in the aorta up to 1.5 m/s, the risk of adverse cardiovascular events increases by 2% (HR 1.02; 95% CI 1.01- 1.02; p <0.001). According to the multivariate model of Strange G et al., by supplementing the flow velocity in the aorta with factors such as male sex, age and LV EF, the authors obtained a probable increase in the risk of adverse cardiovascular events [12].

Thus, using a simple reproducible parameter (age, body weight index TEI LV, peak gradient pressure MK and the maximum flow velocity (Vao) in the aorta) can more accurately estimate the annual prognosis in patients with heart failure, regardless of sex, LV EF and renal function.

Conclusion:
1. Independent risk factors for adverse cardiovascular events (death, myocardial infarction and progressive angina, stroke, progressive heart failure) in patients with CHF should be considered: age and body weight, index TEI LV, peak gradient pressure MK and the maximum flow velocity (Vao) in the aorta, which allows to assess the annual prognosis in patients with CHF regardless of sex, LV EF and renal function.

2. Dependent risk factors for adverse cardiovascular events in patients with CHF are baseline sonographic parameters of E/A and mean pressure gradient MK, plasma sodium concentration, the presence of pulmonary hypertension. Inspiratory IVC collapse of more than 50% is associated with a reduction in the relative risk of adverse cardiovascular events in patients with CHF.

Conflicts of interest: authors have no conflict of interest to declare.

References:


