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LITERATURE REVIEWS
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Determinants of prognosis and management of patients with pulmonary hypertension due to left heart disease: a systematic review

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Patients with pulmonary hypertension (PH) associated with left heart disease usually have a complex comorbidity status and a postcapillary component of PH. The presence and identification of a combined post-/precapillary PH in a cohort of patients with left heart disease is reflected in the more pronounced structural and functional right ventricular changes due to higher pulmonary vascular resistance. Patients with combined post-/precapillary PH have reduced exercise tolerance and PH phenotype similar to pulmonary arterial hypertension. Detection of combined PH is critical as it may influence the prognosis and management of patients. This review presents modern prognosis markers for patients with PH due to left heart disease, which can be used in clinical practice. The results of randomized clinical trials and pilot studies on the expansion of treatment options in group 2 patients, including the use of PAH-specific agents, were analyzed. The prospects for the treatment of this cohort of patients are discussed.

Keywords: pulmonary hypertension due to left heart disease, combined post-/precapillary pulmonary hypertension, prognostic markers, treatment prospects.

Relationships and Activities: none.

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Key messages

- We presented modern prognosis markers for patients with pulmonary hypertension due to left heart disease, based on right ventricular structural and functional parameters, hemodynamic and functional characteristics, respiratory function data, blood biomarkers that can potentially be used in clinical practice.
- An analysis of the results of pilot and randomized studies on the evaluation of efficacy and safety of PAH-specific agents for patients with pulmonary hypertension due to left heart disease was demonstrated.

A common cause of increased pulmonary pressure is the development of post-capillary pulmonary hypertension (PH) against the background of left heart pathology, mainly acquired, which is >80% of all etiological factors for PH [1-3].

According to the national guidelines of the Eurasian Association of Cardiology, PH with left heart disease has following characteristics: mean pulmonary artery (PA) pressure ⩾25 mm Hg and PA wedge pressure (PAWP) ⩾15 mm Hg according to right heart catheterization (RHC) [1, 2]. At the same time, in the updated guidelines of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), released in August 2022, the threshold value of the mean PA pressure (MPAP), as one of the hemodynamic criteria for PH, was reduced from 25 mm Hg to >20 mm Hg [3].

It is not possible to accurately determine the prevalence of PH in the population. According to some data, the incidence of PH in the world is 1% of the population and among people over 65 years of age increases to 10% [4].

According to transthoracic echocardiography, 60% of patients with systolic and 83% of patients with diastolic left ventricular (LV) dysfunction have signs of PH with a level of estimated PA systolic pressure (ePASP) >35 mm Hg [5]. The prevalence of PH among patients with heart failure (HF) with reduced ejection fraction (HFrEF) varies within 40-75%, while among patients with HF with preserved EF (HFpEF) within 36-83% patients [6].

There are two hemodynamic variants of PH in the presence of left heart pathology, which are presented as isolated postcapillary PH (pulmonary vascular resistance (PVR) ⩽3 Wood units and diastolic pressure gradient (DPG) <7 mm Hg [1, 2], according to the updated ESC/ERS guidelines — PVR ⩽2 Woods units [3]) and mixed post-/precapillary PH (PVR >3 Woods units and DPG ⩾7 mm Hg [1, 2], according to the updated ESC/ERS guidelines — PVR >2 Wood units).

Identification of a mixed PH in DPG ⩾7 mm Hg observed in 22,6% of patients with HFpEF and in 18,8% of patients with HFpEF [7].

In mixed post-/precapillary PH, a chronic increase in left atrial pressure in patients with left heart pathology induces a more pronounced pulmonary system remodeling with an increase in PVR and subsequent development of right ventricular (RV) dysfunction, which is practically not typical for isolated postcapillary PH [8 , 9]. That is why patients with a combined post-/precapillary component of PH are characterized by a more pronounced exercise intolerance and PH phenotype similar to pulmonary arterial hypertension (PAH) [10, 11].

The presence and identification of a precapillary component in addition to postcapillary PH is critical, as it may affect the prognosis and principles of patient management [9, 12-14].

The aim of this review is to study the main markers of the prognosis of mortality, worsening of HF and rehospitalizations in patients with PH due to left heart diseases, as well as the role of specific therapy in the treatment of this cohort of patients.

Methodological approaches

The information retrieval algorithm was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) in the PubMed database (132 articles) and included the search for studies using search queries, keywords and logical operators. According to the search goal, abstracts, minutes of meetings, books, case reports and case series were not used. English has been set as the language limit. Two authors independently examined the titles and abstracts of publications for compliance with the inclusion criteria, while the disagreements were resolved through negotiations or with a third author. Primarily, studies were filtered by checking titles and/or abstracts, excluding reviews, duplicate publications, and case reports. The second stage was the selection of studies after reading the full text. The studies were included if they have the following parameters: 1) samples of adult patients with PH associated with left heart pathology (with post-capillary PH or mixed post-/pre-capillary PH) with a description of the clinical and paraclinical characteristics of patients, data on the prognosis and outcomes of the disease; 2) studies demonstrating the changes over time in patients with group 2 PH against the background of interventional or PAH-specific treatment.

The following key words in the PubMed database were used: ((pulmonary hypertension) and (left heart disease)) or (pulmonary hypertension associated with left heart disease) or (postcapillary pulmonary hypertension) or (combined precapillary and postcapillary pulmonary hypertension) or ((heart failure preserved/reduced ejection fraction) and (pulmonary hypertension)).

The last search was carried out on September 28, 2022.

Inclusion/exclusion criteria. The systematic review included only studies with a full description of clinical and paraclinical data, the changes and outcomes of the disease course. The review did not include studies on the effect of PAH-specific therapy alone in patients with acquired heart disease before/after surgery. Animal studies, reviews, case reports and case series were also excluded. The number of patients included in the studies and the established

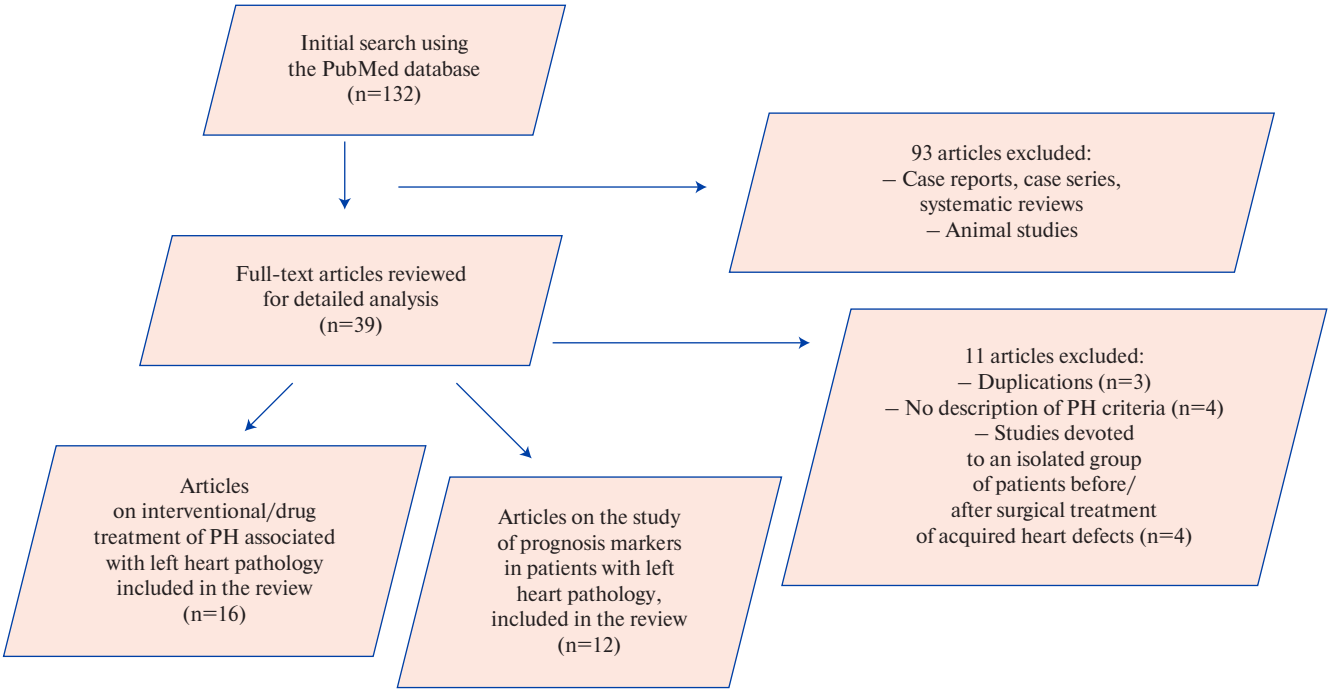

Figure 1. Algorithm for selecting publications for systematic review.
Abbreviation: PH — pulmonary hypertension.

diagnosis of PH by a non-invasive investigation (i.e., using echocardiography) were not the determining factors for selection.

In the primary selection using the above search queries, 132 publications (PubMed) were obtained (Figure 1).

For each study investigating the safety and efficacy of interventional/PAH-specific therapy for the treatment of PH patients with left heart disease, the following data were recorded: first author and/or study title, study population, number of patients included, age, sex, type of left heart pathology and LVEF value, characteristics of PH and the method of its determination, intervention method/drug and duration of therapy, endpoints, achievement of study endpoints. Any disagreements were resolved through discussion.

In total, after the removal of duplicate articles, reviews, and case reports, 31 studies remained on the interventional and/or drug treatment of patients with PH associated with left heart pathology. Two independent researchers reviewed the full-text versions of the remaining publications. After discussion and the involvement of a third expert, an analysis of 16 articles included in this systematic review was carried out. After selection, we also analyzed 12 original studies on prognostic markers in patients with left heart disease and PH (Figure 1).

Determinants of prognosis in patients with PH due to left heart disease

The main prognosis markers in patients with PH and left heart pathology are shown in Figure 2.

RV function as a predictor of prognosis (according to transthoracic echocardiography)

RV function is one of the main determinants of the status and prognosis of patients with PH.

Over a median (Me) of 2 years, the survival rate of patients with HFpEF and RV dysfunction was 56% compared with patients without RV dysfunction (93%) [15]. It demonstrated that RV dysfunction in HFpEF is more typical for male patients with concomitant atrial fibrillation, renal dysfunction and coronary pathology [15].

A number of works describe the contribution of RV systolic function to the prognosis of HFpEF patients [15, 16]. Results of a meta-analysis by Gorter TM, et al. demonstrated that a 5 mm decrease in RV systolic function as measured by transthoracic echocardiography (tricuspid annular plane systolic excursion (TAPSE)) was associated with a 38% increased risk of hospitalization for heart failure (95% confidence interval (CI), 1,21-1,58; p<0,0001) (n=919) and a 26% risk of death (95% CI, 1,16-1,38; p<0,0001) (n=1156) in patients with HFpEF. The TAPSE value, indicative of RV dysfunction, is <17 mm [16].

In a study by Melenovsky V, et al. the presence of RV dysfunction in the form of a decrease in the right ventricular fractional area change (RVFAC) <35% in patients with HFpEF was associated with a 2,2-fold increase in the risk of all-cause death after adjusting for ePASP according to transthoracic echocardiography (95% CI, 1,4-3,5; p=0,001). The lower limit of normal RVFAC is 35% [15].

Data from a meta-analysis by Gorter TM, et al. indicate an increased risk of hospitalization for HF by 9% (95% CI, 1,00-1,19; p=0,07) (n=869) and an increased risk of death by 16% with a decrease in RVFAC by 5% in patients with HFpEF (95% CI, 1,08-1,24; p<0,0001) (n=965) [16].

Such an indicator as the RV-PA coupling, estimated as the ratio of TAPSE to ePASP according to echocardiography, has been studied in a number of studies in patients with HF [17, 18]. This indicator is presented as a powerful predictor of survival in patients with heart failure. TAPSE/ePASP <0,35 mm/mm Hg was associated with a tenfold increase in the death risk in patients with HF (odds ratio (OR), 10,3 (95% CI, 5,4-19,8; p<0,05) [17]. After 4 years of follow-up, patients with HFpEF with a TAPSE/ePASP <0,35 mm/mm Hg had the survival rate of 62%, while at a level of 0,35 to 0,50 mm/mm Hg — 88,4%, and at a level >0,65 mm/mm Hg — 100% [18].

Parameters of cardiac magnetic resonance imaging as predictors of prognosis

Cardiac magnetic resonance imaging (MRI) makes it possible to assess structural changes in the heart, verifying the existing left heart pathology, both the cause of PH and the severity of structural and functional RV changes. Cardiac MRI may also be useful in verifying the phenotype of mixed post-/precapillary PH. Thus, according to cardiac MRI, end-systolic interventricular septal angle (the angle between the ventricles and the middle septal part) correlates with the level of DPG (r=0,74; p<0,001) and PVR (r=0,63; p<0,001). Interventricular septal angle according to cardiac MRI, equal to 160°, is a diagnostic threshold for identifying patients with mixed post-/precapillary PH (with a DPG level of 7 mm Hg and above) with a sensitivity of 67% and a specificity of 93%. According to univariate analysis using Cox proportional hazards regression, a systolic ventricular septal angle of 160° or more can predict all-cause mortality over 2 years (OR, 1,615 (95% CI, 1,253-2,082; p<0,001) [19].

Hemodynamic predictors according to the RHC

PAWP is the main hemodynamic indicator in patients with PH and left heart pathology, reflecting the involvement of venous pulmonary system and isolated postcapillary component of PH (PAWP ⩾15 mm Hg; PVR ⩽3 Wood units) or the addition of combined remodeling as venous, and the arterial pulmonary system with the formation of mixed post-/precapillary PH (PAWP ⩾15 mm Hg; PVR >3 Wood units).

A retrospective analysis of data from 2587 patients with PH and HFpEF at Me follow-up of patients for 1383 days showed that transpulmonary pressure gradient ⩾12 mm Hg, PVR ⩾3 Wood units and DPG ⩾7 mm Hg were predictors of mortality and readmissions for decompensated heart failure. Thus, the risk of death/rehospitalization due to decompensated HF increased by 1,41 times at the level of the transpulmonary pressure gradient ⩾12 mm Hg, (95% CI 1,27-1,56; p<0,001), 1,54 times with PVR ⩾3 Woods units (95% CI, 1,39-1,72; p<0,001) and 1,44 times at the level of DPG ⩾7 mm Hg (95% CI 1,25-1,66; p<0,001), respectively [7].

Right atrial pressure is a component that reflects the volume status of patients with HFpEF, the increase of which is directly related to accession and right ventricular HF.

Measurement of the RV cardiac index for PH patients with left heart pathology with an invasive study is also important for understanding the severity of RV dysfunction, which is a direct mirror of the functional status and prognosis of patients with PH.

Functional status parameters as prognosis determinants

The pathophysiological mechanisms of exercise intolerance in HF are multifactorial and include both impaired cardiac and pulmonary reserves and reduced perfusion and/or peripheral and respiratory skeletal muscle function.

The study demonstrated that a 6-min walk test (6MWT) distance <300 m is an independent predictor of cardiovascular death in patients with NYHA class II-III HFrEF; however, attention is focused on the importance of assessing 6MWT changes over time [20].

The generally accepted gold standard for determining the physical condition of patients with HF is cardiopulmonary exercise test (CPET), which noninvasively assesses the mechanisms that limit physical performance. For patients with both HFpEF and HFrEF during CPET, the value of peak oxygen uptake (VO_2peak) >20 ml/kg/min, ventilatory carbon dioxide equivalent (VE/VCO_2 slope) <30, end-tidal carbon dioxide tension ($PETCO_2$) at rest ⩾33 mm Hg and its increase by 3-8 mm Hg during CPET are associated with the best prognosis in HF patients over 4 years with ⩾90% freedom from adverse events. With a value of VO_2peak of 16-20 ml/kg/min, VE/VCO_2 slope of 30-35,9, $PETCO_2$ at rest ⩾33 mm Hg and its increase by 3-8 mm Hg during CPET, within 1-4 years, freedom from adverse events in patients with heart failure was

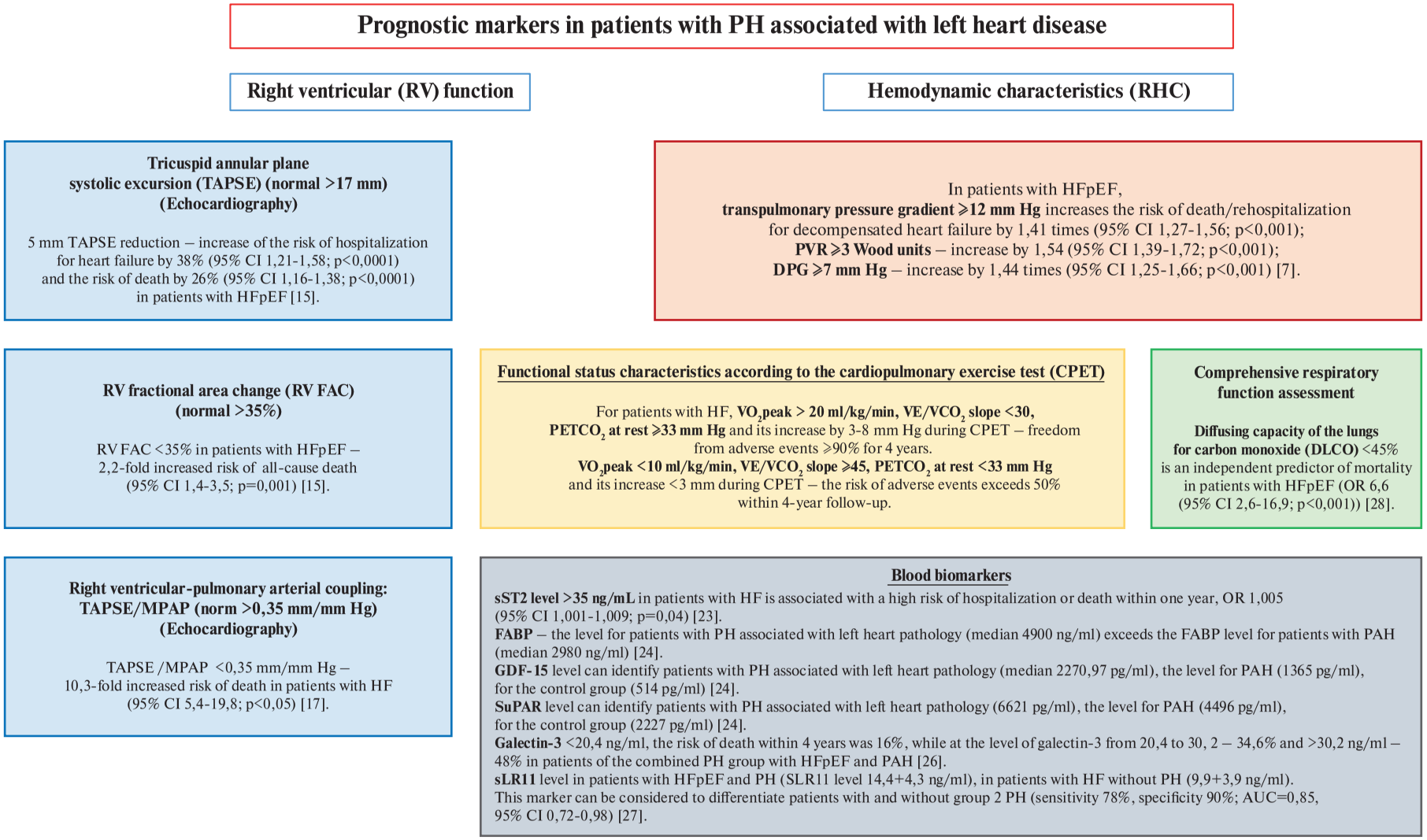

Figure 2. Prognostic markers in patients with PH associated with left heart disease.
Abbreviations: FABP — fatty acid binding protein, DPG — diastolic pressure gradient, CI — confidence interval, CPET — cardiopulmonary exercise testing, RHC — right heart catheterization, PAH — pulmonary arterial hypertension, PH — pulmonary hypertension, PVR — pulmonary vascular resistance, OR — odds ratio, RV — right ventricle, ePAP — estimated pulmonary artery pressure, HF — heart failure, HFpEF — heart failure with preserved ejection fraction, RV FAC RV — right ventricular fractional area change, GDF-15 — growth differentiation factor-15, sLR11 — soluble low density lipoprotein receptor-relative with 11 ligand-binding repeats, sST2 — soluble growth stimulation expressed gene 2, suPAR — soluble urokinase plasminogen activator receptor, $PETCO_2$ — end-expiratory carbon dioxide partial pressure, TAPSE — tricuspid annular plane systolic excursion, VE/VCO_2 slope — ventilatory carbon dioxide equivalent, VO_2peak — peak oxygen uptake.

⩾75%. VO_2peak of 10-15,9 ml/kg/min, VE/VCO_2 slope 36-44,9, $PETCO_2$ at rest ⩾33 mm Hg and its increase by 3-8 mm Hg during CPET in patients with HF is associated with freedom from adverse events ⩾50% during the period of 1-4 years of follow-up. Patients with HF and VO_2peak <10 ml/kg/min, VE/VCO_2 slope ⩾45, $PETCO_2$ at rest <33 mm Hg have a more unfavorable prognosis and its increase by less than 3 mm during CPET, while the risk of adverse events in these patients exceeds 50% during 1-4 years of follow-up [21].

Blood biomarkers as determinants of prognosis

Biomarkers of HF, cardiac remodeling and myocardial stress

Brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are universal markers for diagnosing and predicting the outcomes of a number of cardiovascular pathologies. It is known that an increase in NT-proBNP directly correlates with RV HF manifestations and the risk of death in patients with PH.

For example, for patients with PAH, there are three strata that divide these patients into low/medium/high risk of mortality during the year, taking into account a comprehensive assessment of criteria that also includes the BNP/NT-proBNP level. Levels of BNP <50 ng/L and/or NT-proBNP <300 ng/L correspond to a low risk of death within a year. BNP in the range of 50-300 ng/L and/or NT-proBNP in the range of 300-1400 ng/L, according to national guidelines, correspond to an intermediate risk of death [1]. The updated ESC guidelines changed the range of these markers for intermediate risk: BNP within 50-800 ng/l and/or NT-proBNP within 300-1100 ng/l [3]. BNP levels >300 ng/L and/or NT-proBNP >1400 ng/L, according to national guidelines [1], and BNP >800 ng/L and/or NT-proBNP >1100 ng/L, according to European guidelines for diagnosis and treatment of PH, corresponds to high risk.

At the same time, the level of these markers distinguishes between chronic (BNP ⩾35 pg/ml and NT-proBNP ⩾125 pg/ml) (adjusted for atrial fibrillation)) or acute HF (BNP ⩾100 pg/ml and NT-proBNP ⩾300 pg/ml) [22]. However, there is no established range of BNP and NT-proBNP levels as part of the risk stratification of disease progression and mortality specifically for patients with group 2 PH. Interpretation of NT-proBNP level in any cardiovascular disease should be carried out in conjunction with the clinical status, taking into account comorbidities.

In addition to the natriuretic peptide family, another promising biomarker in PH patients is soluble growth stimulation expressed gene 2 (sST2). sST2 is a biomarker that is expressed in mechanically deformed cardiac fibroblasts and cardiomyocytes and plays a role in remodeling and fibrosis in HF. An increase in sST2 and NT-proBNP in patients with PH is caused by dysfunction and an increase in RV filling pressure, more pronounced myocardial tension, followed by RV dilatation, which determines the severity and prognosis of patients with PH. An sST2 >35 ng/mL in patients with HF is associated with a higher risk of adverse events, defined as hospitalization or death within one year, compared with subjects with an sST2 level below this value [23].

Another promising marker for verification of PH type and its severity is the heart-type fatty acid-binding protein, which is expressed in the cytosol of cardiomyocytes, being a marker of cardiomyocyte damage. In PH patients, fatty acid-binding protein was studied by Mirna M, et al. Its higher level (as an indicator of early myocardial ischemia among all PH types) was found in patients with PH associated with left heart pathology (group 2) and in the group of PH (Me, 4900 ng/ml) associated with lung pathology (group 3), while in patients with PAH its level was 16 times lower (Me, 2980 ng/ml) [24].

Markers of inflammation

There is growing evidence that inflammatory processes play an important role in pulmonary vascular remodeling in patients with PH. However, the inflammatory component may also reflect a response caused by ischemia and increased sympathetic activity due to reduced cardiac output in patients with PH.

Below are relatively new and not widely known markers for patients with group 2 PH.

Growth differentiation factor-15 (GDF-15) is a member of the transforming growth factor beta superfamily. GDF-15 is exposed in various cell types in response to tissue injury, ischemia, or stress. GDF-15 is an inflammatory marker but is also involved in the regulation of cell repair and growth [25]. Detection of a higher GDF-15 level in patients with PH on the background of left heart pathology (group 2 PH) (Me, 2270,97 pg/ml for group 2 PH vs 1365 pg/ml for patients with PAH vs 514 pg/ml for the group control) may be due to pronounced myocardial remodeling and cardiomyocyte death, because the study also included patients with HFrEF against the background of ischemic cardiomyopathy as a cause of group 2 PH [24].

In a study by Mirna M, et al. patients with PH in group 2 also showed a more pronounced increase in the level of soluble urokinase plasminogen activator receptor (suPAR) (6621 pg/ml for group 2 LH vs 4496 pg/ml for patients with PAH vs 2227 pg/ml for the control group). It is a marker of inflammation and organ damage, which is also involved in the process of myocardial remodeling [24].

Another promising marker for PH patients is galectin-3, which is a beta-galactoside-binding lectin expressed in inflammatory cells (macrophages, neutrophils, eosinophils, and mast cells) and endothelial cells in response to tissue injury. Galectin-3 is considered to be a mediator of inflammation and fibrosis, and its activity leads to increased adverse cardiac remodeling. In a study by Mazurek JA, et al. the correlation of the level of this marker with the mortality of patients with PH of various origins was demonstrated. This study included patients (n=37) with PAH and group 2 PH on the background of HFpEF. Me levels of galectin-3 for patients with PAH were 22,33 ng/ml and 28,94 ng/ml for patients with PH group 2 (p=0,07). The results of this study demonstrated the relationship of galectin-3 level with 4-year mortality of patients in the combined group of PAH and group 2 PH, which was 16% with a level of galectin-3 at <20,4 ng/ml, 34,6% from 20,4 to 30,2 and 48% at >30,2 ng/mL [26]. However, this marker has not been studied in isolation for patients with PH against the background of left heart pathology.

Soluble low-density lipoprotein receptor with 11 ligand-binding repeats (sLR11), a marker of smooth muscle cell proliferation and endothelial dysfunction, has demonstrated its role in the severity of patients with group 2 PH. The single-center pilot study included 34 patients with HFpEF and mitral regurgitation. Of these, in 10 patients with PH, the level of sLR11 was significantly higher (14,4±4,3 ng/ml) than in patients without PH (9,9±3,9 ng/ml), p=0,002. Adverse events after 5 years in patients with elevated levels of this marker were represented by 5 hospitalizations (25%) and 2 deaths (10%), while no adverse events were observed in patients with normal levels of sLR11. The authors suggested that this marker can be considered to differentiate patients with and without PH (sensitivity 78%, specificity 90%; AUC=0,85, 95% CI 0,72-0,98), to determine the severity of mitral regurgitation and PH [27]. The main limitations of this marker may be the presence of concomitant coronary artery disease (CAD)/unstable angina, because sLR11 is also used to predict CAD course.

Comprehensive assessment of respiratory function

A marker of prognosis for patients with PH and left heart pathology is also the indicator of the diffusing capacity of the lungs for carbon monoxide (DLCO), which demonstrates the ability of the lungs to transport gas through the alveolar-capillary barrier. Changes in pulmonary capillaries and postcapillary venules can cause functional changes in the lungs, in particular DLCO disturbance. The presence of concomitant chronic obstructive pulmonary disease, a combination of emphysema and pulmonary fibrosis may also be additional reasons for a decrease in DLCO in patients with left heart pathology; however, mechanical disruption of breathing and volume may be absent, as well as the dependence of impaired diffusing capacity of the lungs on PH severity [28].

The study by Hooper MM, et al. included 52 patients with HFpEF with a decrease in DLCO <45% of the predicted value and 56 patients with HFpEF with a DLCO level ⩾45% of the predicted value. The presence of a pronounced decrease in DLCO <45% most often characterized male patients (OR 2,71 (95% CI 1,05-6,88; p=0,039)) with history of smoking (OR 5,01 (95% CI 1,91-13,1; p<0,001)). A DLCO value <45% is an independent predictor of mortality for patients with HFpEF (OR 6,6 (95% CI 2,6-16,9; p<0,001)). The 3-year survival rate of patients with HFpEF and DLCO <45% is 3 times lower than that of patients with DLCO ⩾45% (36,5% vs 87,8%, respectively; p<0,001) [28]. Therefore, pulmonary function test and the assessment of the diffusing capacity of the lungs in group 2 PH helps to diagnose lung pathology and assess its severity, which is necessary to understand its contribution to the severity and origin of PH.

Treatment prospects

In accordance with the current 2022 European guidelines for the diagnosis and treatment of PH, as well as the 2020 guidelines of the Ministry of Health of Russia, the treatment of patients with PH and left heart pathology is aimed at eliminating structural and functional left heart disorders as the main cause of group 2 PH (valve pathology, LV diastolic/systolic dysfunction, LV outflow obstruction, etc.), as well as drug therapy approved for patients with HFrEF and HFpEF [1, 3, 22, 29].

Over the past decade, the search for new ways to treat patients with HF and PH has continued, with the testing of both new drugs and interventional interventions (Table 1).

Interventional treatment

The CHAMPION study analyzing the long-term safety and clinical efficacy of a Wireless Pulmonary Artery Pressure Monitoring System — CardioMEMS Heart Sensor) of implantation of pulmonary artery pressure monitoring system during RHC in patients with HF and LVEF ⩾40% (n=550) during the observation period of 17,6 months stability of clinical status was achieved with a 50% reduction in hospital admissions for heart failure. It is the daily assessment of the hemodynamics of the pulmonary circulation with dynamic control of pressure in the pulmonary artery and the selection of the necessary doses of diuretic therapy, the use of vasodilators in some cases, which made it possible to stabilize the volume status of patients [30].

Table 1

Results of studies on the effect and safety of interventional and drug treatment (PAH-specific therapy) for patients with PH associated with left heart disease

Study	Study population	Studied device/drug	Endpoints	Result
Interventional methods				
CHAMPION [30]	550 patients with HF: 119 of them with LVEF ⩾40% (mean value 50,6%) (of which 66 patients with LV EF ⩾50%); 430 patients with LVEF <40% (mean 23,3%). Patients with LVEF ⩾40% in the treatment group (n=62) had MPAP of 26 mm Hg, PAWP of 14 mm Hg; in the control group, MPAP of 24 mm Hg, PAWP of 13,5 mm Hg (n=57) according to RHC. For patients with LVEF <40% Me, MPAP was 29 mm Hg, PAWP — 19 mm Hg according to RHC.	Implantation of a PAP monitoring system during RHC was performed in all 550 patients: the "treatment group" with daily monitoring of pressure curves included following patients: n=62 with heart failure with LVEF ⩾40% (of which n=35 with LVEF ⩾50%) and 208 patients with LVEF <40%. The "control group" with no control of pressure curves included following patients: n=57 LV EF ⩾40% (of which n=31 with LVEF ⩾50%) and 222 patients with LV EF <40%.	The primary endpoint was hospitalization for HF.	After 6 months, patients with HF with LVEF ⩾40% of the "treatment group" (n=62) were 46% less likely to be hospitalized for HF compared with patients in the control group (n=57), OR 0,54 (95% CI 0,38-0,70; p<0,0001) (11 hospitalizations in the treatment group/19 hospitalizations in the control group). After 6 months, patients with LVEF <40% in the "treatment group" (n=208) were 24% less likely to be hospitalized for heart failure (n=222), OR 0,76 (95% CI 0,61-0,91; p=0,008) (73 hospitalizations in the treatment group/101 hospitalizations in the control group). After 17,6 months, in HF patients with LVEF ⩾40%, hospitalization rates in the treatment group were 50% lower than in the control group, OR 0,50 (95% CI 0,35-0,70; p<0,0001) (29 hospitalizations in the treatment group/59 in the control group). After 17,6 months in patients with heart failure with an LVEF <40%, the rate of hospitalizations in the treatment group was 26% less than in the control group, OR 0,74 (95% CI 0,63-0,89; p=0,001) (153 hospitalizations in treatment group/220 in the control group).
REDUCE-LAP-HF [31]	Patients (n=64) with NYHA class II-IV HF with LVEF >40% with a mean age of 69 years with a mean PAWP of 17 mm Hg and MPAP of 25 mm Hg according to the RHC and without severe right ventricular HF events (central venous pressure <14 mm Hg and TAPSE >1,4 cm).	Through venous access, implantation of a device that creates an interatrial shunt (n=64).	Primary endpoints: periprocedural safety of the intervention and safety in the form of an assessment of cerebrovascular and cardiovascular events 6 and 12 months after the implantation. Secondary endpoints: hospitalization for heart failure within 1 year, as well as changes in echocardiography and hemodynamic parameters, functional status, quality of life.	Within 6 months no patient had perioperative or serious adverse cardiac or cerebrovascular events, including death, stroke, myocardial infarction, pulmonary or systemic embolism, or the need for cardiac surgery for device-related complications. 17 hospitalizations due to HF during the year. One-year survival was 95% (within one year 3 deaths: pneumonia and kidney failure; stroke; cause unknown). Dynamics of the functional status: 6MWTD a year later increased from 331±90 m to 363±93 m; (p=0,001). Significant improvement in quality of life. Improvement in TAPSE from 2,0±0,4 cm to 2,2±0,4 cm after one year (p<0,05). An increase in RV CO from 5,2 to 6,7 l/min a year later (p<0,05) and a decrease in the PAWP/MRAP gradient from 10 to 7 mm Hg.

Table 1. Continuation

Study	Study population	Studied device/drug	Endpoints	Result
PADN-5 [35]	Patients with mixed post-/precapillary PH (n=98) without PAH-specific therapy, 61,2% — patients with HFrEF and 38,8% — patients with HFpEF with MPAP ⩾25 mm Hg, PAWP >15 mm Hg and PVR >3,0 Wood units.	LA denervation group (n=48) and sildenafil + PA denervation simulation group (n=50).	The primary endpoint was an increase in 6MWTD within 6-month follow-up. The secondary endpoint was change in PVR. The primary safety endpoint was pulmonary embolism.	After 6 months, the mean increase in 6MWTD was 83 m in the denervation group and 15 m in the 66 m sildenafil group (95% CI: 38,2-98,8 m; p<0,001). Against the background of denervation, the PVR level was significantly lower (4,2±1,5 Wood units) than in the sildenafil group (6,1±2,9 Wood units; p=0,001). The denervation group experienced less clinical deterioration (16,7%) compared to the sildenafil group (40%), p=0,014. At the end of the study, there were 7 all-cause deaths and 2 cases of pulmonary embolism.
Pharmacotherapy				
FIRST [36]	Patients with HFrEF (n=471) with median age of 65 years with LVEF <25% and NYAH class III-IV HF, PAWP ⩾15 mm Hg, cardiac index ⩽2,2 l/min, median systemic vascular resistance of 20,76 Wood units, median MPAP in the epoprostenol group of 38 mm Hg/in the placebo group of 40 mm Hg according to RHC.	Epoprostenol (n=237) or standard medical therapy for HF (n=234).	Primary: death; a serious event such as the need for mechanical ventilation, inotropic drugs, or mechanical circulatory support. Secondary: 6MWTD, quality of life, dynamics of clinical status after 3 months.	There was a significant increase in cardiac index, a decrease in PAWP and PVR in the group of epoprostenol therapy at a dose of Me 4,0 ng/kg/min. Early termination of the study due to increased mortality from acute HF in the epoprostenol group.
Lewis GD, et al. [37]	HFrEF (n=34) with a median age of 54 years for the sildenafil group and 62 years for the placebo group. LVEF <40% and NYHA class II-IV HF, MPAP >25 mm Hg with an average PVR >4 Wood units according to the RHC data.	Sildenafil 25-75 mg 3 times/day (n=17) or placebo (n=17) for 12 weeks.	Primary: VO_2peak. Secondary: DT6MH, PVR.	In the sildenafil treatment group, the level of VO_2peak, 6MWTD increased, and PVR decreased.
Guazzi M, et al. [38]	HFrEF (n=32) with mean age for sildenafil group 66 years/placebo group 68 years, with LV EF <45%, MPAP of 25-35 mm Hg according to RHC, median PVR of 4,5 Wood units.	Sildenafil 50 mg 3 times/day (n=16) or placebo (n=16) for 1 year.	Cardiopulmonary test parameters after 6 and 12 months. Pulmonary circulation hemodynamics after 6 and 12 months.	In the treatment group, a significant increase in VO_2peak and a decrease in ventilation carbon dioxide equivalent. Significant decrease in PAWP and PVR, increase in CO in the treatment group.
SilHF [39]	HFrEF (n=69) with median age of 68 years, median LVEF of 29%, ePASP ⩾40 mm Hg according to echocardiography (Me 45 mm Hg). Without assessing the parameters of right heart catheterization.	Sildenafil up to 40 mg 3 times/day (n=45) or placebo (n=24) or 24 weeks.	Primary endpoints: improvement in the patient's clinical status and dynamics of 6MWTD after 24 weeks.	Against the background of sildenafil, no significant dynamics of the clinical picture, quality of life and 6MWTD were revealed.

Table 1. Continuation

Study	Study population	Studied device/drug	Endpoints	Result
Guazzi M, et al. [40]	HFpEF with mixed post-/precapillary PH (n=44) with a mean age of 72,5 years and LVEF >50%, NYHA class II-IV HAF with MPAP >40 mm Hg, mean PAWP 22 mm Hg, mean PVR 3,88 Wood units for the sildenafil group and 3,27 Wood units for the placebo group according to transthoracic echocardiography.	Sildenafil 50 mg 3 times/day (n=22) or placebo (n=22) for 52 weeks.	Primary: hemodynamics of the pulmonary circulation, RV function (TAPSE). Secondary: quality of life.	Significant reduction in MRAP, MPAP, PAWP, and PVR; improvement of RV function, CO and quality of life.
Hoendermis ES, et al. [41]	HFpEF with isolated postcapillary PH (n=52), age 74±10 years. LV EF ⩾45%, MPAP >25 mm Hg, PAWP >15 mm Hg, median PVR 4 Wood units (PVR >3 Wood units in 45% of the included patients) according to RHC.	Sildenafil 20 mg 3 times/day (n=26) or placebo (n=26) for 12 weeks.	Dynamics of MPAP, PAWP, SV, VO_2peak.	Significant dynamics was not revealed.
RELAX trial [42]	HFpEF (n=216) with median age of 69 years, median LVEF of 60% and ePASP of 41 mm Hg according to echocardiography (without assessing RHC parameters).	Sildenafil (n=113) 20 mg 3 times/day within 12 weeks with an increase in dose to 60 mg 3 times/day within 12 weeks or placebo (n=103).	Primary endpoint: Change in VO_2peak within 24-week treatment. Secondary endpoints: 6MWTD and comprehensive assessment of clinical status (time to death/to cardiovascular or cardiorenal hospitalization/change in quality of life of participants without cardiovascular or cardiorenal hospitalization after 24 weeks).	There were no significant changes in clinical status and quality of life. Deterioration of renal function in the sildenafil group.
Kramer T, et al. [43]	Chronic HFpEF and mixed post-/precapillary PH (n=40). The mean age of patients was 73 years. Median MPAP of 46,2 mm Hg, median PAWP of 21,2 mm Hg, median DPG of 5,5+7,2 mm Hg, median PVR of 6,2±3,0 Wood units.	Sildenafil 20 mg 3 times/day >1 year	Changes of 6MWTD, NT-proBNP level, RV function according to two-dimensional echocardiography, hospitalization rate due to heart failure.	An increase in 6MWTD, a decrease in the level of NT-proBNP, an improvement in RV function in the form of an increase in TAPSE; reduction in the frequency of hospitalizations for heart failure.

Table 1. Continuation

Study	Study population	Studied device/drug	Endpoints	Result
Belyavskiy E, et al. [44]	HFpEF, patients with mixed post-/precapillary PH prevailed (n=50) with ePASP of 40 mm Hg according to echocardiography (without assessing RHC parameters).	Sildenafil (n=30) 25 mg 3 times/day within 3 months with a further increase in dose to 50 mg 3 times/day within 3 months or placebo (n=20).	Changes of the functional status and RV function.	Increased 6MWTD, decreased PASP, RV and LV filling pressure, LV hypertrophy; improvement in RV function, LV diastolic function, and NYHA class of HF.
LEPHT [45]	HFrEF (n=201) Me age 58,1 years. LV EF <40% with NYHA class II-IV and MPAP ⩾25 mm Hg according to RHC. Mean PVR for the placebo group, riociguat 0,5 mg, 1 mg and 2 mg 3 times/day were 3,81 Wood units, 3,43 Wood units, 2,78, and 3,64 Wood units, respectively.	Riociguat in 4 parallel groups at a dose of 0,5, 1 or 2 mg 3 times/day (n=132) or placebo (n=69) for 16 weeks.	Primary endpoints: MPAP changes. Secondary endpoints: hemodynamic parameters.	The primary endpoint was not reached: there were no significant differences in MPAP changes in the riociguat 2,0 mg group compared to the placebo group. However, in the riociguat 2 mg treatment group, there was a significant increase in cardiac index and a decrease in PVR compared with placebo.
BADDHY [48]	HFpEF (n=20); mean age of 68,1 for the bosentan group/67,4 years for the placebo group. LVEF ⩾50%, MPAP >25 mm Hg, PAWP >15 mm Hg according to the RHC; RV dysfunction according to echocardiography. The value of PVR is not specified.	Bosentan 125 mg daily during the first month with an increase in dose after up to 250 mg per day (n=9) or placebo (n=11) for 12 weeks.	Changes of 6MWTD, MPAP and RA pressure according to echocardiography.	Acute HF in 3 patients in the bosentan group, in the placebo group in 1 patient. In the placebo group, there was a slight trend towards an increase in 6MWTD.
ENABLE [49]	HFrEF (n=1613); mean age for bosentan group of 67,5 years/mean age for placebo group of 66,9 years; LVEF <35%, NYHA class III-IV with median 6MWTD <375 m. Evaluation of RHC was not performed. Two patients were excluded from the analysis due to unwillingness to further participate in the study (total, 1611 patients).	Bosentan (n=804) 125 mg daily during the first month with an increase in dose after up to 250 mg per day or placebo (n=807) for median of 1,5 years.	Primary endpoint: change in clinical status at 9 months; all-cause death or hospitalization for HF.	Bosentan did not affect the clinical status of patients after 9 months. In the bosentan group, fluid retention was observed during the first 2-4 weeks of treatment. 321 patients in the placebo group and 312 patients in the bosentan group died or were hospitalized for HF.
MELODY-1 [50]	HFpEF and HFrEF (n=63); LVEF ⩾35% with NYHA class II-IV with mixed post-/precapillary PH (MPAP ⩾25 mm Hg, PAWP >15 mm Hg, DPG ⩾7 mm Hg, PVR >3 Wood units according to RHC).	Macitentan 10 mg (n=31) or placebo (n=32) for 12 weeks.	Primary points: safety and tolerability (fluid retention, deterioration in NYHA class). Hemodynamic changes, NT-proBNP, 6MWTD.	7 patients in the macitentan group had fluid retention/4 in the placebo group. There were no significant differences between groups in any of the study endpoints.

Abbreviations: DPG — diastolic pressure gradient, CI — confidence interval, PAWP — pulmonary artery wedge pressure, PAP — pulmonary artery pressure, 6MWTD — 6-minute walk test distance, RHC — right heart catheterization, PA — pulmonary artery, PAH — pulmonary arterial hypertension, PH — pulmonary hypertension, LV — left ventricle, PVR — pulmonary vascular resistance, OR — odds ratio, RV — right ventricle, ePASP — estimated pulmonary artery systolic pressure, CO — cardiac output, HF — heart failure, HFrEF — heart failure with reduced ejection fraction, HFpEF — heart failure with preserved ejection fraction, MPAP — mean pulmonary artery pressure, MRAP — mean right atrial pressure, EF — ejection fraction, Me — median, NT-proBNP — N-terminal pro-brain natriuretic peptide, NYHA — New York Heart Association, TAPSE — tricuspid annular plane systolic excursio, VO_2peak — peak oxygen uptake.

The REDUCE-LAP-HF multicenter non-randomized study revealed that implantation of an interatrial shunt device in patients with HF and LVEF >40% (n=64) with a MPAP of 25 mm Hg was safe and resulted in a decrease in LV end-diastolic volume index, PAWP, improvement of RV systolic function, as a result of the functional status and quality of life of patients [31].

PA denervation in PH is still not fully understood, and is used in a few federal centers of the country, mainly as part of research areas for patients with chronic thromboembolic PH in addition to surgical treatment [32], as well as in cardiac surgery patients with acquired heart disease and PH [33]. Russian authors analyzed 8 studies on PA denervation in PH of various origins, including group 2 PH in world practice. It was demonstrated that the method of PA denervation contributed to a decrease in MPAP, the changes of which was -8,59 (95% CI -10,96 — -6,23) mm Hg, and an increase in the 6MWT distance on 60,0 (95% CI 35,74-84,27) meters in patients with PH [34].

The effect of PA denervation was studied in a separate group of patients with NYHA class II-IV HF and mixed post-/precapillary PH (n=98) in the PADN-5 study. In this study, the effectiveness of two approaches was compared: in the first group, PA denervation was performed, while in the second, sildenafil therapy 60 mg per day and PA denervation simulation in patients with mixed post-/precapillary PH on the background of standard medical therapy for HF. After 6 months in the PA denervation group, a significant and more pronounced changes in 6MWT distance was observed, as well as a pronounced decrease in PVR. In this group, clinical deterioration over 6 months was observed 2,4 times less frequently compared with patients in the group of sildenafil and simulated denervation [35].

Large multicenter studies devoted to the study of both short-term and prolonged effects of PA denervation in patients of various etiology and severity of PH should be conducted.

Pharmacotherapy

The potential of specific therapy in patients with PAH, such as endothelin receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators or prostacyclins, is a controversial and not fully resolved issue. However, the studies conducted indicate a safety risk, as well as a low expected efficacy from PAH-specific therapy for patients with PH with left heart pathology. So far, there is no multicenter study that would prove the safety and benefit of treatment with PAH-specific drugs in this group of patients.

Back in 1997, the first attempt to use pulmonary vasodilators for patients with PH on the background of left heart pathology was the The Flolan International Randomized Survival Trial. This study evaluated the effect of epoprostenol infusion therapy in patients with congestive NYHA class III-IV HFrEF FC. The effect of epoprostenol on improving cardiac index and reducing PAWP has been demonstrated, but the study was terminated early due to an increase in deaths with the use of epoprostenol in patients with group 2 PH [36].

The effect of sildenafil therapy in patients with both HFpEF and HFrEF is highly controversial due to the diverse results obtained in studies [37-44] (Table 1).

Lewis GD, et al. in patients with PH and HFrEF with LVEF <40% 12 weeks after sildenafil therapy at a dose of 25 to 75 mg 3 times/day demonstrated a significant improvement in functional status and a decrease in PVR in 17 patients with HF [37].

The prolonged effect of sildenafil at a dose of 50 mg 3 times was studied by Guazzi M, et al. in 16 patients with PH and HF with LVEF <45%. A significant improvement in peak oxygen uptake as measured by CPET from 9,6 to 13,2 ml/min/kg and a reduction in ventilatory carbon dioxide equivalent from 41,1 to 31,5 were demonstrated in addition to an improvement in hemodynamic characteristics, presented in the dynamics of MPAP from 34,8 to 24 mm Hg and PVR level from 360 to 255 dyn/s/cm^{-5} after a 1-year sildenafil therapt compared with the placebo group (p<0,01) [38].

For the first time, a multicenter, randomized, placebo-controlled study of SilHF demonstrated no effect of sildenafil at a dose of 40 mg 3 times/day on clinical and functional status, quality of life in patients with HFrEF (n=45) compared with placebo (n=24) after 24-week therapy [39].

In turn, in 22 patients with HFpEF and mixed post-/precapillary PH therapy with generic sildenafil at a dose of 50 mg 3 times a day within 6 months demonstrated a significant effect on the functional status, improvement of RV systolic function, reduction of PAWP and right atrial pressure [40].

Hoendermis ES, et al. revealed no effect of sildenafil therapy on the functional status and hemodynamic parameters of pulmonary circulation in patients with HFpEF. Against the background of 12-week sildenafil therapy at a dose of 20 mg 3 times/day (n=26) compared with placebo (n=26) in patients with HFpEF (LV EF ⩾45%), there was no significant change in MPAP level, cardiac output, PAWP and VO_2peak [41]. The randomized RELAX trial in a larger cohort of patients with HFpEF with a Me LVEF of 60% (with no invasively verified PH) also showed no effect of sildenafil therapy at a dose of up to 60 mg 3 times (n=113) compared with placebo (n=103) on clinical and functional status and quality of life of patients after 12-week treat-

ment [42]. However, these studies did not separate patients with mixed post-/precapillary PH.

Later studies, mainly including patients with mixed post-/precapillary PH and HFpEF, showed a significant improvement in the functional status and RV function both against the background of short-term use (3 months) and a year after sildenafil therapy in different dose regimens [43, 44] (Table 1).

The LEPHT randomized trial examined the effect of therapy with the soluble guanylate cyclase stimulator riociguat in 201 patients with PH and LV systolic dysfunction. The study whoed that 16-week riociguat therapy in different dose regimens had no effect on hemodynamic parameters of the pulmonary circulation [45].

A representative of the group of soluble guanylate cyclase stimulators, vericiguat, has also been studied in patients with HFrEF and HFpEF. However, the criterion for PH was not a key criterion for including patients with HF in studies. Thus, in the SOCRATES-REDUCED study [46], the safety and effect of vericiguat therapy in different dose regimens (from 1,25 to 10 mg per day) were evaluated in patients with HF with LVEF <45% (n=351) within 12 weeks. During therapy with vericiguat at a maximum dose of 10 mg, syncope was observed in 4,4% of patients, and significant hypotension occurred in 15,4%. Significant NT-proBNP level changes over 12-week vericiguat therapy was not detected. However, the authors attribute this to the presence of included patients with atrial fibrillation, which additionally contributes to the absence of myocardial strain biomarker improvement. At the same time, taking higher doses of riociguat was reflected in a more pronounced decrease in NT-proBNP level.

In 2021, the European guidelines for HF, vericiguat therapy should be considered to reduce the risk of CV death and hospitalizations due to HF in patients with NYHA class II-IV HFrEF [22]. In the SOCRATES-PRESERVED study [47], 12-week therapy with vericiguat 10 mg in patients with HFpEF had a good tolerability profile, with no significant effect on blood pressure changes, but had no effect on either NT-proBNP changes or LA volume reduction. At the same time, in patients with HFpEF, vericiguat therapy significantly improved the quality of life of patients, which encouraged researchers to further study longer-term vericiguat therapy in this cohort of patients with HF [47].

Turning to another class of drugs of specific therapy that has proven effect on patients with PAH, the results of studies on the safety and efficacy of endothelin receptor antagonist therapy in patients with PH and left heart pathology should be highlighted.

The effect of therapy with bosentan at a dose of 250 mg per day for 12 weeks was studied in the BADDHY single-center study in 9 patients with HFpEF. Therapy with bosentan did not improve the functional status of patients and ePASP level according to echocardiography, causing acute HF in 3 patients in the treatment group [48].

Long-term bosentan therapy at a dose of 250 mg per day in the ENABLE study after 9-month treatment did not improve the outcome of patients with NYHA class III-IV HFrEF (LVEF <35%), while causing severe decompensated HF despite the intensification of diuretic therapy. This study was terminated early [49].

The MELODY-1 prospective multicenter study (Macitentan in Subjects With Combined Pre- and Postcapillary Pulmonary Hypertension (CpcPH) Due to Left Ventricular Dysfunction) was the only study that had inclusion criteria specifically for patients with mixed post-/precapillary PH in the presence of left heart disease [50]. During the first month of follow-up in this study, macitentan 10 mg therapy resulted in a 10,1% increased risk of fluid retention in patients with mixed post-/precapillary PH compared with placebo. Fluid retention, most likely, can be explained by insufficient medical leveling and compensation of the postcapillary component, as well as its prevalence over the precapillary component of PH at the time of therapy initiation. After 3 months there were no significant changes in PVR, mean right atrial pressure, and PAWP compared to placebo when taking macitentan.

Until now, we are waiting for the results of multicenter SERENADE (Macitentan is an Effective and Safe Treatment for Patients With Heart Failure With Preserved Ejection Fraction and Pulmonary Vascular Disease) and SOPRANO (Macitentan in Patients With Pulmonary Hypertension After Left Ventricular Assist Device Implantation) studies on the efficacy and tolerability of macitentan 10 mg therapy in patients with mixed post-/precapillary PH on the background of HF with preserved LVEF[1] and in patients with mixed post-/precapillary PH after implantation of left ventricular assist device[2].

[1] ClinicalTrials.gov. A multi-center, double-blind, placebo-controlled phase 2b study to evaluate the efficacy and safety of macitentan in subjects with heart failure with preserved ejection fraction and pulmonary vascular disease (SERENADE). https://clinicaltrials.gov/ct2/show/NCT03153111. Date last updated: July, 2018.

[2] ClinicalTrials.gov. A prospective, multicenter, double blind, randomized, placebo-controlled, parallel group study to assess the efficacy and safety of macitentan in patients with pulmonary hypertension after left ventricular assist device implantation (SOPRANO). https://clinicaltrials.gov/ct2/show/NCT02554903. Date last verified: February, 2018.

Considering no clear evidence of a positive effect of PAH-specific therapy for patients with group 2 PH according to the pilot studies and single multicenter studies, while demonstrating a high risk of pulmonary edema, in the current national clinical guidelines, the appointment of pathogenetic therapy for PAH in patients with PH due to left heart pathology is contraindicated [1]. However, the ESC/ERS guidelines for the diagnosis and treatment of PH recommend individual approach to the choice of therapy for patients with left heart pathology with mixed post-/precapillary PH with a pronounced precapillary component in the form of an increase in PVR ⩾5 Wood units. In this case, the drug of choice for such patients is a phosphodiesterase type 5 inhibitor — tadalafil or sildenafil (registered in the Russian Federation). For these patients, the decision to prescribe sildenafil should be made only with optimal drug therapy for heart failure within the expert PH center, where a comprehensive examination with RHC will be carried out [3].

Thus, the potential of pulmonary vasodilators from the group of PAH-specific therapy for patients with left heart pathology remains controversial. However, in some cases, attempts are being made to prescribe off-label PAH-specific therapy to this cohort of patients. There are following key factors justifying the prescription of pulmonary vasodilators: a combined post-/precapillary PH verified by an invasive diagnostic method with a eliminated/compensated post-capillary component of PH in a patient receiving optimal drug therapy for left heart disease; a personalized approach to prescribing and choosing a treatment, making a decision on prescribing a specific drug only by a multidisciplinary team of highly qualified specialists.

Conclusion

The complex phenotype of patients with PH on the background of left heart pathology implies the need for an integrated approach to assessing the prognosis of this cohort of patients, taking into account their comorbidity status, using both invasive and non-invasive parameters. This will make it possible to timely treat left heart pathology and/or achieve medical compensation. Attempts to use PAH-specific drugs for group 2 PH patients have been unsuccessful in most studies. However, studies are ongoing to study the safety and efficacy of modern drugs in mixed post-/precapillary PH.

Relationships and Activities: none.

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