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Modern Therapeutic Strategies for Chronic Heart Failure: A Review of Pharmaco- and Non-Drug Approaches, New Drugs and Personalized Therapy

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ABSTRACT

Chronic heart failure remains one of the leading causes of hospitalization and mortality worldwide, despite significant progress in drug therapy in recent decades. The leading international recommendations have formed the concept of the "four cornerstones" of pharmacotherapy of heart failure with reduced ejection fraction — inhibitors of the renin-angiotensin-aldosterone system or angiotensin receptor antagonists/non-lysine inhibitors, beta-blockers, antagonists of mineralocorticoid receptors and sodium-glucose cotransporter type 2 inhibitors, supplemented by diuretics and several auxiliary agents. At the same time, the role of non-drug interventions is increasing, including lifestyle modification, cardiac rehabilitation, implantation of resynchronization therapy devices, cardioverter defibrillators, the use of mechanical circulatory support devices and telemedicine monitoring. An active search for new pharmacological targets continues: guanylate cyclase stimulants (vericiguat), selective myosin activators (omecamtiv mecarbil), and new classes of nephron-saving and metabolic drugs are being studied. The purpose of the article is a comprehensive analysis of modern therapeutic strategies for chronic heart failure from the perspective of a combination of pharmacological and non-medicinal approaches, a discussion of the place of new drugs in the structure of therapy and substantiation of the principles of personalized patient management. An overview of current international recommendations and key clinical trials is presented, and data on the impact of various strategies on the prognosis and quality of life of patients are systematized. Special attention is paid to the problem of phenotypic heterogeneity of heart failure (HFrEF, HFmrEF, HFpEF), comorbidity, as well as the need to adapt therapeutic solutions to the individual risk profile, concomitant diseases and patient preferences.

Keywords: *chronic heart failure, pharmacotherapy of heart failure, non-drug treatment, SGLT2 inhibitors, angiotensin receptor antagonists/neprilysin inhibitors, resynchronizing therapy, vericiguat, omecamtiv*

mecarbil, personalized medicine.

INTRODUCTION

Chronic heart failure (CHF) is a clinical and pathophysiological syndrome characterized by the inability of the heart to provide adequate cardiac output in accordance with the metabolic needs of tissues or the need to maintain normal cardiac output due to increased filling pressure. CHF is accompanied by a high frequency of hospitalizations, disability and mortality, as well as a significant economic burden on the healthcare system [3].

In recent decades, ideas about the pathogenesis and treatment of CHF have evolved. From the neurohumoral model, which assumes the key role of activation of the renin-angiotensin-aldosterone and sympathoadrenal systems, cardiology has moved to a multicomponent understanding of the disease, including the role of inflammation, oxidative stress, endothelial dysfunction, disorders of energy and ion homeostasis of the myocardium, cardiorenal and cardiometabolic interactions [11].

These ideas are reflected in a change in therapeutic strategies: from monotherapy with angiotensin converting enzyme inhibitors to the concept of combined pathogenetically oriented therapy, including several classes of proven drugs [12].Of particular importance is the differentiation of CHF by left ventricular ejection fraction: heart failure with a reduced ejection fraction (HFrEF), with a moderately reduced fraction (HFmrEF) and with a preserved fraction (HFpEF) are distinguished. Specific recommendations for drug and non-drug therapy have been developed for each of these categories, reflecting differences in pathophysiological mechanisms and evidence base.

At the same time, there is a growing interest in non-drug approaches. Their role is no longer considered as an auxiliary one, but as an equal component of a comprehensive patient management program involving dietary recommendations, physical activity, psychosocial support, device implantation, and the use of telemedicine [13]. Finally, the rapid development of clinical pharmacology has led to the emergence of new classes of drugs — type 2 sodium-glucose cotransporter inhibitors, soluble guanylate cyclase system stimulants, and myosin activators, which required a revision of existing treatment standards and the formulation of a personalized therapy concept. Thus, the current stage of cardiology development is characterized by the simultaneous coexistence of classical and innovative therapeutic strategies for CHF, which need to be systematized and critically evaluated taking into account the phenotypic heterogeneity of the disease and the principles of personalized medicine.

Materials and methods of research.

This work is an analytical review of modern scientific literature and clinical recommendations based on a systematic search of publications in international databases and official documents of professional cardiological societies in recent years. When interpreting the data obtained, the methods of narrative and comparative analytical generalization based on the principles of evidence-based medicine and critical evaluation of the design of key randomized trials and meta-analyses were used, which made it possible to comprehensively characterize modern pharmacological and non-medicinal approaches to the treatment of chronic heart failure.

Results and discussions.

Modern pharmacotherapy of chronic heart failure

The pharmacotherapy of CHF has undergone a qualitative transformation in recent years. The leading recommendations are based on the need to prescribe four "fundamental" classes of drugs to patients with HFrEF as early as possible and as completely as possible: angiotensin converting enzyme inhibitors or angiotensin receptor blockers, preferably in the form of a combination of sacubitril/valsartan (ARNI), beta-blockers, mineralocorticoid receptor antagonists and SGLT2 inhibitors. The transition from sequential stepwise escalation of therapy to parallel and accelerated implementation of several classes has significantly reduced mortality and hospitalization rates in HFrEF patients [2].

ACE inhibitors and angiotensin receptor blockers remain the basic drugs in the absence of the possibility of prescribing ARNI. Their effect is realized through a decrease in post- and preload, a decrease in myocardial remodeling, and an improvement in clinical symptoms and prognosis. Angiotensin receptor antagonists/non-lysine inhibitor (sacubitril/valsartan) enhance the natriuretic and vasodilating effects of endogenous peptides and have demonstrated an additional reduction in the risk of cardiovascular death and hospitalization compared with ACE inhibitors in patients with HFrEF [7].

Beta-blockers are a key element of treatment by suppressing chronic sympathoadrenal activation, improving diastolic function, and reducing the frequency of ventricular arrhythmias. Mineralocorticoid receptor antagonists (spironolactone, eplerenone) suppress the effects of aldosterone, reduce myocardial fibrosis and remodeling, and improve prognosis, especially in patients with severe symptoms and reduced ejection fraction.

SGLT2 inhibitors (dapagliflozin, empagliflozin, etc.) occupy a special place in modern CHF therapy. Initially developed as hypoglycemic agents, these drugs have demonstrated a marked reduction in the risk of hospitalization for heart failure and cardiovascular mortality in both patients with HFrEF and patients with HFmrEF and HFpEF, regardless of the presence of diabetes mellitus. The mechanisms of their action are multifactorial — osmotic diuretic effect, reduction of afterload, improvement of myocardial energy metabolism, cardiorenal protection. These data led to the inclusion of SGLT2 inhibitors among the first-line drugs in almost all CHF phenotypes [3].

In addition to the basic classes, diuretics (mainly loop diuretics) are widely used to control symptoms of congestion and reduce edema, iron preparations (intravenous forms in patients with iron deficiency), as well as means to control heart rate and rhythm in concomitant atrial fibrillation [5]. To systematize information about modern pharmacological strategies, it is advisable to present them in the form of a summary table 1.

Table 1 – The main classes of drugs in modern pharmacotherapy of chronic heart failure

Drug class	Examples of active substances	Main mechanism of action and key effect	CHF phenotypes with the greatest evidence base	Application features in personalized therapy
ACE / ARB inhibitors	enalapril, ramipril, losartan, valsartan	Blockade of the RAAS, reduction of post- and preload, slowing down the remodeling	Mainly HFrEF	Accounting for blood pressure, kidney function, potassium, concomitant diseases
ARNI (angiotensin receptor antagonist/non-lysine inhibitor)	cubitril/valsartan	Combined inhibition of RAAS and neprilysin, enhanced action of natriuretic peptides	HFrEF, limited data at HFmrEF/HFpEF	Requires switching from ace inhibitors with a "washout period", caution in case of hypotension

				and impaired renal function
Beta-blockers	bisoprolol, metoprolol succinate, carvedilol	Beta-receptor blockade, decreased heart rate, decreased sympathetic activation	HFrEF	Gradual titration, accounting for bradycardia, conduction disturbances, COPD
Antagonists of mineralocorticoid receptors	spironolactone, eplerenone	Blockade of aldosterone effects, antifibrotic effect	HFrEF, part of the HFmrEF/HFpEF patients	Monitoring of potassium and kidney function, caution in case of hyperkalemia
SGLT2 inhibitors	dapagliflozin, empagliflozin	Osmotic diuresis, cardiorenal protection, metabolic effects	HFrEF, HFmrEF, HFpEF	The possibility of use with and without diabetes, taking into account kidney function and the risk of urinary tract infections
Diuretics	furosemide, torasemide	Reducing the volume of circulating blood, relieving symptoms of stagnation	All phenotypes in the presence of stagnant manifestations	Individual dose selection according to symptoms, prevention of dehydration and electrolyte disorders
Iron preparations (IV)	iron carboxymaltosate, etc.	Correction of iron deficiency, improvement of exercise tolerance	Patients with CHF and confirmed iron deficiency	Therapy based on laboratory monitoring of ferritin and transferrin saturation
New drugs (vericiguat, omecamtiv mecarvil, etc.)	vericiguat, omecamtiv mecarbil	sGC stimulation, myosin activation, etc., aimed at improving contractility and hemodynamics	Predominantly HFrEF with a high risk of readmission	Use in carefully selected patients as an adjunct to standard therapy

In recent years, special attention has been paid to the optimal sequence and pace of initiation of these classes, including taking into account age, concomitant pathology (chronic kidney disease, diabetes mellitus, obesity), the CHF phenotype, and socio-economic factors affecting adherence to therapy.

Non-drug approaches in the treatment of chronic heart failure

Non-drug interventions are an integral part of the comprehensive management of patients with CHF and include a wide range of measures aimed at modifying risk factors, improving functional status, preventing decompensation, and improving quality of life. Their effectiveness has been confirmed by numerous studies that have shown a reduction in symptoms, improved exercise tolerance, a decrease in the frequency of hospitalizations and, in some cases, a decrease in mortality [4].

The key areas of non—drug therapy are — dietary interventions with moderate salt and fluid restriction and a focus on nutrition models close to the DASH diet or the Mediterranean diet; — metered exercise and cardio rehabilitation programs; — quitting smoking and limiting alcohol consumption; — psychoeducation, training in self-control of symptoms and body weight; - the use of modern forms of telemedicine

monitoring; — surgical and interventional interventions, including implantation of resynchronization therapy devices, cardioverter defibrillators, mechanical circulatory support devices, and heart transplantation in selected patients [6].

Dietary recommendations are evolving towards the rejection of excessively strict salt and liquid restrictions in favor of a moderate, individually tailored approach. It is believed that an excessively strict diet can lead to a deterioration in the quality of life and a decrease in adherence, while moderate salt restriction combined with a generally healthy diet helps reduce the risk of decompensation without pronounced negative consequences. Cardio rehabilitation includes structured physical training programs under medical supervision aimed at increasing peak oxygen demand, improving endothelial function, reducing symptoms, and increasing exercise tolerance. Despite convincing evidence of benefits, cardio-rehabilitation is still not widely available and is not used in all patients with CHF.

Instrumental non-drug interventions include the implantation of cardio-resynchronizing devices in patients with severe intraventricular block and reduced ejection fraction, cardioverter defibrillators in patients at high risk of life-threatening arrhythmias, the use of left ventricular assistive devices in patients with end-stage CHF, as well as heart transplantation in carefully selected cases. These approaches can significantly improve the prognosis in severe patients, but require strict selection according to indications, a high level of organizational resources and interdisciplinary interaction [8].

To visually present the range of non-drug interventions and their contribution to the management of CHF, we present the corresponding table 2.

Table 2 – The main non-drug interventions in chronic heart failure

The direction of intervention	Specific measures	Expected clinical effects	Features of selection and implementation
Dietary recommendations	Moderate salt and liquid restriction, DASH-type nutrition model, increased proportion of vegetables, fruits, and whole grains	Reducing the risk of decompensation, improving symptom control, and weight loss in obesity	Individualization based on kidney function, concomitant diabetes, cultural and socio-economic characteristics
Physical activity and cardio rehabilitation	Structured training programs, moderate-intensity aerobic and strength exercises	Increased exercise tolerance, reduced symptoms, improved quality of life, potential reduction in mortality	The need for preliminary risk stratification, health monitoring, and motivational support
Behavioral and psychoeducational interventions	Self-control training, keeping a diary of symptoms and body weight, forming a commitment to therapy	Early detection of decompensations, reduction of the number of emergency hospitalizations, improvement of the effectiveness of complex treatment	Adaptation of materials to the level of education and cognitive abilities of the patient, involvement of family members
Telemedicine monitoring	Remote monitoring of symptoms, body weight, blood	Timely detection of deterioration, the possibility of early correction of therapy	It requires technical equipment and the patient's willingness to use digital technologies.

	pressure, and heart rate		
Devices and surgical procedures	CRT, ICD, left ventricular auxiliary devices, heart transplantation	Reducing the risk of sudden death, improving the pumping function of the heart, increasing survival	Application in carefully selected patients, high cost and resource capacity, the need for an interdisciplinary approach

Despite a significant decrease in mortality and the frequency of hospitalizations on the background of standard therapy, a significant proportion of patients with CHF still have a high residual risk, which led to the search for new pharmacological targets. Among the most studied drugs in recent years are the soluble guanylate cyclase stimulator vericiguat and the selective myosin activator omecamtiv mecarbil, as well as a number of other molecules at various stages of clinical development.

Vericiguat belongs to the class of soluble guanylate cyclase stimulants that enhance the effect of endogenous nitric oxide and promote vasodilation, reduce afterload, and improve hemodynamics. According to the results of the VICTORIA study and subsequent analyses, the addition of vericiguat to standard therapy in patients with HFrEF and recent decompensation resulted in a moderate reduction in the risk of a combined endpoint (cardiovascular death or hospitalization for CHF), which allowed the drug to be considered as an option for high-risk patients with continued access to other therapies.

Omecamtiv mecarbil is a selective cardiac myosin activator that improves myocardial systolic function by increasing the duration of the ejection phase without significantly increasing the myocardial oxygen demand. Large clinical studies have demonstrated a decrease in the relative risk of CHF hospitalization when taking omecamtiv mecarbil in HFrEF patients, however, the effect on overall mortality was less pronounced, which led to a cautious approach to its widespread implementation in clinical practice.

A number of studies have been devoted to the study of the combined effect of new drugs and standard classes of therapy, including SGLT2 and ARNI inhibitors. At the same time, the cumulative data indicate that the base classes (SGLT2 and ARNI inhibitors) have the greatest effect, while additional drugs (vericiguat, omecamtiv mecarbil) show a more modest improvement in outcomes and should be used in strictly selected patients with a very high risk. In addition, active research continues on drugs that affect various parts of the cardiorenal continuum and metabolism, such as new—generation nonsteroidal antagonists of mineralocorticoid receptors, drugs that affect the signaling pathways of natriuretic peptides, as well as antidiabetic drugs with proven cardioprotective effects.

Personalized therapy and phenotypic stratification of patients

The concept of personalized medicine in relation to CHF involves the adaptation of standard therapeutic strategies to the individual characteristics of the patient, including the phenotype of heart failure, age, gender, presence of comorbid conditions, functional class, biomarker profile, genetic and socio-economic factors. The HFrEF phenotype is characterized by the most developed evidence base for pharmacotherapy. For this group of patients, the earliest and most complete implementation of four fundamental classes of drugs with the possible addition of new drugs in high-risk patients is indicated. With HFmrEF and HFpEF, the situation is more complicated. Recent updates to the recommendations emphasize that SGLT2 inhibitors are the only class of drugs that have demonstrated a sustained reduction in the risk of CHF hospitalization in these phenotypes, while other classes (ARNI, MPA) may be effective in subgroups of patients with

certain characteristics, for example, if there are signs of remodeling or a slight decrease in ejection fraction [2]. Comorbidity plays a key role in shaping a personalized strategy. In patients with CHF and diabetes mellitus, preference is given to drugs with proven cardiorenal protective effects (SGLT2 inhibitors, some GLP-1 receptor agonists), in patients with chronic kidney disease, careful dose selection and monitoring of drugs affecting the RAAS and mineral metabolism is important, in patients with obesity and metabolic syndrome, the emphasis is on lifestyle modification life expectancy and weight loss.

Taking into account the multifactorial nature of the personalized approach, it is advisable to present the main phenotypes of CHF patients and the corresponding treatment accents in the form of Table 3.

Table 3 – Personalized management strategies for patients with chronic heart failure

Clinical phenotype of the patient	Key characteristics	Priority pharmacological strategies	Most important non-drug and organizational accents
HFrEF without pronounced comorbidity	Reduced LVEF, relatively young patients, low comorbidity	Early initiation of the complete GDMT complex (ARNI/ACE inhibitor/ARB, beta-blocker, MPA, SGLT2), if necessary, the addition of diuretics	Cardiorehabilitation, self-control training, lifestyle optimization, telemedicine monitoring according to indications
HFrEF with frequent decompensations and high risk	Repeated hospitalizations, high functional grade, possible decrease in blood pressure	Maximizing the doses of basic therapy, considering vericiguat, omecamtiv mecarbil and other innovative drugs in selected patients	Intensive telemedicine monitoring, early referral for evaluation of device indications, transplant/IVF consultation
HFmrEF/HFpEF in the presence of obesity and metabolic syndrome	Preserved or moderately reduced LVEF, obesity, insulin resistance	SGLT2 inhibitors, selection of RAAS blockers and MRA in subgroups, control of blood pressure and heart rate	Active lifestyle modification, weight loss programs, dietary support, increased physical activity
CHF with concomitant chronic kidney disease	Decreased GFR, impaired water and electrolyte balance	Careful use of RAAS blockers and MPas with frequent monitoring of laboratory parameters, if possible, the use of SGLT2	Personalized dietary recommendations, coordination with a nephrologist, prevention of nephrotoxic effects
CHF in patients of the older age group and with severe polymorbidity	Advanced age, multiple concomitant diseases, polypharmacotherapy	Individualization of therapy goals, possibly lower target doses, emphasis on safety and tolerability of treatment	Assessment of cognitive status, involvement of family and social services, if necessary, elements of palliative care

Thus, personalized therapy does not contradict, but complements standardized treatment, allowing it to be adapted to the realities of a particular patient. It requires active interdisciplinary interaction between a cardiologist, therapist, nephrologist, endocrinologist, rehabilitologist, psychologist and other specialists, as well as consideration of the patient's preferences and values.

Conclusion.

Modern therapeutic strategies for chronic heart failure are a multicomponent system in which the early and maximally complete appointment of basic pharmacological classes occupies a central place, which formed the concept of therapeutic "cornerstones" for HFrEF and a significant part of patients with HFmrEF/HFpEF.

The leading role in this complex is played by RAAS and ARNI inhibitors, beta-blockers, mineralocorticoid receptor antagonists and SGLT2 inhibitors, the use of which in various combinations can significantly improve survival and reduce the risk of hospitalization. Non—drug approaches — dietary interventions, cardiac rehabilitation, psychoeducation and self-monitoring programs, telemedicine monitoring, surgical and instrumental methods - are an equal component of a comprehensive patient management program. Their integration into daily practice can significantly reduce the symptomatic burden, increase exercise tolerance, reduce the frequency of decompensation, and improve the quality of life of patients. New pharmacological agents, such as vericiguat and omecamtiv mecarbil, expand the arsenal of therapy for high-risk patients, but currently their use is mainly complementary to standard therapy and requires careful selection of indications, which is reflected in modern recommendations and reviews. The evolution of ideas about CHF as a heterogeneous syndrome with different phenotypes and a complex spectrum of comorbid conditions has naturally led to the formation of the concept of personalized therapy. A promising area of further research is the integration of clinical, laboratory, instrumental, genetic, and digital data into unified risk stratification models that automatically select optimal combinations of pharmacological and non-medicinal interventions for a particular patient. Taken together, the analysis of modern pharmacological and non-medicinal approaches, new drugs, and principles of personalized therapy for chronic heart failure allows us to consider the future management of this syndrome as a transition from universal schemes to dynamically adaptable, data-based, multicomponent strategies focused simultaneously on improving clinical outcomes, quality of life, and rational use of health system resources.

References

1. Boytsov S.A. Chronic heart failure: the evolution of etiology, prevalence and mortality over the past 20 years //Therapeutic archive. – 2022. – Vol. 94. – No. 1. – pp. 5-8.
2. Galyavich A. S. et al. Chronic heart failure. Clinical guidelines for 2024 //Russian Journal of Cardiology. – 2024. – Vol. 29. – No. 11. – p. 6162.
3. Glezer M. G. Chronic heart failure: focus on differences between men and women //Cardiology. – 2024. – Vol. 64. – No. 11. – pp. 117-131.
4. Demidova T.Yu., Ushanova F.O., Panteleeva S.V. Review of international clinical guidelines for the management of arterial hypertension in patients with diabetes mellitus //FOCUS. Endocrinology. – 2024. – Vol. 5. – No. 1. – pp. 42-51.
5. Ismoilova Yu.A. Modern approaches to drug therapy of CHF of ischemic genesis //SHOKH LIBRARY. – 2026. – VOL. 1. – No. 1. pp. 45-51
6. Kalyuzhin V.V. Promising areas of treatment for chronic heart failure: improvement of old or development of new ones? //Bulletin of Siberian medicine. – 2022. – Vol. 21. – No. 3. – pp. 181-197.
7. Kodirova S. S. Modern approaches to the treatment of chronic heart failure (literature review) //Biology and integrative medicine. – 2022. – №. 2 (55). – Pp. 45-71.
8. Larina V. N., Skiba I. K., Skiba A. S. A brief overview of the updates of the clinical guidelines on chronic heart failure of the European Society of Cardiology in 2021 //Russian Journal of Cardiology. – 2022. – Vol. 27. – No. 2. – pp. 97-105.
9. Melekhov A.V. Cardiology news //Atmosphere. Cardiology news. – 2025. – No. 1. – pp. 18-21.
10. Semenkin A. A. and others. Hypertensive heart: from left ventricular hypertrophy to chronic heart failure //Arterial hypertension. – 2023. – Vol. 29. – No. 2. – pp. 138-149.
1. Mascolo A. Current and future therapeutic perspective in chronic heart failure //Pharmacological research. – 2022. – T. 175. – C. 106035.
2. Metra M. Worsening of chronic heart failure: definition, epidemiology, management and prevention. A clinical consensus statement by the Heart Failure Association of the European Society of Cardiology //European Journal of Heart Failure. – 2023. – T. 25. – №. 6. – C. 776-791.

3. Shumba A. T. Wearable technologies and AI at the far edge for chronic heart failure prevention and management: a systematic review and prospects //Sensors. – 2023. – Т. 23. – №. 15. – С. 6896.