

COMPLEX THERAPY OF CHRONIC HEART FAILURE: CLINICAL AND PHARMACOLOGICAL ASPECTS

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Abstract: *Background:* Chronic heart failure is one of the key causes of reduced life expectancy and quality of life, as well as a leading factor in repeated hospitalizations in therapeutic and cardiological practice. In recent years, medicine has developed a comprehensive treatment program focused on early parallel initiation of key medical interventions, targeted escalation in high-risk patients, correction of associated iron metabolism disorders, and the rational use of devices such as cardiac resynchronization therapy and implantable systems for preventing sudden cardiac death. This article presents a consistent clinical and pharmacological analysis of modern complex therapy, provides an in-depth discussion of the mechanisms of action and the expected effects of various components on vital outcomes, evaluates the real clinical effectiveness over a two-year horizon using approximate absolute benefits, and provides practical approaches to the selection and sequence of prescriptions, taking into account the safety, tolerability, and phenotypic characteristics of the patient. The proposed integrative scheme allows the primary care physician and the cardiologist to build a continuous trajectory of disease management from early stabilization to long-term control of symptoms and prevention of repeated decompensations.

Keywords: Chronic heart failure, left ventricular ejection fraction, clinical and pharmacological analysis, combination therapy, cardiac resynchronization, implantable sudden death prevention, iron deficiency, hospitalization, mortality, quality of life.

INTRODUCTION

Chronic heart failure is a clinical syndrome that occurs in structural or functional damage to the myocardium and manifests itself in the inability of the heart to provide adequate cardiac output in accordance with the metabolic needs of the tissues.

The pathogenesis involves a complex interaction between central and peripheral hemodynamics, systemic neurohumoral activation, and metabolic dysfunction, leading to progressive myocardial remodeling and multi-organ consequences. At the level of systemic reactions, stable cascades are formed, in which the renin-angiotensin-aldosterone system, the sympathetic nervous system, natriuretic peptides, endothelial dysfunction, imbalance of nitric oxide and cyclic guanosine monophosphate, and disorders of sodium and glucose transport in the renal tubules play a key role. As a result, pumping function deteriorates, fluid retention increases, tolerance to physical activity decreases, and chronic low-intensity inflammation and myocardial energy inefficiency develop.

Historically, treatment was based on the sequential, step-by-step administration of individual classes of medications with a long period of dose titration. Despite the proven benefits of each step, this strategy led to a prolonged phase of suboptimal therapy, during which patients remained vulnerable to repeated episodes of decompensation. The modern treatment paradigm radically shifts the focus towards the simultaneous early initiation of key directions, which allows for the suppression of key pathogenetic axes in the first weeks after diagnosis or after discharge from the hospital, achieving rapid clinical stabilization, reducing congestion, and creating a foundation for sustainable impact on survival and hospitalization rates.

Individualization of therapy depending on the left ventricular ejection fraction is of particular importance. In patients with reduced ejection fraction, the priority is to aggressively influence neurohumoral mechanisms, remodeling, and sodium and water retention, which is achieved by a combination of drugs that simultaneously block angiotensin receptors and enhance the action of natriuretic peptides, inhibit sympathetic activity,

suppress mineralocorticoid-dependent fibrosis, and improve renal-cardiac sodium and glucose metabolism. In patients with preserved ejection fraction, pressure overload, myocardial rigidity, and age-related and metabolic comorbidities predominate, which necessitates a shift in focus towards reducing congestion, improving renal-cardiac interaction, controlling blood pressure and body weight, and preventing hospitalizations [1].

An integral part of the modern strategy is taking into account the period of increased vulnerability in the first months after decompensation, when the risk of a repeated adverse event is highest. It is during this period that it is advisable to add agents that improve vascular-myocardial signaling through the soluble guanylate cyclase and cyclic guanosine monophosphate pathway, which leads to a reduction in the residual risk in the context of already initiated basic therapy. For small but clinically severe phenotypes with extremely low ejection fraction and limitations on blood pressure, direct activation of cardiomyocyte myosin is relevant, allowing for an increase in stroke volume without a significant increase in myocardial oxygen demand and without a pronounced effect on systemic hemodynamics/

Special attention should be paid to iron deficiency, which is found in a significant proportion of patients with chronic heart failure and is associated with rapid fatigue, shortness of breath at low loads, frequent hospitalizations, and a decrease in the quality of life. The use of intravenous iron preparations has an advantage over oral forms, as it allows for the rapid restoration of functional reserves and the achievement of a clinically significant improvement in load tolerance and symptoms [8].

Finally, in patients with electrical desynchrony according to electrocardiography, cardiac resynchronization therapy restores interventricular coordination of contractions, reduces mitral regurgitation, improves stroke volume, and reduces the frequency of hospitalizations. Implantable devices for the prevention of sudden cardiac death are considered in patients with persistently low ejection fraction and an appropriate electrical substrate after optimization of drug therapy [3].

Thus, the modern concept of managing chronic heart failure is an integrated system that combines early

The results of the analysis confirm that the early parallel launch of four key areas of drug therapy in patients with reduced ejection fraction provides the maximum contribution to reducing mortality and the frequency of hospitalizations. The combination that simultaneously blocks angiotensin receptors and enhances the effect of natriuretic peptides outperforms monotherapy with traditional angiotensin-converting enzyme inhibition in terms of its impact on outcomes. Drugs that inhibit the transport of sodium and glucose in

parallel start of drug therapy, subsequent targeted escalation in high-risk groups, correction of iron deficiency, rehabilitation measures, and the use of devices, all of which are based on strict indications. The goal is not only to prolong life, but also to improve its quality, reduce the need for hospitalization, and maintain the patient's autonomy in daily activities.

MATERIALS AND METHODS

The article provides an analytical review of large randomized studies and practical treatment protocols that reflect the current state of the evidence base for key drug areas and devices.

A unified approach to interpreting the results was used for the clinical and pharmacological evaluation: the relative effects described in the primary publications were converted into approximate absolute benefits in a two-year horizon, taking into account the typical baseline risks associated with outpatient populations. For patients with reduced ejection fraction, the baseline risk of a combined outcome of cardiovascular death and hospitalization for heart failure was approximately one-third over a two-year period, which is consistent with observed rates in real-world clinical practice. For patients with preserved or mildly reduced ejection fraction, the baseline risk was approximately one-fifth over a two-year follow-up period. Based on this, the expected absolute reduction in risk and the approximate number of patients who need to be treated to prevent one combined event were calculated.

To ensure the clinical applicability of the results, safety and tolerability issues were further analyzed: the effect on blood pressure, heart rate, potassium and creatinine levels, glomerular filtration dynamics, the risk of urinary tract infection and dehydration, as well as possible drug interactions. For devices, electrical and morphological selection criteria, expected life expectancy, combination with drug therapy, and the impact on quality of life were considered. The statistical analysis was descriptive in nature, as the study aimed to provide a clinical decision-making illustration that allows a doctor to quickly compare relative and absolute effects with the actual baseline risks of a particular patient.

RESULTS AND DISCUSSIONS

the renal tubules have a rapid and sustained effect in both patients with reduced ejection fraction and those with preserved ejection fraction, reducing the likelihood of hospitalization in the first few months. Mineralocorticoid receptor antagonists stabilize remodeling and reduce the risk of death, while beta-blockers reduce sympathetic overload, normalize heart rate, and improve diastolic filling.

In the period after a decompensation, when the risk of a repeated episode is especially high, the addition of a soluble guanylate cyclase stimulator reduces the residual risk against the background of the already initiated basic therapy. The effect is most noticeable in cohorts with high baseline risk, where even a moderate relative reduction turns into a significant absolute benefit, expressed in the prevention of repeated hospitalizations in the coming months [2].

In selected patients with extremely low ejection fraction and limitations on blood pressure, a direct myosin activator increases the mechanical efficiency of myocardial contraction without significantly increasing the oxygen demand. In this group, the clinical benefit is manifested in a reduction in the frequency of decompensations and improved exercise tolerance, especially when it is not possible to achieve the target doses of other medications [4]. Correction of iron deficiency with intravenous drugs leads to a decrease in fatigue, an increase in physical activity tolerance, and a decrease in the likelihood of repeated hospitalizations. Screening for iron deficiency should be carried out

regularly, focusing on ferritin and transferrin saturation indicators, as it is functional iron deficiency that often underlies limited skeletal muscle performance and insufficient rehabilitation effectiveness.

The use of cardiac resynchronization therapy in patients with a wide ventricular complex on the electrocardiogram and a characteristic morphology of electrical desynchrony restores the coordination of contractions, reduces secondary mitral regurgitation, and increases stroke volume. In combination with optimized medical therapy, this leads to a decrease in mortality and the frequency of hospitalizations [1]. Implantable systems for the prevention of sudden cardiac death remain the basis for preventing lethal arrhythmias in patients with persistent systolic dysfunction after the completion of the drug optimization phase.

To demonstrate the scale of the impact of various therapy components on vital outcomes over a two-year horizon, the first summary Table 1 is presented. It summarizes the clinical treatment directions, target patient groups, the expected impact on combined outcomes, and key safety considerations.

Table 1. Main Directions of Modern Therapy

Treatment direction	Target clinical group	Estimated effect on combined outcomes over two years	Important aspects of safety and monitoring
Combination of sacubitril with valsartan	Patients with reduced left ventricular ejection fraction	A significant reduction in the risk of cardiovascular death and hospitalizations compared to traditional angiotensin-converting enzyme inhibition monotherapy	Monitoring blood pressure and kidney function, and following the transition period when changing therapy
Drugs that inhibit the transport of sodium and glucose in the renal tubules	Patients with reduced and preserved left ventricular ejection fraction	A significant reduction in the frequency of hospitalizations and combined events, regardless of the presence of diabetes mellitus	Monitoring of water balance, prevention of urogenital infections, and controlled assessment of kidney function
Mineralocorticoid receptor antagonists	Patients with persistent symptoms despite basic therapy	Reduction in mortality and hospitalizations, and limitation of myocardial fibrosis	Regular monitoring of potassium and creatinine levels, and caution in case of chronic kidney disease
Beta-blockers in proven doses	Patients with reduced ejection fraction	Reduced mortality, reduced risk of decompensation, improved remodeling	Step-by-step titration with monitoring of heart rate and blood pressure
Soluble guanylate cyclase stimulator	Patients who have recently experienced decompensation	Moderate relative reduction in risk with large absolute benefit in high-risk patients	Use after stabilization, monitoring blood pressure and electrolytes
Direct activator of cardiac muscle myosin	Patients with very low ejection fractions and limitations on blood pressure	Additional reduction in the frequency of adverse events in selected subgroups	Monitoring of hemodynamics and symptoms during concomitant therapy
Intravenous iron preparations	Patients with confirmed iron deficiency	Reduced frequency of repeated hospitalizations and improved quality of life	Regular screening of iron stores and transferrin saturation, with an advantage of intravenous administration

Combination of sacubitril with valsartan provides additional protection compared to the traditional approach, while drugs that affect sodium and glucose transport demonstrate a universal effect across all ejection fraction ranges.

Mineralocorticoid receptor antagonists and beta-blockers remain cornerstone agents that enhance the modification of the prognosis and promote the regression of pathological remodeling [9].

A soluble guanylate cyclase stimulator and a myosin activator are not indicated for everyone, but they provide significant additional benefits in carefully selected

phenotypes, especially in the immediate post-hospital period and in cases with extremely low ejection fractions. Correcting iron deficiency improves functional capacity and reduces the burden on the inpatient unit, which is particularly important for the organization of medical care [5]. For practical application, a doctor needs a roadmap that describes the sequence of actions from the moment of diagnosis or discharge until stable stability is achieved.

Table 2 presents a practical strategy for managing a patient with chronic heart failure from early initiation to targeted escalation

Table 2. Practical strategy for managing a patient with chronic heart failure from early initiation to targeted escalation

Stage of the clinical trajectory	Content of the interventions	Immediate goal within three to six months	Expected result within two years
Early parallel start of therapy	Simultaneous administration of a combination of sacubitril with valsartan, beta-blockers, mineralocorticoid receptor antagonists, and a drug that inhibits sodium and glucose transport; diuretics are used to achieve euvolemia	Rapid reduction of congestion, stabilization of hemodynamics, suppression of neurohumoral cascades, and improvement of load tolerance	A significant decrease in mortality and the likelihood of hospitalizations, and the formation of a stable regression of remodeling
Monitoring the vulnerable period after decompensation	Addition of a soluble guanylate cyclase stimulator in patients at high risk of recurrent events on stable background therapy	Prevention of early re-admissions and maintenance of achieved stability	Decreased frequency of combined events in the coming months, increased likelihood of achieving target doses of the main therapy
Targeted enhancement in special phenotypes	Consideration of a direct myosin activator in patients with extremely low ejection fraction and limitations on blood pressure; mandatory correction of iron deficiency with intravenous medications if laboratory confirmation is available	Increased stroke volume with limited titration of other medications, reduced fatigue and shortness of breath, and improved rehabilitation tolerance	Additional reduction of the risk of decompensation, reduction of the need for emergency care and inpatient treatment
Technological interventions in the presence of indications	Cardiac resynchronization therapy in patients with electrical desynchrony; implantable systems for preventing sudden death in patients with persistent systolic dysfunction after optimization of drug therapy	Restoration of interventricular coordination, prevention of fatal arrhythmias	Additional reduction in mortality and hospitalizations, and improvement in functional class

An analysis of Table 2 shows that the main determinant of success is not the sequence of individual assignments, but rather the early and parallel implementation of basic components.

This approach creates a short "therapeutic window" for a significant reduction in sympathoadrenal and renin-angiotensin-aldosterone overload, facilitates

the achievement of euvolemia, and accelerates the restoration of daily activity. The transition to targeted escalation should occur after the minimum necessary stabilization and confirmation of a high residual risk, ensuring the rational use of drugs targeting the vascular-myocardial signaling system and agents enhancing the mechanical efficiency of contraction [8].

In parallel, iron deficiency screening and timely correction are performed, which contributes to a more complete realization of the benefits of drug therapy and rehabilitation measures. In the final stage of the trajectory, in patients with appropriate electrical and morpho functional characteristics, the use of devices provides a synergistic reduction in risk that cannot be achieved with medications alone [6].

An extended analysis of the results highlights that the greatest absolute clinical benefit is concentrated in the first months of treatment, when a well-organized start can prevent a significant proportion of repeated hospitalizations and lay the foundation for long-term survival gains [10]. In outpatient practice, it is the combination of clinical and pharmacological logic with clear safety monitoring, regular laboratory control, dose adjustment based on tolerability, patient education on self-monitoring, and early intervention for signs of fluid retention that determines the sustainability of the results. Multidisciplinary coordination involving a cardiologist, a general practitioner, a rehabilitation specialist, and a clinical pharmacologist is also important, as it enhances adherence, reduces medication conflicts, and ensures timely escalation or de-escalation of treatment based on changes in clinical status.

CONCLUSION

Comprehensive therapy of chronic heart failure should begin as early as possible with the simultaneous prescription of the main drug directions affecting the key pathogenetic axes and the renal-cardial interaction. This strategy leads to a rapid reduction of congestion, a decrease in the level of neurohumoral activation and a creation of a platform for a sustainable impact on mortality and the frequency of hospitalizations.

During the period of increased vulnerability after decompensation, it is advisable to add a drug that activates the soluble guanylate cyclase pathway, which reduces the risk of repeated adverse events. In patients with a specific phenotype of extremely low ejection fraction and limitations on blood pressure, the use of a direct myosin activator to increase stroke volume is justified.

Regular screening and intravenous correction of iron deficiency improve exercise tolerance and reduce the

need for inpatient treatment. In the presence of electrical and morpho functional criteria, cardiac resynchronization therapy and implantable sudden death prevention significantly enhance the medical strategy. The success of treatment depends on the speed and completeness of implementation, careful safety monitoring, continuous communication with the patient, and a multidisciplinary approach.

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