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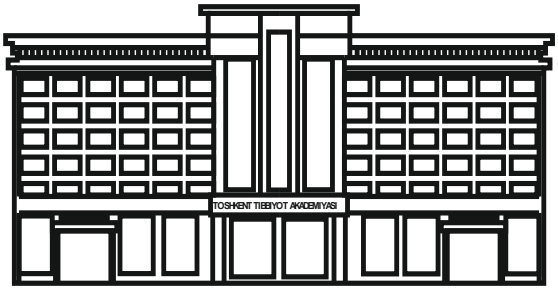

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ADVANCEMENTS IN HEART FAILURE TREATMENT: CURRENT STRATEGIES AND FUTURE DIRECTIONS OF PHARMACOTHERAPY

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The importance and necessity of further research into this pathological syndrome are determined by the high incidence of chronic heart failure (CHF) in the population (1-2%), an increase in the average age of newly diagnosed patients, a progressive course, the need for inpatient treatment, and an unfavorable prognosis. This article discusses new, effective directions for the pharmacological and non-drug correction of cardiac dysfunction in the treatment of CHF patients, numerous evolutionary changes in the heart failure problem, strategies for enhancing quality of life, and life expectancy for CHF patients.

Key words: *chronic heart failure, pharmacotherapy, pathogenetic treatment*

Among the various cardiovascular diseases, a special place is occupied by chronic heart failure (CHF). Its high prevalence in the population (1-2%), the increasing average age of patients newly diagnosed with CHF, its progressive course, the need for hospitalizations, and an unfavorable prognosis emphasize the relevance and necessity for further research into this pathological syndrome [5,21]. Moreover, the development of CHF is projected to occur in one out of four individuals throughout their lifetime [20]. Within 5 years after the diagnosis of CHF is established, only half of the patients survive, and the risk of death in individuals with heart failure increases with each hospitalization [16].

As we know, the causal or comorbid conditions that contribute to the development of CHF are numerous. According to C. Lawson and colleagues [13], the most common causal or comorbid conditions that contribute to the development of CHF include arterial hypertension (65%), ischemic heart disease (IHD) (50%), chronic kidney disease (43%), atrial fibrillation (41%), post-infarction cardiac fibrosis (27%), and diabetes mellitus (27%), obesity (23%), malignancies (23%), chronic obstructive pulmonary disease (23%), anemia (12%), and stroke (12%). Among these, there is a strong association with the likelihood of death and hospitalization, as well as a high level of clinical research evidence regarding changes in CHF outcomes when influencing the corresponding pathology, such as IHD, aortic stenosis, diabetes, and chronic kidney disease [15].

In light of this, the high demand for fundamental and applied research aimed at improving existing disease-modifying approaches to treating patients with CHF becomes evident. On one hand, there is a need to enhance current strategies, and on the other hand, to explore new breakthroughs in pharmacological and non-pharmacological interventions for heart dysfunction.

Over the past 20 years, there have been significant changes in the field of chronic heart failure (CHF), which can be characterized as evolutionary. In 2021, updated clinical guidelines were published by the European Society of Cardiology (ESC) and the Heart Failure Association, followed by the American College of Cardiology's recommendations in 2022. These updated clinical guidelines are a response to the accumulation of new scientific advancements from an evidence-based medicine perspective. Notable changes among these updates include questions related to etiology, a new definition of CHF, diagnostic algorithms, and treatment strategies for CHF according to phenotypes, as well as new indications for certain medications.

The treatment approaches for CHF are numerous, encompassing general measures, pharmacotherapy, electrophysiological interventions, surgical procedures, and mechanical circulatory support. Naturally, these methods are used in various combinations for each specific case[2].

Enhancing the quality and duration of life for patients with CHF can be achieved through etiotropic and pathogenetic therapies. A personalized approach to treatment primarily emphasizes the necessity to consider the etiological heterogeneity among CHF patients [8,18]. Since the conditions leading to the development of heart failure have diverse pathogenesis, creating universal treatment algorithms is challenging [8,17]. However, it's evident that properly tailored treatment for the underlying condition causing CHF can significantly reduce the severity of heart failure symptoms and, in some cases, eliminate them (for instance, after successful surgical correction of a heart defect) [3,16]. This primarily involves treating ischemia and acute myocardial infarction, preventing recurrent infarctions, identifying and actively treating individuals with arterial hypertension, diabetes, obesity, and dyslipidemia, as well as addressing the causes of specific myocardial damage, and promptly correcting valve pathology and heart defects [16].

All modern methods of treating heart failure aimed at improving prognosis can be categorized into several main groups, each with specific targets[1]:

. Blockade of Cardiomyocyte Death: This involves preventing necrosis and apoptosis of cardiomyocytes, as well as preserving cellular organelles through mechanisms like autophagy.

. Enhancement of Cardiac Contractile Function: This includes improving the force and speed of heart contraction (positive inotropy), increasing cardiac output, resynchronizing heart activity, and modulating the heart's contractility.

. Reduction of Pathological Cardiac Remodeling: This aims to counteract the pathological changes in heart structure, such as chamber dilation, spherical deformation, and myocardial hypertrophy.

. Preservation and Proliferation of Contractile Cardiomyocytes: This involves preventing cardiomy-

ocytes from entering a state of hibernation or creating new cardiomyocytes to maintain an active contractile population.

The goals of pharmacotherapy for patients with heart failure include:

. Reducing mortality.

. Preventing recurrent hospitalizations due to worsening heart failure.

. Enhancing clinical status, functional capabilities, and overall quality of life.

Currently, there is no doubt that the most significant improvement in the survival of heart failure patients is achieved through neurohumoral modulation of the cardiovascular system. This includes the use of angiotensin-converting enzyme inhibitors (or angiotensin II receptor antagonists), beta-adrenergic blockers, and mineralocorticoid receptor antagonists[11]. However, even with the combined use of these medications (referred to as triple neurohormonal blockade), they have not become a panacea for heart failure treatment. The recognized limitations of the capabilities of neurohormonal modulators, with mortality risk reduction not exceeding 23-35%, have prompted the search for fundamentally new targets for pharmacological intervention in the functional state of the neuroendocrine systems activated in this syndrome. This search is focused not only on the circulatory level but, more importantly, on the tissue level [7].

In the search for preferred directions in the development of pharmaceutical substances, the focus has shifted from isolated counteraction of so-called adverse neuroendocrine reactions to a balanced modulation with simultaneous stimulation of the activity of "beneficial" hormonal regulatory axes [9]. The success of this concept has been confirmed in clinical trials, where the neprilysin inhibitor sacubitril in combination with valsartan [12] demonstrated superiority over a "pure" renin-angiotensin-aldosterone system blocker like enalapril in terms of improving prognosis and quality of life in heart failure patients. This approach has led to innovative therapeutic strategies that not only address the negative hormonal responses but also harness the potential of favorable hormonal pathways to achieve better clinical outcomes[7] .

The results of the subgroup analysis from the PARAGON-HF study and the meta-analysis combining data from the PARAGON-HF and PARADIGM-HF trials demonstrated the disease-modifying potential of sacubitril/valsartan, highlighting a reduction of the number of heart failure decompensation-related hospitalizations. These effects extended beyond heart failure patients with reduced left ventricular ejection fraction (LVEF), suggesting the feasibility of considering the use of this combination therapy irrespective of LVEF values [14].

In patients experiencing acute decompensation with normal or elevated systemic arterial pressure, who exhibit refractoriness to diuretics, the addition of hormonal vasodilators can be considered. Among these, the use of serelaxin (a recombinant analog of human relaxin-2) and low doses of nesiritide (a recombinant human brain natriuretic peptide) appear to be the most promising [10].

Ultimately, it is possible to modulate the biological effects of certain hormones and neurotransmitters in the desired direction by targeting their secondary messengers. For instance, the salutary effects (vasodilation and reduction of coronary microvascular dysfunction, attenuation of myocardial fibrosis and hypertrophy, enhancement of cardiomyocyte relaxation speed and completeness during diastole, improvement in ventricular-arterial coupling, as well as augmentation of cardiac reserve) provided by the soluble guanylate cyclase stimulator vericiguat can lead to improved prognosis (and reduced need for decompensation-related hospitalizations) when administered over an extended period in patients with heart failure and reduced left ventricular ejection fraction [4].

When it comes to exploring new directions in treating heart failure, the most successful approach has been the focus on the use of antihyperglycemic agents from the sodium-glucose cotransporter 2 (SGLT-2) inhibitor class. Convincing evidence of the efficacy of these so-called "gliflozins" has led the European Society of Cardiology experts to designate two selective SGLT-2 inhibitors, dapagliflozin, and empagliflozin, as the fourth component of the first-line optimal heart failure therapy (the "fantastic four") in 2021, alongside the discussed neurohormonal modulators. Administering these medications to patients with functional class II–IV heart failure and reduced left ventricular ejection fraction (LVEF) results in decreased cardiovascular mortality and hospitalization needs due to decompensated heart failure, regardless of the presence or severity of carbohydrate metabolism disturbances [16].

Cardiac glycosides, which were considered "classic" drugs for heart failure treatment until the end of the last century, currently hold a place only in the arsenal of adjunctive measures. They do not influence the prognosis but can improve symptoms in specific clinical situations. These situations include manifest heart failure associated with atrial fibrillation and a high heart rate, as well as clinically evident heart failure with reduced left ventricular ejection fraction (LVEF) in patients with sinus rhythm. In such cases, symptoms persist despite treatment with angiotensin-converting enzyme inhibitors (or sacubitril/valsartan), beta-adrenergic blockers, and mineralocorticoid receptor antagonists [19].

A ray of hope for patients with severe heart failure, characterized by low cardiac output and hemodynamic instability, and for whom modern pharmacotherapy options are limited, could be the use of a representative of a new class of myotropic compounds called omecamtiv mecarbil. This compound acts as a selective activator of cardiac myosin. A post hoc analysis of the results from the randomized clinical trial GALACTIC-HF, which considered episodes of heart failure decompensation or cardiovascular death as the primary endpoint, demonstrated the positive impact of omecamtiv mecarbil on the prognosis of patients with severe heart failure corresponding to functional class III and IV, and with reduced left ventricular ejection fraction (LVEF) (<30%) [6].

Conclusion

Unprecedented achievements in secondary prevention have significantly improved the prognosis for patients with heart failure. However, regrettably, heart failure continues to be associated with high mortality. The continuous progress in addressing this issue appears to lie in the comprehensive utilization of all available and evolving treatment methods for heart failure in clinical practice, which have demonstrated their effectiveness in randomized controlled trials.

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