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Promising directions in the treatment of chronic heart failure: improving old or developing new ones?

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ABSTRACT

Unprecedented advances of recent decades in clinical pharmacology, cardiac surgery, arrhythmology, and cardiac pacing have significantly improved the prognosis in patients with chronic heart failure (CHF). However, unfortunately, heart failure continues to be associated with high mortality. The solution to this problem consists in simultaneous comprehensive use in clinical practice of all relevant capabilities of continuously improving methods of heart failure treatment proven to be effective in randomized controlled trials (especially when confirmed by the results of studies in real clinical practice), on the one hand, and in development and implementation of innovative approaches to CHF treatment, on the other hand. This is especially relevant for CHF patients with mildly reduced and preserved left ventricular ejection fraction, as poor evidence base for the possibility of improving the prognosis in such patients cannot justify inaction and leaving them without hope of a clinical improvement in their condition. The lecture consistently covers the general principles of CHF treatment and a set of measures aimed at inotropic stimulation and unloading (neurohormonal, volumetric, hemodynamic, and immune) of the heart and outlines some promising areas of disease-modifying therapy.

Keywords: chronic heart failure, treatment, neurohormonal modulators, sacubitril / valsartan, pecavaptan, fineron, vericiguat, sodium – glucose cotransporter type 2 inhibitors, omecamtiv mecarbil, gene therapy, cardiac resynchronization therapy, cardiac contractility modulation, heart transplantation, implantation of a circulatory assist device

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Перспективные направления лечения хронической сердечной недостаточности: совершенствование старых или разработка новых?

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РЕЗЮМЕ

Беспрецедентные достижения последних десятилетий в области клинической фармакологии, кардиохирургии и имплантационной аритмологии значительно улучшили прогноз у пациентов с хронической сердечной недостаточностью (ХСН), однако, к сожалению, сердечная недостаточность продолжает ассоциироваться с высокой смертностью. Решение этой проблемы видится одновременно в максимально полном применении в клинической практике всех актуальных возможностей непрерывно совершенствующихся методов лечения сердечной недостаточности, доказавших свою эффективность в рандомизированных контролируемых исследованиях (особенно при подтверждении результатами исследований реальной клинической практики), с одной стороны, а также в разработке и оперативном внедрении инновационных подходов к терапии ХСН – с другой. Больше всего в этом нуждаются пациенты с ХСН с умеренно сниженной и сохранной фракцией выброса левого желудочка, бедная доказательная база возможности улучшения прогноза у которых не может обосновывать бездействие и оставление их без надежды хотя бы на клиническое улучшение состояния. В лекции последовательно рассмотрены общие принципы лечения ХСН, комплекс мероприятий, направленный на инотропную стимуляцию и разгрузку (нейрогормональную, объемную, гемодинамическую и иммунную) сердца, а также обозначены некоторые перспективные направления болезнь-модифицирующей терапии.

Ключевые слова: хроническая сердечная недостаточность, лечение, нейрогормональные модуляторы, сакубитрил/валсартан, пекаваптан, финерон, верицигуат, ингибиторы натрий-глюкозного котранспортера 2-го типа, омекамтив мекарбил, генная терапия, сердечная ресинхронизирующая терапия, модуляция сердечной сократимости, трансплантация сердца, имплантация аппарата вспомогательного кровообращения

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Due to the development of clinical pharmacology, cardiac surgery, and implantation arrhythmology, we have seen significant advances in the treatment of patients with chronic heart failure (CHF) in the last decades. However, the long-term results of the so-called optimal medical therapy are often still disappointing [1–4]. The prognosis in patients with CHF is one of the worst, though this fact is often poorly understood by practitioners [5–10].

On the one hand, it becomes clear that there is a high need for fundamental and applied research aimed at improving existing disease-modifying approaches to the treatment of patients with CHF. On the other hand, this research should be also aimed at finding new breakthrough directions for the pharmacological and non-pharmacological treatment of heart dysfunction.

The aim of this paper was to discuss promising treatment options for patients with CHF.

GENERAL PRINCIPLES OF TREATMENT FOR HEART FAILURE

Therapeutic approaches to treating CHF are numerous and include general interventions, pharmacotherapy, electrophysiology therapies, surgery, and mechanical circulatory support. Naturally, in each specific case, these methods are combined differently [11, 12]. Achieving sustainable treatment effect is hindered by unreasonably ignoring any of these treatments (for example, non-pharmacological options) [12].

Etiotropic and pathogen-specific therapy can improve the quality of life and life expectancy of patients with CHF. A personalized approach to treatment primarily makes it necessary to take into account the etiological heterogeneity of the group of patients with CHF [13–15]. Since the conditions that are complicated by the development of HF differ in their pathogenesis, it is difficult to create universal therapy algorithms [11, 14]. Nevertheless, it is obvious that properly selected treatment of the disease underlying CHF in many cases can significantly reduce the severity of manifestations of cardiac decompensation and sometimes allows to eliminate them completely (for example, after successful surgical correction of heart disease) [1, 16]. First of all, we refer to treatment of ischemia and acute myocardial infarction, prevention of recurrent heart attacks, careful identification and active treatment of people with arterial hypertension, diabetes mellitus, obesity and dyslipidemia, elimination of the causes of specific myocardial damage, and timely correction of valvular pathology and heart defects [1, 11].

In a clinical situation, when it is temporarily impossible to eliminate the cause of the disease (for example, if due to severe circulatory failure, radical treatment of the underlying disease is not feasible), pathogen-specific and symptomatic therapy should be aimed at reducing the clinical manifestations of CHF and creating conditions that would allow physicians to reconsider etiotropic treatment [16].

All modern methods of treating CHF aimed at improving the prognosis can be divided into several main groups with a specific target [4, 17]: 1) blockade of cardiomyocyte death (necrosis and apoptosis) and loss of cell organelles (autophagy); 2) improvement of lusitropic and inotropic functions of the heart (increased cardiac output, cardiac resynchronization, and cardiac contractility modulation); 3) decreased severity of pathological cardiac remodeling (chamber dilatation and spherification, increase in myocardial mass); 4) preservation of and increase in the number of actively contracting cardiomyocytes (when cardiomyocytes are no longer in the hibernation state; myocardial stunning or generation of new cardiomyocytes). The discreteness of these targets is rather conditional, since in many cases the use of specific modern methods for treating CHF (for example, angiotensin-converting enzyme (ACE) inhibitors) provides a complex of sanogenic effects that go beyond one goal.

Since heart failure is typically an aging-associated disease, it is often associated with other diseases and syndromes, such as diabetes mellitus, obesity, anemia, kidney failure, chronic obstructive pulmonary disease, sleep disorders, depression, and hyperkalemia, which increase the likelihood of a negative outcome and should be scrupulously recorded in the diagnostic report [18–21]. Adaptation of existing and new regimens for CHF treatment aimed at solving these problems simultaneously can theoretically improve the survival rate of patients with comorbid pathology, especially those with preserved left ventricular ejection fraction (LVEF) [1, 22–24].

NEUROHORMONAL MODULATORS

The modern concept of medical treatment of patients with CHF can be narrowed down to two main principles: inotropic stimulation and unloading

(volumetric, hemodynamic, neurohormonal, and immune) of the heart [16, 25]. As inotropic stimulants did not prove to be very effective, at the end of the last century, the dominant role of contractile myocardial insufficiency in HF mechanisms (especially at an early stage) was revised as part of the evolution of the HF pathogenesis paradigm [26–29]. In the early 2000s, undoubtedly, the greatest increase in the survival rate of patients with CHF was provided by neurohumoral unloading of the cardiovascular system, and the use of ACE inhibitors (or angiotensin II receptor antagonists), beta-blockers, and mineralocorticoid receptor antagonists was considered reasonable [30, 31]. However, even with the combined use (the so-called triple neurohormonal blockade), the drugs of these groups did not become a "panacea" in the treatment of CHF, and known possibilities of neurohormonal modulators (risk of death is reduced by 23–35%) made researchers search for fundamentally new targets for drug exposure to affect the functional state of neuroendocrine systems activated in this syndrome at the circulatory and, more importantly, at the tissue level [17, 22, 30, 32, 33].

Unfortunately, testing the hypothesis that the addition of new selective blockers of the neurohormonal system may still bring additional benefits has resulted in obtaining unsatisfying results when studying the effectiveness of endopeptidase inhibitors (omapatrilat), renin inhibitors (aliskiren) or endothelin receptor antagonists (bosentan, darusentan) [30]. Well-known cardiologists did not see much sense in creating new effective neurohormonal inhibitors for the treatment of CHF due to the fact that in reality it was quite difficult to achieve a complete neurohormonal blockade (largely due to the effect of neurohormonal escape), which is not physiological, since endocrine, paracrine, and autocrine regulatory effects of hormones in the HF development should not be considered as purely pathological [17, 34].

When pharmacology seemed to have stopped creating new effective neurohormonal modulators for the prevention and treatment of HF with reduced LVEF, in the search for preferred directions for the development of pharmaceutical substances, the researchers began to focus on balanced modulation with simultaneous stimulation of the activity of "beneficial" hormonal regulatory axes rather than on isolated fight against the so-called "bad" neuroendocrine responses [22, 34, 35]. This concept was proven to be successful in clinical studies, in which the neprilysin inhibitor sacubitril as part of a single crystalline supramolecular complex, containing six molecules of sacubitril and six molecules of valsartan [36], was more efficient than the "pure" renin – angiotensin – aldosterone system (enalapril) in terms of improving the prognosis and quality of life in patients with CHF [17, 37–40]. Restoration of the normal balance of neurohormones with different directions of action was achieved by inhibiting the degradation of vasoactive peptides (natriuretic peptide, bradykinin, substance P, and calcitonin gene-related peptide), which provided sanogenic effects (vasodilation, increased level of diuresis / natriuresis, and slower pathological remodeling of cardiomyocytes and cardiac extracellular matrix).

The latest European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic HF emphasized the need for timely triple therapy, including a beta-blocker, a mineralocorticoid receptor antagonist, and a neurohumoral modulator sacubitril / valsartan, which prolongs life in patients with CHF with reduced LVEF [1]. However, J. Lindenfeld and M. Jessup were right to quote C.E. Koop saying that "drugs do not work in patients who do not take them" [41], which also contributes to the common practice when doctors do not actively prescribe such therapy, which altogether increases the patient's risk of death by 2–3 times [42, 43]. Unsatisfactory adherence of internists to modern principles of CHF therapy, the effectiveness of which was proven in large-scale clinical trials, requires great educational efforts [11]. Physicians should understand that despite the known limited possibilities of neurohormonal modulators, the best practical way to increase the effectiveness (increase life expectancy) of the treatment for both decompensated and stable patients with CHF and reduced LVEF is to prescribe this therapy to a larger number of patients [44–47]. In other words, while waiting for a miracle cure, practicing physicians should not expose CHF patients to an unacceptably high risk of death by not taking the needed measures. The use of all relevant possibilities of continuously improving neurohumoral modulation should become a fundamental rule for them.

Moreover, the results of a sub-analysis of the PARAGON-HF study and a meta-analysis of the PARAGON-HF and PARADIGM-HF studies, which demonstrated the potential for disease-modi-

fying activity of sacubitril / valsartan and a decrease in the number of hospitalizations due to HF decompensation, which could not be attributed to CHF with reduced LVEF, make it possible to discuss the advisability of using a combination of these drugs, regardless of the value for this LV contractile function parameter [1, 48, 49]. In this regard, there is a reason to expect the evolution of the evidence base [50–52].

The discussed direction of pathogen-specific CHF therapy is still to be developed further. In particular, the known role of the hypothalamic peptide hormone vasopressin (antidiuretic hormone) accumulating in the posterior lobe of the pituitary gland (neurohypophysis) in the mechanisms of fluid retention and the role of cardiac and vascular remodeling and dysfunction in patients with CHF allow to consider the latter as a target for pharmacological intervention [53, 54]. The so-called aquaretics (vaptans) are successfully used in patients with CHF associated with severe hypervolemic hyponatremia [1]. Since therapy with tolvaptan, which is the most studied selective, competitive V2 receptor antagonist, does not affect the prognosis of a patient with CHF, the current focus is placed on the use of dual vasopressin receptor antagonists, which have a potential advantage due to simultaneous blockade of vasopressin V1a receptors [55, 56]. In particular, several experimental and clinical studies are currently underway focused on the analysis of the efficacy and safety of the non-selective V1a / V2 receptor antagonist pecavaptan [57, 58].

Sixty years after H. Selye's publications, which emphasized the importance of aldosterone in the mechanisms of heart and kidney fibrosis, several pharmaceutical companies, inspired by the success of using its steroid antagonists (spironolactone, eplerenone) for the treatment of CHF, began to search for new non-steroidal mineralocorticoid receptor antagonists with certain pharmacokinetic and pharmacodynamic properties that can make them more beneficial than first- and second-generation drugs [59]. Several substances of third-generation mineralocorticoid receptor antagonists are under development, but fineron seems to meet the search criteria to the greatest extent. The first results of its clinical use indicated that its advantages over classical first- and second-generation drugs are not only theoretical, but also practical [60–64].

In patients with acute decompensated heart failure whose systemic blood pressure is normal or elevated, hormonal vasodilators can be added to overcome refractoriness to diuretics, of which the use of serelaxin (a recombinant analogue of human relaxin-2) and low doses of nesiritide (recombinant human brain natriuretic peptide) is the most promising [65, 66].

Finally, it is possible to modulate in the required direction (increase or decrease) the biological effects of a number of hormones and neurotransmitters by influencing their second messengers. For example, sanogenic effects of the stimulator of the soluble guanylate cyclase vericiguat receptor (vasodilation and a decrease in the severity of coronary microvascular dysfunction, slowdown in the development of fibrosis and myocardial hypertrophy, an increase in the speed and degree of cardiomyocyte relaxation in diastole, an improvement in the ventricular – arterial coupling, and an increase in cardiac reserve) improve the prognosis (reduced risk of death caused by cardiovascular diseases) and reduce the need for hospitalization due to decompensation in patients with HF with reduced LVEF if used on a long-term basis [25, 67, 68].

The latest European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic HF indicate that vericiguat may be considered in CHF patients with functional class II–IV reduced LVEF with aggravating heart failure despite combination therapy with an ACE inhibitor, beta-blocker, and mineralocorticoid receptor antagonist [1]. Another soluble guanylate cyclase stimulator, riociguat, is currently recommended (also in combination with endothelin receptor antagonists or prostanoids) for the correction of pulmonary arterial hypertension and portopulmonary hypertension [69].

SODIUM-GLUCOSE COTRANSPORTER TYPE 2 INHIBITORS

As for the search for new directions in the treatment of CHF, the most successful option involved the use of hypoglycemic drugs from the group of the sodium-glucose cotransporter type 2 (SGLT2) inhibitors. Convincing evidence of the effectiveness of the so-called gliflozins allowed the experts of the European Society of Cardiology to designate in 2021 two selective SGLT2 inhibitors (dapagliflozin and empagliflozin) as the 4th component of optimal

first-line CHF therapy, including the neurohormonal modulators discussed above [1, 70]. At the same time, the diuretic (osmotic diuresis) and slight natriuretic effects of the considered SGLT2 are not associated with blood glucose level, and their administration to patients with functional class II–IV CHF and reduced LVEF decreases cardiovascular mortality and the need for hospitalization due to decompensated heart failure, regardless of the presence and severity of carbohydrate metabolism disorders [70, 71].

The positive additive effect of these drugs on the survival of CHF patients with reduced LVEF already receiving optimal therapy based on a triple neurohormonal blockade (sacubitril / valsartan or an ACE inhibitor, a beta-blocker, a mineralocorticoid receptor antagonist) should encourage practitioners to transfer the achievements of clinical research into practice more quickly [47]. At the same time, it would appear that accumulating data on the high efficacy of the discussed gliflozins in a wide range of LVEF values will make it possible in the near future to justify the addition of indications for their prescription in cases of CHF with mildly reduced and preserved LVEF [52, 72–74].

It is supposed that SGLT2 has a so-called class effect, and we can expect addition to the line of drugs in this group of drugs which are intended for the treatment of CHF due to other selective cotransporter type 2 inhibitors (for example, canagliflozin and ertugliflozin) and non-selective cotransporter type 1 and 2 inhibitors (for example, sotagliflozin) [75–79].

Perhaps, other hypoglycemic agents can be as effective as SGLT2. Long-acting analogues of glucagon-like peptide-1 were the most likely to prove their efficacy in treating heart failure [80–82].

INOTROPIC DRUGS

Until the end of the 20th century, cardiac glycosides were mostly used for the treatment of CHF, currently they are only used as adjuvants (digoxin and, possibly, digitoxin) that do not affect the disease prognosis, but improve symptoms in certain clinical situations. In practice, there are only two such clinical situations. The first one is overt heart failure associated with atrial fibrillation and a high heart rate, when other therapeutic approaches (e.g., pulmonary vein isolation or effective doses of beta-blockers for arterial hypotension) cannot be applied [1]. We should also keep in mind that in sinus rhythm with a resting heart rate of 70 bpm or more, when, despite combination therapy with optimal doses of first-line drugs, tachysystole persists, it is recommended to add the selective sinus node If channel inhibitor ivabradine for patients with symptomatic heart failure and the LVEF value of 35% or less, in order to reduce the risk of hospitalization and death from cardiovascular causes [1, 83]. The second case includes symptomatic CHF with reduced LVEF in patients with sinus rhythm, when symptoms persist despite treatment with an ACE inhibitor (or sacubitril / valsartan), a beta-blocker, and a mineralocorticoid receptor antagonist [1, 55].

It should be noted that the main mechanism of digoxin at low doses recommended for clinical practice is associated not with the inotropic effect of the drug, but with its neuromodulatory activity. We are talking about weakening of sympathetic nervous activity and a decrease in renin secretion, associated with inhibition of K^+-Na^+-dependent ATPase in the afferent fibers of the vagus nerve and renal tubules, respectively [12, 55].

Short-term use of non-glycoside inotropic stimulating agents is limited by the clinical situation with reduced cardiac output and hemodynamic instability in progressive and acute heart failure [1, 4, 55]. Vasoconstrictors (e.g., norepinephrine, midodrine, and vasopressin), inotropes with vasoconstrictor properties (e.g., dopamine, epinephrine, and droxidopa), cardiotonic agents (e.g., dobutamine, milrinone), and inodilators, among which, according to some experts, levosimendan is the most promising one and can be used in the absence of a pronounced decrease in systolic blood pressure – > 85 mm Hg [1, 84, 85]. However, despite a short-term improvement in hemodynamics and clinical status in patients with decompensated heart failure, long-term therapy with non-glycoside inotropic drugs may be associated with an increased risk of death [12, 86].

The use of a representative of a new class of myotropic compounds, omecamtiv mecarbil, which is a selective activator of cardiac myosin, may become a treatment option for patients with severe heart failure associated with low cardiac output and hemodynamic instability, as modern pharmacotherapy options are limited for such patients [87, 88]. Post hoc analysis of the results of the randomized clinical

trial GALACTIC-HF, which took into account an episode of CHF decompensation or cardiovascular death as the primary endpoint, demonstrated a positive effect of omecamtiv mecarbil on the prognosis of patients with severe functional class III and IV heart failure and reduced LVEF (< 30%) [88].

Another relatively new direction of inotropic support is the modulation of the sarcoplasmic reticulum Ca2+-ATPase 2a (SERCA2a), the expression and activity of which is reduced in CHF, which leads to disruption of intracellular calcium movement between the cytosol and the lumen of the sarcoplasmic reticulum and negatively affects the mechanics of systole and diastole. Modulation of SERCA2a in patients with CHF can be achieved through gene therapy (intracoronary or endomyocardial administration of viral and plasmid vectors encoding SERCA2a or other proteins of the Ca^{2+}-modulating protein family) [89, 90].

Since the excitation – contraction coupling in myocardium in CHF is impaired at various levels (receptors, ion channels, and transporters, phosphorylation of proteins that modify the function of the cardiomyocyte, etc.), a wide variety of targets can be chosen for the targeted correction of maladaptation shifts: from enzymes to structural proteins and cytoprotective factors. These approaches are especially important when treating patients suffering from hereditary diseases with heart damage. Despite the controversial results that followed attempts to transfer the promising results of laboratory studies on the modification of genetic programs and additional translational mechanisms into practice, this direction of research is still of interest, but much remains to be done to prove the perfection of delivery and intracellular transfer systems, as well as the effectiveness and safety of the discussed approaches to therapy for CHF before gene therapy and postgenomic medicine are included in standard treatment protocols [90–94].

ELECTROPHYSIOLOGY THERAPIES

In addition to optimal medical therapy in selective groups of patients with CHF with reduced LVEF, for more than 20 years electrophysiology treatment has been successfully used, namely implantation of conventional pacemakers (relevant for patients with sick sinus syndrome and high-grade atrioventricular block), cardiac resynchronization therapy (effectiveness of triple chamber pacing has been proven in patients with severe systolic dysfunction and wide QRS) and implantation of a cardioverter – defibrillator (used for primary and secondary prevention of life-threatening cardiac arrhythmias). The last two methods that can be combined (a pacemaker with a defibrillator function) in one patient are recommended in all modern guidelines for treatment of CHF with detailed indications, which depend on the duration of the QRS, the reduction of the LVEF value, the CHF functional class, the main heart rhythm (sinus or atrial fibrillation), the risk of fatal arrhythmia, the etiology of heart failure, the presence and severity of comorbidity, age, and life expectancy [1, 12, 95, 96].

Electrophysiology therapies are continuously being improved, and currently the effectiveness and safety of cardiac contractility modulation devices implanted in patients with symptomatic CHF with reduced LVEF, who cannot undergo cardiac resynchronization therapy (with narrow QRS) or who have not received sufficient clinical effect from this therapy, are still actively studied. Cardiac contractility modulation is based on two-electrode stimulation of the interventricular septum with a biphasic high-voltage signal in the absolute refractory period, and its use provides an increase in heart contractility due to positive changes in intracellular calcium homeostasis (increased expression of SERCA2a or other proteins of the Ca2+-modulating protein family) without increasing myocardial oxygen consumption and also improves the functional state and quality of life and, possibly, prevents hospitalization of these patients [1, 97].

So far, there are still insufficient data regarding the evaluation of the efficacy and safety of other implantable electrotherapy devices in patients with CHF, in particular, of those aimed at modifying the autonomic nervous system activity (for example, baroreflex activation therapy), in order to decide on the possibility of their use in clinical practice [1, 98, 99].

TREATMENT OF ADVANCED HEART FAILURE

Patients with symptoms of CHF corresponding to functional classes III and IV that persist despite optimal medical therapy and cardiac resynchronization therapy (if indicated) and are associated with objective signs of severe cardiac dysfunction, such

as severe systolic and (or) diastolic LV dysfunction, elevated ventricular filling pressure, and increased plasma natriuretic peptide levels, require timely referral to a specialized center, where advanced methods of treating heart failure are used, which are not available in a clinic [1, 100–102].

If other methods of dehydration are ineffective in these patients, extracorporeal ultrafiltration (sparing modes are preferable with a minimum volume of extracorporeal blood and an ultrafiltration rate of no more than 250 ml / h), and peritoneal dialysis can be used [12, 102–104].

Considering that a well-founded conclusion about advanced heart failure leaves little hope for the success of pharmacotherapy, the only options for patients include surgical treatment, heart transplantation, or implantation of a circulatory assist device [102, 105, 106].

Conventional surgical treatment is aimed at correcting the etiological factors, as well as the main mechanisms underlying CHF. For instance, this treatment would include revascularization of ischemic but viable myocardium in patients with LVEF value not exceeding 35%, aortic valve replacement (transcatheter implantation is preferable when perioperative risk is high) in severe symptomatic aortic valve stenosis with an average pressure gradient above 40 mm Hg or in severe aortic regurgitation in all symptomatic and asymptomatic patients with LVEF of less than or equal to 50%, as well as surgery to correct mitral regurgitation (endovascular mitral valve clip placement theoretically seems more reasonable in a situation of high perioperative risk), also in secondary (due to LV dilatation) severe mitral regurgitation (especially in patients with LVEF less than 30%), which cannot be corrected with pharmacotherapy and electrophysiology treatment [102, 105, 107, 108].

Despite the lack of well-designed controlled studies, it is widely believed in the cardiology community that heart transplantation in end-stage CHF significantly improves survival (one-year survival rate of about 90%, median survival rate of 12.2 years), physical performance, and quality of life compared with conventional treatment, provided that appropriate selection criteria are carefully observed (the mainstay for the treatment of refractory CHF) [102, 109].

Long-term mechanical circulatory support is increasingly being considered as an alternative to heart transplantation in patients with end-stage CHF, in whom transplantation is not feasible for objective or subjective reasons [1, 102, 110, 111].

OTHER PROMISING DIRECTIONS OF TREATMENT FOR PATIENTS WITH CHF

A list of some promising approaches to the treatment of patients with CHF which are currently being developed or have already proven their effectiveness but need wider application in clinical practice is presented in the table.

CONCLUSION

Unprecedented advances in secondary prevention significantly improved the prognosis in patients with CHF, but, unfortunately, heart failure is still associated with high mortality. Sustainable progress in solving this problem is seen in the fullest possible application of all relevant continuously improving methods of treating heart failure in clinical practice, which have proven their effectiveness in randomized controlled trials (especially when confirmed by the results of studying real clinical practice), as well as in development and rapid implementation of innovative approaches to the treatment of CHF. CHF patients with mildly reduced and preserved LVEF need this most of all, the poor evidence base for the possibility of improving their prognosis cannot justify a lack of measures taken by physicians and leaving patients without a hope for even a clinical improvement [174].

Table

Some promising approaches to the treatment of patients with CHF

Treatment approaches	Note
Correction of iron deficiency (serum ferritin concentration of less than 100 mg / l or in the range from 100 to 300 mg / l in combination with the iron transferrin saturation coefficient of less than 20%), which is detected in approximately every second patient with CHF [112]	Anemia, which is iron-deficiency in 75% of patients with CHF, is an independent factor of poor prognosis for any etiology of heart failure and any value of LVEF [12, 113, 114]. Iron deficiency should be considered as an independent clinically significant concomitant condition and, therefore, in order to reduce the need for hospitalization, reduce the clinical severity of CHF, as well as improve the functional capabilities and quality of life of patients, it is advisable to correct even latent iron deficiency [1, 113].

Table (continued)

	The results of the Cochrane Review confirm that the effectiveness of iron salt preparations (mainly divalent) and Fe^{3+} preparations based on hydroxide polymaltose complex in the treatment of iron-deficiency anemia is the same in the general population, with a better tolerability profile in the latter [115, 116]. Nevertheless, there is a widespread opinion among cardiologists that oral iron preparations are ineffective in the treatment of patients with CHF, and in most modern guidelines for iron deficiency, only intravenous administration of iron carboxymaltose is recommended [1, 113, 117]. It should be noted that the ferinject annotation states that it should be used in hospital departments with the necessary equipment to provide emergency medical care in case of anaphylactic reactions. Erythropoietin should not be used in the treatment of patients with CHF even with a reduced hemoglobin level [1, 113].
Stimulation of the potential for cardiac muscle regeneration	In advanced scientific centers, material is being accumulated in four main areas [118–128]: – Some researchers are investigating the efficacy and safety of various methods of transplantation (endovascular, transthoracic or during heart surgery) of own or autologous stem cells and myoblasts isolated from skeletal muscle, as well as other cells (including genetically modified ones). Researchers encounter pending problems related to the need to prepare sufficient material for transplantation, develop methods for cell preconditioning, their targeted administration, survival / rejection of transplanted cells, and their commitment towards cardiomyogenesis. – Other researchers are developing a technique for stimulating the production and release of own stem cells into the bloodstream from the bone marrow (for example, using granulocyte and granulocyte – macrophage colony-stimulating factors), which does not require surgery or complex invasive intervention and can be a good alternative to cell transplantation. – Still others are exploring the possibility of direct reprogramming of cardiac fibroblasts, allowing the transformation of terminally differentiated cells into cardiomyocytes. At the same time, the search is underway for optimal cell reprogramming factors (transcription factors, such as GATA4, MEF2c, and TBX5, which are usually combined in different ratios, cytokines, microRNAs, and other epigenetic modifiers), and delivery systems are being improved. – Finally, there are researchers convinced that heart regeneration can be achieved by re-activating the proliferation of own cardiomyocytes (no more than 5% of cells express proliferative activity marker Ki-67) and try to stimulate the potential of cardiac muscle regeneration using, for example, acellular biomaterials. The results of these experimental and clinical studies have not yet allowed to revise clinical guidelines for the treatment of CHF [129, 130].
Myocardial cytoprotection	Despite a rather impressive list of drugs that can be attributed to the so-called myocardial cytoprotectors, from the standpoint of evidence-based medical practice, only the use of long-acting trimetazidine is justified for the treatment of patients with ischemic CHF, in whom it demonstrates high antianginal and anti-ischemic efficacy and provides increased tolerance to physical activity, positive dynamics of indicators characterizing LV remodeling and its functional state, as well as a decrease in the risk of death and repeated hospitalizations [1, 12, 131, 132]. The development and clinical trials on myocardial cytoprotectors continue; myocardial cytoprotectors under study are potentially effective in CHF and are aimed at inhibiting fatty acid oxidation, stimulating glucose oxidation, activating the cytochrome chain, optimizing the transport of an energy substrate into mitochondria, and increasing the antioxidant potential of cardiomyocytes [4, 133–143].
Correction of hyperkalemia classified as mild (5.0–5.4 mmol / l), moderate (5.5–6.0 mmol / l), and severe (> 6.0 mmol / l).	Associated with an increased risk of adverse (including fatal) outcomes, hyperkalemia is becoming more common in patients with CHF, partly due to an increase in the incidence of comorbidities, but, apparently, to a greater extent due to the widespread use of combination therapy with neurohumoral modulators [144]. The prescription of potassium sequestrants (for example, patiromer or sodium zirconium cyclosilicate) increases the safety of such therapy and the likelihood of achieving target doses of renin – angiotensin – aldosterone system inhibitors [1, 96, 145–147]. Whether the correction of hyperkalemia with these drugs will improve clinical outcomes in patients with CHF is still to be determined [96].
Interventions aimed at slowing down the cardiac extracellular matrix remodeling	All neurohormonal modulators, which have become the core of CHF therapy, have antifibrotic activity to a greater or lesser extent. In recent years, the possibility of potentiating this effect by targeting the key mechanisms of pathological collagen accumulation and changing its composition in the interstitium has been studied; the search is underway for possible therapeutic targets (galectin-3, matrix metalloproteinases, metallopeptidase inhibitor 1, growth differentiation factor-15, osteopontin, etc.) [148–157].
Correction of proinflammatory status	It is a well-proven fact that the pathology of the immune system is essentially important in the mechanisms of CHF [158–161]. Toll-like receptors, inflammasomes (including NOD-like receptors), cytokines, and apoptotic and pyroptotic effector mechanisms are most often considered as promising targets of therapy aimed at reducing the severity of proinflammatory shifts at the systemic and local levels, as well as the readiness of cardiomyocytes to implement apoptosis, pyroptosis, and autophagy programs [162–172]. The use of nonsteroidal anti-inflammatory drugs can reduce the effectiveness of the main drugs used to treat CHF, provoke the development of acute decompensation, and increase the risk of thrombotic events (especially selective cyclooxygenase blockers) [1, 173].

REFERENCES

1. McDonagh T.A., Metra M., Adamo M., Gardner R.S., Baumbach A., Böhm M. et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* 2021;42(36):3599−3726. DOI: 10.1093/eurheartj/ehab368.
2. Salah H.M., Minhas A.M.K., Khan M.S., Khan S.U., Ambrosy A.P., Blumer V. et al. Trends in hospitalizations for heart failure, acute myocardial infarction, and stroke in the United States from 2004 to 2018. *Am. Heart J.* 2022; 243:103−109. DOI: 10.1016/j.ahj.2021.09.009.
3. Roger V.L. Epidemiology of heart failure: A contemporary perspective. *Circ. Res.* 2021;128(10):1421−1434. DOI: 10.1161/CIRCRESAHA.121.318172.
4. Kalyuzhin V.V., Teplyakov A.T., Kalyuzhin O.V. Heart failure. Moscow: Meditsinskoe informatsionnoe agentstvo, 2018:376 (in Russ.).
5. Groenewegen A., Rutten F.H., Mosterd A., Hoes A.W. Epidemiology of heart failure. *Eur. J. Heart Fail.* 2020; 22 (8):1342−1356. DOI: 10.1002/ejhf.1858.
6. Teplyakov A.T., Tarasov N.I., Isakov L.K., Grakova E.V., Sinkova M.N., Kopieva K.V., Garmaeva O.B., Ogurkova O.N., Kalyuzhin V.V., Kalyuzhina E.V. Prognosis of cardiovascular events after implantation of a cardioverterdefibrillator in patients with chronic heart failure: the value of increasing concentration of endothelin-1 and soluble forms of ST2 protein in blood plasma. *Bulletin of Siberian Medicine*. 2018;17(3):140−150 (in Russ.). DOI: 10.20538/1682-0363-2018-3-140-150.
7. Bottle A., Faitna P., Aylin P., Cowie M.R. Five-year survival and use of hospital services following ICD and CRT implantation: comparing real-world data with RCTs. *ESC Heart Fail.* 2021;8(4):2438−2447. DOI: 10.1002/ehf2.13357.
8. Spitaleri G., Lupón J., Domingo M., Santiago-Vacas E., Codina P., Zamora E. et al.. Mortality trends in an ambulatory multidisciplinary heart failure unit from 2001 to 2018. *Sci. Rep.* 2021;11(1):732. DOI: 10.1038/s41598-020-79926-3.
9. Virani S.S., Alonso A., Aparicio H.J., Benjamin E.J., Bittencourt M.S., Callaway C.W. et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation.* 2021;143(8):e254−e743. DOI: 10.1161/CIR.0000000000000950.
10. Polyakov D.S., Fomin I.V., Belenkov Yu.N., Mareev V.Yu., Ageev F.T., Artemyeva E.G., et al. Chronic heart failure in the Russian Federation: what has changed over 20 years of follow-up? Results of the EPOCH-CHF study. *Kardiologiia.* 2021;61(4):4−14 (in Russ.). DOI: 10.18087/cardio.2021.4.n1628.
11. Remme W.J., Swedberg K. Task Force for the Diagnosis and Treatment of Chronic Heart Failure, European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur. Heart J.* 2001;22(17):1527–1560. DOI: 10.1053/euhj.2001.2783.
12. Mareev V.Yu., Fomin I.V., Ageev F.T., Begrambekova Yu.L., Vasyuk Yu.A., Garganeeva A.A., et al. Russian Heart Failure Society, Russian Society of Cardiology. Russian Scientific Medical Society of Internal Medicine Guidelines for Heart failure: chronic (CHF) and acute decompensated (ADHF). Diagnosis, prevention and treatment. *Kardiologiia*. 2018;58(6S):8−161 (in Russ.). DOI: 10.18087 / cardio. 2475.
13. Kalyuzhin V.V., Teplyakov A.T., Chernogoryuk G.E., Kalyuzhina E.V., Bespalova I.D., Terentyeva N.N., et al. Chronic heart failure: syndrome or disease? *Bulletin of Siberian Medicine.* 2020;19(1):134–139 (in Russ.). DOI: 10.20538/1682-0363-2020-1-134–139.
14. Triposkiadis F., Xanthopoulos A., Parissis J., Butler J., Farmakis D. Pathogenesis of chronic heart failure: cardiovascular aging, risk factors, comorbidities, and disease modifiers. *Heart Fail. Rev.* 2022;27(1):337−344. DOI: 10.1007/s10741-020-09987-z.
15. Fayol A., Wack M., Livrozet M., Carves J.B., Domengé O., Vermersch E. et al. Aetiological classification and prognosis in patients with heart failure with preserved ejection fraction. *ESC Heart Fail.* 2022;9(1):519−530. DOI: 10.1002/ehf2.13717.
16. Roitberg G.E., Strutynsky A.V. Internal diseases. Cardiovascular system: study guide. Moscow: MEDpress-inform, 2019:904 (in Russ.).
17. Mareev V.Yu., Belenkov Yu.N. Prospects in the treatment of chronic heart failure. *Journal - Heart Failure.* 2002;3(3):109–114 (in Russ.).
18. Xanthopoulos A., Tryposkiadis K., Giamouzis G., Dimos A., Bourazana A., Papamichalis M. et al. Coexisting morbidity burden in hospitalized elderly patients with new-onset heart failure vs acutely decompensated chronic heart failure. *Angiology.* 2022;33197211062661. DOI: 10.1177/00033197211062661.
19. Kalyuzhin V.V., Teplyakov A.T., Bespalova I.D., Kalyuzhina E.V., Ostanko V.L., Terentyeva N.N., et al. Correct diagnostic conclusion in patients with chronic heart failure: a reality or a pipe dream? *Bulletin of Siberian Medicine*. 2020;19(3):128 −136 (in Russ.). DOI: 10.20538/1682-0363-2020-3-128-136.
20. Zheng C., Han L., Tian J., Li J., He H., Han G. et al. Hierarchical management of chronic heart failure: a perspective based on the latent structure of comorbidities. *ESC Heart Fail.* 2022;9(1):595−605. DOI: 10.1002/ehf2.13708.
21. Maeda D., Matsue Y., Kagiyama N., Jujo K., Saito K., Kamiya K. et al. Inaccurate recognition of own comorbidities is associated with poor prognosis in elderly patients with heart failure. *ESC Heart Fail.* 2022. DOI: 10.1002/ehf2.13824.
22. Kaye D., Krum H. Drug discovery for heart failure: a new era or the end of the pipeline? *Nat. Rev. Drug Discov.* 2007;6:127–139. DOI: 10.1038/nrd2219.
23. Marra A.M., Bencivenga L., D'Assante R., Rengo G., Cittadini A. Heart failure with preserved ejection fraction: Squaring the circle between comorbidities and cardiovascular abnormalities. *Eur. J. Intern. Med.* 2022:S0953-6205(22)00018-8. DOI: 10.1016/j.ejim.2022.01.019.
24. Sabouret P., Attias D., Beauvais C., Berthelot E., Bouleti C., Gibault Genty G. et al. Diagnosis and management of heart failure from hospital admission to discharge: A practical expert guidance. *Ann. Cardiol. Angeiol. (Paris).* 2022;71(1):41−52. DOI: 10.1016/j.ancard.2021.05.004.

25. Ghionzoli N., Gentile F., Del Franco A.M., Castiglione V., Aimo A., Giannoni A. et al. Current and emerging drug targets in heart failure treatment. *Heart Fail. Rev.* 2021;27(4):1119–1136. DOI: 10.1007/s10741-021-10137-2.
26. Swedberg K. Importance of neuroendocrine activation in chronic heart failure. Impact on treatment strategies. *Eur. J. Heart Fail.* 2000;2(3):229−233. DOI: 10.1016/s1388-9842(00)00102-1.
27. Kalyuzhin V.V., Teplyakov A.T., Solovtsov M.A. The role of systolic and diastolic LV dysfunction in the clinical manifestation of chronic heart failure in patients with myocardial infarction. *Therapeutic archive*. 2002;74(12):15−18 (in Russ.).
28. Kalyuzhin V.V., Teplyakov A.T., Vechersky Yu.Yu., Ryazantseva N.V., Khlapov A.P. Pathogenesis of chronic heart failure: change of dominating paradigm. *Bulletin of Siberian Medicine*. 2007;6(4):71−79 (in Russ.). DOI: 10.20538/1682-0363-2007-4-71-79.
29. Kalyuzhin V.V., Teplyakov A.T., Ryazantseva N.V., Vechersky Yu.Yu., Khlapov A.P., Kolesnikov R.N. Diastole of the heart. Physiology and clinical pathophysiology. Tomsk: TPU Publishing House, 2007:212 (in Russ.).
30. Gheorghiade M., De Luca L., Bonow R.O. Neurohormonal inhibition in heart failure: insights from recent clinical trials. *Am. J. Cardiol.* 2005;96(12A):3L−9L. DOI: 10.1016/j.amjcard.2005.09.059
31. Teplyakov A.T., Popov S.V., Kalyuzhin V.V., Garganeeva A.A., Kurlov I.O., Nilogov V.L., et al. Evaluation of the effect of carvedilol, atenolol and their combination with fosinopril on heart rate variability, clinical and functional status and quality of life in patients with postinfarction left ventricular dysfunction. *Therapeutic archive*. 2004;76(9):62−65 (in Russ.).
32. Jneid H., Moukarbel G.V., Dawson B., Hajjar R.J., Francis G.S. Combining neuroendocrine inhibitors in heart failure: reflections on safety and efficacy. *Am. J. Med.* 2007;120(12):1090.e1−1090.e8. DOI: 10.1016/j.amjmed.2007.02.029.
33. Dobrek Ł., Thor P. Neuroendocrine activation as a target of modern chronic heart failure pharmacotherapy. *Acta Pol. Pharm*. 2011;68(3):307−316.
34. Ferrari R., Cardoso J., Fonseca M.C., Aguiar C., Moreira J.I., Fucili A. et al. ARNIs: balancing "the good and the bad" of neuroendocrine response to HF. *Clin. Res. Cardiol.* 2020;109(5):599−610. DOI: 10.1007/s00392-019-01547-2.
35. Berliner D., Bauersachs J. New drugs: big changes in conservative heart failure therapy? *Eur. J. Cardiothorac. Surg.* 2019;55(1):i3−i10. DOI: 10.1093/ejcts/ezy421.
36. Gu J., Noe A., Chandra P., Al-Fayoumi S., Ligueros-Saylan M., Sarangapani R. et al. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). *J. Clin. Pharmacol.* 2010;50(4):401−414. DOI: 10.1177/0091270009343932.
37. McMurray J.J., Packer M., Desai A.S., Gong J., Lefkowitz M.P., Rizkala A.R. et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur. J. Heart Fail.* 2013;15(9):1062−1073. DOI: 10.1093/eurjhf/hft052.
38. Berg D.D., Samsky M.D., Velazquez E.J., Duffy C.I., Gurmu Y., Braunwald E. et al. Efficacy and Safety of Sacubitril/Valsartan in High-Risk Patients in the PIONEER-HF Trial. *Circ. Heart Fail.* 2021;14(2):e007034. DOI: 10.1161/CIRCHEARTFAILURE.120.007034.
39. Wachter R., Senni M., Belohlavek J., Straburzynska-Migaj E., Witte K.K., Kobalava Z. et al. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. *Eur. J. Heart Fail.* 2019; 21 (8):998−1007. DOI: 10.1002/ejhf.1498
40. Chandra A., Lewis E.F., Claggett B.L., Desai A.S., Packer M., Zile M.R. et al. Effects of Sacubitril/Valsartan on Physical and Social Activity Limitations in Patients With Heart Failure: A Secondary Analysis of the PARADIGM-HF Trial. *JAMA Cardiol.* 2018;3(6):498−505. DOI: 10.1001/jamacardio.2018.0398.
41. Lindenfeld J., Jessup M. 'Drugs don't work in patients who don't take them' (C. Everett Koop, MD, US Surgeon General, 1985). *Eur. J. Heart Fail.* 2017;19(11):1412−1413. DOI: 10.1002/ejhf.920.
42. Cole G.D., Patel S.J., Zaman N., Barron A.J., Raphael C.E., Mayet J. et al. "Triple therapy" of heart failure with angiotensin-converting enzyme inhibitor, beta-blocker, and aldosterone antagonist may triple survival time: shouldn't we tell patients? *JACC Heart Fail.* 2014;2(5):545−548. DOI: 10.1016/j.jchf.2014.04.012/
43. Zaman S., Zaman S.S., Scholtes T., Shun-Shin M.J., Plymen C.M., Francis D.P., Cole G.D. The mortality risk of deferring optimal medical therapy in heart failure: a systematic comparison against norms for surgical consent and patient information leaflets. *Eur. J. Heart Fail.* 2017;19(11):1401−1409. DOI: 10.1002/ejhf.838.
44. Bhatt A.S., Vaduganathan M., Claggett B.L., Liu J. Packer M., Desai A.S. et al. Effect of sacubitril/valsartan vs. enalapril on changes in heart failure therapies over time: the PARADIGM-HF trial. *Eur. J. Heart Fail.* 2021;23(9):1518−1524. DOI: 10.1002/ejhf.2259.
45. Cabral J., Vasconcelos H., Maia-Araújo P., Moreira E., Campelo M., Amorim S. et al Sacubitril/valsartan in everyday clinical practice: an observational study based on the experience of a heart failure clinic. *Cardiovasc. Diagn. Ther.* 2021;11(6):1217−1227. DOI: 10.21037/cdt-21-312.
46. Yoshikawa T. New paradigm shift in the pharmacotherapy for heart failure-where are we now and where are we heading? *J. Cardiol.* 2022:S0914-5087(22)00031-4. DOI: 10.1016/j.jjcc.2022.02.008.
47. Mareev Yu.V., Mareev V.Yu. The ability of modern therapy to improve the prognosis of patients with HF: role of angiotensin neprilysin inhibitors and sodium-glucose cotransporter inhibitors. *Kardiologiia.* 2021;61(6):4−10 (in Russ.). DOI: 10.18087/cardio.2021.6.n1678.
48. Vaduganathan M., Claggett B.L., Greene S.J., Aggarwal R., Bhatt A.S., McMurray J.J.V. et al. Potential implications of expanded US food and drug administration labeling for sacubitril/

valsartan in the US. *JAMA Cardiol.* 2021;6(12):1415−1423. DOI: 10.1001/jamacardio.2021.3651.
49. Lin Y., Wu M., Liao B., Pang X., Chen Q., Yuan J. et al. Comparison of Pharmacological Treatment Effects on Long-Time Outcomes in Heart Failure With Preserved Ejection Fraction: A Network Meta-analysis of Randomized Controlled Trials. *Front. Pharmacol.* 2021;12:707777. DOI: 10.3389/fphar.2021.707777.
50. Bozkurt B., Ezekowitz J. Substance and Substrate: LVEF and Sex Subgroup Analyses of PARAGON-HF and PARADIGM-HF Trials. *Circulation.* 2020;141(5):362−366. DOI: 10.1161/CIRCULATIONAHA.120.045008
51. Yancy C.W. An expanded heart failure indication for sacubitril/valsartan: evolving the evidence bar. *JAMA Cardiol.* 2021;6(12):1357−1358. DOI: 10.1001/jamacardio.2021.3658.
52. Gallo G., Volpe M., Battistoni A., Russo D., Tocci G., Musumeci M.B. Sacubitril/valsartan as a therapeutic tool across the range of heart failure phenotypes and ejection fraction spectrum. *Front. Physiol.* 2021;12:652163. DOI: 10.3389/fphys.2021.652163.
53. Vaz-Salvador P., Adão R., Vasconcelos I., Leite-Moreira A.F., Brás-Silva C. Heart failure with preserved ejection fraction: a pharmacotherapeutic update. *Cardiovasc. Drugs Ther.* 2022:1–18. DOI: 10.1007/s10557-021-07306-8.
54. Aikins A.O., Nguyen D.H., Paundralingga O., Farmer G.E., Shimoura C.G., Brock C. et al. Cardiovascular neuroendocrinology: emerging role for neurohypophyseal hormones in pathophysiology. *Endocrinology.* 2021;162(8):bqab082. DOI: 10.1210/endocr/bqab082.
55. Urbach J., Goldsmith S.R. Vasopressin antagonism in heart failure: a review of the hemodynamic studies and major clinical trials. *Ther. Adv. Cardiovasc. Dis.* 2021;15:1753944720977741. DOI: 10.1177/1753944720977741.
56. Vishram-Nielsen J.K.K., Tomasoni D., Gustafsson F., Metra M. Contemporary drug treatment of advanced heart failure with reduced ejection fraction. *Drugs.* 2022:1−31. DOI: 10.1007/s40265-021-01666-z.
57. Bhatt A.S., Yanamandala M., Konstam M.A. For vaptans, as for life, balance is better. *Eur. J. Heart Fail.* 2021;23(5):751−753. DOI: 10.1002/ejhf.2042.
58. Goldsmith S.R., Burkhoff D., Gustafsson F., Voors A., Zannad F., Kolkhof P. et al. Dual Vasopressin Receptor Antagonism to Improve Congestion in Patients With Acute Heart Failure: Design of the AVANTI Trial. *J. Card. Fail.* 2021;27(2):233−241. DOI: 10.1016/j.cardfail.2020.10.007.
59. Mondritzki T., Mai T.A., Vogel J., Pook E., Wasnaire P., Schmeck C. et al. Cardiac output improvement by pecavaptan: a novel dual-acting vasopressin V1a/V2 receptor antagonist in experimental heart failure. *Eur. J. Heart Fail.* 2021;23(5):743−750. DOI: 10.1002/ejhf.2001.
60. Kolkhof P., Bärfacker L. 30 years of the mineralocorticoid receptor: Mineralocorticoid receptor antagonists: 60 years of research and development. *J. Endocrinol.* 2017;234(1):T125−T140. DOI: 10.1530/JOE-16-0600.
61. Kolkhof P., Bärfacker L. 30 years of the mineralocorticoid receptor: Mineralocorticoid receptor antagonists: 60 years of research and development. *J. Endocrinol.* 2017;234(1):T125−T140. DOI: 10.1530/JOE-16-0600.
62. Filippatos G., Anker S.D., Böhm M., Gheorghiade M., Køber L., Krum H. et al. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. *Eur. Heart J.* 2016;37(27):2105−2114. DOI: 10.1093/eurheartj/ehw132.
63. Capelli I., Gasperoni L., Ruggeri M., Donati G., Baraldi O., Sorrenti G. et al. New mineralocorticoid receptor antagonists: update on their use in chronic kidney disease and heart failure. *J. Nephrol.* 2020;33(1):37−48. DOI: 10.1007/s40620-019-00600-7.
64. Rico-Mesa J.S., White A., Ahmadian-Tehrani A.., Anderson AS. Mineralocorticoid Receptor Antagonists: a Comprehensive Review of Finerenone. *Curr. Cardiol. Rep.* 2020;22(11):140. DOI: 10.1007/s11886-020-01399-7.
65. Filippatos G., Anker S.D., Agarwal R., Ruilope L.M., Rossing P., Bakris G.L. et al. Finerenone Reduces Risk of Incident Heart Failure in Patients With Chronic Kidney Disease and Type 2 Diabetes: Analyses From the FIGARO-DKD Trial. *Circulation.* 2022;145(6):437−447. DOI: 10.1161/CIRCULATIONAHA.121.057983.
66. Cox Z.L., Hung R., Lenihan D.J., Testani J.M. Diuretic strategies for loop diuretic resistance in acute heart failure: the 3t trial. *JACC Heart Fail.* 2020;8(3):157−168. DOI: 10.1016/j.jchf.2019.09.012.
67. Batool A., Salehi N., Chaudhry S., Cross M., Malkawi A., Siraj A. Role of vasodilator therapy in acute heart failure. *Cureus.* 2021;13(8):e17126. DOI: 10.7759/cureus.17126.
68. Armstrong P.W., Pieske B., Anstrom K.J., Ezekowitz J., Hernandez A.F., Butler J. et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N. Engl. J. Med.* 2020;382(20):1883−1893. DOI: 10.1056/NEJMoa1915928.
69. Calamera G., Moltzau L.R., Levy F.O., Andressen K.W. Phosphodiesterases and compartmentation of cAMP and cGMP signaling in regulation of cardiac contractility in normal and failing hearts. *Int. J. Mol. Sci.* 2022;23(4):2145. DOI: 10.3390/ijms23042145.
70. Klinger J.R., Chakinala M.M., Langleben D., Rosenkranz S., Sitbon O. Riociguat: clinical research and evolving role in therapy. *Br. J. Clin. Pharmacol.* 2021;87(7):2645−2662. DOI: 10.1111/bcp.14676.
71. McMurray J.J.V., Solomon S.D., Inzucchi S.E., Køber L., Kosiborod M.N., Martinez F.A. et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N. Engl. J. Med.* 2019;381(21):1995−2008. DOI: 10.1056/NEJMoa1911303.
72. Packer M., Anker S.D., Butler J., Filippatos G., Pocock S.J., Carson P. et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N. Engl. J. Med.* 2020;383(15):1413−1424. DOI: 10.1056/NEJMoa2022190.
73. Solomon S.D., de Boer R.A., DeMets D., Hernandez A.F., Inzucchi S.E., Kosiborod M.N. et al. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. *Eur. J. Heart Fail.* 2021;23(7):1217−1225. DOI: 10.1002/ejhf.2249.
74. Butler J., Packer M., Filippatos G., Ferreira J.P., Zeller C., Schnee J. et al. Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction. *Eur. Heart J.* 2022;43(5):416−426. DOI: 10.1093/eurheartj/ehab798.

75. Yadava O.P. Heart failure - does ejection fraction hold any relevance? *Indian J. Thorac. Cardiovasc. Surg.* 2022;38(1):1–4. DOI: 10.1007/s12055-021-01295-x.
76. Bethel M.A., McMurray J.J.V. Class effect for sodium glucose-cotransporter-2 inhibitors in cardiovascular outcomes: implications for the cardiovascular disease specialist. *Circulation.* 2018;137(12):1218–1220. DOI: 10.1161/CIRCULATIONAHA.117.030117.
77. Volpe M., Patrono C. Do VERTIS-CV trial results question a class-effect of cardiovascular protection with sodium-glucose cotransporter 2 inhibitors? *Eur. Heart J.* 2020;41(44):4232–4233. DOI: 10.1093/eurheartj/ehaa891.
78. Teo Y.H., Yoong C.S.Y., Syn N.L., Teo Y.N., Cheong J.Y.A., Lim Y.C. et al. Comparing the clinical outcomes across different sodium/glucose cotransporter 2 (SGLT2) inhibitors in heart failure patients: a systematic review and network meta-analysis of randomized controlled trials. *Eur. J. Clin. Pharmacol*. 2021;77(10):1453–1464. DOI: 10.1007/s00228-021-03147-4.
79. Savarese G., Butler J., Lund L.H., Bhatt D.L., Anker S.D. Cardiovascular effects of non-insulin glucose-lowering agents: a comprehensive review of trial evidence and potential cardioprotective mechanisms. *Cardiovasc. Res.* 2021:cvab271. DOI: 10.1093/cvr/cvab271.
80. Täger T., Frankenstein L., Atar D., Agewall S., Frey N., Grundtvig M. et al. Influence of receptor selectivity on benefits from SGLT2 inhibitors in patients with heart failure: a systematic review and head-to-head comparative efficacy network meta-analysis. *Clin. Res. Cardiol.* 2022;111(4):428–439. DOI: 10.1007/s00392-021-01913-z.
81. Correale M., Lamacchia O., Ciccarelli M., Dattilo G., Tricarico L., Brunetti N.D. Vascular and metabolic effects of SGLT2i and GLP-1 in heart failure patients. *Heart Fail. Rev.* 2021. DOI: 10.1007/s10741-021-10157-y.
82. Helmstädter J., Keppeler K., Küster L., Münzel T., Daiber A., Steven S. Glucagon-like peptide-1 (GLP-1) receptor agonists and their cardiovascular benefits-The role of the GLP-1 receptor. *Br. J. Pharmacol.* 2022;179(4):659–676. DOI: 10.1111/bph.15462.
83. Tanday N., Flatt P.R., Irwin N. Metabolic responses and benefits of glucagon-like peptide-1 (GLP-1) receptor ligands. *Br. J. Pharmacol.* 2022;179(4):526–541. DOI: 10.1111/bph.15485.
84. Rashki Kemmak A., Dolatshahi Z., Mezginejad F., Nargesi S. Economic evaluation of ivabradine in treatment of patients with heart failure: a systematic review. *Expert Rev. Pharmacoecon. Outcomes Res.* 2022;22(1):37–44. DOI: 10.1080/14737167.2021.1941881.
85. Heringlake M., Alvarez J., Bettex D., Bouchez S., Fruhwald S., Girardis M. et al. An update on levosimendan in acute cardiac care: applications and recommendations for optimal efficacy and safety. *Expert Rev. Cardiovasc. Ther.* 2021;19(4):325–335. DOI: 10.1080/14779072.2021.1905520.
86. Asai Y., Sato T., Kito D., Yamamoto T., Hioki I., Urata Y. et al. Combination therapy of midodrine and droxidopa for refractory hypotension in heart failure with preserved ejection fraction per a pharmacist's proposal: a case report. *J. Pharm. Health Care Sci.* 2021;7(1):10. DOI: 10.1186/s40780-021-00193-z.
87. Nagao K., Kato T., Yaku H., Morimoto T., Inuzuka Y., Tamaki Y. et al. Current use of inotropes according to initial blood pressure and peripheral perfusion in the treatment of congestive heart failure: findings from a multicentre observational study. *BMJ Open.* 2022;12(1):e053254. DOI: 10.1136/bmjopen-2021-053254.
88. Cotter G., Davison B.A., Edwards C., Takagi K., Cohen-Solal A., Mebazaa A. Acute heart failure treatment: a light at the end of the tunnel? *Eur. J. Heart Fail.* 2021;23(5):698–702. DOI: 10.1002/ejhf.2116.
89. Felker G.M., Solomon S.D., Claggett B., Diaz R., McMurray J.J.V., Metra M. et al. Assessment of Omecamtiv Mecarbil for the Treatment of Patients With Severe Heart Failure: A Post Hoc Analysis of Data From the GALACTIC-HF Randomized Clinical Trial. *JAMA Cardiol.* 2022;7(1):26–34. DOI: 10.1001/jamacardio.2021.4027.
90. Bernardo B.C., Blaxall B.C. From bench to bedside: new approaches to therapeutic discovery for heart failure. *Heart Lung Circ.* 2016;25(5):425–434. DOI: 10.1016/j.hlc.2016.01.002.
91. Greenberg B. Gene therapy for heart failure. *Trends Cardiovasc. Med.* 2017;27(3):216–222. DOI: 10.1016/j.tcm.2016.11.001.
92. Gabisonia K., Recchia F.A. Gene therapy for heart failure: new perspectives. *Curr. Heart Fail. Rep.* 2018;15(6):340–349. DOI: 10.1007/s11897-018-0410-z.
93. Yamada K.P., Tharakan S., Ishikawa K. Consideration of clinical translation of cardiac AAV gene therapy. *Cell Gene Ther. Insights*. 2020;6(5):609–615. DOI: 10.18609/cgti.2020.073.
94. Devarakonda T., Mauro A.G., Cain C., Das A., Salloum F.N. Cardiac gene therapy with relaxin receptor 1 overexpression protects against acute myocardial infarction. *JACC Basic Transl. Sci*. 2021;7(1):53–63. DOI: 10.1016/j.jacbts.2021.10.012.
95. Sayed N., Allawadhi P., Khurana A., Singh V., Navik U., Pasumarthi S.K. et al. Gene therapy: comprehensive overview and therapeutic applications. *Life Sci.* 2022;294:120375. DOI: 10.1016/j.lfs.2022.120375.
96. Palmiero G., Florio M.T., Rubino M., Nesti M., Marchel M., Russo V. Cardiac resynchronization therapy in patients with heart failure: what is new? *Heart Fail. Clin.* 2021;17(2):289–301. DOI: 10.1016/j.hfc.2021.01.010.
97. Heidenreich P.A., Bozkurt B., Aguilar D., Allen L.A., Byun J.J., Colvin M.M. et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2022:101161CIR0000000000001062. DOI: 10.1161/CIR.0000000000001062.
98. Chinyere I.R., Balakrishnan M., Hutchinson M.D. The emerging role of cardiac contractility modulation in heart failure treatment. *Curr. Opin. Cardiol.* 2022;37(1):30–35. DOI: 10.1097/HCO.0000000000000929.
99. Jorbenadze A., Fudim M., Mahfoud F., Adamson P.B., Bekfani T., Wachter R. et al. Extra-cardiac targets in the management of cardiometabolic disease: Device-based therapies. *ESC Heart Fail.* 2021;8(4):3327–3338. DOI: 10.1002/ehf2.13361.
100. Reed S.D., Yang J.C., Rickert T., Johnson F.R., Gonzalez J.M., Mentz R.J. et al. Quantifying Benefit-Risk Prefer-

ences for Heart Failure Devices: A Stated-Preference Study. *Circ. Heart Fail.* 2022;15(1):e008797. DOI: 10.1161/CIRCHEARTFAILURE.121.008797.
101. Baumwol J. "I Need Help" − A mnemonic to aid timely referral in advanced heart failure. *J. Heart Lung Transplant.* 2017;36(5):593594. DOI: 10.1016/j.healun.2017.02.010.
102. Kalyuzhin V.V., Teplyakov A.T., Bespalova I.D., Kalyuzhina E.V., Terentyeva N.N., Sibireva O.F. et al. Advanced heart failure. *Bulletin of Siberian Medicine*. 2021;20(1):129−146 (in Russ.). DOI: 10.20538/1682-0363-2021-1-129-146.
103. Crespo-Leiro M.G., Metra M., Lund L.H., Milicic D., Costanzo M.R., Filippatos G. et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. *Eur. J. Heart Fail.* 2018;20(11):1505−1535. DOI: 10.1002/ejhf.1236.
104. Shi X., Bao J., Zhang H., Wang H., Li L., Zhang Y. Patients with high-dose diuretics should get ultrafiltration in the management of decompensated heart failure: a meta-analysis. *Heart Fail. Rev.* 2019;24(6):927−940. DOI: 10.1007/s10741-019-09812-2.
105. Grossekettler L., Schmack B., Meyer K., Brockmann C., Wanninger R., Kreusser M.M. et al. Peritoneal dialysis as therapeutic option in heart failure patients. *ESC Heart Fail.* 2019;6(2):271−279. DOI: 10.1002/ehf2.12411.
106. Masarone D., Kittleson M., Petraio A., Pacileo G. Advanced heart failure: state of the art and future directions. *Rev. Cardiovasc. Med.* 2022;23(2):48. DOI: 10.31083/j.rcm2302048.
107. Hullin R., Meyer P., Yerly P., Kirsch M. Cardiac surgery in advanced heart failure. *J. Clin. Med.* 2022;11(3):773. DOI: 10.3390/jcm11030773.
108. Tadic M., Sala C., Cuspidi C. The role of TAVR in patients with heart failure: do we have the responses to all questions? *Heart Fail. Rev.* 2022;27:1617–1625. DOI: 10.1007/s10741-021-10206-6.
109. Yousef S., Arnaoutakis G.J., Gada H., Smith A.J.C., Sanon S., Sultan I. Transcatheter mitral valve therapies: State of the art. *J. Card. Surg.* 2022;37(1):225−233. DOI: 10.1111/jocs.15995.
110. Lund L.H., Khush K.K., Cherikh W.S., Goldfarb S., Kucheryavaya A.Y., Levvey B.J. et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Heart Transplantation Report-2017; Focus Theme: Allograft ischemic time. *J. Heart Lung Transplant.* 2017;36(10):1037−1046. DOI: 10.1016/j.healun.2017.07.019.
111. Kormos R.L., Cowger J., Pagani F.D., Teuteberg J.J., Goldstein D.J., Jacobs J.P. et al. The society of thoracic surgeons intermacs database annual report: evolving indications, outcomes, and scientific partnerships. *Ann. Thorac. Surg.* 2019;107(2):341−353. DOI: 10.1016/j.athoracsur.2018.11.011.
112. Hullin R., Meyer P., Yerly P., Kirsch M. Cardiac surgery in advanced heart failure. *J. Clin. Med.* 2022;11(3):773. DOI: 10.3390/jcm11030773.
113. Rizzo C., Carbonara R., Ruggieri R., Passantino A., Scrutinio D. Iron deficiency: a new target for patients with heart failure. *Front. Cardiovasc. Med.* 2021;8:709872. DOI: 10.3389/fcvm.2021.709872.
114. Mareev V.Yu., Gilyarevsky S.R., Mareev Yu.V., Begrambekova Yu.L., Belenkov Yu.N., Vasyuk Yu.A., et al. Position Paper. The role of iron deficiency in patients with chronic heart failure and current corrective approaches. *Kardiologiia*. 2020;60(1):99 −106 (in Russ.). DOI: 10.18087/cardio.2020.1.n961.
115. Pintér A., Behon A., Veres B., Merkel E.D., Schwertner W.R., Kuthi L.K. et al. The prognostic value of anemia in patients with preserved, mildly reduced and recovered ejection fraction. *Diagnostics (Basel).* 2022;12(2):517. DOI: 10.3390/diagnostics12020517.
116. Toblli J.E., Brignoli R. Iron(III)-hydroxide polymaltose complex in iron deficiency anemia / review and meta-analysis. *Arzneimittelforschung.* 2007;57(6A):431−438. DOI: 10.1055/s-0031-1296692.
117. Zdravkovic S.C., Nagorni S.P., Cojbasic I., Mitic V., Cvetkovic P., Nagorni I. et al. Effects of 6-months of oral ferrous and ferric supplement therapy in patients who were hospitalized for decompensated chronic heart failure. *J. Int. Med. Res.* 2019;47(7):3179−3189. DOI: 10.1177/0300060519847352.
118. Loncar G., Obradovic D., Thiele H., von Haehling S., Lainscak M. Iron deficiency in heart failure. *ESC Heart Fail.* 2021;8(4):2368−2379. DOI: 10.1002/ehf2.13265.
119. Shen T., Xia L., Dong W., Wang J., Su F., Niu S. et al. A Systematic Review and Meta-Analysis: Safety and Efficacy of Mesenchymal Stem Cells Therapy for Heart Failure. *Curr. Stem Cell Res. Ther.* 2021;16(3):354−365. DOI: 10.2174/1574888X15999200820171432.
120. Kir D., Patel M.J., Munagala M.R. What is the status of regenerative therapy in heart failure? *Curr. Cardiol. Rep.* 2021;23(10):146. DOI: 10.1007/s11886-021-01575-3.
121. Pourtaji A., Jahani V., Moallem S.M.H., Karimani A., Mohammadpour A.H. Application of G-CSF in congestive heart failure treatment. *Curr. Cardiol. Rev.* 2019;15(2):83−90. DOI: 10.2174/1573403X14666181031115118
122. Sadahiro T., Ieda M. *In vivo* reprogramming as a new approach to cardiac regenerative therapy. *Semin. Cell Dev. Biol.* 2022;122:21−27. DOI: 10.1016/j.semcdb.2021.06.019.
123. Testa G., Di Benedetto G., Passaro F. Advanced Technologies to Target Cardiac Cell Fate Plasticity for Heart Regeneration. *Int. J. Mol. Sci.* 2021;22(17):9517. DOI: 10.3390/ijms22179517
124. Pascale E., Caiazza C., Paladino M., Parisi S., Passaro F., Caiazzo M. MicroRNA Roles in Cell Reprogramming Mechanisms. *Cells.* 2022;11(6):940. DOI: 10.3390/cells11060940
125. Zhou W., Ma T., Ding S. Non-viral approaches for somatic cell reprogramming into cardiomyocytes. *Semin. Cell Dev. Biol.* 2022;122:28−36. DOI: 10.1016/j.semcdb.2021.06.021
126. Garbern J.C., Lee R.T. Heart regeneration: 20 years of progress and renewed optimism. *Dev. Cell*. 2022;57(4):424−439. DOI: 10.1016/j.devcel.2022.01.012.
127. Sharma V., Dash S.K., Govarthanan K., Gahtori R., Negi N., Barani M. et al. Recent advances in cardiac tissue engineering for the management of myocardium infarction. *Cells.* 2021;10(10):2538. DOI: 10.3390/cells10102538.
128. Goonoo N. Tunable biomaterials for myocardial tissue regeneration: promising new strategies for advanced biointer-

face control and improved therapeutic outcomes. *Biomater. Sci.* 2022;10(7):1626–1646. DOI: 10.1039/d1bm01641e.
129. Hoeeg C., Dolatshahi-Pirouz A., Follin B. Injectable hydrogels for improving cardiac cell therapy *in vivo* evidence and translational challenges. *Gells.* 2021;7(1):7. DOI: 10.3390/gels7010007.
130. Doimo S., Pavan D. Novelties in therapy of chronic heart failure. *Heart Fail. Clin.* 2021;17(2):255–262. DOI: 10.1016/j.hfc.2021.01.006.
131. Eschenhagen T., Ridders K., Weinberger F. How to repair a broken heart with pluripotent stem cell-derived cardiomyocytes. *J. Mol. Cell. Cardiol.* 2022;163:106–117. DOI: 10.1016/j.yjmcc.2021.10.005.
132. Kalyuzhin V.V., Solovtsov M.A., Kamaev D.Yu. The effectiveness of cytocardioprotection of patients with the moderately expressed post infarct dysfunction of left heart ventricle: the results of the randomization research of trimetazidine and athenolole. Bulletin of Siberian Medicine. 2002;1(1):40–44 (in Russ.). DOI: 10.20538/1682-0363-2002-1-40-44.
133. Shu H., Peng Y., Hang W., Zhou N., Wang D.W. Trimetazidine in heart failure. *Front. Pharmacol.* 2021;11:569132. DOI: 10.3389/fphar.2020.569132.
134. Jong C.J., Sandal P., Schaffer S.W. The role of taurine in mitochondria health: more than just an antioxidant. *Molecules.* 2021;26(16):4913. DOI: 10.3390/molecules26164913.
135. Yuan S., Schmidt H.M., Wood K.C., Straub A.C. Coenzyme Q in cellular redox regulation and clinical heart failure. *Free Radic. Biol. Med.* 2021;167:321–334. DOI: 10.1016/j.freeradbiomed.2021.03.011.
136. Raddysh M.E., Delgado D.H. Integrating supplementation in the management of patients with heart failure: an evidence-based review. *Expert. Rev. Cardiovasc. Ther.* 2021;19(10):891–905. DOI: 10.1080/14779072.2021.1999806.
137. Oppedisano F., Mollace R., Tavernese A., Gliozzi M., Musolino V., Macrì R. et al. PUFA supplementation and heart failure: effects on fibrosis and cardiac remodeling. *Nutrients.* 2021;13(9):2965. DOI: 10.3390/nu13092965.
138. Liu J., Meng Q., Zheng L., Yu P., Hu H., Zhuang R. et al. Effect of omega-3 polyunsaturated fatty acids on left ventricular remodeling in chronic heart failure: a systematic review and meta-analysis. *Br. J. Nutr.* 2022;1–35. DOI: 10.1017/S0007114521004979.
139. Mareev V.Yu., Mareev Yu.V., Begrambekova Yu.L. Coenzyme Q-10 in the treatment of patients with chronic heart failure and reduced left ventricular ejection fraction: systematic review and meta-analysis. *Kardiologiia*. 2022;62(6):3–14 (in Russ.). DOI: 10.18087/cardio.2022.6.n2050.
140. Samuel T.Y., Hasin T., Gotsman I., Weitzman T., Ben Ivgi F., Dadon Z. et al. Coenzyme Q10 in the Treatment of Heart Failure with Preserved Ejection Fraction: A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial. *Drugs R. D.* 2022;22(1):25–33. DOI: 10.1007/s40268-021-00372-1.
141. Mongirdienė A., Skrodenis L., Varoneckaitė L., Mierkytė G., Gerulis J. Reactive oxygen species induced pathways in heart failure pathogenesis and potential therapeutic strategies. *Biomedicines.* 2022;10(3):602. DOI: 10.3390/biomedicines10030602.
142. Schwemmlein J., Maack C., Bertero E. Mitochondria as therapeutic targets in heart failure. *Curr. Heart Fail. Rep.* 2022;19(2):27–36. DOI: 10.1007/s11897-022-00539-0.
143. Bisaccia G., Ricci F., Gallina S., Di Baldassarre A., Ghinassi B. Mitochondrial Dysfunction and Heart Disease: Critical Appraisal of an Overlooked Association. *Int. J. Mol. Sci.* 2021;22(2):614. DOI: 10.3390/ijms22020614.
144. Ghionzoli N., Gentile F., Del Franco A.M., Castiglione V., Aimo A., Giannoni A. et al. Current and emerging drug targets in heart failure treatment. *Heart Fail. Rev.* 2022;27(4):1119–1136. DOI: 10.1007/s10741-021-10137-2.
145. Ismail U., Sidhu K., Zieroth S. Hyperkalaemia in heart failure. *Card. Fail. Rev.* 2021;7:e10. DOI: 10.15420/cfr.2020.29.
146. Murphy D., Ster I.C., Kaski J.C., Anderson L., Banerjee D. The LIFT trial: study protocol for a double-blind, randomised, placebo-controlled trial of K^+-binder Lokelma for maximisation of RAAS inhibition in CKD patients with heart failure. *BMC Nephrol.* 2021;22(1):254. DOI: 10.1186/s12882-021-02439-2
147. Montagnani A., Frasson S., Gussoni G., Manfellotto D. Optimization of RAASi Therapy with New Potassium Binders for Patients with Heart Failure and Hyperkalemia: Rapid Review and Meta-Analysis. *J. Clin. Med.* 2021;10(23):5483. DOI: 10.3390/jcm10235483.
148. Silva-Cardoso J., Brito D., Frazão J.M., Ferreira A., Bettencourt P., Branco P. et al. Management of RAASi-associated hyperkalemia in patients with cardiovascular disease. *Heart Fail. Rev.* 2021;26(4):891–896. DOI: 10.1007/s10741-020-10069-3.
149. Ostanko V.L., Kalacheva T.P., Kalyuzhina E.V., Livshits I.K., Shalovai A.A., Chernogoryuk G.E., et al. Biological markers in risk stratification and progression of cardiovascular disease: present and future. *Bulletin of Siberian Medicine*. 2018;17(4):264–280 (in Russ.). DOI: 10.20538/1682-0363-2018-4-264-280.
150. Sainio A., Järveläinen H. Extracellular matrix macromolecules as potential targets of cardiovascular pharmacotherapy. *Adv. Pharmacol.* 2018;81:209–240. DOI: 10.1016/bs.apha.2017.09.008.
151. Castiglione V., Aimo A., Vergaro G., Saccaro L., Passino C., Emdin M. Biomarkers for the diagnosis and management of heart failure. *Heart Fail. Rev*. 2022;27(2):625–643. DOI: 10.1007/s10741-021-10105-w.
152. Sygitowicz G., Maciejak-Jastrzębska A., Sitkiewicz D. The diagnostic and therapeutic potential of galectin-3 in cardiovascular diseases. *Biomolecules.* 2021;12(1):46. DOI: 10.3390/biom12010046.
153. Shirakawa K., Sano M. Osteopontin in cardiovascular diseases. *Biomolecules.* 2021;11(7):1047. DOI: 10.3390/biom11071047.
154. Maruyama K., Imanaka-Yoshida K. The pathogenesis of Cardiac Fibrosis: A Review of Recent Progress. *Int. J. Mol. Sci.* 2022;23(5):2617. DOI: 10.3390/ijms23052617.
155. Aimo A., Spitaleri G., Panichella G., Lupón J., Emdin M., Bayes-Genis A. Pirfenidone as a novel cardiac protective treatment. *Heart Fail. Rev.* 2022;27(2):525–532. DOI: 10.1007/s10741-021-10175-w.
156. Trinh K., Julovi S.M., Rogers N.M. The role of matrix pro-

teins in cardiac pathology. *Int. J. Mol. Sci.* 2022;23(3):1338. DOI: 10.3390/ijms23031338.
157. May B.M., Pimentel M., Zimerman L.I., Rohde L.E. GDF-15 as a biomarker in cardiovascular disease. *Arq. Bras. Cardiol.* 2021;116(3):494−500. DOI: 10.36660/abc.20200426 .
158. Lewis G.A., Rosala-Hallas A., Dodd S., Schelbert E.B., Williams S.G., Cunnington C. et al. Predictors of myocardial fibrosis and response to anti-fibrotic therapy in heart failure with preserved ejection fraction. *Int. J. Cardiovasc. Imaging.* 2022. DOI: 10.1007/s10554-022-02544-9.
159. Zhang Y., Bauersachs J., Langer H.F. Immune mechanisms in heart failure. *Eur. J. Heart Fail.* 2017;19(11):1379−1389. DOI: 10.1002/ejhf.942.
160. Murphy S.P., Kakkar R., McCarthy C.P., Januzzi J.L. Jr. Inflammation in Heart Failure: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* 2020;75(11):1324−1340. DOI: 10.1016/j.jacc.2020.01.014.
161. Kumar P., Lim A., Poh S.L., Hazirah S.N., Chua C.J.H., Sutamam N.B. et al. Pro-Inflammatory Derangement of the Immuno-Interactome in Heart Failure. *Front. Immunol.* 2022;13:817514. DOI: 10.3389/fimmu.2022.817514.
162. Bertero E., Dudek J., Cochain C., Delgobo M., Ramos G., Gerull B. et al. Immuno-metabolic interfaces in cardiac disease and failure. *Cardiovasc. Res.* 2022;118(1):37−52. DOI: 10.1093/cvr/cvab036.
163. Everett B.M., Cornel J.H., Lainscak M., Anker S.D., Abbate A., Thuren T. et al. Anti-inflammatory therapy with canakinumab for the prevention of hospitalization for heart failure. *Circulation.* 2019;139(10):1289−1299. DOI: 10.1161/CIRCULATIONAHA.118.038010.
164. Abbate A., Toldo S., Marchetti C., Kron J., Van Tassell B.W., Dinarello C.A. Interleukin-1 and the inflammasome as therapeutic targets in cardiovascular disease. *Circ. Res.* 2020;126(9):1260−1280. DOI: 10.1161/CIRCRESAHA.120.315937.
165. Hanna A., Frangogiannis N.G. Inflammatory cytokines and chemokines as therapeutic targets in heart failure. *Cardiovasc. Drugs Ther.* 2020;34(6):849−863. DOI: 10.1007/s10557-020-07071-0.
166. Libby P. Targeting inflammatory pathways in cardiovascular disease: the inflammasome, interleukin-1, interleukin-6 and beyond. *Cells.* 2021;10(4):951. DOI: 10.3390/cells10040951.
167. Reina-Couto M., Pereira-Terra P., Quelhas-Santos J., Silva-Pereira C., Albino-Teixeira A., Sousa T. Inflammation in human heart failure: major mediators and therapeutic targets. *Front. Physiol.* 2021Oct.11;12: 746494. DOI: 10.3389/fphys.2021.746494
168. Szabo T.M., Frigy A., Nagy E.E. Targeting mediators of inflammation in heart failure: a short synthesis of experimental and clinical results. *Int. J. Mol. Sci.* 2021;22(23):13053. DOI: 10.3390/ijms222313053.
169. Olsen M.B., Gregersen I., Sandanger Ø., Yang K., Sokolova M., Halvorsen B.E. et al. Targeting the inflammasome in cardiovascular disease. *JACC Basic Transl. Sci.* 2021;7(1):84−98. DOI: 10.1016/j.jacbts.2021.08.006.
170. Ridker P.M., Rane M. Interleukin-6 signaling and anti-interleukin-6 therapeutics in cardiovascular disease. *Circ. Res.* 2021;128(11):1728−1746. DOI: 10.1161/CIRCRESAHA.121.319077.
171. Corcoran S.E., Halai R., Cooper M.A. Pharmacological inhibition of the nod-like receptor family pyrin domain containing 3 inflammasome with MCC950. *Pharmacol. Rev.* 2021;73(3):968−1000. DOI: 10.1124/pharmrev.120.000171/
172. Zhuang C., Chen R., Zheng Z., Lu J., Hong C. Toll-like receptor 3 in cardiovascular diseases. *Heart Lung Circ.* 2022:S1443-9506(22)00080-4. DOI: 10.1016/j.hlc.2022.02.012.
173. Zhang F.S., He Q.Z., Qin C.H., Little P.J., Weng J.P., Xu S.W. Therapeutic potential of colchicine in cardiovascular medicine: a pharmacological review. *Acta Pharmacol. Sin.* 2022;43(9):2173–2190. DOI: 10.1038/s41401-021-00835-w.
174. Arfè A., Scotti L., Varas-Lorenzo C., Nicotra F., Zambon A., Kollhorst B. et al. Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study. *BMJ.* 2016;354:i4857. DOI: 10.1136/bmj.i4857.
175. Mareev V.Yu., Ageev F.T., Arutyunov G.P., Koroteev A.V., Mareev Yu.V., Ovchinnikov A.G., et al. Russian Heart Failure Society, Russian Society of Cardiology. Russian Scientific Medical Society of Internal Medicine Guidelines for diagnosis and treatment of CHF (fourth revision). *Journal – Heart Failure.* 2013;14(7):379–472 (in Russ.).

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