Corresponding author / Адреса для кореспонденції
Lukyantseva Halyna Volodymyrivna / Лук'янцева Галина Володимирівна
National University of Ukraine on Physical Education and Sport / Національний університет фізичного виховання і спорту України
Ukraine, 02000, Kyiv, 1 Fizkultury str. / Адреса: Україна, 02000, м. Київ, вул. Фізкультури 1
Tel.: +380975777765 / Тел.: +380975777765
E-mail: lukjantseva@gmail.com

A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article / **A** – концепція роботи та дизайн, **B** – збір та аналіз даних, **C** – відповідальність за статичний аналіз, **D** – написання статті, **E** – критичний огляд, **F** – остаточне затвердження статті

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Zaikina T. S., Rynchak P. I., Tytova G. Yu., Zaliubovska O. I., Lantukhova N. D.

NEW ERA IN THE TREATMENT OF CHRONIC HEART FAILURE

Kharkiv National Medical University (Kharkiv, Ukraine)
ts.zaikina@knmu.edu.ua

Heart failure remains one of the leading medical problems in the world. In recent years, there have been significant changes in approaches to the treatment of patients with chronic heart failure.

The aim of the study - summarization of existing scientific data on the effects of recently discovered drugs and analysis of current clinical trials aimed at evaluating of experimental drugs in patients with chronic heart failure.

Positive effects of sodium-glucose cotransporter-2 inhibitors found in the several studies allowed to include them in the European guidelines for the treatment of patients with chronic heart failure regardless of the ejection fraction of the left ventricle.

Vericiguat is recommended for patients with chronic heart failure NYHA class II-IV and reduced left ventricular ejection fraction, who experienced decompensation of heart failure in the recent 3 months, despite receiving optimal therapy of chronic heart failure.

Omecamtiv mecarbil, an activator of cardiac myosin, was considered one of the promising drugs for the treatment of heart failure due to its ability to reduce primary composite endpoint compared to placebo. However, in 2023 the US Food and Drug Administration refused to approve omecamtiv mecarbil for the treatment of adult patients with heart failure with reduced left ventricular ejection fraction, citing a lack of sufficient evidence of the drug's effectiveness.

Development of new medicines for patients with chronic heart failure provides new opportunities for improving the quality of life and prognosis of patients. Sodium-glucose cotransporter-2 inhibitors, vericiguat, which are already on the pharmaceutical market, show impressive results in reducing symptoms, preventing decompensation and prolonging the life of patients. Ongoing clinical studies of experimental drugs give hope for breakthrough results.

Key words: *chronic heart failure, drug therapy, sodium-glucose cotransporter-2 inhibitors, vericiguat, omecamtiv mecarbil.*

Connection of the publication with planned research works.

This work is a fragment of the research work «Pathogenetic substantiation of clinical-diagnostic, prognostic and therapeutic markers in patients with coronary artery disease under conditions of polymorbidity». State registration number: 0123U100331.

Introduction.

Heart failure remains one of the key medical problems in the world. According to recent estimates, heart failure affects more than 64 million people and this number is constantly increasing. Obviously, this is due to the aging of the population in developed countries, the increase in survival rates after a myocardial infarction, and the extension of the life expectancy of patients with heart failure itself due to the improvement of treatment tactics. Nevertheless, given the significant functional limitations, poor quality of life, need for rehospitalization, and high risk of mortality, heart failure places a significant burden on health care systems in many countries [1].

In recent years, we have witnessed serious changes in approaches to drug therapy of patients with chronic heart failure (CHF). The arsenal of drugs for the treatment of this cohort of patients has been replenished with new groups of drugs, which in numerous multicenter randomized clinical trials demonstrated a positive effect on the course and prognosis of CHF, which allowed experts to include them in treatment protocols [2, 3, 4]. We will talk about sodium-glucose cotransporter -2 inhibitors, vericiguat and other promising drugs.

The aim of the study.

Summarization of existing scientific data on the effects of recently discovered drugs, such as sodium-glucose cotransporter-2 inhibitors, vericiguat and omecamtiv mecarbil, on the clinical course and prognosis

in patients with chronic heart failure. Analysis of current clinical trials aimed at evaluating hemodynamic effects, tolerability and safety of experimental drugs in patients with chronic heart failure.

Main part.

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are a new class of antidiabetic drugs, whose mechanism of action is the blockade of the low-affinity protein SGLT2, located in the proximal convoluted tubule of the nephron. This protein is responsible for the reabsorption of approximately 90% of the filtered glucose, while the rest of the glucose is reabsorbed thanks to the SGLT1 protein, which is located in the distal part of the proximal convoluted tubule. That is, suppression of the SGLT2 protein prevents the reabsorption of glucose in the nephron and leads to its active excretion with urine. Due to the unique mechanism of action, SGLT2i occupy an important place in the treatment of patients with type 2 diabetes.

But as recent studies have shown, in addition to glucosuria, SGLT2i increase natriuresis and diuresis, which contributes to a significant reduction in preload on the left ventricle. However, unlike loop diuretics, which reduce the volume of intravascular fluid, SGLT2i mainly reduce the volume of interstitial fluid, without worsening the perfusion of internal organs and without causing reflex neurohumoral stimulation [5].

The revealed peculiarities of the action of SGLT2i prompted scientists to investigate the effect of drugs of this group on the course of cardiovascular diseases, in particular CHF.

Thus, in the international placebo-controlled clinical trial DAPA-HF, which included 4744 patients with chronic heart failure NYHA class II, III, IV and reduced left ventricular ejection fraction (≤40%), it was established that the addition of dapagliflozin at a dose of 10 mg once daily before standard therapy reduced the risk of cardiovascular death or worsening heart failure by 26% compared with placebo. Moreover, a similar effect was observed both in patients with concomitant type 2 diabetes mellitus and without violations of carbohydrate metabolism [6].

In the international placebo-controlled clinical trial EMPEROR-Reduced, which included 3730 participants with chronic heart failure NYHA class II, III, IV and reduced left ventricular ejection fraction (≤40%), the effect of empagliflozin was investigated. The results showed a 25% relative reduction in the risk of cardiovascular death and hospitalization for heart failure in the group of patients treated with empagliflozin 10 mg once daily compared to the placebo group [7].

Impressive results obtained in the DAPA-HF and EMPEROR-Reduced trials prompted experts to revise the drug therapy recommendations for patients with chronic heart failure and reduced left ventricular ejection fraction and to add SGLT2i to the list of mandatory drugs [3, 4].

In 2022, scientific data appeared on the positive effect of SGLT2i in patients with CHF and moderately reduced or preserved left ventricular ejection fraction (>40%). The results of the DELIVER study with dapagliflozin demonstrated a significant reduction in the risk of cardiovascular death and hospitalization for heart failure in patients treated with dapagliflozin compared with placebo [8]. In the EMPEROR-Preserved trial, empagliflozin showed a 21% risk reduction for the composite primary endpoint due to a reduction in heart failure hospitalizations [9].

The stunning effects of SGLT2i, demonstrated in the DELIVER and EMPEROR-Preserved studies, allowed to expand the indications for the use of SGLT2i and to include them in the updated European guidelines for the treatment of patients with CHF and moderately reduced or preserved left ventricular ejection fraction [2].

According to scientists, the impressive effect of SGLT2i on the course and prognosis in patients with CHF may be related not only to glucosuria and natriuresis, but also to other mechanisms, in particular, a decrease in intraglomerular pressure, a decrease in blood pressure and the level of uric acid in the blood serum, improvement of the metabolic energetic processes in cardiomyocytes, a decrease in the level of proinflammatory cytokines, suppression of the sympathetic nervous system, an increase in autophagy and lysosomal degradation, a decrease in the mass of epicardial fat, an increase in the level of erythropoietin, an increase in circulating provascular progenitor cells, a decrease in oxidative stress and an improvement in vascular function [10].

Sodium-glucose cotransporter-2 inhibitors have proven to be extremely effective therapeutic agents, which, thanks to their unique effects, are able to modify the course of chronic heart failure. We hope that further scientific research will reveal the full potential of SGLT2i and expand the scope of their application in clinical practice.

It is well known that heart failure is associated with insufficient synthesis of NO and reduced activity of soluble guanylate cyclase, which can lead to myocardial and vascular dysfunction. Directly stimulating soluble guanylate cyclase, vericiguat increases the level of intracellular cyclic guanylate monophosphate (cGMP) which contributes to smooth muscle relaxation, vasodilation, inhibition of hypertrophy, reduction of inflammation and fibrosis, and slowing of cardiac remodeling [11].

The first data on the use of vericiguat in patients with heart failure and reduced left ventricular ejection fraction were obtained in the SOCRATES-REDUCED clinical trial which confirmed the safety and effectiveness of this drug [12].

In the multicenter randomized placebo-controlled trial VICTORIA, which included 5050 patients with CHF NYHA class II-IV and left ventricular ejection fraction <45%, vericiguat at a target dose of 10 mg once daily demonstrated advantages over placebo in reducing the risk of cardiovascular mortality and hospitalization for heart failure [13].

Taking into account obtained results, vericiguat is recommended to be prescribed to patients with CHF NYHA class II-IV and reduced left ventricular ejection fraction, who experienced decompensation of heart failure in the recent 3 months, despite receiving optimal therapy with ACE inhibitors (or sacubitril/valsartan), beta-adrenergic blockers, mineralocorticoid receptor antagonists [14]. It should be noted that vericiguat should not be prescribed to patients taking other soluble guanylate cyclase stimulators, in particular riociguat for pulmonary hypertension, as well as phosphodiesterase-5 inhibitors due to the risk of

symptomatic hypotension. Vericiguat should also be avoided in patients with severe anemia [15].

However, the use of vericiguat is not limited to patients with heart failure and reduced ejection fraction of the left ventricle. Given the existing deficiency of NO synthesis and the decrease in the activity of soluble guanylate cyclase in patients with preserved myocardial contractility of the left ventricle, clinical trials aimed at evaluating the effect of the drug on the clinical course and prognosis of heart failure against the background of preserved left ventricular ejection fraction are ongoing. First results of these trials are quite contradictory, because the positive effect of vericiguat on the quality of life of a patient with heart failure, revealed in the SOCRATES-PRESERVED study [16], was not confirmed in the VITALITY-HFpEF study [17]. This suggests the need for continued clinical studies of the effects of vericiguat in this cohort of patients.

To date, two clinical trials with vericiguat are ongoing – the VICTOR trial (VerICiguaT in adults with chronic heart failure and Reduced ejection fraction) and the VALOR trial. The VICTOR trial aimed to evaluate the effect of vericiguat on the course and prognosis of heart failure with reduced left ventricular ejection fraction in patients without recent decompensation of heart failure. The VALOR trial evaluates the effect of vericiguat on NT-proBNP levels in children with dilated cardiomyopathy [18].

Despite significant positive changes in approaches to drug therapy of chronic heart failure that have taken place over the past few years, the search for new highly effective drugs does not stop.

For a long time, omecamtiv mecarbil, an activator of cardiac myosin, was considered one of the promising drugs for the treatment of heart failure. Mechanism of its action is associated with the activation of cardiac myosin and an increase in the rate of hydrolysis of adenosine triphosphate (ATP), which leads to an increase in the formation of the actin-myosin complex and an increase in cardiomyocyte contraction [19].

In the GALACTIC-HF trial, that was conducted in patients with heart failure and reduced left ventricular ejection fraction (LVEF ≤35%), omecamtiv mecarbil was associated with a reduction in the primary composite endpoint compared to placebo. These differences were especially significant in the group of patients with left ventricular ejection fraction ≤28% and in the group of patients with systolic blood pressure ≤100 mm Hg. [20].

The encouraging results gave hope to the most severe patients with heart failure. However, in 2023 the US Food and Drug Administration (FDA) refused to approve omecamtiv mecarbil for the treatment of adult patients with heart failure with reduced left ventricular ejection fraction, citing a lack of sufficient evidence of the drug's effectiveness [21].

Preclinical and clinical studies of other drugs, potentially able to improve the course and prognosis of patients with heart failure, are ongoing currently. Vemtoberant is among them. Vemtoberant (APD418) belongs to beta3-adrenoceptor inhibitors that can be effective in the treatment of conditions accompanied by activation of the sympathetic nervous system, in particular, heart failure. To date, a phase 2 of the multicenter, randomized, double-blinded, placebo-controlled clinical study of vemtoberant has been completed. Its primary objective was to evaluate the hemodynamic effects, safety, tolerability, and pharmacokinetics of the vemtoberant in patients with heart failure and reduced left ventricular ejection fraction [22].

Considering the crucial role of the activation of the renin-angiotensin-aldosterone system in the development and progression of heart failure, an innovative drug was developed that inhibits the synthesis of angiotensinogen by binding to the mRNA encoding angiotensinogen. A significant decrease in angiotensinogen levels was found in the group of hypertensive patients who received evazarsen sodium compared with patients who received placebo [23]. The positive effect of evazarsen sodium on the level of angiotensinogen prompted scientists to investigate the effect of the drug on the course and prognosis of heart failure. We hope that the results of this research will become known to the scientific community in the near future.

Conclusions.

The emergence of new drugs has opened a new era in the treatment of chronic heart failure. These innovative tools demonstrate significant success in improving the quality of life and prognosis of patients with this pathology. Currently, clinical studies of other drugs are ongoing, which already show positive results and give hope for breakthrough findings. This will generally add to the progress in the treatment of heart failure in the near future.

Prospects for further research.

Further research into the development of new drugs for the treatment of chronic heart failure, as well as the expansion of indications for existing drugs, is extremely urgent. Movement in these directions can lead to important breakthroughs in the therapy of chronic heart failure, which will improve the quality of life and prognosis of patients with this pathology.

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НОВА ЕРА В ЛІКУВАННІ ХРОНІЧНОЇ СЕРЦЕВОЇ НЕДОСТАТНОСТІ

Заїкіна Т. С., Ринчак П. І., Титова Г. Ю., Залюбовська О. І., Лантухова Н. Д.

Резюме. Серцева недостатність є однією з найбільш актуальних проблем медицини, адже число пацієнтів, які страждають на цю патологію, продовжує неухильно зростати. Арсенал препаратів для лікування хронічної серцевої недостатності поповнився новими зразками, які продемонстрували значну ефективність у поліпшенні перебігу та прогнозу пацієнтів цієї когорти. Утім, пошук інших перспективних препаратів триває.

Метою нашої роботи є узагальнення існуючих наукових даних щодо впливу інгібіторів натрійзалежного котранспортера глюкози 2-го типу, веріцигуату, омекамтиву мекарбіл на клінічний перебіг та прогноз у пацієнтів із хронічною серцевою недостатністю, а також аналіз поточних клінічних досліджень, спрямованих на оцінку гемодинамічних ефектів, переносимості та безпеки експериментальних препаратів у пацієнтів з хронічною серцевою недостатністю.

Виявлені позитивні ефекти інгібіторів натрійзалежного котранспортера глюкози 2-го типу дозволили включити їх до європейських рекомендацій для лікування пацієнтів із хронічною серцевою недостатністю незалежно від фракції викиду лівого шлуночка.

Веріцигуат рекомендований пацієнтам із хронічною серцевою недостатністю II-IV класу за NYHA та зниженою фракцією викиду лівого шлуночка, у яких протягом останніх 3 місяців спостерігалася декомпенсація серцевої недостатності, незважаючи на те, що вони отримували оптимальну терапію хронічної серцевої недостатності.

Омекамтиву мекарбіл-це активатор серцевого міозину, який впродовж тривалого часу вважався одним із перспективних препаратів для лікування серцевої недостатності завдяки його здатності знижувати первинну комбіновану кінцеву точку порівняно з плацебо. Однак у 2023 році Управління з контролю за якістю харчових продуктів і медикаментів США відмовилося схвалити омекамтив мекарбіл для лікування дорослих пацієнтів із серцевою недостатністю зі зниженою фракцією викиду лівого шлуночка, посилаючись на відсутність достатніх доказів ефективності препарату.

Розробка нових лікарських засобів для пацієнтів із хронічною серцевою недостатністю відкриває нові можливості для покращення якості життя та прогнозу пацієнтів. Триваючі клінічні дослідження експериментальних препаратів дають надію на проривні результати.

Ключові слова: хронічна серцева недостатність, медикаментозна терапія, інгібітори натрійзалежного котранспортера глюкози 2-го типу, веріцигуат, омекамтив мекарбил.

NEW ERA IN THE TREATMENT OF CHRONIC HEART FAILURE

Zaikina T. S., Rynchak P. I., Tytova G. Yu., Zaliubovska O. I., Lantukhova N. D.

Abstract. Heart failure is one of the most urgent problems of medicine, because the number of patients suffering from this pathology continues to grow steadily. The arsenal of drugs for the treatment of chronic heart failure has been replenished with new samples that have demonstrated significant effectiveness in improving the course and prognosis of patients in this cohort. However, the search for other promising drugs continues.

The aim of our work is to summarize existing scientific data on the effect of sodium-glucose cotransporter-2 inhibitors, vericiguat, omecamtiv mecarbil on the clinical course and prognosis in patients with chronic heart failure, as well as the analysis of current clinical studies aimed at evaluating hemodynamic effects, tolerability and safety of experimental drugs in patients with chronic heart failure.

The positive effects of sodium-glucose cotransporter-2 inhibitors have led to their inclusion in European guidelines for treating patients with chronic heart failure, regardless of left ventricular ejection fraction.

Vericiguat is recommended for patients with NYHA class II-IV chronic heart failure and reduced left ventricular ejection fraction who have decompensated heart failure within the past 3 months despite receiving optimal chronic heart failure therapy.

Omecamtiv mecarbil has been considered a promising drug for the treatment of heart failure due to its ability to reduce the primary composite endpoint compared to placebo for many years. However, in 2023, the US Food and Drug Administration refused to approve omecamtiv mecarbil for the treatment of adult heart failure patients with reduced left ventricular ejection fraction, citing insufficient evidence of the drug's effectiveness.

Development of new drugs for patients with chronic heart failure opens up new opportunities to improve the quality of life and prognosis of patients. Ongoing clinical trials of experimental drugs give hope for breakthrough results.

Key words: chronic heart failure, drug therapy, sodium-glucose cotransporter-2 inhibitors, vericiguat, omecamtiv mecarbil.

ORCID and contributionship:
Zaikina T. S.: https://orcid.org/0000-0003-1587-2146 ADF
Rynchak P. I.: https://orcid.org/0000-0002-7413-0970 BD
Tytova G. Yu.: https://orcid.org/0000-0001-6876-083X AE
Zaliubovska O. I.: https://orcid.org/0000-0003-2165-6386 BE
Lantukhova N. D.: https://orcid.org/0000-0003-4713-7971 BE

Conflict of interest:
The authors declare that there is no conflict of interest.

Corresponding author
Zaikina Tetiana Serhiivna
Kharkiv National Medical University
Ukraine, 61022, Kharkiv, 4 Nauky avenue
Tel.: 0508127688
E-mail: ts.zaikina@knmu.edu.ua

A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article.

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Ivanov R. O., Zverkhanovskyi O. A., Sarafiniuk L. A., Androshchuk O. V., Tatarina O. V.

MAIN METHODOLOGICAL ASPECTS OF DETERMINING THE CHEWING EFFICIENCY

National Pirogov Memorial Medical University (Vinnytsya, Ukraine)
lsarafinyuk@gmail.com

In modern dentistry, one of the problems that needs to be urgently addressed is the determination and evaluation of masticatory efficiency, in particular, a reliable assessment of masticatory pressure at the time of occlusion. Occlusion is a system of integrated structures that ensure the interconnection of tooth contacts, which is based on the morphological and functional state of the maxillary joint and the neuromuscular system in general. The purpose of our study is to analyse the existing data on methods for determining and evaluating chewing efficiency, in particular, bite force and chewing pressure in people of different ages and genders. We conducted a systematic review and analysis of the literature with a depth of 10 years based on PubMed, Google Scholar, ScienceDirect, Scopus,