



RESEARCH ARTICLE
3.1.20. Кардиология

УДК 616.12-008.464

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K., Musagalieva A., Junusbekova G., Alieva G., Artemenko S.N. - 2024

*** | Accepted:
20.12.2024

<http://dx.doi.org/10.26787/nydha-2686-6838-2024-26-12-35-45>

МЕДИКАМЕНТОЗНАЯ И СЕРДЕЧНАЯ РЕСИНХРОНИЗИРУЮЩАЯ ТЕРАПИЯ В ЛЕЧЕНИИ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ (ОБЗОР ЛИТЕРАТУРЫ)

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Аннотация. В статье рассматривается роль фармакологических средств и имплантируемых устройств в лечении хронической сердечной недостаточности (ХСН) с различной фракцией выброса (ХСНнФВ, ХСНунФВ, ХСНсФВ). Авторами подчеркивается, что, несмотря на широкое внедрение в практику ангиотензиновых рецепторов и непрямого ингибитора (АРНИ), бета-блокаторов, антагонистов минералокортикоидных рецепторов (АМКР) и ингибиторов натрий-глюкозного котранспортера (SGLT2), у больных как ХСНнФВ, так и ХСНунФВ, ХСНсФВ сохраняется высокий остаточный риск неблагоприятных исходов. В связи с этим развиваются методы лечения с использованием имплантируемых кардиовертеров-дефибрилляторов (ИКД) и сердечной ресинхронизирующей терапии (СРТ). Обзор основан на данных из баз PubMed и Google Scholar за последние 5 лет.

Ключевые слова: хроническая сердечная недостаточность, имплантируемые кардиовертеры-дефибрилляторы, сердечная ресинхронизирующая терапия.

DRUG AND CARDIAC RESYNCHRONIZATION THERAPY IN THE TREATMENT OF CHRONIC HEART FAILURE (LITERATURE REVIEW)

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Abstract. The article deals with the role of pharmacological agents and implantable devices in the treatment of chronic heart failure (CHF) with different ejection fraction: preserved ejection fraction, mildly reduced ejection fraction and reduced ejection fraction (HFpEF, CHFmrEFV, CHFrfV). The authors emphasise that despite the widespread introduction of angiotensin receptor and neprilysin inhibitor (ARNI), beta-blockers, mineralocorticoid receptor antagonists (MCRAs) and sodium-glucose cotransporter inhibitors (SGLT2) into practice, there is still a high residual risk of unfavorable outcomes in patients with both HFpEF and CHFmrEFV, CHFrfV. Therefore, therapies using implantable cardioverter-defibrillators (ICDs) and cardiac resynchronisation therapy (CRT) are evolving. The review is based on data from PubMed and Google Scholar databases for the last 5 years.

Keywords: chronic heart failure, implantable cardioverter-defibrillators, cardiac resynchronisation therapy.

Background. Chronic heart failure (CHF) is one of the major problems of our time due to increasing its prevalence and associated mortality rates. The basic pharmacological agents: angiotensin receptor and neprilysin inhibitor (ARNI), beta-blockers, mineralocorticoid receptor antagonists (MCRAs) and sodium-glucose cotransporter inhibitors (SGLT2), have been established for the treatment of CHF with the reduced ejection fraction (CHFrfV) [1, 2, 3]. Recent studies have established a positive role for SGLT2 in patients with CHF with the preserved ejection fraction CHFpEFV) and with moderately reduced ejection fraction (CHFmrEFV). In spite of this, there is still a significant residual risk of unfavourable outcomes in patients with both CHFmrEFV and CHFrfV. Therefore, implantable cardioverter-defibrillators (ICDs) and cardiac resynchronisation therapy (CRT) have been developed in parallel with medical methods [4, 5, 6]. Just recently, devices such as the cardiac contractility modulation and baroreflex activation therapy have been approved by the FDA, although they have not yet been included in any clinical guidelines [6]. Obviously, it is necessary to analyse the state of the problem on the influence of complex therapy including, along with the pharmacotherapy, the implantation of various assistive devices on the course and prognosis of CHF.

Purpose of the study. The aim of this literature review is to analyse the effectiveness of pharmacotherapy and CRT in patients with chronic heart failure.

Materials and methods of the study. The review is based on data from PubMed and Google Scholar databases for the last 5 years.

Results. According to the literature, the prevalence of CHF varies considerably in different regions of the world, from 0.3 % in India to 5.3 % in the indigenous population of Australia. In Western Europe, Germany has the highest prevalence (4 %). It is important to note the presence of gender differences in the detection of different forms of CHF: men are more likely to have CHF with the preserved ejection fraction (98 cases per 100,000 population), while women have predominantly low ejection fraction CHF (141 cases per 100,000) [7].

The most frequent causative or comorbid diseases contributing to the development of CHF are arterial hypertension (65 %), ischaemic heart disease (50 %), chronic kidney disease (43 %), atrial fibrillation (41 %), postinfarction cardiosclerosis (27 %), diabetes mellitus (27 %), obesity (23 %), malignant neoplasms (23 %), chronic obstructive pulmonary disease (23 %), anaemia (12 %), stroke (12 %). It should be noted that coronary heart disease (CHD), aortic stenosis, diabetes mellitus (DM) and chronic kidney disease have a strong association with the probability of death and hospitalisation for CVD, as well as a high degree of evidence of clinical studies confirming the effectiveness of treatment of the corresponding pathology to improve the outcomes of CVD [8].

When analysing the dynamics of mortality from CVD in England and Wales over a fifty-year period (1950-2000), several key trends were found: between 1950 and 1973, mortality from CVD in men increased 3-fold and in women 2.6-fold; by 1993, mortality from CVD in men decreased 1.8-fold and in women 2-fold [9]. Among the reasons for the increase in mortality, an increase in the prevalence of arterial hypertension and CHD is recognised along with an increase in overall life expectancy. In the 1990s, the

era of evidence-based medicine began, and as a result of numerous randomised trials and introduction of new drugs (beta-blockers, ACE inhibitors, statins) it was possible to improve the control of the arterial hypertension and hyperlipidaemia. The success of the smoking cessation has led to a reduction in cardiovascular diseases, including CVD. Despite the country differences, a significant decrease in mortality from CVD during 20 years (from 1985 to 2005) was recorded in the following countries: Greece, Germany, Spain, France, Finland, Sweden [10].

In Russia, the analysis of the Federal State Statistics Service data showed that in the structure of cardiac deaths the share of chronic CHD is 61 %, and the share of CVD is less than 1 %. At the same time, according to the results of in-depth analysis of medical death certificates, the total share of deaths from CVD among deaths in various forms of chronic CHD was 35 % [11]. Undoubtedly, is the widespread introduction of electronic medical records (EMR), united in one vertically integrated medical information system (MIS), the most important condition for a full-fledged and operative analysis of the frequency of CVD cases and mortality from CVD in outpatient and hospital practice. As these processes are still slow in Russia, the available data should be taken in a balanced way.

Modern guidelines for the treatment of CCN recommend to start the treatment with ACE/ARA (angiotensin receptor antagonists) as the first line [1, 2, 3]. The 'classical' ACE inhibitors, which have not lost their importance – enalapril and captopril (IA) – have the highest degree of evidence in the treatment of CHF of all stages; however, 9 others can be used: benazepril, zofenopril, xinapril, lisinopril, perindopril, spirapril, ramipril, fosinopril, cilazapril. All of them have varying degrees of evidence in patients with stable CHF and the previous myocardial infarction [12, 13, 14]. Dry cough occurring on iACE can range from mild to quite severe, that led researchers to study the effects of ARAs (give full name before abbreviation). ARAs, although not shown in clinical trials to have better results (compared to iACEs) in terms of effects on the endpoints, but they very rarely cause cough, and therefore are recommended for the treatment of CHF in cases of iACE intolerance.

Angiotensin receptor and neprilysin inhibitor creates a dual neurohormonal blockade: renin-angiotensin-aldosterone system to block an excessive vasoconstriction, a fluid retention, an aldosterone activation, an organ proliferation and a remodelling, and a neprilysin enzyme blockade by the activating antiproliferative, diuretic and vasodilatory effects of natriuretic peptides [15, 16, 17]. The efficacy of

valsartan/sacubitril (LCZ 696) in patients with CHF was proved in the multicentre randomised phase III PARADIGM-HF study. The study enrolled 8442 patients with CHF, functional class (FC) II-IV (NYHA) and the low left ventricular ejection fraction (LVEF), who did not require intravenous diuretics and had a systolic blood pressure (SBP) level greater than 100 mmHg (above 95 mmHg on treatment). The patients were randomised into two groups: those receiving enalapril at a dose of 10 mg twice daily and C/B at a dose of 100 mg twice daily followed by titration to 200 mg twice daily. The median follow-up period was 27 months. The study was prematurely terminated because of the obvious advantage of valsartan/sacubitril over enalapril, which was traditionally considered the 'gold standard' of therapy for CHF [15].

The main idea behind of the using of b-adrenoblockers (BABs) in the treatment of patients with CHF, was that hyperactivation of the sympathoadrenal system (SAS) contributes to a significant increase in both the risk of the sudden death and the risk of decompensation progression [18]. However, now it is proved that BABs have a blocking effect on some other neurohormonal systems responsible for the progression of CHF: the renin-angiotensin-aldosterone system (RAAS), endothelin system and the cytokine system. There are currently about 30 known randomised clinical trials (RCTs): MDC (metoprolol tartrate study), CIBIS -II (bisoprolol study), MERIT – HF (metoprolol succinate delayed release study), COPERNICUS (carvedilol study), SENIORS (nebivolol study) and others, which showed a positive role of BABs in reducing the risk of the sudden death, the progression of CHF, the hospitalisations due to decompensation of CHF [19].

Mineralocorticoid receptor antagonists affect the secondary aldosteronism that occurs in CHF. Two large studies RALES (study of spironolactone) and EPHESUS (evaluation of eplerenone) demonstrated an additional reduction in the incidence of endpoints in patients with CHF (combined index of mortality from CVD and the incidence of first hospitalisation for CHF decompensation) [20, 21].

Two studies, DAPA-HF (evaluating dapagliflozin) and EMPEROR-Reduced (evaluating empagliflozin), showed that inhibition of sodium-glucose cotransporter-2 (SGLT2) reduced the combined risk of cardiovascular death or hospitalisations in patients with heart failure with reduced ejection fraction with or without diabetes mellitus. A meta-analysis of these studies found a 13 % reduction in all-cause mortality and a 14 % reduction in cardiovascular mortality, as well as a relative reduction in combined cardiovascular risk of

26 % (death or first hospitalisation for heart failure) and combined risk of 25 % (repeat hospitalisations for heart failure and cardiovascular death) [22, 23, 24, 25].

The combined use of ARNI/iACE/ARA, beta-blockers, MCRA (mineralocorticoid receptor antagonists) and SGLT2 inhibitors can reduce the relative risk of cardiovascular death by almost 75 % and translate into an absolute risk reduction of about 25 % when treated for 2 years. This position – quadrotherapy – is leading in clinical recommendations of European, American, national levels [1, 2, 3].

Atrioventricular (AV) blockades, inter- and intraventricular conduction disorders, which are manifested by dilated QRS complexes on ECG, occur quite often in CHF. AV conduction disorders lead to the separation of atrial and ventricular contractions, and slowing of conduction through the Guis-Purkinje system is accompanied by uncoordinated contraction of ventricular myocardial segments. As a result, there is a dyssynchrony of heart chamber contractions. Left bundle branch blockade (LBBB) is registered on ECG in 25 % of persons with CHF; QRS complex dilation >120 ms is associated with a more severe course of CHF and is a predictor of the increased overall risk of death and the risk of sudden cardiac death. To eliminate the ventricular dyssynchrony, cardiac resynchronisation therapy, developed in the late 1990s to treat patients with severe CHF, is used [1, 2, 3, 26].

Cardiac resynchronisation therapy is atrial-synchronised biventricular electrocardiostimulation, the consequence of which is the modification of interventricular, intraventricular and atrial-ventricular activation in individuals with the desynchronisation of the heart chambers. At present, according to the positions of evidence-based medicine, the main indication (class I, level of evidence A) for CRT is clinically manifested CHF in the presence of left bundle branch blockade (LBBB) with QRS complex duration ≥ 130 ms. In this case, either a pacemaker for the resynchronisation therapy (CRT-P) or a combination of cardiac resynchronisation therapy and the implantable cardioversion-defibrillation (CRT-D) may be indicated in a patient with CHF [27–31].

The results of effective CRT in the long term are increased survival and the improved quality of life of patients, the reduction in the number of hospitalisations due to the progression of CHF, the reduction (improvement) of NYHA chronic heart failure class. To achieve these goals, the successful elimination of dyssynchrony and the degree of reverse cardiac remodelling processes on the background of the resynchronisation therapy are

important. There is information in the literature about the use of various methods to determine the effect of CRT based on the study of the dynamics of electrophysiological, clinical and hemodynamic data, but today there are no unified, generally accepted criteria for assessing the response to CRT. The most common positive response is considered to be a decrease in NYHA heart failure class ≥ 1 , ≥ 25 % increase in distance at the six-minute walk test, the ≥ 15 % decrease in left ventricular end-systolic volume (LVEF), ≥ 15 % increase in LVEF [32–34]. At the same time, the results of some studies suggest that 20–40 % of patients with CHF have do not positive response to CRT [28–31]. In the absence of changes or increasing (worsening) of the functional class of CHF, the insufficient degree of the cardiac reverse remodelling or negative dynamics of the indicated hemodynamic parameters, a number of authors refer patients to the category of non-responders to CRT (non-responders) [35–38]. In their opinion, the most common reasons for the absence or the insufficient response to the resynchronisation therapy may be the heterogeneity of patients selected for CRT (difference in the underlying disease leading to CHF, including the presence of myocardial scarring), suboptimal positions of the ventricular electrode and the low percentage of the biventricular stimulation. There is also no unanimity in determining the time frame for assessing true response to CRT, although most published studies have chosen 6 or 12 months as an intermediate time frame for determining the efficacy of CRT [39].

Over the past 20 years, the question of the benefits between the two main methods, CRT-P and CRT-D, has remained unresolved. Thus, in the early 2000s, the COMPANION phase III randomised trial was conducted. In it, patients with clinical indications for the cardiac resynchronisation therapy were randomised into three groups as follows: CRT-D, CRT-P and therapy without device (control group) [38]. All patients received optimal drug treatment for chronic heart failure (CHF) according to the guidelines of the time. Unfortunately, the analysis plan included only a comparison between CRT-D and the control group on the one hand, and CRT-P and control group on the other hand. A direct comparison between CRT-D and CRT-P was not planned, although the sample size allowed for this, with 600 patients in each active group versus 300 in the control group. The endpoints of the study involved assessment of all-cause mortality or hospitalisations for the decompensation of CHF. After a fairly short mean follow-up period (14 months), CRT-D and CRT-P showed almost identical effects compared with the controls: an OR of 0.65 (95% CI 0.53-0.80) for CRT-P and 0.60 (95% CI 0.49-0.75) for CRT-D

for the two endpoints. The mortality was 19% in the control group, 15 % in the CRT-P group, and 12 % in the CRT-D group; the difference was statistically significant for CRT-D comparing with the control group [HR 0.64 (0.48-0.86)] but not for CRT-P [0.76 (0.58-1.01)].

The open randomised trial 'Re-evaluation of the optimal resynchronisation therapy in patients with chronic heart failure' or RESET-CRT study was conducted by the Leipzig Cardiology Centre with the aim to demonstrate that CRT-P is not inferior to CRT-D in patients with chronic heart failure and indications for CRT. The primary endpoint was all-cause mortality [40]. The rationale for the RESET-CRT trial was based on data from a national registry in Germany that included patients with de novo CRT device implantation between 2014 and 2019. The patients with indications for implantation of a cardiac defibrillator for secondary prevention of sudden cardiac death were excluded. Data from 847 patients with CRT-P and 2722 patients with CRT-D were analysed. Overall, there were 714 deaths (20%) during a mean follow-up period of 2.35 years. In the initial unadjusted time-to-event analysis, there was a higher cumulative incidence of the all-cause mortality in patients who underwent CRT-P [HR 1.63 (95%CI 1.38-1.92)]; however, after the adjustment for age [HR 1.13 (95%CI 0.95-1.35)] and after the correction for entropy (better by another expression) [0.99 (95%CI 0.81-1.20)], differences in survival between age groups were not found. The enrolment in the RESET-CRT study has now been stopped because of lack of funding, so there is no certainty that the study will have sufficient power of reasoned conclusions.

In the landmark CARE-HF trial, conducted with the inclusion of patients with CHCF FC III-IV according to NYHA, CRT per se was compared with drug therapy [41]. CRT was shown to reduce the incidence of the combined primary endpoint (what is included) by 37 % [HR 0.63 (95%CI 0.51-0.77)], which is similar to COMPANION, and all-cause mortality (secondary endpoint) by 36% [HR 0.64 (95%CI 0.48-0.85)]. It is important to say that, the median duration of follow-up was twice as long in CARE-HF (29.4 months) as in COMPANION. In the 1-year follow-up (extended) phase of the trial, CRT was also shown to significantly reduce the risk of sudden cardiac death [HR 0.54 (95%CI 0.35-0.84)]. These data strongly suggest that CRT itself improves the survival in patients with moderate and severe CHF.

Two large-scale RCTs evaluated the value of adding CRT to ICDs in patients with CHF with the reduced ejection fraction (<30 %). The RAFT study included 1798 patients with NYHA class II-III who were followed for a mean of 40 months [42]. The MADIT-CRT study included 1820 patients with

NYHA class I-II with a shorter mean duration of follow-up (28 months) [43]. Although the clinical benefit of the primary combined endpoint (disclose) in these two studies was expected, the results were not consistent with the secondary endpoint, the all-cause mortality. In RAFT, the mortality was significantly reduced with CRT-D: 20.8 % vs 26.1 % [HR 0.75 (95%CI 0.62-0.91)], while any significant benefit was not observed in MADIT-CRT: 6.8 % vs 7.3 % [HR 1.00 (95%CI 0.69-1.44)]. These data suggest that the additional survival benefit of adding CRT to ICD may depend on the baseline severity and the duration of follow-up in the study [42, 43, 44].

It was shown in a meta-analysis of five randomised trials comparing CRT without or with a defibrillator (MIRACLE, MIRACLE-ICD, CARE-HF, RAFT, REVERSE), that when CRT/CRT-D patients were compared with controls from the whole population, the OR for the all-cause mortality was 0.66 (95%CI 0.57-0.77) and for the death or hospitalisation for the decompensation of CHF was 0.65 (95%CI 0.58-0.74). However, there was not found any difference between CRT and CRT-D subgroups [45]. Another method was to analyse the effect of implantable cardiac devices (CRT-D, CRT-P or ICD) on the mortality in patients with CHF and reduced PV according to 13 RCTs [46]. In the unadjusted analyses, the CRT-D implantation was the most effective treatment with a mean reduction in the all-cause mortality of 19 % compared with CRT-P and 18 % compared with ICD. Adjusted analyses showed that patients with QRS duration >150 ms, presence of complete VLNPH, age >60 years and female gender benefited more from CRT-P and CRT-D.

And what do we know from observational studies? A recent meta-analysis included 128,030 patients, of whom 55,469 had CRT-P devices implanted and 72,561 had CRT-D devices implanted. The patient baseline characteristics are not described in detail, but it is reported that overall the results show an overall 15 % reduction in all-cause mortality with CRT-D compared with CRT-P [HR 0.85 (95%CI 0.76-0.94)]. However, this difference was statistically insignificant in some patient subgroups, particularly in elderly patients over 75 years of age [HR 0.95 (95%CI 0.79-1.15)] and patients with non-ischaemic cardiomyopathy [HR 1.08 (95%CI 0.96-1.21)] [47].

In the DANISH study, in which 1116 patients with the symptomatic left ventricular dysfunction (left ventricular ejection fraction <35%) not because of to ischaemic heart disease were randomised into two groups: with ICD implantation and no ICD. In both groups, 58 % of patients had CRT. During a median follow-up period (67.6 months), 21.6 % of patients died in the group with ICD compared with

23.4 % in the group without ICD, the difference was not statistically significant [HR 0.87 (95%CI 0.68-1.12)]. A preliminary subgroup analysis didn't show no dependence on whether patients received CRT or not ($p = 0.73$) [48].

The newer alternatives to conventional biventricular cardiac resynchronisation therapy include the stimulation of the conduction system such as the stimulation of the Hiss bundle, the stimulation of the left leg of the Hiss bundle (main trunk or anterior/posterior branches) and the left ventricular stimulation including the left ventricular septal stimulation and the left ventricular endocardial stimulation. All these new ways have a smaller evidence base, but few studies have shown a reduction in QRS duration, the improvement in

NYHA EF, the reduction in the size and the increase in left ventricular ejection fraction [49, 50, 51, 52, 53].

Thus, the results of the studies reported in the review confirm the international guidelines: because of the lack of reliable clinical data, they do not provide strict recommendations on the choice of device, CRT-D or CRT-P, in patients with indications for CRT class I or IIa, including the using new of methods of conduction stimulation. It is recommended that decisions should be made on the basis of individual patient characteristics, as the age and etiology of CHF, as well as the factors such as the life expectancy, the major comorbidities, the renal function and, of course, the patient preference.

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Authors' contribution. All authors declare an equal contribution to the article- conception and design of the study, approval of the final version for publication, full responsibility for the content, literature review, writing the article.

Conflict of Interest Statement. The authors declare no conflict of interest.

CHF – chronic heart failure

ARNI – angiotensin receptor and neprilysin inhibitor

MCRA – mineralocorticoid receptor antagonists

SGLT2 – sodium-glucose cotransporter inhibitors

ACE inhibitors – angiotensin-converting enzyme

ARA – angiotensin receptor antagonists

CRT-D – cardiac resynchronization therapy with defibrillation

CRT-P – cardiac resynchronization therapy with pacemaker

ICD – implantable cardioverter-defibrillator

CHFrFV – CHF with the reduced ejection fraction

CHFpFV – CHF with the preserved ejection fraction

CHFmrEFV – CHF with moderately reduced ejection fraction

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For citation: Akhyt B., Lozhkina N.G., Berkinbaev S., Pashimov M., Koshumbaeva K., Musagalieva A., Junusbekova G., Alieva G., Artemenko S.N. DRUG AND CARDIAC RESYNCHRONIZATION THERAPY IN THE TREATMENT OF CHRONIC HEART FAILURE (LITERATURE REVIEW) // Medical & pharmaceutical journal "Pulse". – 2024;26(12):35-45. <http://dx.doi.org/10.26787/nydha-2686-6838-2024-26-12-35-45>.

Вклад авторов. Все авторы заявляют о равном вкладе в подготовку статьи – концепция и дизайн исследования, утверждение окончательной версии для публикации, полная ответственность за содержание, обзор литературы, написание статьи.

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

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Для цитирования: Ахыт Б., Ложкина Н.Г., Беркинбаев С., Пашимов М., Кошумбаева К., Мусагалиева А., Джунусбекова Г., Алиева Г., Артеменко С.Н. МЕДИКАМЕНТОЗНАЯ И СЕРДЕЧНАЯ РЕСИНХРОНИЗИРУЮЩАЯ ТЕРАПИЯ В ЛЕЧЕНИИ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ (ОБЗОР ЛИТЕРАТУРЫ) // Медико-фармацевтический журнал "Пuls". 2024;26(12):35-45. <http://dx.doi.org/10.26787/nydha-2686-6838-2024-26-12-35-45>.