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ALGORITHM FOR THE TREATMENT OF PATIENTS WITH CHRONIC HEART FAILURE WITH REDUCED LEFT VENTRICULAR EJECTION FRACTION

Abstract:

Despite a significant number of publications devoted to the management of patients with chronic heart failure (CHF), a practicing doctor is not always easy to navigate in the use of medicines and indications for high-tech methods of treatment in these patients. The largest evidence base is currently accumulated in patients with CHF with a reduced left ventricular ejection fraction (CHFrEF), which is characterized by a significant decreasing in the quality of life, decreased/lost ability to work, disability of patients and high mortality. This article details all the essential medicines used for therapy of CHFrEF, the sequence and practical aspects of their prescribing in accordance with contemporary guidelines. The issue of treating patients with CHF refractory to standard therapy, including with the help of a new class of medicines from the group of angiotensin receptor-neprilysin inhibitors, cardiac resynchronization therapy, implantation of cardioverter-defibrillators and application of devices for mechanical circulatory support and heart transplantation is considered. The publication is illustrated by tables, figures, charts, which makes it accessible for understanding and memorizing.

Key words: *chronic heart failure, ejection fraction, therapy algorithm, drug therapy, cardiac resynchronization therapy, ARNI, prognosis*

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ICD — implantable cardioverter-defibrillator, MCS — mechanical circulatory support, CHF — chronic heart failure, EF — ejection fraction, CHFrEF — chronic heart failure with reduced ejection fraction, CRT — cardiac resynchronization therapy

Introduction

Despite significant advances in the management of various cardiovascular diseases, the prevalence of chronic heart failure (CHF) continues to increase [1]. A total of 37 million people worldwide are affected by CHF. In European countries, this disease is diagnosed in 1–2.6 % of the population [2], in 2.2 % of the population of the USA [3, 4], and in 7–10 % of the population of the Russian Federation [5, 6], i.e. the prevalence of this disease in

our country is much higher than in the European countries and the USA.

In Europe, CHF accounts for 5 % of all hospital admissions [7]. In the USA, CHF leads to 1.023 million hospital admissions per year (6.5 million bed-days) [4]. In Russian Federation, CHF is the main cause of admission in 16.7 % of the patients admitted with CVD. This disease is the most common cause of inpatient treatment among people over 65 years old [5, 8]. Moreover, about 50 % of patients with CHF are rehospitalized

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within 6 months; 20–25 % of patients are rehospitalized within 30 days after discharge from the hospital [9]. Seventy percent of rehospitalizations are associated with CHF decompensation [10].

A further increase in the number of patients with CHF is expected due to an increase in the prevalence of cardiac risk factors, an improvement in the survival of patients with various cardiovascular disorders, and the aging of the population in future [8]. By 2030, the number of patients with CHF is expected to increase by 46 % [4].

The cost of CHF treatment amounted to 30.7 billion dollars in the USA in 2012 [3]. By 2030, it is expected to increase by 127 % to 69.7 billion dollars per year [3, 4].

CHF progression is accompanied by a significant decrease in life quality, decreased/lost ability to work, disability of patients, and increased mortality. The loss of working-age population due to cardiovascular morbidity and mortality in the European Union is 45 billion euro per year [11].

CHF is the leading cause of cardiovascular mortality. The mortality in patients with CHF is 4–10.3 times higher than that in the general population of the corresponding age, and is comparable to, or even in excess of, the mortality rate for a number of oncological diseases. The five-year mortality rate in patients with CHF from the moment of diagnosis was 60–70 % of patients until the 1990's. In recent years, a small but significant decrease to 50 % was recorded [12]. The annual CHF mortality is 17.4–33 % [13]: in the USA, accounting for 250,000 people per year, and in the Russian Federation 612,000 people die per year from the disease [6]. Mortality in patients with CHF with reduced ejection fraction (CHFrEF, EF < 40 %) is higher than in patients with CHF with preserved EF (CHFpEF, EF ≥ 50%) regardless of the age, gender, and etiology of CHF [14]. The hospital mortality in patients with CHF is 2–20 %. The 30-day post-discharge mortality is 11.3 % [15].

Due to this, the objective of healthcare is to significantly improve the quality of medical care for patients with CHF. This lecture presents a procedure and practical recommendations for the treatment of patients with CHF, and in particular those with CHFrEF, from the standpoint of current local and international guidelines.

The Goal of CHF Management

The goal of treatment for patients with CHF is to improve their clinical status, functional ability, and prognosis [16].

The Objectives of CHF Management

1. Decrease the severity of clinical symptoms.
2. Increase the exercise tolerance.
3. Improve the quality of life.
4. Prevent disability.
5. Prevent the progression of CHF.
6. Improve hemodynamics and organ perfusion and reverse target organ damage.
7. Decrease the frequency of decompensation and the number of hospitalizations.
8. Prevent thromboembolic and other complications.
9. Increase life expectancy, and reduce mortality in patients with CHF [17].

CHF and EF Treatment Procedure

All medications for the treatment of CHF and decreased EF can be divided into two main categories in accordance with the strength of evidence. The first is medicines that reduce mortality in patients with CHF. The second is medicines that do not affect the prognosis for patients with this disease (Figure 1) [17]. While taking into consideration the goals and objectives of treatment, it is necessary to primarily prescribe medicines that have been proven to be able to reduce mortality, i.e., to prolong the life expectancy of patients with CHF.

The procedure for managing patients with CHF and EF is presented in Figure 2.

Angiotensin Converting Enzyme (ACE) Inhibitors

ACE inhibitors should be prescribed to a patient with heart failure with reduced ejection fraction of the left ventricle (CHFrEF). It is necessary to begin treatment with the starting dose and gradually

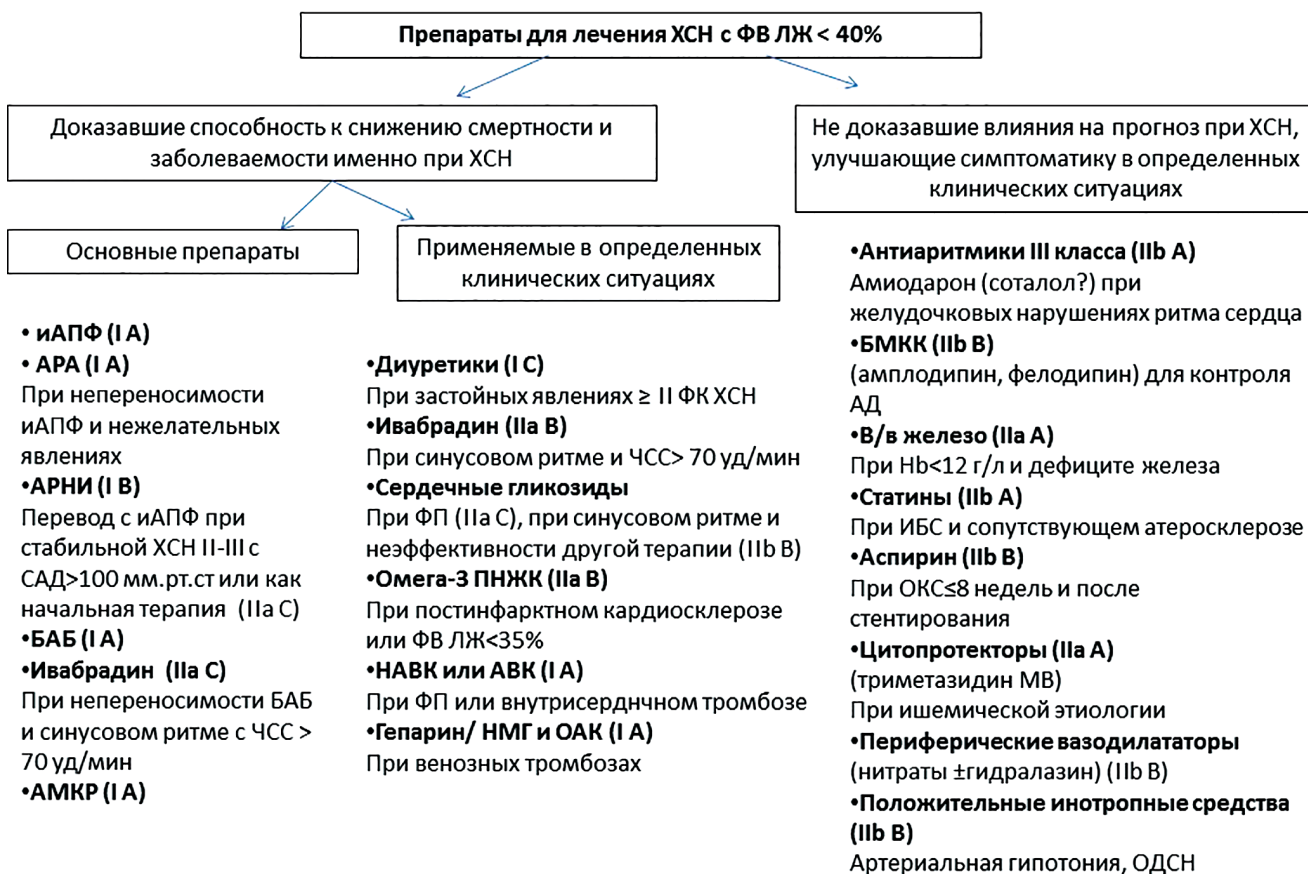


Figure 1. Medicines for treatment of CHF with EF < 40% [17].

Caption to Figure 1. The classes of recommendations and the levels of evidence are graded in parentheses. Classes of recommendations: I — **sufficient evidence** and/or the general agreement that a given treatment or procedure is **beneficial, useful and effective** — **such a course of treatment must be prescribed**; IIa — weight of evidence/opinion is in favor of usefulness/efficacy of treatment (**the benefit** of the procedure/treatment **exceeds the risk** of adverse events, but further studies are needed) — **it is reasonable to prescribe such a course of treatment**; IIb — usefulness/efficacy is less well established (**the benefit** of the procedure/treatment **is either somewhat greater than or equal to the risk** of adverse effects; additional studies are needed to clarify the appropriateness of the prescribing the course of treatment) — **may be prescribed if clinically indicated**; III — **sufficient evidence** and/or general agreement that the given treatment or procedure **is not useful/effective** and in some cases **may be harmful** — **such a course of treatment should not be prescribed**.

Levels of evidence: A — the recommendation is based on the results of **multiple, randomized** clinical trials or meta-analyses; B — the recommendation is based on results of **a single randomized** clinical trial **or several large non-randomized** clinical trials; C — the recommendation is based **on the opinion of experts** and/or small studies, retrospective studies, and register data.

increase the dose to the target (optimal) value while monitoring blood pressure (BP), serum creatinine and potassium values (Table 1).

ACE inhibitors reduce the risk of death by 44 %. In this regard, they should be used in all patients with CHFrEF to reduce the risk of death and rehospitalization and improve the medical state of the patient. Not prescribing ACE inhibitors to patients with low EF cannot be considered justified at a SBP > 85 mm Hg, and leads to an increased risk of

death in patients with CHF (Class of recommendations Ia, Level of evidence A). ACE inhibitors have not yet proven their ability to improve the prognosis in patients with CHF with a midrange left ventricular ejection fraction (CHFmrEF, EF 40–49 %). However, due to improvement of the functional status of patients and the reduction in the frequency of hospitalizations, ACE inhibitors are indicated for all patients with CHF and mid-range EF [16, 17].

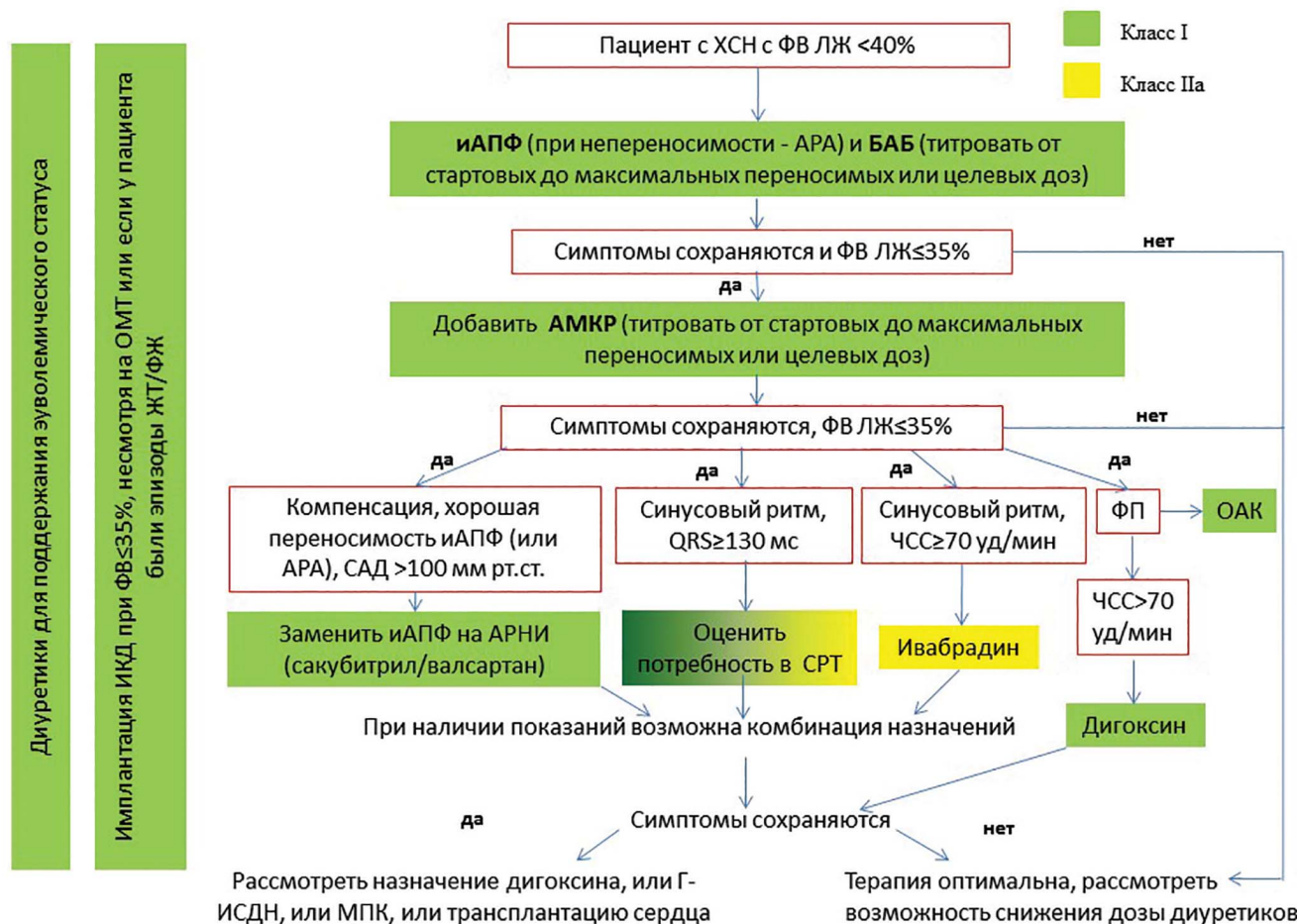


Figure 2. The algorithm of patients management with CHFrEF (EF <40%) [16, 17]

Table 1. Angiotensin-converting enzyme (ACE) inhibitors and their doses used in CHF [16, 17]

ACE inhibitors	Starting dose (mg)	Target dose (mg)
Captopril	6,25/t.i.d.	50/t.i.d.
Enalapril	2,5/b.i.d.	10-20/b.i.d.
Lisinopril	2,5-5,0/o.d	20-35/o.d.
Ramipril	2,5/o.d.	10/o.d.
Trandolapril	0,5/o.d	4/o.d.

Note: b.i.d. — bis in die (twice daily); o.d. — omne in die (once daily); t.i.d. — ter in die (three times a day).

Table 2. Angiotensin receptor blocker (ARBs) and their doses used in CHF [16, 17]

ARB	Starting dose (mg)	Target dose (mg)
Candesartan	4-8/o.d.	32 * 1 р/сутки/o.d.
Valsartan	40/b.i.d.	160 * 2 р/сутки/b.i.d.
Losartan	50/o.d.	150 * 1 р/сутки/o.d.

Table 3. Beta-blockers and their doses used in CHF [16, 17]

Beta-blocker	Starting dose (mg)	Target dose (mg)
Bisoprolol	1,25 o.d.	10 o.d.
Carvedilol	3,125 b.i.d.	25 b.i.d.
Metoprolol succinate (CR/XL)	12,5-25 o.d.	200 o.d.
Nebivolol	1,25 o.d.	10 o.d.

Contraindications to ACE inhibitors and ARBs:

1. Allergic reaction (angioedema, rash, etc.).
2. Bilateral stenosis of the renal arteries or stenosis of the renal artery of a single kidney.
3. Pregnancy.
4. Clinically apparent hypotension (SBP < 85 mm Hg).

Angiotensin II Receptor Blockers (ARBs)

If the patient is intolerant to ACE inhibitors due to allergic reactions or cough, ARBs should be prescribed to reduce the combination of risk of death and hospitalization (Table 2). It is necessary to begin treatment with the starting dose and gradually increase the dose to the target one while monitoring BP, serum creatinine and potassium values. Contraindications to ARBs are the same as for ACE inhibitors (Table 2).

Beta-Adrenergic Blockers

β -blockers as well as ACE inhibitors should be used in all patients with CHF_rEF to reduce the risk of death and rehospitalizations because they reduce mortality by 34–35 %. This has been proved only for 4 β -blockers. These β -blockers should be prescribed to patients with CHF (Table 4). Patients with CHF with midrange EF and CHF_pEF can be prescribed β -blockers to reduce heart rate and severity of LVH. Nebivolol is also able to reduce the risk of hospitalization and death in patients with CHF with midrange EF [16, 17].

Treatment with β -blockers in CHF should begin cautiously, starting with an initial dose, which is 1/4 of the therapeutic dose. Doses should be increased (titrated) slowly (not more than once every 2 weeks, and in case of doubtful tolerability and excessive decrease in blood pressure — once per month) until the optimal dose is achieved. In each patient with CHF and sinus rhythm, the optimal dosage of β -blockers is defined as the one that will decrease heart rate to < 70 beats per minute. For every 5 beats that the heart rate is decreased, the risk of CHF death is reduced by 18 %. Patients who are receiving treatment with non-recommended β -blockers (most often atenolol or short-acting

metoprolol tartrate) should be prescribed with the recommended β -blockers (Table 3) [16, 17].

Contraindications to β -blockers:

1. Asthma. COPD is not a contraindication to β -blockers. The physician must make an attempt to prescribe them, starting with small doses and titrating slowly. Treatment with β -blockers should be avoided only in case of exacerbation of bronchial obstruction symptoms when being on β -blockers treatment. The drugs of choice in this situation are highly selective β_1 -blockers, bisoprolol and nebivolol.
2. Clinically apparent bradycardia (< 50 bpm)
3. Clinically apparent hypotension (SBP < 85 mm Hg)
4. AV block 2 or 3.
5. Severe obliterating endarteritis and atherosclerosis of the lower extremities.

In case of intolerance and contraindications to β -blockers in patients with CHF_rEF with sinus rhythm and heart rate > 70 beats per minute, the physician should consider prescribing the I_f inhibitor ivabradine to reduce the risk of death and hospitalizations.

Diuretics

If congestion signs are present (edemas, fine crackles in the lower lung fields, jugular vein distention, hydrothorax, hydropericardium, ascites, etc.), the prescription of diuretics is necessary for patients with CHF in addition to ACE inhibitors/ARBs and β -blockers to improve clinical symptoms and reduce the risk of rehospitalization (Figure 3, Table 4) [16, 17].

Treatment with diuretics should begin with small doses (especially in patients who have not received any previous diuretics). Afterwards the dose should be chosen in accordance with the principle of quantum satis — as much as necessary. A careless approach to dehydration will only cause side effects and rebound fluid retention [16, 17].

There are 2 phases of diuretic therapy in CHF:

1. **Active phase** (if congestion signs are present): the amount of urine excreted should be 4–4.5 liters per day more than the amount of fluid taken, weight

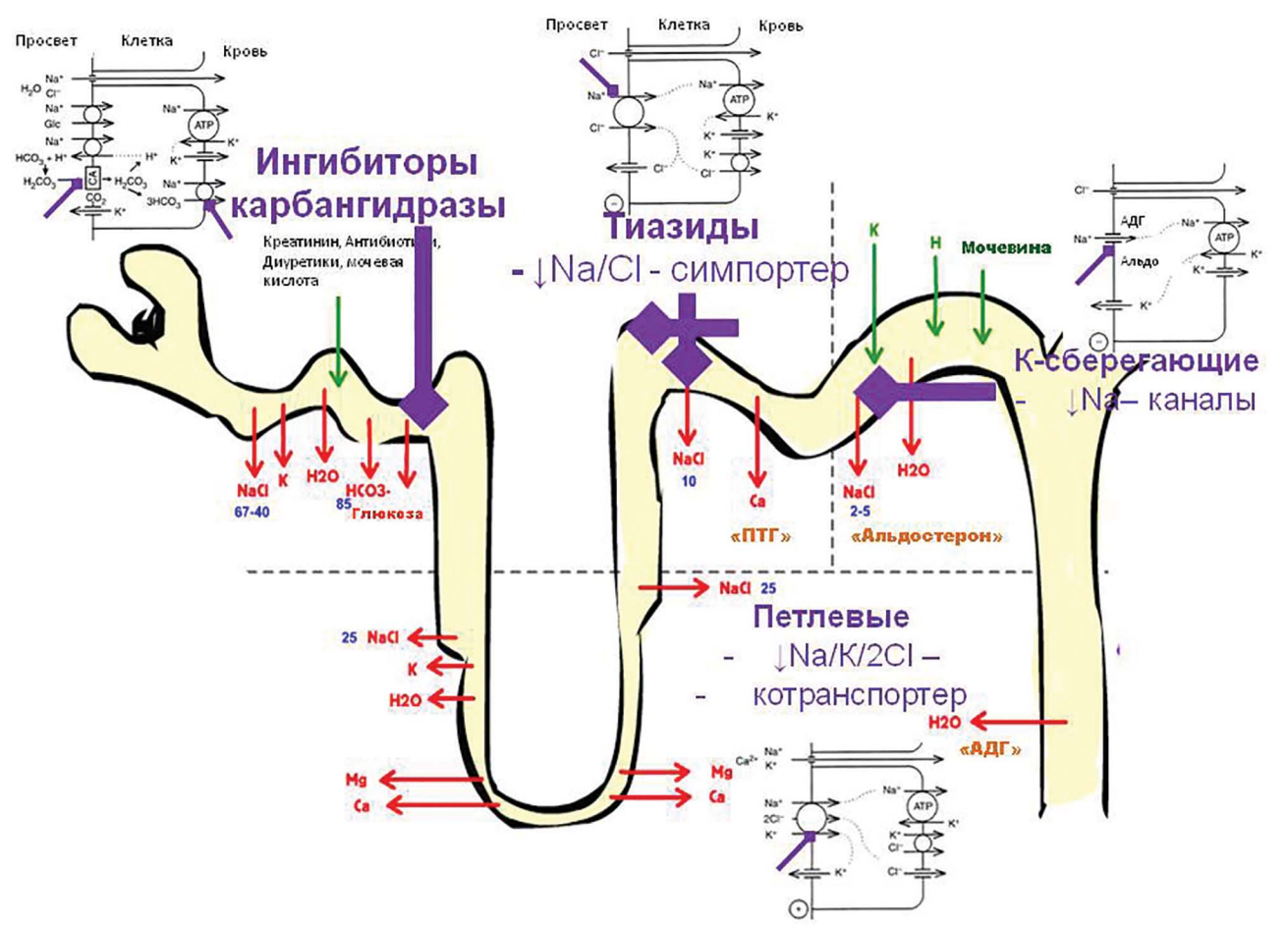


Figure 3. Groups of diuretics recommended for the treatment of CHF, localization and mechanism of their action

Table 4. Diuretics and their doses used in CHF [16, 17]

Diuretic	Starting dose (mg)		Target dose (mg)	
Loop diuretics				
Furosemide	20-40		40-240	
Bumetanide	0,5-1,0		1-5	
Torsemide	5-10		10-20	
Thiazides and non-thiazide sulfonamide				
Bendroflumethiazide	2,5		2,5-10	
Hydrochlorothiazide	25		12,5-100	
Metolazone	2,5		2,5-10	
Indapamide	2,5		2,5-5	
Potassium-sparing diuretics				
	+ACE-I/ARB	-ACE-I/ARB	+ACE-I/ARB	-ACE-I/ARB
Spironolactone/eplerenone	12,5-25	50	50	100-200
Amiloride	2,5	5	5-10	10-20
Triamterene	25	50	100	200

Table 5. Mineralcorticoid receptor antagonists (MRA) and their doses used for the treatment of CHF [16, 17]

MRA	Starting dose (mg)	Target dose (mg)
Eplerenone	25 o.d.	50 o.d.
Spironolactone	25 o.d.	50 o.d.

loss of ~1 kg per day. More rapid dehydration leads to excessive hyperactivation of neurohormones, rebound fluid retention in the body as well as the development of electrolyte, hormonal, arrhythmic and thrombotic complications. Loop diuretics torasemide or furosemide are combined with a diuretic dose of mineralocorticoid-receptor antagonists (MRA) 100–300 mg/day. Torasemide has advantages over furosemide in terms of the strength of its effect, degree of absorption (ease of ingestion), duration of effect (better tolerability, lower incidence of urination), and positive effect on neurohormones (fewer electrolyte disturbances, decreased progression of myocardial fibrosis, and improved diastolic filling of the heart). It also reliably reduces the risk of rehospitalizations that are necessitated due to exacerbation of CHF. For severe cavitory and refractory edemas, additional mechanical evacuation of fluid from the cavities (para-, pleuro- or pericardiocentesis) or isolated ultrafiltration are also possible solutions [16, 17].

2. Maintenance phase (to maintain a euvolemic state after achieving compensation for CHF events): the amount of fluid excreted should be 150–200 ml per day more than the amount of consumed/injected fluid (diuresis + 150–200 ml per day) and body weight should remain stable during the period of daily intake of diuretics. After the patient reaches euvolemia, diuretics should be prescribed on a daily basis in minimal doses, which make it possible to maintain a balanced diuresis. When diuretics are prescribed occasionally (bolus doses once every 3–4–5–7 days), the impact quality on life and the prognosis may be negative. Four to five day courses of the carbonic anhydrase inhibitor acetazolamide (0.75/day) are recommended once every 2 weeks to maintain optimal acid-base balance, preserve sensitivity to loop diuretics and normalize renal blood flow [16, 17].

When prescribing diuretics, it is necessary to remember that you cannot use thiazides if GFR is less than 30 mL/min/1.73 m², with the exception of some cases when they are prescribed together with loop diuretics to overcome diuretic resistance.

If the patient with CHF is prescribed a combination of 3 drugs (ACE inhibitor / ARBs,

β-blocker and diuretic), and there are no clinical symptoms of CHF (dyspnea, weakness, fatigue, palpitations, and swelling), **then it is necessary to continue treatment with these drugs!!!** You can try to reduce the dose of diuretics over time. If clinical symptoms appear after that, return to the initial dose of the diuretic [16, 17].

Mineralocorticoid Receptor Antagonists (MRA)

If, in spite of the fact that the patient with CHF_{rEF} is treated with a 3 drug-combination (**ACE inhibitor / ARBs, β-blocker and diuretic**) **clinical symptoms of CHF** (dyspnea, weakness, fatigue, palpitations, and swelling) **persist**, then **it is necessary** to add a **mineralocorticoid receptor antagonist** (aldosterone antagonists, MRA, Table 5) to this combination to reduce the risk of death and rehospitalization as well as to improve the medical state. MRA can be prescribed for patients with CHF_{pEF} and CHF with midrange EF to reduce the number of hospitalizations due to CHF [16, 17].

Contraindications to MRA:

1. GFR < 30 ml/min/1.73 m², especially in combination with another RAAS blocker, because of the risk of developing kidney dysfunction and hyperkalemia.
2. Hyperkalemia > 5.5 mmol/L

In cases when **clinical symptoms of CHF** (dyspnea, weakness, fatigue, palpitations, and swelling) **persist** despite the 4 drug-combination (**ACE inhibitor / ARBs, β-blocker, diuretic, and MRA**) and EF is 35 % or below, it is necessary to consider the following 3 options of patient management:

1. In case of good tolerability of ACE inhibitors or ARBs, replace ACE inhibitor or ARBs with an angiotensin receptor-neprilysin inhibitor (ARNI).
2. If there is sinus rhythm, and the heart rate is 70 beats per minute or higher, add ivabradine to the 4 drug-combination.
3. If the rhythm is sinus and QRS duration is 130 ms or more, cardiac resynchronization therapy (CRT) should be considered.

Angiotensin Receptor-Neprilysin Inhibitors (ARNI)

If, in spite of the fact that the patient with CHF_{rEF} is prescribed a 4 drug-combination (ACE inhibitor / ARBs, β -blocker, diuretic, and MRA) clinical symptoms of CHF persist, then ACE inhibitor / ARBs should be replaced with angiotensin receptor-neprilysin inhibitor (ARNI).

Neprilysin is a neutral endopeptidase that cleaves natriuretic peptides, bradykinin, and other peptides. Inhibition of neprilysin leads to an increased level of natriuretic peptides in the blood, increased diuresis, natriuresis, improved relaxation of the myocardium, and a decrease in the secretion of renin and aldosterone. Currently, there is one drug in the ARNI group, which is a cross-linked molecule of valsartan (ARBs) and sacubitril (neprilysin inhibitor). It is able to reduce mortality by 20 % better than an ACE inhibitor (enalapril).

ARNI is recommended for patients with stable CHF_{rEF} (without decompensation, intravenous administration or doubling of the dose of oral diuretics and SBP > 100 mm Hg), and in case of intolerance to ACE inhibitors (or ARBs). This category of patients is moved onto ARNI (at the starting dose of 100 (49/51) mg b.i.d., no earlier than 36 hours after the last dose of ACE inhibitors (ARBs), followed by titration of the dose to the optimal 200 (97/103) mg b.i.d.) to further reduce the risk of death and subsequent hospitalizations for CHF. The use of ARNI in patients with stable CHF_{rEF} can be considered as an initial therapy (instead of ACE inhibitors) to reduce the risk of death and hospitalizations. A combination of two RAAS blockers (excluding MRA) is not recommended for the treatment of patients with CHF due to a significant increase in serious adverse events, including hypotension and impaired renal function [16, 17].

Triple neurohormonal blockade: ACE inhibitors (in case of ARBs intolerance) or ARNI (in case of stable CHF with SBP > 100 mm Hg) in combination with β -blocker and MRA provide the basis of therapy for CHF_{rEF} and reduce the mortality rate of patients with CHF by a total of 45 % [16, 17].

Ivabradine

If, in spite of the fact that the patient with CHF_{rEF} is prescribed a 4 drug-combination (ACE inhibitor / ARBs, β -blocker, diuretic, and MRA) clinical symptoms of CHF (dyspnea, weakness, fatigue, palpitations, and swelling) persist, then, in case of sinus rhythm with heart rate of 70 beats per minute and more ivabradine should be added to the prescribed combination to reduce the risk of death and rehospitalizations. The starting dose is 5 mg b.i.d., the target dose is 7.5 mg b.i.d. [16, 17].

Ivabradine slows heart rate by inhibiting If-channels in the sinus node, and therefore it should be used only for patients with a sinus rhythm [16].

Cardiac Resynchronization Therapy (CRT)

If, in spite of the fact that the patient with CHF_{rEF} is prescribed a 4 drug-combination (ACE inhibitor / ARBs, β -blocker, diuretic, and MRA) clinical symptoms of CHF (dyspnea, weakness, fatigue, palpitations, and swelling) persist, then in the case of a sinus rhythm with QRS of 130 ms and more the physician should consider the need for cardiac resynchronization therapy (CRT) [16, 17].

CRT is a method of restoring the heart function by means of correction of impaired intracardiac conduction. The simplest indicator of impaired intracardiac conduction (interventricular dyssynchrony) is a wide QRS complex or bundle branch block on the ECG. Besides that, interventricular and intraventricular dyssynchrony are detected using doppler ultrasound and/or myocardial perfusion scintigraphy synchronized with ECG. CRT includes setting the electrode in the right atrium and biventricular stimulation that synchronizes the work of the ventricles. Indications for CRT are given in Table 6. CPT is contraindicated when QRS duration is less than 130 ms. In many cases, devices that combine the ability to resynchronize the rhythm and cardioverter-defibrillator (CRT-D) functions are used [16, 17].

Table 6. Indications for cardiac resynchronization therapy (CRT) in patients with CHF [16, 17]

Recommendations	Class	Level
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥ 150 msec and LBBB QRS morphology and with EF $\leq 35\%$ despite OMT in order to improve symptoms and reduce morbidity and mortality	I	A
CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration ≥ 150 msec and non-LBBB QRS morphology and with EF $\leq 35\%$ despite OMT in order to improve symptoms and reduce morbidity and mortality	IIa	B
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and LBBB QRS morphology and with EF $\leq 35\%$ despite OMT in order to improve symptoms and reduce morbidity and mortality	I	B
CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and non-LBBB QRS morphology and with EF $\leq 35\%$ despite OMT in order to improve symptoms and reduce morbidity and mortality	IIb	B
CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity. This includes patients with AF	I	A
CRT should be considered for patients with EF $\leq 35\%$ in NYHA Class III–IVd despite OMT in order to improve symptoms and reduce morbidity and mortality, if they are in AF and have a QRS duration ≥ 130 msec provided a strategy to ensure bi-ventricular capture is in place or the patient is expected to return to sinus rhythm	IIa	B
Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF	IIb	B
CRT is contra-indicated in patients with a QRS duration < 130 msec	III	A

Note: LBBB — left bundle branch block; OMT — optimal medical therapy; RV — right ventricular

Implantable Cardioverter-Defibrillator (ICD)

The implantation of a cardioverter-defibrillator (ICD) is recommended for all patients with CHFrEF, who had hemodynamically significant ventricular tachycardia or ventricular fibrillation. For the purpose of primary prevention of sudden cardiac death, the ICD is indicated in patients with CHFrEF and persisting clinical symptoms despite having received optimal medical therapy for 3 months if the life expectancy with a good NYHA class is more than one year and they have IHD (ischemic heart disease) or DCM (dilated cardiomyopathy). ICD is not recommended for 40 days after MI (myocardial infarction). ICD is not recommended for patients with NYHA IV with the exception of candidates for CRT, implantation of LVAD (left ventricular assist device), or heart transplantation (Table 7) [16, 17].

Cardiac Glycosides in Patients with CHFrEF

To reduce the risk of rehospitalizations, it is useful to prescribe digoxin for patients with CHFrEF and sinus rhythm and persisting clinical symptoms despite optimal drug therapy, including all the approaches described above, and who have also experienced several episodes of CHF decompensation during the year, low EF $\leq 25\%$, LV dilatation and high NYHA class (III–IV), if CHF is compensated [16, 17]. In patients with CHFrEF, the prescription should be considered for tachysystolic form of atrial fibrillation (AF) [16, 17]. Oral β -blockers are safe for use in patients with I–III NYHA class, and therefore they are recommended as a **first-line** therapy for monitoring ventricular rate (VR) in AF. The use of digoxin should be considered in patients with CHF, if, despite the use of β -blockers, high VR persists or in the case of resistance or contraindications to β -blockers [16, 17].

Table 7. Recommendations for implantable cardioverter-defibrillator (ICD) in patients with CHF [16, 17]

Recommendations	Class	Level
Secondary prevention: An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for >1 year with good functional status.	I	A
Primary prevention: An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA Class II–III), and an EF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than one year with good functional status, and they have: — Ischemical Heart Disease	I	A
— Dilated cardiomyopathy	I	B
ICD implantation is not recommended within 40 days of an MI as implantation at this time does not improve prognosis	III	A
ICD therapy is not recommended in patients in NYHA Class IV with severe symptoms refractory to pharmacological therapy unless they are candidates for CRT, a ventricular assist device, or cardiac transplantation	III	C
Patients should be carefully evaluated by an experienced cardiologist before generator replacement, because management goals and the patient's needs and clinical status may have changed	IIa	B
A wearable ICD may be considered for patients with HF who are at risk of sudden cardiac death for a limited period or as a bridge to an implanted device	IIb	C

An optimal ventricular rate (VR) for patients with HF and AF has not been established, but most of the data suggest that strict VR control may be harmful. Heart rate at rest should be considered in the range of 60–100 bpm [16]. Digoxin should be prescribed when the level of the drug in the blood is controlled (a dose reduction is necessary at a concentration of more than 1.1–1.2 ng/ml), both in case of sinus rhythm and AF (optimal digoxin concentration in blood is less than 0.9 ng/ml) if contraindications are absent. If it is not possible to determine the digoxin concentration, the use of the drug can be continued in small doses (0.25–0.125 µg) if there is no data on glycoside poisoning (at a dose of not more than 0.125 mg with a body weight of less than 60 kg (especially in women) aged 75 years and more and with GFR of less than 60 mL/min/1.73 m²) [16, 17].

Oral Anticoagulants (OAC)

The CHA2DS2-VASc and HAS-BLED scales are recommended for assessing the risk of TC (thromboembolic complications) and bleeding (Appendix).

OAC (Figure 4, Table 8) should be prescribed to reduce the risk of death and hospitalization for patients with CHF with paroxysmal, persistent and permanent AF with a score according to the CHA2DS2VASc scale ≥ 2 or intracardiac thrombosis. For patients with CHF and non-valvular AF who have indications to anticoagulant therapy, the prescription of new oral anticoagulants (non-vitamin K antagonist oral anticoagulants, NOACs) should be preferred over vitamin K antagonists (VKA), given the fact that they are better able to reduce the risk of death and thromboembolic complications while also lowering the risk of bleeding, including intracranial hemorrhage in particular, at the same time. The use of NOACs is contraindicated in the presence of mechanical valves, mitral stenosis, GFR of less than 30 mL/min/1.73 m² [16, 17].

Heparin

Prescription of heparin or low-molecular-weight heparin (LMWH) for a minimum of 7 days should be considered in patients with CHF_rEF in the presence of venous thrombosis, PE (pulmonary

embolism) or decompensation requiring bed rest (≥ 3 days) to reduce the risk of thromboembolism, improve prognosis, and reduce the risk of hospitalization followed by transfer to the VKA (with INR control) or NOACs [16, 17].

In case of venous thrombosis and PE in patients with CHF, alternative therapy with oral Xa factor inhibitors is possible in place of heparin: apixaban at 10 mg b.i.d. for 7 days followed by a transfer

to 5 mg b.i.d., or rivaroxaban at 15 mg b.i.d. for 21 days with a transfer to 20 mg once daily [16, 17].

The duration of anticoagulant therapy for patients who have experienced a single episode of venous thrombosis or PE is up to 3 months, and for those who have experienced repeated episodes it should be longer; NOACs should be preferred in these cases. If anticoagulant therapy is not possible, acetylsalicylic acid can be prescribed [16, 17].

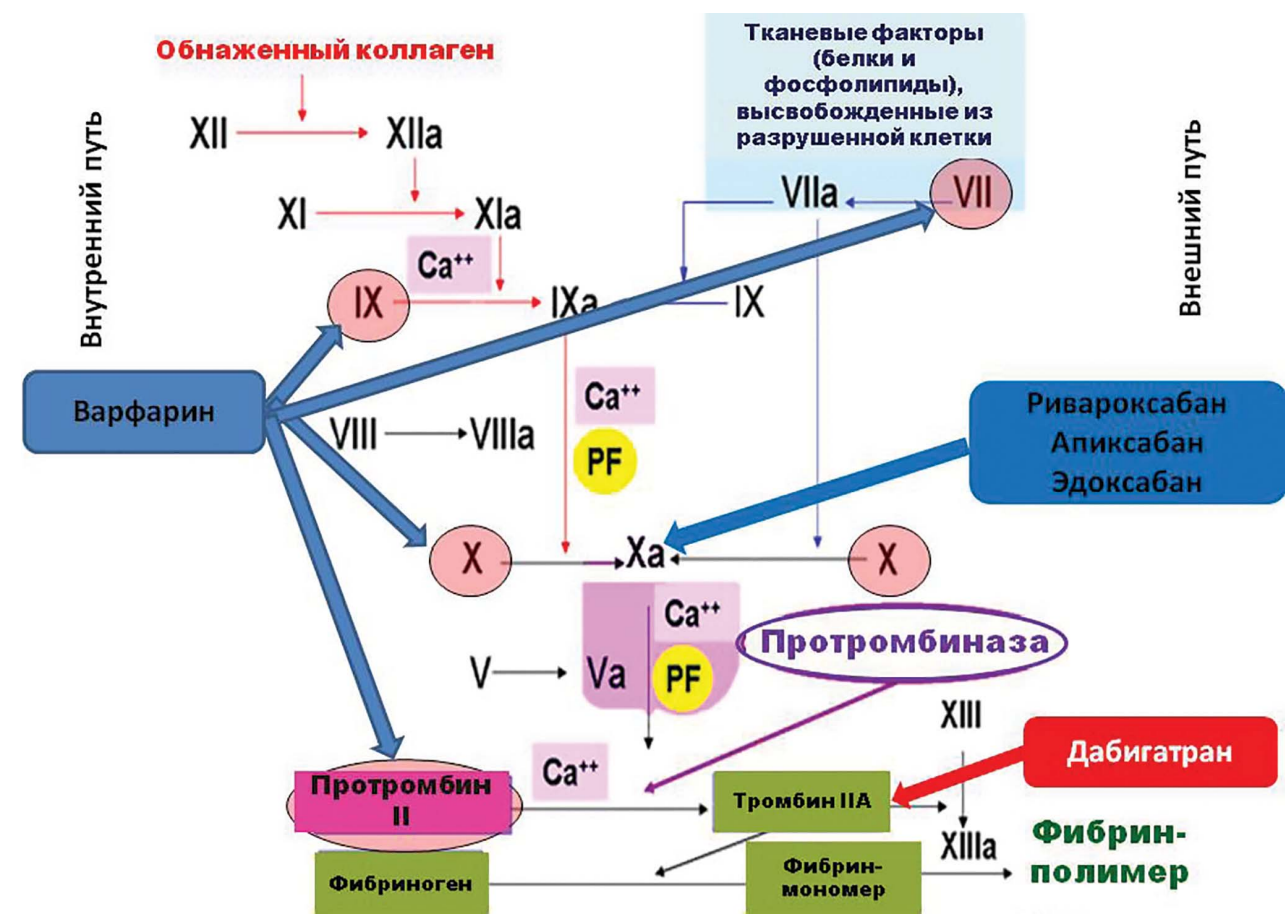


Figure 4. Effect of oral anticoagulants on coagulation

Table 8. Oral anticoagulants

	Vitamin K antagonist	Nonvitamin K antagonist (NOAC)	
Drugs	Warfarin	Dabigatran	Rivaroxaban, Apixaban, Edoxaban
Effect	Blockade of the synthesis of II, VII, IX, X coagulation factors in the liver	Inhibition of factor II coagulation — thrombin	Antagonist Xa factor
Indication	1. Atrial Fibrillation in mechanical heart valves or at least moderate mitral stenosis 1. CKD 3-4 (GFR <60 ml/min/1.73 m ²)		
Control	INR 2-3, in mitral valve disease >2,5		

Acetylsalicylic Acid (ASA)

The prescription of ASA does not affect the prognosis in patients with CHF and can weaken the effect of ACE inhibitors and other essential drugs. Therefore, the prescription of ASA can only be considered for patients who had ACS within the last 8 weeks and who underwent percutaneous coronary intervention in the last year [16, 17].

Peripheral Vasodilators

The use of peripheral vasodilators (hydralazine and/or nitrates) can be considered only for the management of angina pectoris and when all other methods of treatment described above are ineffective.

Circulatory Assistance Devices: MCS (Mechanical Circulatory Support), LVMSD (Left Ventricle Mechanical Support Device), LVAD (Left Ventricular Assist Device)

If all of these strategies for the CHF treatment are ineffective, mechanical circulatory support can be considered (Table 9, 10).

Heart Transplantation

Heart transplantation is a common treatment method for end-stage HF. Although no controlled studies have been conducted, it is believed that heart transplantation (if the patient selection criteria are

Table 9. Terms describing various indications for mechanical circulatory support [16, 17]

Bridge to decision (BTD)/ Bridge to bridge (BTB)	Use of short-term MCS (e.g. ECLS or ECMO) in patients with cardiogenic shock until haemodynamics and end-organ perfusion are stabilized, contra-indications for long-term MCS are excluded (brain damage after resuscitation) and additional therapeutic options including long-term VAD therapy or heart transplant can be evaluated
Bridge to Candidacy (BTC)	Use of MCS (usually LVAD) to improve end-organ function in order to make an ineligible patient eligible for heart transplantation
Bridge to transplantation (BTT)	Use of MCS (LVAD or BiVAD) to keep patient alive who is otherwise at high risk of death before transplantation until a donor organ becomes available
Bridge to recovery (BTR)	Use of MCS (typically LVAD) to keep patient alive until cardiac function recovers sufficiently to remove MCS
Destination therapy (DT)	Long-term use of MCS (LVAD) as an alternative to transplantation in patients with end-stage HF ineligible for transplantation or long-term waiting for heart transplantation

Abbreviations: BiVAD — biventricular assist device; BTB — bridge to bridge; BTC — bridge to candidacy; BTD — bridge to decision; BTR — bridge to recovery; BTT — bridge to transplantation; DT — destination therapy; ECLS — extracorporeal life support; ECMO — extracorporeal membrane oxygenation; LVAD — left ventricular assist device; MCS — mechanical circulatory support; VAD — ventricular assist device.

Table 10. Patients potentially eligible for implantation of a left ventricular assist device [16, 17]

Patients with >2 months of severe symptoms despite optimal medical and device therapy and more than one of the following:
EF <25% and, if measured, peak V _{O2} <12 mL/kg/min
≥3 HF hospitalizations in previous 12 months without an obvious precipitating cause
Dependence on i.v. inotropic therapy
Progressive end-organ dysfunction (worsening renal and/or hepatic function) due to reduced perfusion and not to inadequate ventricular filling pressure (PCWP ≥20 mmHg and SBP ≤80–90 mmHg or CI ≤2 L/min/m ²)
Absence of severe right ventricular dysfunction together with severe tricuspid regurgitation

Abbreviations: SBP — systolic blood pressure, SI — cardiac index, HF — heart failure, EF — left ventricular ejection fraction, PCWP — wedge pressure in pulmonary capillaries

met) significantly increases the patient survival rate, and it also improves exercise tolerance, quality of life, and the ability to return to work as compared to conventional treatment [16].

The main problems in heart transplantation are the lack of donor hearts, the consequences of the limited effectiveness of the method and the complications of immunosuppressive therapy over the long term (for example, antigen-antibody mediated rejection of the transplant, infectious complications, hypertension, kidney failure, malignancy, and vasculopathy of the coronary arteries) [16].

Indications for heart transplantation [16]:

1. The end-stage of HF, severe clinical symptoms, unfavorable prognosis, and inability to use alternative therapies.
2. Motivated, well-informed, emotionally stable patients.
3. Ability of a patient to comply with a course of intensive treatment in the postoperative period.

Contraindications to heart transplantation [16]:

1. Active infection.
2. Severe damage to peripheral and/or cerebral arteries.
3. Pharmacologically irreversible pulmonary hypertension.
4. Cancer (cooperation with oncologists is necessary to assess the risk of tumor recurrence).
5. Irreversible kidney injury (e.g., creatinine clearance < 30 mL/min).
6. Systemic diseases involving multiple organs.
7. Other comorbidities with poor prognosis.

8. BMI (body mass index) > 35 kg/m² (weight loss is recommended to achieve BMI < 35 kg/m²).
9. Alcohol and drug abuse.
10. Patients with insufficient social support.

It should be considered that some contraindications are temporary. In patients with potentially reversible or compensable comorbidities, such as obesity, kidney failure, pulmonary hypertension, the use of MCS, particularly LVMSD, should be considered, followed by a reassessment of indications and contraindications for heart transplantation [16].

Drug Products That Can Harm Patients with CHF_rEF

In addition, the use of drugs that can harm patients with CHF should be avoided in these patients (Table 11).

Thus, currently, a clear procedure for managing patients with CHF_rEF has been developed on the evidence-based data. Unfortunately, in real clinical practice, patients rarely follow this procedure sufficiently closely to obtain tangible benefits. In addition, patients often fail to adhere to the treatment regimen and do not take prescribed medications even when a course of therapy has been properly prescribed. It is necessary to have a clear understanding of the procedures for managing patients with CHF and to follow them in real clinical practice. This will make it possible to achieve the set goals and resolve the specified objectives for managing patients with CHF.

Table 11. Treatments that may cause harm in patients with CHF_rEF [16, 17]

Recommendation	^a Class	^b Level
Thiazolidinediones (glitazones) are not recommended in patients with CHF, as they increase the risk of CHF worsening and CHF hospitalization	III	A
Non-steroidal anti-inflammatory drug and cyclooxygenase-2 inhibitor are not recommended in patients with CHF, as they increase the risk of CHF worsening and CHF hospitalization	III	B
Diltiazem or verapamil are not recommended in patients with CHF _r EF, as they increase the risk of CHF worsening and CHF hospitalization	III	C
The addition of an ARB (or renin inhibitor) to the combination of an ACE-I and an MRA is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalaemia	III	C

Appendices

Приложение. Шкала CHA₂DS₂-VASc для оценки риска ТЭО:

Congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥ 75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex (female)

Факторы риска		Балл
Клиника ХСН или ФВ ЛЖ $\leq 40\%$		1
Артериальная гипертония		1
Возраст ≥ 75 лет		2
Сахарный диабет		1
Инсульт / ТИА/ тромбоэмболия в анамнезе		2
Сосудистое заболевание (инфаркт миокарда, атеросклероз аорты, периферических артерий)		1
Возраст 65-74 года		1
Женский пол		1
Категория риска	Сумма баллов	Тактика антитромботической терапии
Низкий	0	Нет необходимости
Средний	1	Пероральные антикоагулянты (предпочтительнее) или дезагреганты
Высокий	≥ 2	Пероральные антикоагулянты

Приложение. Шкала HAS-BLED для оценки риска кровотечений: Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly

Факторы риска	Балл
Артериальная гипертензия (САД > 160 мм.рт.ст.)	1
Нарушение функции почек и печени (1 балл каждое)	1 или 2
Инсульт	1
Склонность к кровотечениям	1
Лабильность МНО (на фоне варфарина)	1
Возраст > 65 лет	1
Лекарственные препараты (например, аспирин, НПВС) или злоупотребление алкоголем (1 балл каждое)	1 или 2
При сумме баллов ≥ 3 необходимо с осторожностью назначать пероральные антикоагулянты и регулярно контролировать МНО	

Conflict of interests

The authors declare no conflict of interests.

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