REVIEW PAPER

PHARMACOLOGICAL TREATMENT OF CHRONIC CONGESTIVE HEART FAILURE

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ABSTRACT

Chronic congestive heart failure is a clinical syndrome based on the progressive deterioration of contractile (systolic) heart function due to structural or functional disorders. The incidence of the disease increases with age, so the prevalence in people older than 75 years is greater than 10%. Due to the different clinical presentation, the pharmacological approach to the patient is individual, and most patients are treated on an outpatient basis, according to the guidelines taken from the recommendations of professional associations. Hospitalization is necessary in severe forms of CHF or acute exacerbations. Patients with severe hemodynamic disturbances due to acute CHF require treatment in intensive care units, due to specific cardiovascular therapy, respiratory support and vital functions monitoring. Individualized, stepwise and rational pharmacological therapy achieves significant symptomatic and functional improvement in most patients.

Keywords: *Congestive heart failure, renal failure, ejection fraction, pharmacological treatment, diuretics, inotropic drugs.*

ABBREVIATIONS

ACEi - angiotensin-converting enzyme inhibitors
ACH - acute heart failure
ACHF - acutisation of chronic compensated heart failure
ADHF - acutely decompensated heart failure
ADCHF - acutisation of chronic decompensated heart failure
ARBs - angiotensin II receptor blockers
AV block - atrioventricular block
AV node - atrioventricular node
BNP – B-type natriuretic peptide
CHF – congestive heart failure
CK – creatin kinase
CKD – chronic kidney disease
CK-MB – creatin kinase in heart muscle cells
CVP – central venous pressure
EF - ejection fraction
e-GFR – estimated glomerular filtration rate
g/d – grams per day
FE_{Na} - fractional excretion of sodium
HF – heart failure
HFmrEF - heart failure with mid-range ejection fraction
HFpEF - heart failure with preserved ejection fraction
HFrEF – heart failure with reduced ejection fraction
cTnI – cardiac Troponin I

cTnT – cardiac Troponin T
IHD - ischemic heart disease
L/d – liters per day
LD - Henley's loop diuretic
LDH - lactate dehydrogenase
LV – left ventricle
MDD – maximum daily dose
MV – minute volume
NSAID - nonsteroidal anti-inflammatory drugs
NT-proBNP - N-terminal proBNP
NYHA - The New York Heart Association
PCI - Percutaneous Coronary Intervention
PCWP - pulmonary capillary wedge pressure
PVO2 - partial pressure of oxygen in venous blood
R – receptor
RAAS - Renin-Angiotensin-Aldosterone System
RAS - Renin - Angiotensin system
RF – renal failure
SGLT2i - sodium-glucose co-transporter-2 inhibitors
SIADH - syndrome of inappropriate antidiuretic hormone secretion
SNB - sequential nephron blockade
TEE – transesophageal echocardiogram
TTE- transthoracic echocardiogram

CLASSIFICATION OF HEART FAILURE

The general definition of heart failure is defined as a condition in which the pumping function of the heart cannot provide the current metabolic needs of the organism, or it is able to achieve so by increasing endocavitary pressure and/or volume [1,2].

Congestive heart failure is a clinical syndrome that is most often characterized by an initial disorder of left ventricle contractile function, with consequent damage to the right ventricle, stress intolerance, pulmonary and systemic congestion [3].

Like other chronic diseases, CHF evolves through asymptomatic/symptomatically tolerant periods ("stationary phases/compensated CHF"), which become shorter over time as they are replaced by more frequent periods of symptoms and signs of the disease ("worsening phases/decompensated CHF"). The patient is in a "stable state" if the achieved improvement is unchanged or with tolerant symptoms and signs, for at least a month [4]. Based on hemodynamic parameters (ejection fraction - EF%) and clinical manifestations, heart failure can be classified as following [1,4]:

A. Left-sided heart failure:

- Systolic heart failure/HFrEF: EF ≤ 40%
- Diastolic heart failure/HFpEF: EF ≥ 50%
- Systolic-diastolic heart failure/HFmrEF: EF 40-49%

a. Acute and acutely decompensated heart failure:
- De novo: pulmonary edema, cardiogenic shock, etc.: 25%
- Acutisation of chronic compensated heart failure (ACHF): 70%
- Acutisation of chronic decompensated heart failure (ADCHF): 5%

b. Chronic/congestive heart failure:
- Progressive reduction of the ejection fraction with clinical signs of systemic and pulmonary stasis.

B. Right-sided heart failure:

a. **Acute:** due to disorders leading to a sudden increase in endocavitary pressure and/or volume in the right heart.
b. **Chronic**: most often the consequence of primarily left-sided heart failure, lung diseases, heart defects, conditions with chronically increased load on the right heart, etc.

DIAGNOSTICS

Although revised compared to the original version, the modified Framingham criteria still represent a reliable way of initial clinical assessment of HF probability, with high enough sensitivity and specificity if 2 major, or 1 major and 2 minor criteria are met [5].

A. Major criteria: paroxysmal nocturnal dyspnea, orthopnea, swollen jugular veins, S3-gallop, cardio-thoracic index (CTI) > 0.5, visual evidence of pulmonary stasis, and bilateral cracks.

B. Minor criteria: peripheral edema, nocturnal cough, dyspnea on exertion, hepatomegaly, pleural effusion, and tachycardia / tachyarrhythmia ≥ 100/min.

The NYHA functional classification is based on the subjective statement of the patient and serves to assess the severity of symptoms and exercise tolerance. Data are often unreliable, especially in the lower functional classes, when some recognizable symptoms typical of CHF are absent [1].

In addition, the functional class can be changed, sometimes within minutes or hours (e.g., after remediation of pulmonary edema).

Objectification of heart failure severity, choice of therapy and prognostic significance can be predicted with high reliability based on classification criteria depending on the

severity of structural heart abnormalities (A-D). Returning to the "lower clinical stage" is not possible (*American Cardiology Foundation - ACCF and American Association of Cardiologists - AHA*) [1,6].

Echocardiographic (TTE / TEE) examination determines the type and hemodynamic weight of HF based on agreed parameters and provides us with other relevant information such as: assessment of volemia, pulmonary stasis/edema, analysis of transvalvular flows, intracavitary pressures, mobility of LV walls, presence of thrombus masses, vegetation, pericardial diseases, etc. [6].

Electrocardiogram, standard markers of heart damage (CK/CK-MB, cTnI/cTnT, LDH, BNP/NT-proBNP) and **standard biohumoral examinations**, hemogram and other, situationally necessary analyzes, are an integral part of the recommendations for the diagnosis of CHF, accompanying disorders and assessing the effectiveness of treatment.

Semi invasive procedures (CVP, right-heart catheterization) are often necessary in acute heart failure, cardiogenic shock, and other conditions treated in ICU [1,7].

PREVENTION AND PRINCIPLES OF STANDARD TREATMENT

Moderate physical activity, reduced intake of salt (2-3 g/d) and water, including beverages and food (1.0 -1.5 L/d), regular monitoring of body weight by morning measurements, avoidance of certain medications (NSAID, non-dihydropyridine calcium antagonists (n-DHP/CaCBs), proarrhythmogenic and cardiodepressant antiarrhythmics, some antibiotics, cytostatics, etc.), treatment of anemia, dyslipidemia, obstructive sleep-apnea syndrome (25% of patients) and other concomitant diseases and disorders, are basic preventive measures that should be permanently applied [1,8].

The standard protocol for the treatment of heart failure necessarily implies the application of pharmacological, and in some cases various non-pharmacological measures and procedures (*Table 1)* [1,4,9].

Table 1. Stepwise approach to the treatment of heart failure

ACC/AHA	B	C		D
NYHA	I	II	III	IV
Pharmacological treatment	Asymptomatic	Symptoms, current or prior		Persistent symptoms
	Have not been hospitalized before		Frequent hospitalizations	
ACEI/ARB/ARB+sacubitril	ACEI	ACEI or ARB or ARB+sacubitril		
β - blockers	+	+	+	+
Loop diuretic	-	±	+	+
SNB	-	±	±	+
Aldosterone antagonists	-	+	+	+
IDN/Hydralazine	-	±	±	+
Digoxin	-	±	±	±
Ivabradine	-	-	±	±
Anticoagulation	CHF associated with paroxysmal or persistent AF (according to CHA_2DS_2-VASc and HAS BLED score) in the absence of contraindications			
Non-pharmacological measures				
Mechanical ultrafiltration	-	-	±	±
ICD	Reduces the risk of sudden cardiac death in symptomatic CHF (NYHA II–III), dilatative CMP and IHD with EF ≤ 35% after ≥ 3 months of optimize medicament therapy			

ACC/AHA	B	C		D
NYHA	I	II	III	IV
CRT (BiVD/CCM)	Indicated in CHF in sinus rhythm with EF ≤ 35% and QRS ≥ 150 msec with morphology of LBBB Cardiac contractility modulator (CCM) for QRS < 120 msec			
M.V./IABP	Indicated in conditions of severe hemodynamic instability of various etiologies, after PCI or cardiac surgery			
Revascularisation	PCI or CABG based on clinical presentation, coronary anatomy, and associated disorders			
LVAD/Transplantation	LVAD as part of preparation for transplantation ("bridging time") and according to current recommendations: EF ≤ 25%, pVO2 < 12 ml/kg/min, inotropic dependence, multiorgan dysfunction, increased hospitalizations...			

PHARMACOLOGICAL TREATMENT

a. Drugs that affect the natural course of CHF by preventing LV remodeling, reducing hemodynamic and nonhemodynamic stress, sympathetic hyperstimulation, and RAAS hyperactivity: antihypertensives/cardioprotectors (ACEI/ARBs), aldosterone antagonists, β-blockers, neprilysin inhibitors, arteriovenous dilators (combination of hydralazine and nitrate), etc.
b. Drugs that reduce symptoms and morbidity: diuretics, inotropic drugs, ivabradine, SGLT2 inhibitors, etc. [4,5,9]

CHF treatment at a lower NYHA class (controlled symptoms) typically involves ambulatory patient treatment and periodical controls. Some patients in this category may be hospitalized occasionally, usually for a shorter period to optimize therapy or eliminate precipitating factors such as infections, anemia, heart rhythm disorders, associated insufficiency of other organs (kidney, lung, diabetes, etc.) [10]

I DIURETICS

Adequate diuresis of healthy individuals is achieved with 10 mg of furosemide given intravenously or 40 mg given orally, and it mostly amounts more than 500 mL for 30-60 min., or 60-120 min, respectively. In CHF and/or associated renal failure, adequate diuresis should be higher than physiological, because it implies a mandatory loss increased by the loss of part of the body water surplus and is achieved more slowly and only at higher/more frequent single doses of diuretics. Dose titration is individual and depends on the severity of CHF, the severity of edema, associated renal failure, albuminemia and albuminuria (diuretics are also bound to albumin in urine).

Oral administration of **loop diuretics** (LD), most often *furosemid*e given in single doses of 20-40 mg once or twice a day. More frequent administration reduces the subsequent, distal reabsorption of filtered Na^+ by other transport mechanisms [5]. By measuring the morning body weight (BW), the patient's compliance and/or the effect of a prescribed diuretic dose is simply checked. If it is 0.8 -1.25 kg higher than the measurement from 3-5 days ago, there is a fundamental suspicion of non-compliance or refractoriness. The rise of BW is registered 2 weeks after the increase in BNP, but a few days before the onset of manifest dyspnea or hospitalization.

In such patients, the morning dose of furosemide is doubled, or evening dose of the drug is administered temporarily or permanently, until optimal diuresis of 2.5-3.0 L/d is achieved, symptoms are subsided, and BNP is normalized. Frequent decompensations require hospitalization, to optimize therapy or eliminate precipitating factors [9,10].

In case of recurrent exacerbations/decompensation or inadequate diuresis (< 1.5 L/d) at oral doses of 80-160 mg/d, especially in case of inadequate response to parenteral administration of LD, a diuretic acting on the second reabsorbtive segment of the nephron should be added - sequential nephron blockade **(**SNB**).** So-called "second lines" diuretics should be given for at least 30 minutes before the administration of loop diuretic. If there is an impairment of kidney function, they should be use with caution. Although many diuretics are available, in our country this choice is limited [4,11,12]:

- *Metolazone* (Zaroxolyn®, Mykrox®, tbl. 2,5/5,0 mg), can be used in RF: MDD: 10 mg.
- *Hydrochlorthiazide* (Diunorm®, tbl. 25/50/100mg): MDD: 200 mg.
- *Chlorothiazide* (Diuril®, tbl. 500/1000 mg/d.): MDD: 0,5 -1,0 g.
- *Spironolactone* (Aldactone® tbl. á 25/100 mg): MDD: 25-100 mg.
- *Eplerenone* (Inspra® tbl. á 25/100 mg): MDD: 25 -100 mg.

II CONTROL OF NEUROHUMORAL AND METABOLIC DYSREGULATION

a) Treatment with **beta-blockers** (β-B) should be started with minimal initial doses that are increased on two-week period, only when euvolemia and hemodynamic stability are achieved as they may worsen the symptoms of CHF (initial negative inotropism). If edema worsens or recurs during dose titration, increase the dose of the diuretic, and then reduce the dose of β-B. With long-term use, they undoubtedly have beneficial effects: they slow down and lead to partial reversion of remodeling, improve EF%, prevent arrhythmias, reduce the frequency of hospitalizations and mortality. The most important limitations are: AV block gr. I^0- III^0, severe CHF, systolic blood pressure (SBP) ≤ 80 mmHg, bradyarrhythmia/bradycardia ≤ 55/min. If bradycardia (even asymptomatic) develops during treatment, first reduce the doses of digitalis and amiodarone, and only then reduce the dose of β-B [1,4,9]:

- *Metoprolol***:** selective β_1-B: 12.5-25 mg/24h; MDD: 200 mg/24h. Indicated in acute and chronic arrhythmias, complications of ischemic heart disease, etc.
- *Carvedilol*: selective β_1-B, β_2-B, α_1-B: start with 3.125 mg/12h; MDD: 25 mg/12h. It is well tolerated in patients with borderline blood pressure. It has a better anti-adrenergic effect, and a weaker chronotropism than metoprolol. Body weight should also be considered when dosing.
- *Bisoprolol***:** selective β_1-B: titrate the dose starting from 1.25/2.5 to 10 mg/24h; and in associated RF, reduce the dose to 25-50 percent. Maximum daily dose: 10 mg/24h.

b) **Angiotensin-converting enzyme inhibitors** (ACEi) and **angiotensin II receptor blockers** (ARBs). They slow down remodeling, improve hemodynamic performance and survival. These drugs should be used with caution in hypotension (SBP ≤ 80 mmHg) and in advanced CKD due to hyperkalemia. Start the combined use with β-B with small doses of ACEi/ARBs, then add small doses of β-B the next day, then carefully titrate for 7-14 days until the full dose. After reaching the maximum dose of β-B, increase the dose of ACEi/ARBs [9,11,13]:

- **Entresto®** is an integral chemical combination of neprilysin inhibitors (*sacubitril*) and ARBs (*valsartan*). Sacubitril inhibits the degradation of natriuretic peptides, which further increases natriuresis and diuresis, and valsartan also prevents fibrous pseudoreparative processes (remodeling). Before the initiation, a break in the application of ACEi/ARBs is required for 36 hours. It is available in fixed combinations: tbl. á 24/26 | 49/51 | 97/103 mg. The starting dose is 24/26 mg every 12 hours and is increased on a 4 week period up to 49/51 mg at 12h, or up to 97/103 mg, which is the maximum daily dose [1,4,9].

c) **Aldosterone receptor antagonists** (*spironolactone, eplerenone*) improve the diuretic response often without the need for potassium substitution, slow down remodeling, reduce the need for hospitalizations, improve the NYHA class, and are especially useful in the presence of ascites. Use with caution if renal insufficiency exists (e-GFR < 30 ml/min). [2,4,9].

- Aldactone® (*spironolactone*): tbl. á 25/100 mg; MDD: 25-100 mg.
- Inspra® (*eplerenone*): tbl. á 25/100 mg; MDD: 25-100 mg.

d) **Digitalis** as inotropic drug is indicated in CHF with EF ≤ 30% in NYHA III/IV class, with cardiomegaly in sinus rhythm or atrial fibrillation (AF) with rapid ventricular response (> 80/min). They improve the quality of life and tolerance of efforts [1,4,6].

- Digoxin® amp. á 0.5 mg/2ml; tbl. á 0.125/0.25 mg; MDD: 0.125-0.25 mg/24h
- Digitaline® (*digitoxin*) has an advantage over *digoxin* in case of RF.

e) **Coraxan®**/Bixebra® (*ivabradine*) is a specific inhibitor of the Na-K dependent channel in the SA node, so it slows down pacing. It does not affect the A-V node, conduction system and myocardial repolarization. It is indicated in stable patients with CHF and EF < 35%, in sinus rhythm and frequency ≥ 75/min. It may also be useful in the treatment of stable ischemic heart disease**,** when the use of β-B is not possible, or the maximum tolerated dose has been reached. Contraindications: bradycardia ≤ 70/min., acute coronary syndrome (ACS), S-A block, A-V block gr. III, pacemaker, cardiogenic shock, sick-sinus sy., arterial hypotension.

- It is available as a tablet. á 5/7.5mg; MDD: 15 mg/24h [1,14].

f) **Forxiga®:** (*dapagliflozin* tbl. 10/25 mg): MDD: 25 mg/24h.

- SGLT2 inhibitor blocks the reabsorption of glucose and salt in the proximal tubule, has antidiabetic, natriuretic and antiproteinuric effect. It is also given in non-diabetic patients, but only if e-GFR ≥ 40 ml/min [15].

g) **Oral anticoagulants** (VKA/NOAK) for the prevention of thromboembolic events, in AF with CHA_2DS_2-VASc score ≥ 2 [4,9].

TREATMENT OF REFRACTORY CONGESTIVE HEART FAILURE

A special problem in clinical practice is CHF refractory to the application of standard pharmacological therapy, including diuretics. Such conditions require the usage of other pharmacological and non-pharmacological measures, due to which the patient should be hospitalized [6,16].

The diagnosis of refractory (advanced) congestive heart failure is made on the basis of criteria proposed by referent associations, such as *European Heart Failure Association* of

the *ESC-2018*. Refractory CHF exists if after at least 2 weeks of drug therapy according to the guidelines from the good clinical practice (furosemide in repeated doses of 80 mg or more than 240 mg/d with SNB, ACE inhibitors, nitrate/hydralazine, with/without digitalis) and at least one hospitalization in the last six months, symptoms further persist [17, 18]. Some of suggested criteria are:

1. Severe symptoms and signs of HF including severe dyspnea and a feeling of tiredness at rest or minimum effort (NYHA III/IV).
2. On the use of diuretics refractory systemic (peripheral edema, hepatomegaly, ascites, swollen jugular veins...) and pulmonary congestion (orthopnea, pulmonary edema, pleural effusion):

a. Diuresis intensity ≤ 1.0 L/d with furosemide (repeated 80 mg or ≥ 160 mg/d),
b. $FE_{Na^+} < 0.2\%$ ($UE_{Na^+} < 90$ mmol/day),
c. Other causes of "unexplained" weight gain.

3. Imaging evidence of cardiac dysfunction: EF < 30%; transmitral flow disorder; PCWP > 16 mmHg and/or right atrial pressure > 12 mmHg; elevated serum BNP.

4. At least one indicator of reduced functional capacity: intolerance of minimal effort, 6-minute walking distance < 300m, pVO2 < 12-14 ml/kg/minute on cardiopulmonary exercise test.

Patients who meet most of the above criteria should be hospitalized in semi-/intensive care units for hemodynamic monitoring including monitoring of vital signs, fluid balance and diuresis monitoring, oxygen therapy and re-monitoring of relevant biochemical parameters. Therapeutic guidelines include intensification of diuretic therapy and application of other pharmacological measures for hemodynamic support.

A. CHANGE OF DIURETIC PRESCRIPTION REGIME

As a rule, the pharmacological approach is more "aggressive" because in addition to intensifying diuretic therapy, it is necessary to use various inotropic agents. Intensified diuretic therapy involves the use of fast-acting diuretics (furosemide), usually as follows [19,20]:

a. The initial i.v. bolus dose equivalent to the previous daily oral dose, given at 8 - 12 h. Adequate diuresis response in emergency, hemodynamically intolerant conditions (threatening or manifest pulmonary edema) is 0.5 L/30 - 60 min. Adequate diuresis response in hemodynamically tolerant hypervolemia implies a net diuresis of 3.5 -5.0 L/d.
b. If diuresis does not improve within a reasonable period, start with a continuous infusion of furosemide, with or without SNB. First, the initial i.v. bolus dose of 0.1 mg/kg, followed by infusion with 0.1 mg/kg/h with an increase to 0.4 mg/kg/h (5-20 mg/h) until diuresis > 1.0 ml/kg/h is established. The maximum daily dose (80-160 mg/h) depends on the current clinical presentation, the severity of hypervolemia and the state of renal function [6, 20, 21].

c. Replacement of furosemide with other loop diuretics is justified due to "tubular resistance" to furosemide and better bioavailability of some diuretics under gastrointestinal stasis:

- *Bumetanide* (Yurinex® tablet á 0.5/1.0 mg; amp. á 0.5 mg/2 ml): MDD: 5-10.0 mg; [amp. iv/im. 0.5-1.0 mg/12-24 h; inf: 0.5 mg/h/24h],
- *Torsemide* (Diuver® tablet á 5/10/20 mg; amp. á 20 mg/2 ml): MDD: 200 mg; [amp. iv. 10-20 mg/24h; inf: 0.5 mg/h/24h].

d. Infusion of loop diuretics with hypertonic NaCl solutions can be useful maneuver in refractory CHF with hypervolemic hyponatremia [6, 22]:

- Infusion of furosemide at a dose of 250-2,000 mg/d in 150 ml of hypertonic NaCl solution (1.4% -4.6% depending on the current concentration of s-Na^+) for 12 hours during 6 -12 days.
- The choice of concentration of NaCl solution depends on the current serum sodium concentration:
    - 4.6% NaCl for s-Na ≤ 125 mmol/L;
    - 3.5% NaCl for s-Na: 126 - 135 mmol/L;
    - 1.4% - 2.1% NaCl for s-Na > 135 mmol/L.

Worsening of azotemia in patients with stable/compensated HF is a sign that the diuretic dose is too high and should be reduced, unless there are other reasons for its increase [4, 23].

B. USE OF INOTROPIC MEDICINES

Majority of drugs from this pharmacological group are most often indicated for severe or life-threatening hemodynamic disorders. In general, they improve refractory hypotension, reduce systemic resistance, increase venous system capacity, improve inotropic effect on the heart, and ultimately tissue perfusion, including improved glomerular ultrafiltration, which in conjunction with diuretics leads to diuresis restitution.

Congestive heart failure with small minute volume, refractory to high-dose diuretic infusions (≥ 500-1000 mg/d) or its acute decompensation (ADHF) are the most common indications for inotropic drug use. Other reasons include conditions such as high-risk PCI, after cardiac surgery, conditions accompanied by cardiogenic shock or other urgent cardiovascular disorders in ICU [11,24].

a) **Dopamine®** (*dopamine*): [amp. á 50 mg/5 ml; amp. á 200 mg/10 ml] is an endogenous catecholamine, a precursor of norepinephrine with a dose-dependent effect on: $\alpha_{1/2}/\beta_{1/2}/D_{1/2}$ R. It increases stroke volume, heart rate, renal blood flow (D_1/D_2 R) and natriuresis [1, 2].

• As a rule, smaller (so-called "splanchnic") doses are given in inf. 2 μg/kg/min.

b) **Dobutrex®** (*dobutamine*): [amp. á 250mg/20 ml/50ml] is a synthetic catecholamine for the treatment of CHF refractory to conventional therapy. By stimulating β_1R and α_1R, it increases contractility and heart rate, and by stimulating β_1R >> α_1R it lowers venous tone and PCWP, so it is more suitable in patients with CHF and IHD [1, 2, 25].

• Initial dose of 1.0-2.5 μg/kg/min. which is continued by titration at 10-20 μg/kg/min.

c) **Digitalis**/cardiotonic glycosides [Digoxin amp. á 0.5 mg/ 2 ml; tbl. á 0.125/0.25 mg; MDD: 0.125 - 0.5 mg/24h]. Indicated in CHF with EF ≤ 30% in NYHA III/IV class, with cardiomegaly in sinus rhythm or atrial fibrillation with rapid ventricular response. They improve quality of life and effort tolerance [11, 26].

d) **Phosphodiesterase III (PDI3) inhibitors** - non-glycosidic inotropes [*amrinone*, *milrinone*, *enoximone*]. They increase intracellular cAMP and thus intracellular Ca^{2+}, so it exhibits a positive inotropic effect. They are used in severe forms of ADHF: cardiogenic shock, sepsis, cardiac surgery, less often in standard CHF treatment, etc. In RF the dose is reduced by 25-50% [1, 2].

e) **Calcium sensitizer** [**Simdax®** (*levosimendan*): [amp. á 12.5 mg/5 ml] increases the sensitivity of troponin C to cytosolic calcium without additional transport of Ca^{2+} into the cytosol. It increases the contractility of the myofilamentary apparatus and exhibits arteriolodilatory and anti-inflammatory effects. Effectively increases MV (30%) and reduces PCWP (25%). The effect may last for several days and is not given if the e-GFR is ≤ 30 ml/min. [27, 28].

• It is initially given 6-12 μg/kg/10 min, then in a slow infusion 0.05-0.2 μg/kg/min/24h.

f) **AVP - V2 receptor antagonist** [Samsca® (*tolvaptan*): tbl. á 15/30 mg; MDD: 60 mg/dosis therapy interval of 24h]. They increase serum Na^+ and aqueous diuresis by selective blockade of AVP - V2R, in the collecting tubule (reduces the expression of AQP-2 channels). They are indicated in conditions of hyper-/euvolemic hyponatremia (s-Na ≤ 125 mEq/L) in CHF and SIADH syndrome [2, 25].

g) **Myosin activators** (*omecamtiv mecarbil*) are drugs of the latest generation that increase the efficiency of the contractile apparatus without additional increase of Ca^{2+} ions in the cytosol. They have shown very good effects in patients with CHF in NYHA III/IV class [11, 29].

h) **Recombinant human BNP** [Natrecor® (*nesiritide*): amp. á 1,5mg] is an arterio/venous and coronary dilator, reduces pre-/after load, antagonizes the effects of RAS and ADH in refractory CHF and ADCHF, when nitroglycerin and/or Na-nitroprusside are not effective.

• Initially given iv. 2 mcg/kg, then in inf. 0.01 mcg/kg/min, not longer than 3 days [2,11]

NON-PHARMACOLOGICAL TREATMENT

It implies a set of different non-pharmacological measures and procedures that are applied together with medical support in severe clinical forms of refractory CHF [16].

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