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The use of diuretics in chronic heart failure. Position paper of the Russian Heart Failure Society

The document focuses on key issues of diuretic therapy in CHF from the standpoint of current views on the pathogenesis of edema syndrome, its diagnosis, and characteristics of using diuretics in various clinical situations.

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Keywords Diuretics; CHF; fluid retention; edema; decompensation; salt-water regimen; euvolemia

For citation Mareev V. Yu., Garganeeva A. A., Ageev F. T., Arutunov G. P., Begrambekova Yu. L., Belenkov Yu. N. et al. The use of diuretics in chronic heart failure. Position paper of the Russian Heart Failure Society. Kardiologiia. 2020;60(12):13–47. [Russian: Мареев В.Ю., Гарганеева А.А., Агеев Ф.Т., Арутюнов Г.П., Беграмбекова Ю.Л., Беленков Ю.Н. и др. Экспертное мнение по применению диуретиков при хронической сердечной недостаточности. Общество специалистов по сердечной недостаточности. Кардиология. 2020;60(12):13–47]

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Introduction

Epidemiology of chronic heart failure

Chronic heart failure (CHF) is a syndrome that results from the disability of the heart to fill and/or empty, occurring when the vasoconstriction and vasodilation neurohormonal systems are imbalanced, which is accompanied by the inadequate perfusion of the body's organs and tissues, and manifested by a complex of symptoms: shortness of breath, weakness, palpitation, fatigue, and fluid retention [1]. CHF is diagnosed in 1–4% of the adult population in developed countries, with the prevalence of CHF significantly increasing among the population over the age of 70 years old and reaching 10% [1–5]. According to the EPOCH trial, 7–10% of the Russian adult population suffer from CHF [1, 6, 7]. Among patients admitted to cardiac units, CHF is diagnosed in 89–92%, with about 70% of cases being CHF with

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1427

preserved left ventricular ejection fraction (HFpEF) [8, 9]. The annual mortality of patients with CHF is from 6.9 to 15.6%, which significantly exceeds the mean population values [10, 11].

Acute HF (AHF) is a clinical syndrome characterized by the rapid onset and/or augmentation of heart failure (HF) symptoms associated with cardiac dysfunction, and requiring emergency intervention [12]. The percentage of patients with acute decompensated HF among those with AHF syndrome reaches 80–90% [13]. Acute decompensated HF (ADHF) is a key cause of death and repeated hospitalizations of CHF patients. The in-hospital mortality is 9%, the total 30-day mortality after an episode of ADHF reaches 22%, and the 12-month mortality after discharge from the hospital is 43% [11]. ADHF is characterized by a high rate of hospitalizations. Thus, according to the Russian ORACUL-RF registry, the rate of hospitalizations within 30, 90, 180, and 360 days is 31, 11, 11, and 9.5%, respectively [11].

Place of diuretic therapy in the treatment of chronic heart failure

Diuretic therapy (DT) is directly indicated in the onset or exacerbation of symptoms and signs of fluid retention in CHF. There are many triggers, such as alimentary disorders of fluid and electrolyte consumption, use of alcohol, hemodynamically significant tachyarrhythmia and bradyarrhythmia, acute coronary insufficiency, exacerbation of concomitant pathology, infectious process, thyroid dysfunction, anemia, nephropathy, chronic lung diseases, use of some drugs, and other factors causing the depletion of compensatory mechanisms of the circulatory system and the development of fluid retention syndrome [14–17].

There have been no large randomized clinical trials (RCTs) to assess the effects of diuretics (except for mineralocorticoid receptor antagonists (MCRAs)) on the course and outcomes of CHF. The findings regarding their efficacy and safety are based mainly on the sub-analysis results. In some observational post-marketing studies, the administration of diuretics to CHF patients was associated with increased mortality and repeated hospitalizations due to decompensated CHF [18–21].

However, the adverse effects of diuretics on the prognosis of CHF has been repeatedly argued against by the scientific evidence, which proves the association of adverse course and outcome of HF. This leads to the need for high doses of diuretics and the development of diuretic resistance, rather than the fact of their administration [22–24]. Despite the existing contradictions, the administration of DT in fluid retention and decompensated CHF is almost inevitable. According to the European Heart failure Survey, 74% of patients with CHF need DT, 36% of them receive loop diuretics, 34% use thiazide diuretics, and 17% receive MCRAs [25].

The decision of whether it is reasonable to use diuretics and their dosages is made based on the diagnosis of body hyperhydration, accompanied by the increased chamber filling pressure and the activation of compensatory and adaptive neurohumoral reactions. The progression of water and electrolyte imbalance is manifested by symptoms and signs of developing circulatory congestion, which requires active DT [1, 26, 27]. However, if CHF is compensated and the volume of intravascular and interstitial fluids is normalized, the doses of the diuretic may be significantly reduced [27, 28]. Diuretic therapy can be reasonably reduced in the state of euvolemia, which is a cut-off point when the body reaches an optimal fluid volume, which allows meeting the metabolic needs of organs and systems, in the absence of excessive amounts of interstitial fluid and a pathologic increase in a cardiac chamber filling pressure [27].

Neuroendocrine regulation of body fluid volume

The fluid is 60% of human body weight and is distributed between intracellular (up to 40%) and extracellular (up to 20%) sectors. The osmolarity of blood plasma is the main indicator of water homeostasis, which is determined by the number of dissolved atoms, molecules, molecule complexes per kilogram of plasma. The normal osmolarity of blood serum is 290 (285–295) mOsmol/L in middle age. The regulation of osmolarity is mainly maintaining the consistency of the water-to-sodium (Na^+) ratio. Antidiuretic hormone (ADH) is the main hormone that regulates the volume of urine released. The interaction of ADH with the V_2 vasopressin receptors in the discharging tubules leads to the incorporation of the aquaporin 2 protein, which forms water-permeable pores, into the cell membrane and increases water reabsorption.

Renin-angiotensin-aldosterone system (RAAS) and natriuretic peptides (NPs) regulate sodium excretion. The reduction of blood flow through the afferent artery and the decrease in sodium and

chlorine levels in the distal nephron have a powerful effect, which stimulates the synthesis of renin by the juxtaglomerular apparatus and triggers a cascade of reactions. The latter leads to the increased synthesis of angiotensin II, which acts as a vasopressor and stimulates the synthesis of aldosterone in the adrenal glands. Aldosterone regulates the volume of extracellular fluid by increasing sodium reabsorption in the kidney tubules and large intestine, which is accompanied by water retention. The increase in sodium levels in the distal nephron perceived by macula densa cells, conversely, leads to the reduced synthesis of renin, angiotensin II, and aldosterone.

The secretion of NPs increases when circulating blood volume (CBV) and myocardial stress increase, due to a higher left ventricular filling pressure. Atrial tissue is normally the main source of peptides. The increased preload accelerates the synthesis of atrial NPs, then the synthesis of cerebral NPs increases significantly during long-term volume overload and cardiac chamber remodeling. The effect of NPs on a nephron consists in the dilation of the efferent arteriole and narrowing of the efferent arteriole: increased hydrostatic intra-glomerular pressure and higher glomerular rate, reduced tone of the mesangial cells and higher effective surface area of the kidney filter, lower reabsorption of sodium in the distal convoluted tubule, inhibiting the secretion of renin and reducing the secretion of aldosterone. In fact, NPs have an antagonistic effect against RAAS.

Fluid retention syndrome in chronic heart failure

Pathogenesis of fluid retention and development of congestion

Kidneys are involved in fluid retention pathogenesis at the earliest stage of HF [29, 30]. The retention of sodium and water in CHF occurs in response to a decrease in effective CBV and simultaneous activation of three critical systems: sympathetic nervous system, RAAS, and NP system [31].

The activation of the neurohormonal pressor system is originally compensatory and is aimed at maintaining adequate perfusion pressure in organs and tissues by accumulating extracellular and interstitial fluid, which acts as a buffer and provides compensatory increase in the intravascular volume, recovery of effective CBV, increase of venous return back to the heart, and normalization of its filling pressure [32, 33]. Increased activity of NPs at the stage of asymptomatic stable CHF is considered as a compensatory mechanism of reduced initial cardiovascular maladaptation, which is achieved by increased natriuresis [34], inhibition of aldosterone synthesis [35], enhancement of vasodilation [36], suppression of cell proliferation, and inflammation [37, 38].

However, the formation of peripheral resistance to NPs during the long-term increased activity of the pressure systems provides no adequate response to the effects of RAAS, which leads to the development of excessive sodium and water

Table 1. Sensitivity and specificity of clinical signs of congestion. Adapted from Gheorghiade et al. [27, 55, 56]

Clinical signs	Sensitivity	Specificity	Comment
Signs (on the right) consistent with RAP >7 mm Hg			
Jugular venous pressure >8 cmH_2O	48%	78%	Difficult to identify in obese patients, patients with COPD
Hepatojugular reflux	50%	75%	Difficult to identify in obese patients
Hepatomegaly	51%	62%	Difficult to identify in obese patients; non-cardiac causes
Bilateral peripheral edema	94%	10%	False-positive value in the presence of non-cardiac causes
Signs (on the left) consistent with PAWP >18 mm Hg			
Shortness of breath	50%	73%	Many other reasons for shortness of breath
Shortness of breath during physical exercise	66%	52%	Many other reasons for shortness of breath
Orthopnea	66%	47%	Non-cardiac etiology; absent in many patients
Third heart sound	73%	42%	Erratic manifestation of the symptom
Pulmonary rales	13%	90%	Non-cardiac etiology; absent in many patients

RAP, right atrial pressure; PAWP, pulmonary arterial wedge pressure; COPD, chronic obstructive pulmonary disease

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1427

retention, vasoconstriction, and volume overload [39–41].

There are two conventional stages in the pathogenesis of fluid retention and the development of congestion: hemodynamic and clinically significant [42]. Initially, there is a slight increase in the pulmonary and/or right-heart pressure, which is preserved at a certain level for a long time (up to several weeks) and is asymptomatic [43, 44]. The chamber filling pressure can then increase rapidly, and hemodynamic congestion transforms into clinically significant congestion, with the onset of symptoms and signs of ADHF.

The onset of clinical signs and symptoms indicates the actual retention of a significant amount of fluid in patients with CHF. It is important to note that a higher total volume of fluid circulating in the vascular bed in ADHF is always associated with a three-fold increase in its interstitial volume, owing to the heterogeneous distribution of sodium retained by the kidneys [45]. At the same time, the venous system can accommodate 60–70% of the total blood volume, mainly localized in the high-capacity visceral section [46, 47]. Thus, taking into account the iso-osmotic retention of sodium and water as the primary reason for increased cardiac filling pressure, weight gain should occur weeks before the onset of symptoms of ADHF [48, 49]. CBV can increase by more than 100% (mean increase is about 40%) in such patients [49]. However, the long-term development of venous congestion weeks before the onset of apparent clinical decompensation suggests its significant independent contribution to the development of ADHF [48].

At the same time, several studies show that more than 50% of patients with clinically apparent ADHF did gain significant weight before the onset of decompensation symptoms, and the weight gain in these patients was less than 1 kg one month before hospitalization [50, 51]. As such, it is generally accepted that the redistribution of blood from the venous depot to the central part of the circulatory system, as well as the absolute volume, can increase cardiac filling pressure with both mechanisms often not excluding, but supplementing each other [1, 32, 52, 53].

Thus, it is necessary to distinguish between acute redistribution of fluid and real volume overload, caused by fluid retention in patients hospitalized with symptoms and signs of congestion, as it can have possible effects on further patient management [1, 53]. The main purpose of using diuretics in patients with HF is to eliminate volume overload, edema syndrome, circulatory congestion symptoms, and signs associated with volume overload, which are discussed in the following sections.

Clinical signs of congestion in heart failure

The onset of clinical signs and symptoms of congestion in CHF patients is associated with increased cardiac filling pressure and excessive accumulation of extravascular fluid.

The most important clinical signs that reflect the development of congestion are used as surrogate markers of increased cardiac filling pressure [54]. The diagnostic precision of using non-invasive clinical signs of congestion in CHF patients is specified in Table 1.

Dilation (engorgement) of the jugular veins is the most accurate clinical sign of congestion that reflects cardiac filling pressure and right atrium pressure (RAP) [57]. Conventionally, jugular venous pressure is determined in the internal jugular veins, but the external jugular veins are also useful for this purpose [58]. Both increased pressure and jugular vein dilation accurately reflect the severity of systemic congestion in patients with CHF and right heart dysfunction. These signs are also closely correlated (sensitivity 70%, specificity 79%) with the left cardiac filling pressure [59–61], which predetermined the presence of an elevated pulmonary arterial wedge pressure (PAWP) of >18 mm Hg accompanying biventricular HF [62]. However, accurate measurement of the jugular venous pressure requires skill, which can have limited success and therefore reproducibility of this sign in clinical practice [63].

Hepatojugular reflux

This clinical sign is useful when combined with the jugular venous pressure measurement [62, 64, 65] to identify cardiac congestion and elevated cardiac filling pressure. The presence of hepatojugular reflux is detected with prolonged pressure on the abdomen, for 10 seconds, which, in the presence of congestion in CHF, elevates the top of the jugular venous pulsation by more than 3 cm and then drops it. The higher the top of the jugular venous pulsation becomes when the abdomen is pressed, the higher the venous pressure is. Hepatojugular reflux increases the likelihood of high ventricular filling pressure, since its detection in HF and normal right ventricular systolic function predetermines

an increased level of PAWP >15 mm Hg [66]. The evaluation of this parameter is often limited in clinical practice to the patient's physique, such as obesity or associated respiratory pathology.

Shortness of breath is the most common symptom, which is used as a clinical marker of a change/reduction of the severity of congestion in patients with decompensated HF. However, the specificity and sensitivity of this sign are reduced due to many other reasons for its development. Moreover, patients with CHF may have no shortness of breath if they have other signs of congestion [67, 68].

Orthopnea is a clinical sign of severe congestion associated with increased PAWP (sensitivity 90%) [69].

Attacks of paroxysmal nocturnal dyspnea (cardiac asthma) are a major symptom that often precedes pulmonary edema development in the coming days and nights. However, this sign is much less common in patients with initial fluid retention events.

Pulmonary rales are a clinical sign of fluid overload in HF patients. However, this sign is extremely unspecific and can be found in patients with pulmonary pathology. However, the absence of rales is not a sensitive marker of the absence of congestion in CHF due to increased lymphatic drainage in such patients. Moreover, patients with elevated cardiac filling pressure may have no pulmonary changes, even radiographic ones [59].

The onset of peripheral edema in CHF patients, which is based on the development of left heart pathology, is a late clinical sign of congestion and fluid retention. Peripheral edema is mainly bilateral in patients with CHF. This symptom is not specific and barely informative about the levels of cardiac filling pressure. The development of peripheral edema can also be caused by other diseases and conditions, such as liver cirrhosis, venous insufficiency, lymphedema, nephrotic syndrome, hypoalbuminemia, anemia, obesity, etc.

Weight change

Patients with CHF are recommended to weigh daily and to keep records. A rapid weight gain of more than 2 kg within 24–72 hours usually indicates sodium and water retention in patients with CHF and the risk of decompensation (recommendation class I, evidence level A) [1, 70]. Clinical signs of congestion can progress in patients with HF without weight gain due to the redistribution of the volume of fluid, leading to a rapid change in the cardiac filling pressure, which is particularly true for patients with HFpEF [71]. Moreover, fluid retention can often be masked by a simultaneous decrease in actual body weight as a result of gastrointestinal congestion, bowel wall edema with impaired nutrient absorption, and loss of appetite. Many patients with severe CHF develop cachexia over time. In this respect, even in the presence of severe congestion events, a patient's weight can change insignificantly. Therefore, the specificity of this clinical sign for the detection of congestion in HF is extremely low, even with high sensitivity.

Laboratory markers for detection of congestion

According to existing guidelines, NPs can be used to detect congestion in CHF. They were included in the corresponding clinical and laboratory scores [1, 72]. The rest of the routine laboratory markers are more useful for assessing the safety of the ongoing DT and its correction, monitoring the elimination of congestion, achieving euvolemia in patients with ADHF [33, 73, 74], as well as for excluding non-cardiac causes of fluid retention [1, 53].

NPs are well-studied biomarkers that can be used in patients with congestion to confirm its presence or absence. The NP cut-off values most accurately predetermine the absence of cardiac causes of fluid retention: with brain natriuretic peptide (BNP) <100 pg/mL, N-terminal pro-brain natriuretic peptide (NT-proBNP) <300 pg/mL, and midregional pro-atrial natriuretic peptide (MR-proANP) <120 pg/mL, congestion and ADHF are unlikely [1, 53, 75-77]. The higher the concentration of NPs, the higher the likelihood of the correlation of shortness of breath and other clinical signs of congestion with HF. When NPs are used to confirm the presence of congestion and decompensated HF, BNP > 400–500 pg/mL should be considered [78–80]. Its age-specific cut-off values are used to improve the positive predictive strength of NT-proBNP. According to the age groups (<50 / 50–75 / >75 years), the useful cut-off values of the hormone to confirm the presence of congestion and ADHF are the levels of the peptide > 450/900/1800 pg/mL, respectively [77, 78, 81]. However, as in patients with stable HF, the negative predictive value of BNP and NTproBNP is higher (0.94–0.98) than the positive predictive value (0.66–0.67).

A lower predictive value of existing NP cut-off levels used to confirm the development of decompensation is due to the fact that patients with stable CHF can initially have significantly elevated levels of BNP and NTproBNP, euvolemic (dry) le-

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1427

vels of NPs. Therefore, it is essential to study the initial levels of NPs in every CHF patient, which were determined in the state of euvolemia, assuming for the highly likely development of decompensation, when the levels of these biomarkers increase by 100% or more in a shorter time period [78, 82, 83]. At the same time, congestion and fluid retention can be suspected in patients with stable HF at an earlier stage of hemodynamic changes, days and weeks before the development of a full picture of decompensated HF. Cardiac filling pressure is highly likely to increase even when NT-proBNP is elevated by >50% and BNP by >60% compared to the baseline levels [78, 84, 85]. Other possible causes of increased NP levels (acute myocardial infarction, pulmonary embolism, etc.), and impaired kidney function should also be excluded. The cut-off value used to confirm the diagnosis of ADHF in patients older than 50 years, who have a glomerular filtration rate of ≥60 mL/min/1.73 m^2, is NTproBNP ≥900 pg/mL. This value increases to to the level of 1200 pg/mL in patients of the same age group but with GFR <60 mL/min/1.73 m^2 [86].

Thus, the comprehensive assessment of the clinical signs of congestion, as well as the determination of NP levels over time, is the best option for early detection of decompensation in patients with a history of cardiovascular diseases and/or CHF.

Hemoconcentration markers

The assessment of blood thickness (increase in serum protein, albumin, hemoglobin and/or hematocrit) on the admission of an HF patient is a surrogate marker of congestion and its elimination. Its further development is associated with better short- to medium-term prognosis in ADHF [73, 87], even if kidney function is impaired [88].

However, if changes in hemoglobin levels and hematocrit values can be used to estimate changes in intravascular volume status and prognosis, it is not reasonable to use absolute values of these laboratory markers to verify the presence of congestion [89].

Markers of kidney function

Evaluation of the kidney function and determination of creatinine, urea, GFR, and albuminuria, as well as the urea-to-creatinine and albumin-to-creatinine ratios, are also routine and standard laboratory parameters estimated in patients with CHF or ADHF. It has been shown that the onset and progression of venous congestion accompanied by elevated central venous pressure (CVP) is a significant hemodynamic factor of kidney function deterioration in patients with decompensated HF [90, 91]. Impaired kidney function confirmed by the increased initial levels of plasma creatinine ≥0.3 mg/dL (≥26.4 umol/L), or decreased GFR, negatively affects the prognosis for patients with HF [92].

Increased urea reabsorption and its increased blood levels in HF can be caused by the development of congestion and increased neurohormonal activity and impaired kidney function, whereas increased creatinine is more specific only for changes in GFR [93]. For this reason, urea levels do not always increase proportionately with changes in the creatinine levels, and are not so much indicative of kidney function as their increase is comparable to the severity of congestion and HF. It was also established that the urea levels indirectly reflect the degree of neurohormonal activation [93–95].

Markers of liver dysfunction

The signs of cholestatic liver damage and hepatocyte dysfunction develop in patients with HF mainly when CVP and RAP values are already high at the late stages of congestion. Thus, bilirubin and gamma-glutamyl transpeptidase can also be considered as laboratory biomarkers of congestion [96].

Instrumental methods of measuring the volumetric status

Direct methods

Volemia usually refers to CBV, which is not entirely accurate from a clinical point of view, since the ratio of blood volume and the capacity of the vascular bed where it circulates is essential for adequate filling of the cardiac chambers with blood and, accordingly, creating the necessary pressure in the aorta and pulmonary artery [97]. Therefore, volemia is described as an absolute indicator, i.e., an estimated blood volume normally contained in the circulatory bed, and a relative indicator showing the degree of the vessel filling with blood [97].

The blood pressure in the superior or inferior vena cava right where it inserts into the right atrium is usually called CVP, which corresponds to RAP. In clinical practice, CVP is measured in the superior vena cava through the inserted subclavian catheter for infusion and transfusion therapy [98, 99]. It is used to indicate the volume of venous return to the heart and its filling in diastole [100, 101]. When RA pressure drops from 0 to –4 mm Hg, the venous blood flow to the heart increases by 20–30%.

Table 2. Classification of diuretics by focus of action in the nephron structure and diuretic efficiency

Class of diuretics	Focus of drug action	Diuretic efficiency
Carbonic anhydrase inhibitors	Proximal tubule	Low, sodium excretion 1–2%
Loop diuretics	Ascending limb of the loop of Henle	High, sodium excretion 20–25%
Thiazide and thiazide-like diuretics	The first part of the distal tubule, the corneal segment of the nephron	Moderate, sodium excretion 5–10%
Potassium-saving (sodium channel blockers and aldosterone antagonists)	The terminal part of the distal tubule and collecting tubules	Low, sodium excretion 1–2%

However, when the pressure drops below –4 mm Hg, further decrease in pressure does not cause an increase in venous blood flow, due to the collapse of veins entering the chest caused by a sharp drop in the blood pressure in these veins. When RAP increases by 1 mm Hg, venous return to the heart decreases by approximately 14% [102].

A decrease in CBV that occurs in dehydration, including during excessive DT or significant blood loss, causes a decrease in venous pressure. Thus, CVP is indicative of the right ventricle's ability to pump the entire volume of incoming blood, which is why it is an objective criterion of right ventricular pumping function. CVP increases in right ventricular failure.

Blood pressure should be measured in the pulmonary vein system to evaluate the pumping function of the left heart objectively. PAWP is determined for this purpose. It is one of the main hemodynamic indicators of the heart's pumping function and is always, with a few exceptions, with left atrial pressure and left ventricular end-diastolic pressure, thus showing the state of the pulmonary capillary circulation, and the risk of pulmonary edema in patients with left ventricular heart failure. Normal PAWP is 6 to 12 mm Hg; when it is less than 6 mm Hg, the left ventricle is not filled enough. The performance of the heart will be definitely limited by such a low preload. When PAWP is more than 12 mm Hg, there is usually no increase in the heart performance. Moreover, the risk of volume overload of the pulmonary circulation increases.

Indirect methods

Dynamic measurements of blood pressure and cardiac preload parameters (e.g., pulse pressure, systolic and end-diastolic left ventricular volume), and echocardiographic measurement of cardiac chamber pressures can be used to assess a patient's volemic status indirectly in the clinical setting [103–105]. The normal cardiac chamber pressure values are provided in the supplementary materials to this article and on the journal's website.

Table 3. Main pharmacokinetic parameters of loop diuretics

Drug	Bio-availability,%	Elimination: kidneys/ liver, %	Duration of action, hours
Furosemide	10-90	65 / 35	4–6
Torasemide	80-90	20 / 80	12–18
Etacrynic acid	100	67 / 33	6
Bumetanide	60-90	62 / 38	6–8

Ultrasound study of the inferior vena cava (IVC) and measuring of its diameter during respiratory cycles is an informative method for assessing volemic status. A deep inhale causes a decrease in intrathoracic pressure and an elevation in the RA filling by increasing the blood flow coming from the IVC, as a result the IVC collapses and its diameter is reduced. The situation is the opposite in a deep exhale, and the IVC dilates [106–108]. The so-called inferior vena cava collapsibility index (IVCCI) was proposed to estimate the severity of IVC lumen changes during respiration [109]. It is calculated using the following formula:

$$IVCCI = [IVC\ max\ diameter - IVC\ min\ diameter / IVC\ max\ diameter] \times 100\%.$$

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1427

IVCCI more than 75% corresponds to hypovolemia; 40–75% indicates euvolemia, and inspiratory IVC collapse less than 40% is characteristic of hypervolemia. A small diameter of the IVC (1.2 cm or less) suggests absolute hypovolemia.

Chest X-ray cannot detect signs of pulmonary congestion in one in five patients with decompensated CHF [27]. Lung ultrasound shows higher sensitivity and specificity than X-ray. Lung ultrasound is based on the definition of the B-line artifacts that occur due to an accumulation of extravascular (interstitial and alveolar) fluid in the lungs [110]. The detection of more than three B-lines in more than two intercostal spaces on both sides is the diagnostic symptom of congestion [27]. The relatively high sensitivity of the lung ultrasound in detecting congestion allows it to be diagnosed at the asymptomatic stage. It was shown that 81% of CHF patients having B-lines in the lungs could have no auscultatory signs of congestion [110, 111]. However, the presence of asymptomatic congestion increases the risk of adverse cardiovascular outcomes [112]. Moreover, in the LUS study, a DT correction based on lung ultrasound data reduced the risk of the primary endpoint (emergency department visits, hospitalizations for CHF, all-cause death), in patients with CHF after discharge from the hospital by 48%, compared to the standard approach [113]. The CHF patient management protocols based on regular lung ultrasound appear to need further investigation.

Bioelectrical analysis of the intrathoracic (pulmonary) impedance may be another quantitative method of assessing congestion, including the asymptomatic stage. Although this analysis is not yet widely used, the treatment of ambulatory patients with CHF based on the regular evaluation of pulmonary impedance, and the correction of treatment depending on its changes, reduced the number of hospitalizations for CHF during the 12 months of follow-up in the IMPEDANCE-HF study [114].

Diuretic agents

Diuretics are medicines that inhibit the reabsorption of water and salts in the kidney tubules and increase their excretion in the urine, thereby increasing the rate of urine formation and reducing the fluid content in tissues and serous cavities.

Classification

Diuretics used for the treatment of CHF are classified according to the localization of their action in nephron [115], as well as the force, rate of onset, and duration of action [116] (Table 2). The force of the diuretic effects correlates with the drug's ability to interfere with sodium reabsorption, i.e., its natriuretic effect.

Loop diuretics are the most effective diuretics that block sodium reabsorption throughout the ascending limb of the loop of Henle. Loop diuretics bind to the Na^+-K^+-$2Cl^-$ carrier in the thick segment of the ascending limb of the loop of Henle and inhibit it, suppressing the reabsorption of Na^+, K^+, and Cl^- in this part of the nephron. Loop diuretics contribute to inhibiting tubuloglomerular feedback, which is why they do not reduce GFR and renal blood flow. Loop diuretics remain active when the renal filtration rate is >5 mL/min [116–118].

Loop diuretics (especially furosemide) have a direct vasodilating effect. They quickly increase the capacity of the venous bed and reduce the left ventricular preload.

Loop diuretics are currently the basic method to treat edema syndrome in CHF.

Furosemide is used both as intravenous injections (in decompensated CHF) and tablets for long-term maintenance treatment [1]. The diuretic effect of the drug continues for 6–8 hours. The presence of serious adverse reactions requires using minimally effective doses of furosemide, combined with RAAS blockers and potassium-saving diuretics [1, 115].

Torasemide is the most effective and safe loop diuretic in use today, with an optimal pharmacokinetic profile. Its pharmacokinetic properties are superior to furosemide. It has better and predictable absorption independent of food intake [1, 119]. The half-life of torasemide does not change in kidney failure because 80% of the drug is metabolized by the liver (Table 3).

Two formulations of torasemide, immediate-release (IR) and extended-release (ER), are available. The maximum concentration occurs in 1–2 hours after the administration of torasemide IR and it decreases rapidly to subtherapeutic levels. Extended-release torasemide (ER) passes gradually into the blood plasma, which allows avoiding peak-to-trough fluctuations in plasma concentrations and increased post-diuretic reabsorption [120, 121].

The main positive difference between torasemide and other loop diuretics is its additional effects, such as those associated with the simultaneous blockade of the local RAAS, and the sympathetic nervous system. Torasemide has anti-aldosterone effects accompanied by a decrease in myocardial fibrosis,

Table 4. Main diuretics used in CHF: indications, dosing, required glomerular filtration rate [1]

Drug	Indication	GFR, mL/min/ 1.73 m²	Starting dose, mg, frequency	Maximum daily dose, mg
Furosemide	FC II–IV	>5	20 x 1–2	600
Torasemide	FC II	>5	2,5 x 1	5
Torasemide	FC II–IV	>5	10 x 1	200
Hydrochlorothiazide	FC II–IV	>30	25 x 1–2	200
Indapamide	FC II	>30	1,5 x 1	4,5
Spironolactone	Decompensated CHF FC III–IV	>10	50 x 2	300
Acetazolamide	Combination therapy in decompensated CHF, diuretic resistance (alkalosis)	>10	250 x 1–3–4 days with pauses (10–14 days)	750

with a simultaneous improvement of its diastolic characteristics [122, 123].

In controlled comparative studies, torasemide demonstrated higher clinical efficacy and tolerability, as well as the capacity to reduce repeated hospitalizations for CHF exacerbation, improving the prognosis for patients by decreasing all-cause and cardiovascular mortality compared to furosemide [124–126].

Thus, torasemide is a diuretic of choice used to treat congestion events in CHF, especially in the long-term treatment of clinically severe decompensation (recommendation class I, evidence level B) [1].

The diuretic properties of etacrynic acid differ little from those of furosemide, although it is the only diuretic that does not contain sulfanilic acid residues in the molecule. Therefore, if diuretic-dependent patients become addicted and the efficacy of furosemide (or torasemide) decreases, a temporary transfer to etacrynic acid can be justified.

Bumetanide also has diuretic properties similar to those of furosemide and etacrynic acid, but it is the most short-acting loop diuretic, which is why it is less reasonable to use it to treat CHF.

Thiazide and thiazide-like diuretics that inhibit co-transport of Na^+-Cl^-, interfere with the reabsorption of Na^+ and Cl^- in the distal convoluted tubules. However, their effect is relatively moderate with the excreted Na^+ not more than 5–10%. Thiazide and thiazide-like diuretics, as well as loop diuretics, increase the excretion of K^+ and H^+, increasing the inflow of Na^+ into the distal tubules. They increase diuresis and natriuresis by 30–50%, and are effective at the filtration rates of more than 30 mL/min [116, 117].

During the long-term use, thiazide and thiazide-like diuretics (especially indapamide) reduce the sensitivity of the vascular wall to noradrenaline and angiotensin II, which is due to the lower levels of sodium in the cytoplasm of the vascular smooth muscle cells. They stimulate the synthesis of prostaglandins, thus reducing the overall peripheral vascular resistance.

Hydrochlorothiazide is the main thiazide diuretic, which can be used in patients with moderate CHF (functional class (FC) II) or in combination with other diuretics.

It should be kept in mind that, despite all its positive effects, hydrochlorothiazide is a drug that requires careful and correct administration to avoid serious adverse events [1].

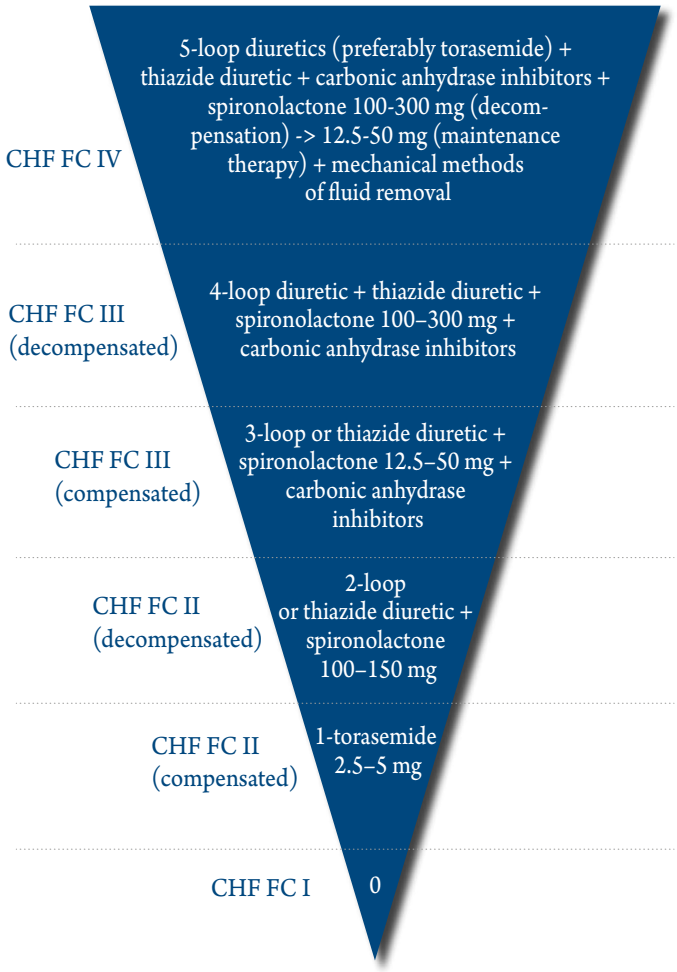
The safety profile of indapamide is significantly superior to that of hypothiazide, but there is still not enough data on its use to treat CHF. Another thiazide diuretic is chlorthalidone, which is commonly used to treat patients with arterial hypertension. However, similar to indapamide, it can be used in patients with primary CHF and preserved kidney filtration function.

Potassium-saving diuretics that act on the distal renal tubules and collector tubule are used together with active diuretics. Drugs of this group slightly increase the excretion of sodium; they are usually administered to reduce the renal loss of K^+ induced by other diuretics.

Their clinical efficacy is proportional to the aldosterone levels and the higher it is, the higher the

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1427

Figure 1. Algorithm of dehydration treatment of patients with chronic heart failure



effect of spironolactone and eplerenone on renal excretion.

Spironolactone is used in diuretic therapy as a potassium-saving drug combined with active diuretics [127]. The criteria of spironolactone efficacy in the complex treatment of persistent edema syndrome are a 20–25% increase in diuresis, less pronounced thirst, dry mouth, disappearance of the particular hepatic breath smell, and stable plasma levels of potassium and magnesium. The concentration of spironolactone reaches a plateau by day 3 of treatment. When the compensation is achieved, high doses of spironolactone are discontinued.

Spironolactone is a non-selective MCRA highly affinitive to androgen and progesterone receptors, which is why it can cause gynecomastia and impotence in male patients and menstrual disorders in female patients.

Eplerenone, unlike spironolactone, is a selective MCRA having a weak anti-androgen effect, which significantly reduces the risk of side effects. The RCT findings currently indicate recommending eplerenone 25–50 mg/day as a third neurohormonal modulator to improve the prognosis for patients with HF with reduced left ventricular ejection fraction (HFrEF) [1, 128], whereas high-dose spironolactone remains the drug of choice in decompensated CHF.

Other potassium-saving drugs (triamterene) are uncommon and are used only in case of MCRA intolerance.

Carbonic anhydrase inhibitors act on the proximal renal tubules. They have a small diuretic effect and are used to treat CHF to increase the efficacy of loop diuretics. These compounds are administered at a dosage of 250 mg tid for 3 to 4 days with a two-week break. Acetazolamide has been shown to reduce renal blood flow and protect the glomeruli from increased stress, especially high stress, during the use of loop diuretics [129].

It is particularly important to combine active diuretics and acetazolamide in patients with CHF and concomitant pulmonary pathology, which contributes to the excretion of HCO3- with urine (recommendation class IIa, evidence level B) [1, 129]. Moreover, it was shown that taking acetazolamide 250 mg one hour before going to bed reduces sleep apnea, which can complicate the course of the disease in 40% of patients with CHF (recommendation class IIa, evidence level C) [1, 130–132].

Indications and contraindications for the diuretic treatment in heart failure

The main indication for using diuretics in CHF is the presence of edema syndrome (hyperhydration) diagnosed by the clinical and paraclinical signs of congestion. Diuretics are administered in patients with CHF to eliminate edema syndrome and reduce clinical symptoms [1].

Dehydration therapy in CHF is conducted in two phases, active treatment (during hyperhydration) and maintenance (to maintain the achieved state of euvolemia). During the active treatment, a positive diuresis should be achieved and the volume of the excreted urine should be more than the fluid intake by 1–2 liters, with the mean weight loss of 1 kg a day. Faster dehydration can lead to severe neuroregulatory disorders and rebound fluid retention, thus resulting in the development of diuretic resistance.

During the maintenance treatment, the diuresis should be balanced (the volume of urine excreted should be at least 75% of the volume of fluid intake), and the bodyweight should be stable. The loading

regimen of diuretics, i.e., once every few days, is unacceptable. Dehydration therapy should be used every day in minimally effective doses during the complex nosotropic therapy of HF.

DT should be initiated if CHF FC II (NYHA) is diagnosed, whereas diuretics are not required in the absence of symptoms of congestion and the satisfactory tolerance to physical activity (FC I) (Table 4).

Contraindications to diuretics

The main contraindications to the use of all groups of diuretics, as well as individual intolerance of the active substance and excipients, are severe electrolyte disorders (should be corrected before beginning the therapy), terminal renal failure with anuria, liver cirrhosis, and encephalopathy (risk of increasing levels of endogenous toxins and worsening the severity), hypovolemia and dehydration, pronounced disorders of urine outflow, contraindications to the administration of main diuretics are provided in the supplementary materials to this article and on the journal's website.

Combined use of diuretics

The combination of diuretics is based on the mechanisms of action of the drugs to produce a synergistic effect and is determined by the severity of the symptoms of congestion in CHF. Figure 1 shows an algorithm of combining diuretics depending on FC and the hydration status of HF patients.

Combination diuretic treatment

Tactics for managing patients with congestive heart failure and diuretic resistance

Identifying diuretic resistance (DR) in clinical practice is limited by the standard approaches to quantitative analysis of diuresis. The recent years have witnessed an increasing interest in using natriuresis as an indicator of DT response in CHF patients [133–137]. Moreover, the HF events are expected to progress if sodium excretion levels are <35.4 mmol within one hour after the administration of the diuretic with a 100% sensitivity [138]. With an estimated 6-hour sodium urine excretion >100 mmol depending on 24-hour diuresis (~3–4–5 L of urine), 24-hour natriuresis is potentially between 230 and 500 mmol [139].

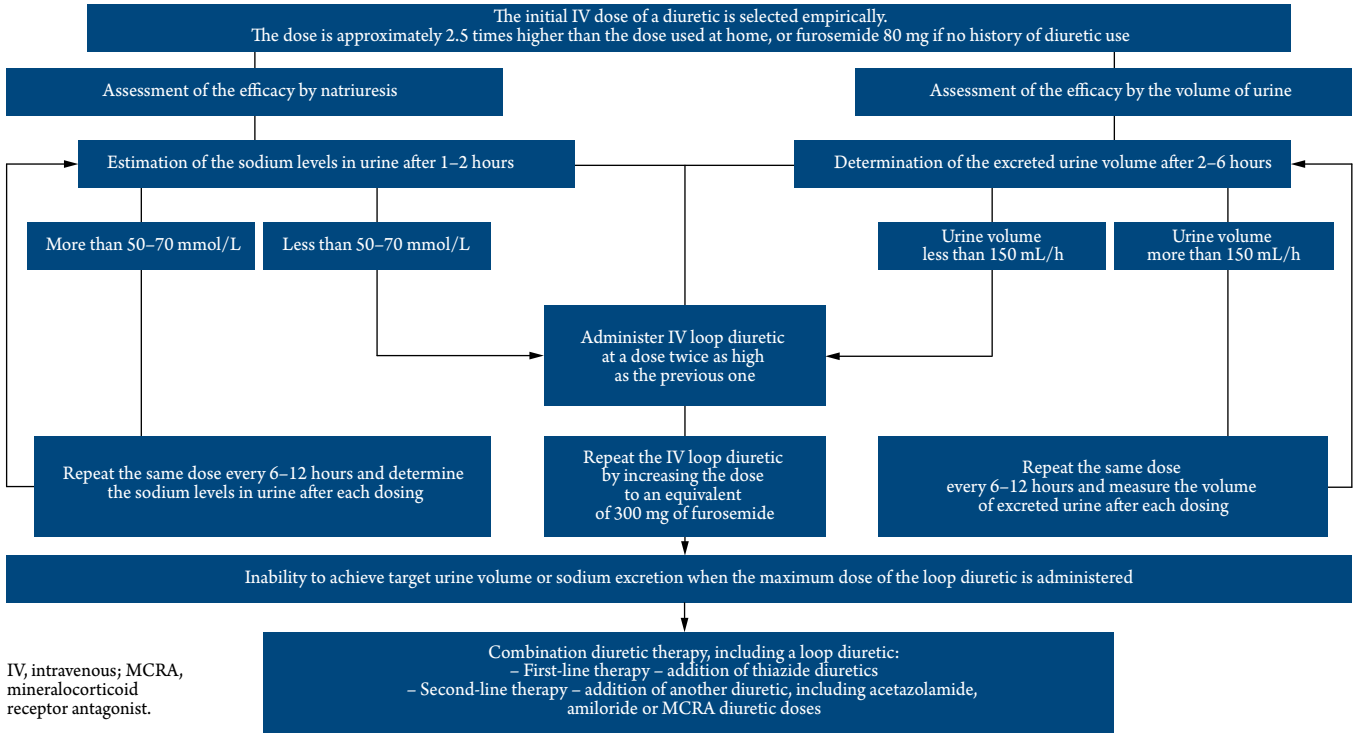
However, it is important to keep in mind that the urine levels of sodium change significantly during DT of patients with congestion. When diuresis increases, natriuresis decreases with each passing day due to the changes in neurohormonal activity, renal hemodynamics, and kidney structure [140].

Table 5. Types and mechanisms of diuretic resistance (adapted from Felker et al.) [141]

Significance of specific causes or mechanisms of diuretic resistance	Types of diuretic resistance			
	Prerenal	Intrarenal		
		Before the loop of Henle	At the level of the loop of Henle	After the loop of Henle
High significance	–	–	Dose of loop diuretic	Compensatory reabsorp-tion of sodium in distal tubules
Not known but sug-gestively significant	Venous stasis	–	Response at the level of the loop of Henle	Proteolytic activation of epithelial sodium channels
	Increased intraperi-toneal pressure			
Minor and mild to moderate impair-ments in most pa-tients with heart fail-ure	Decreased cardiac output	Increased sodium re-absorption in the prox-imal tubules	Hypochloremic alkalosis	Increased regulation of sodium chloride cotransporter, pendrin, sodium-driven chloride bicarbonate exchanger, epithelial sodium channel
	Hypoalbuminemia	Reduced glomerular filtration rate		
	High sodium intake	Increased number of organic anions		
		Albuminuria		

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1427

Figure 2. Possible algorithm of diuretic administration in patients with heart failure and diuretic resistance. Adapted from Felker et al. [141]



IV, intravenous; MCRA, mineralocorticoid receptor antagonist.

Mechanisms for development of diuretic resistance

Before assessing DR, it is reasonable to check whether the absence of a response to diuretics can indicate a risk of using the diuretic in this patient, since the mechanisms that inhibit the diuretic effect prevent potential fatal loss of sodium and fluid [141].

It can be useful to specify the anatomical structures responsible for the development of DR in order to choose the best possible tactics to overcome resistance. Under this approach, DR is divided into two categories prerenal and renal resistance. In turn, renal DR is divided depending on the anatomical segments of the nephron, in which DR develops (Table 5).

Prerenal mechanisms of DR are less important in patients with HF than intrarenal mechanisms [90, 142]. In the absence of severe hemodynamic disorders, vasodilators, dopamine, and milrinone do not increase diuresis, reduce body weight and/or sodium urine excretion in patients with ADHF [143–146]. However, the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) in combination with intravenous administration of loop diuretics is accompanied by increased natriuresis and higher efficacy of diuretics with preserved kidney function [147, 148].

Arterial hypotension or HFrEF contributes significantly to the development of DR in individual patients, and the elimination of these disorders improves the response to diuretics [141]. However, the development of DR is generally not caused by hemodynamic disorders, and the additional use of drugs with positive inotropic action solely to increase diuresis is usually ineffective [141]. It is considered that the consumption of a large amount of sodium causes prerenal pseudo-diuretic resistance [149]. During a comparative study on the use of high-sodium and low-sodium diets in patients with ADHF, the same reaction to the use of diuretics was shown when different amounts of sodium were consumed [150]. It was also reported that the administration of hypertonic solution combined with high-dose loop diuretic resulted in greater diuresis and increased volume of urine compared to the use of only high-dose loop diuretic in patients with ADHF and DR [151–153].

Intrarenal DR Abnormal kidney function is the main determinant of resistance to the development of DR in patients with HF, as in patients with chronic kidney disease (CKD) [154]. However, it should be noted that estimated GFR is not really related to the total diuretic response in patients with HF [155, 156]. Patients with lower GFR tend to have less pronounced tubular DR than patients with

Table 6. Changes in electrolyte metabolism associated with diuretic therapy

Effect/ drug group	Changes in plasma pH	Electrolyte excretion				
		Ca^{2+}	HCO^{3-}	K^+	Mg^{2+}	Na^+
Thiazides and indapamide	0 or ↑	–	0 or +	++	++	++
Loop diuretics	0 or ↑	++	0	++	++	+++
Potassium-saving diuretics	0 or ↓	–	0	–	–	+
Acetazolamide	↓	0 or +	+++	+	–	+

0 – no changes; ↑ – increase; ↓ – decrease; + – mild; + + – moderate; +++ – severe.

higher GFR, having almost twice the level of sodium excretion per nephron [157]. Thus, the reduced number of nephrons is compensated in patients with HF and low GFR by the fact that each nephron excretes more sodium [141]. It was established long ago that hypochloremic metabolic alkalosis caused by the administration of sodium bicarbonate leads to a significant decrease in response to diuretics. Thus, hypochloremic alkalosis is an important factor in the development of DR in patients hospitalized with ADHF [158]. The effects of this mechanism may include a decrease in chloride concentration in the tubular lumen, or a direct effect of the reduced intracellular chloride content on the factors regulating sodium avidity.

Tactics to overcome diuretic resistance

Although an approach to overcome DR depends on the prevailing mechanisms of its development in a particular patient, the overall treatment goal in such cases is to reduce objective signs and subjective symptoms of congestion and achieve a negative sodium balance [141].

The following approaches are offered to overcome DR in patients with HF who have stable hemodynamics and hypervolemia signs. It is unknown whether maximizing doses of loop diuretics or combining different diuretics is advantageous [141]. According to most experts, it is reasonable to postpone the combined use of diuretics until an attempt is made to administer the best possible dose of a loop diuretic. At the same time, there is no consensus as to the dose level of the loop diuretic before adding a thiazide diuretic.

Although the use of combination DT appears to be reasonable from a physiological point of view, there is a significant risk of electrolyte disorders, which may be quite severe [159]. The CARRESS-HF RCT showed that the stepwise dosing algorithm that included a combination of gradually increasing the dose of a loop diuretic and adding a thiazide diuretic (metolazone), if necessary [160], was superior to the use of ultrafiltration on the effects of kidney function within 96 hours after beginning treatment without changes in weight loss [161].

The efficacy of an empirical dose of the loop diuretic can be estimated by the amount of urine excreted and, if possible, by measuring the amount of sodium excreted. Figure 2 shows an algorithm representing general approaches to the use of

Table 7. Types of hyponatremia in heart failure and correction tactics

Type/ period of development	Pathogenesis/ laboratory data	Therapy
Dilutional hyponatremia (hemodilution). Usually in ADHF	ГHypervolemia due to reduced water excretion/ High urine osmolality (Uosm >100 mOsmol/L)	Temporarily withdraw diuretics acting in distal tubules, reduce water intake to 1 L/day, improve distal tubular flow: administer a loop diuretic, hypertonic solution of sodium chloride, acetazolamide, SGLT2 inhibitors (gliflozins), vaptans, K^+ and Mg^{2+} correction
Absolute sodium deficiency. Usually, during massive long-term DT with reduced sodium intake	Hypovolemia. Low Uosm (<100 mOsmol/L). Low Una (<50 mEq/L)	Withdraw distal diuretics, IV repletion of sodium, repletion of K^+ and Mg^2

ADHF, acute decompensated heart failure; Uosm, urine osmolarity;
Una, sodium levels in urine, SGLT2, sodium-glucose cotransporter type 2; DT, diuretic therapy.

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1427

Table 8. Hypokalemia treatments

Stage	Moderate hypokalemia (K >2 mmol/L)	Severe hypokalemia (K >2 mmol/L)
Correction of predisposing factors	Resolve: – Alkalosis – Hypomagnesemia, withdrawal of thiazide diuretics	
Therapy	IV infusion of KCl at the rate of ≤10 mmol/hour	IV infusion of KCl at the rate of ≤40 mmol/hour ECG monitoring. In life-threatening condition (VT, VF): bolus injection 5–6 mmol.

IV, intravenous; ECG, electrocardiogram; VT, ventricular tachycardia; VF, ventricular fibrillation.

diuretics in patients with DR [27]. The dose of the intravenous diuretic is insufficient if, two hours after the injection, sodium concentration in the urine sample is less than 50–70 mmol/L or urine excretion rate is less than 150 mL/h. In such cases, the dose should be usually doubled and, if there is no effect, it should be increased to the maximum (the maximum dose is not established formally, but it is often considered to be bolus furosemide 200–300 mg or an equivalent dose of another loop diuretic). During the effective dose selection, sodium urine concentration and the volume of urine excreted are re-measured [27]. Once sufficient diuretic response (a cer tain diuretic and/or natriuretic effect) is achieved, the selected dose may be re-administered every 6 to 12 hours to achieve negative sodium or fluid balance.

If congestion persists despite the use of sufficiently high doses of the loop diuretic, the next stage is sequential nephron blockade with a thiazide (or thiazide-like) diuretic. There is no evidence showing the benefits of one drug over another, even in patients with low GFR [159]. The efficacy of using acetazolamide in combination with intravenous loop diuretics is still being studied e.g. the ADVISOR RCT is ongoing [162]. The diuretic dose of MCRA (more than 50 mg/day) is believed to have a natriuretic effect, which in theory can complement the effects of loop diuretics. Other complementary drugs were not studied in an RCT on patients with HF and DR or at high risk of developing DR. Those were dopamine [163], low-dose nesiritide [163], and vasopressin antagonist tolvaptan [164]. Although low-dose dopamine had no beneficial clinical effects in the ROSE-AHF RCT, the results of the subanalysis of patients with HFrEF suggest that dopamine may be effective in such cases [163]. Sodium-glucose cotransporter inhibitors have diuretic effects and improve the prognosis for patients with chronic HFrEF [165], but their effects on DR have not yet been studied.

Adverse events and drug interactions in the diuretic treatment

Adverse events in the diuretic therapy

Hypovolemia is an excessive decrease in CBV, which can often develop due to persistent fluid retention in tissues. It can complicate any stage of DT, but is more common at the beginning of the treatment of decompensated HF after excessive diuresis. Hypovolemia naturally leads to a drop in stroke volume, tissue hypoperfusion, and reduced renal blood flow [166], which may contribute to the development of DR due to renal failure. It is manifested by hypotension, orthostatic hypotension, progression of azotemia, and drop in diuresis.

Acute urinary retention can be caused by an obstruction of excessive urine flow, such as prostate enlargement, if it develops during the active DT.

Dyselectrolythemia

Changes in electrolyte exchange associated with the use of modern DT are presented in Table 6.

Hyponatremia (reduced plasma sodium <135 mmol/L) can develop both early and late during the DT. It is identified in 20% of patients on admission and develops in another 10–15% of patients in the course of the DT during their hospital stay [27].

Hyponatremia is more common in older women with low weight and in patients with severe CHF. Carriers of the SLCO2A1 gene inactivating the prostaglandin transporter are at high risk of thiazide-mediated hyponatremia [167]. This adverse event is more likely to develop in patients receiving thiazide therapy and a combination of loop diuretic+thiazide diuretic+acetazolamide and those who comply fully with a low-sodium diet.

Thiazides lead to hyponatremia more often within the first week, and loop diuretics usually cause it within several months of treatment. However, this complication can develop within 1-2 days if diuresis is forced. The DT-associated decrease in CBV contributes to the production of ADH and the retention of free water, which can result in dilutional hyponatremia. Another reason is a decrease in the osmolar gradient and concentrating capability of the renal medulla. Hyponatremia may be a result of the combined use of potassium-saving diuretics and ACE inhibitors/ARBs. This complication is even more common than hyperkalemia for this combination of drugs.

Hyponatremia is manifested by anorexia, nausea, sleepiness, apathy and frequently hypovolemia. In severe cases disorientation, agitation, seizures, suppression of reflexes, focal neurological symptoms and Cheyne–Stokes breathing develop. This complication causes polydipsia, which then contributes to the decompensation and the development of refractory edema. It is necessary to distinguish between hyponatremia associated with sodium loss and dilutional hyponatremia (Table 7).

When the DT is discontinued, sodium levels recovery rapidly, but canceling diuretics is of little promise in CHF, and the repeated administration will lead to a recurrence of the complication. Therefore, hyponatremia is treated HF without canceling the DT; thiazides are withdrawn, fluid intake is limited to 1 L, K^+ and Mg^{2+} are replenished, and sodium chloride solution is injected. Sodium replenishment should be gradual and the rate of administration should not exceed 8 mmol/L per day [168, 169]. Usually, 1–2 mmol/h is injected in the first 24 to 48 hours, until the blood level reaches 130 mmol/L and the symptoms disappear. The administration of more than 20 mmol/L in the first 24 hours or rapid saline injection leads to pontine myelinolysis and increased risk of death.

In dilutional hyponatremia, fluid (not more than 1 L/day) and salt intake, the use of v2 vasopressin receptor antagonists are restricted (not approved in the Russian Federation).

The prevention of hyponatremia should include the administration of hypertonic sodium chloride solution, at the same time with the initiation of the active phase of the DT and with careful control of the electrolyte levels in the blood.

Hypokalemia

Hypokalemia is reduced plasma levels of potassium less than 3 mmol/L, which develops during the use of loop and thiazide diuretics. A 0.5 mmol/L decrease in potassium levels is common (in more than 50% of cases) [170] and is caused by the unnecessarily active DT used to treat patients with decompensated HF. Secondary hyperaldosteronism during the DT, metabolic alkalosis and increased tubular flow are the important reasons. However, it is uncommon during the scheduled DT for CHF. When the optimal full-dose therapy for CHF is implemented, including RAAS blockers and beta-blockers, hypokalemia develops relatively rarely since these compounds contain potassium.

This is why hypokalemia in CHF during the scheduled DT should be a matter of concern by other causes, such as hyperaldosteronism. Hypokalemia is manifested by muscle weakness, seizures, heart rate and conduction disorders, weakness, fatigue, depression, disinterest in almost everything, anorexia, constipation, nausea, vomiting, paresthesia, leg cramps, polyuria, rhabdomyolysis, metabolic alkalosis, impaired cardiac activity (atrial and ventricular premature beats), and increased sensitivity to cardiac glycosides. Acute hypokalemia causes hyperpolarization and increased ectopic activity of cardiomyocytes, development of re-entry paroxysmal tachycardia and conduction disorders [171].

Typical electrocardiographic changes in hypokalemia include low T voltage, the appearance of U wave, and ST-segment depression [172]. Hypokalemia raises the risks of digoxin overdose. The risks of clinically significant hypokalemia are increased in patients with severe CHF when secondary aldosteronism and liver dysfunction develop. The approaches to treatment are provided in Table 8 [173]. When potassium levels in the blood are moderately reduced (3–3.5 mmol/L), there is no need for parenteral potassium therapy, potassium-containing oral formulations, MCRA dose correction, and occasionally the combination with potassium-saving diuretics is preferable.

The rate of intravenous injection of potassium depends on the severity of hypokalemia and is carried out under careful electrocardiographic monitoring, with control of K^+ levels in the blood to avoid the development of hyperkalemia [174]. The bolus administration of potassium is possible under the life-threatening conditions of severe hypokalemia. The correction of hypokalemia without the treatment of hypocalcemia can cause convulsive syndrome.

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1427

Hypomagnesemia can result from the use of loop and thiazide diuretics. Potassium-saving diuretics retain magnesium. The normal blood levels of magnesium are 1.5–1.9 mEq/L (0.75–0.95 mmol/L or 1.7–2.2 mg/dL). Clinical manifestations of hypomagnesemia ($Mg2^{+}$ <1.8 mg/dL) are the same as in hypocalcemia (see below), but muscle symptoms are usually not as pronounced as in calcium deficiency. However, magnesium deficiency potentiates ventricular rhythm disorders. It is corrected by intravenous infusion of magnesium sulfate.

Metabolic alkalosis

Metabolic alkalosis develops during the use of thiazide and loop diuretics, contributes to DR [175], and has a typical clinical presentation (nausea, vomiting). It is caused by the excessive excretion of hydrogen ions in the tubules. The correction included the administration of potassium chloride, potassium-saving diuretics, and acetazolamide [176].

Creatinine build-up (and some decrease in GFR) often accompanies the initial stages of the active and/or combined DT, is most likely associated with both hypovolemia and the development of prerenal failure, as well as the increased sodium passage through nephron [177]. As edema syndrome resolves, azotemia usually decreases, and GFR increases. In any case, if renal dysfunction progresses in patients with decompensated CHF, exposure to nephrotoxic drugs (antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), etc.) should be avoided, and hypovolemia should be actively detected (e.g. by measuring blood pressure during the transition to orthostasis). A temporary increase in creatinine levels is not very clinically significant [177].

Hypocalcemia (ionized Ca^{2+} <4.0 mg/dL or <1.0 mmol/L) develops during the use of loop diuretics. Long-term calcium deficiency provokes hair loss, brittle nails, multiple tooth decay, and osteoporosis. Clinical manifestations appear when ionized Ca^{2+} decreases <0.7 mmol/L and include: convulsions of striated muscles and smooth muscle symptoms (intestinal colic, frequent urination), heart rate disorders, and decreased sensitivity to digitalis. They modify the diurnal rhythm of the parathyroid hormone, which can negatively affect bone density in elderly patients.

Hypocalcemia is corrected when the level of ionized Ca^{2+} is <0.7 mmol/L or in the presence of symptoms. First, 10 mL of 10% calcium gluconate solution is administered intravenously for 10 min, then 50–100 mg of elemental calcium is given orally in combination with a vitamin D supplement every 6 hours.

The use of calcium supplements combined with vitamin D may contribute to the correction of osteopenia associated with the long-term use of loop diuretics [178].

Hypercalcemia (ionized Ca^{2+} >1.5 mmol/L, total Ca^{2+} >10.5 mg/dL) can develop during a long-term monotherapy with thiazide and thiazide-like diuretics. This is a rare complication, which is more common in older women (at the age of 70–79 years, 55/100000) and develops in several years (6 years on average) after the beginning of the therapy. The mean level of ionized calcium is 2.7 (2.54–2.88) mmol/L [179]. Clinical presentation of total Ca^{2+} >11.5 mg/dL includes muscle weakness, depression, memory impairment, emotional lability, arrhythmias, atrioventricular conduction disorders, and hypersensitivity to digitalis. Significant hypercalcemia can develop when thiazide and calcium supplements are used in combination, [180] and always require an additional examination to exclude hyperparathyroidism. Due to the latter, it is recommended to stop the use of hydrochlorothiazide if hypercalcemia develops until parathyroid hyperfunction is ruled out.

Hyperuricemia results from increased urate reabsorption in the proximal tubules, when GFR decreases during the DT and is also caused by the decreased secretion of uric acid in the proximal tubules. The condition severity depends on the dose of diuretics. However, hyperuricemia is associated with the development of gout only in 3–5% of patients [181]. Gout develops more frequently during the use of loop diuretics, mainly in those users of thiazides with obesity and alcohol misuse.

The clinical value of DT-associated hyperuricemia is not well established. In the recent European Society of Cardiology (ESC) guidelines, correction of hyperuricemia for CHF to maintain <357 umol/L (<6 mg/dL) is indicated only for patients with gout [182]. This strategy is based on the EXACT-HF RCT findings, in which allopurinol therapy was not shown to be beneficial in patients with CHF without gout and with hyperuricemia [183]. These results agree well with those obtained in more recent trials [184]. The onset of hyperuricemia and even gout in patients with HF in need of the DT is not a reason to stop the use of or reduce the diuretic doses. However,

gout should be treated according to the current guidelines (See purine metabolism disorders).

Dyslipoproteinemia

Thiazides and loop diuretics increase the levels of low-density and very-low-density lipoprotein cholesterol, total cholesterol, and triglycerides in 5–20% of cases [185]. This is a dose-dependent effect, which develops early in the DT. The effect on high-density lipoprotein cholesterol is variable. The mechanisms are not clear, but this effect might be associated with impaired insulin secretion, or decreased circulating blood volume, i.e. caused by thick blood. By month 3–12 of therapy, these lipid changes usually disappear [185, 186]. There is no reliable information about the effects of potassium-saving diuretics on the lipid profile.

Hyperglycemia

Hyperglycemia is usually detected in the first 4–8 weeks of the DT. The causes are increased insulin resistance and reduced insulin secretion in hypokalemia, and diabetes mellitus (DM) develops only in 1–3% of patients who use diuretics. Non-ketone hyperglycemia is possible in the presence of DM. Extended-release diuretics cause hyperglycemia more often. Thiazides cause dose-dependent hyperglycemia and require careful assessment of glycemic levels during the entire course [187].

After the DT withdrawal, impaired glucose tolerance usually disappears within a few months. Hyperglycemia and dyslipidemia, which develop during the use of modern diuretics, are not currently considered significant adverse events and do not have significant adverse effects on the course of cardiovascular diseases.

Sexual disorders during the use of thiazides and thiazide-like diuretics are observed in male patients with wide variability (3–32%) and include reduced sexual desire, erectile dysfunction, and ejaculation disorders. The significance of these disorders is not apparent [188]. No sexual disorders were described in female patients during the DT.

Specific adverse events inherent in certain diuretic treatments

Thiazides cause photosensitization, retain calcium, and contribute to the development of allopurinol hypersensitivity syndrome. Their long-term use is associated with an increased risk of skin cancer and is dose-dependent [189].

Hypernatremia may result from inadequate free water excretion during the use of loop diuretics [190, 191].

Furosemide-dependent kidney syndrome [192] is the dependence of renal function on the use of furosemide. When the dosage is reduced, or the drug is withdrawn in some patients who have been using the drug for a long time, diuresis decreases sharply and even discontinues. In addition, edema appears and progresses, shortness of breath occurs, body weight increases rapidly, acute kidney failure may occur, and the patient may need renal replacement therapy. During the long-term use of this drug, pseudo-Bartter syndrome (hypokalemia, alkalosis, RAAS activation with normal or low blood pressure) can develop. Furosemide-dependent nephropathy can manifest by glomerulonephritis and renal interstitial hyperplasia.

In such cases, either the dose of furosemide is gradually reduced with the acid-base state corrected, and hypertonic solution of sodium chloride is administered, or furosemide is replaced with thiazides, which allows cancelling the DT gradually [193]. It takes 1.5–4 weeks to restore physiological diuresis fully.

Symptomatic metabolic acidosis is a specific side effect of acetazolamide, which is described in 50% of patients with glaucoma. The risk of acidosis is higher in the elderly with DM or CKD. Increased ammonia levels in the blood may contribute to encephalopathy in patients with liver cell failure. The best prevention of metabolic acidosis is the intermittent regimen of this therapy in patients with HF.

Sodium bicarbonate can reduce weakness, sluggishness, malaise, taste disturbance, paresthesia, gastrointestinal disorders, and reduced sexual desire developing during the use of acetazolamide, but it increases the risk of nephrocalcinosis and nephrolithiasis [194].

Acetazolamide increases the risk of nephrolithiasis more than 10-fold, sometimes causes allergic reactions, hepatitis, hematopoiesis disorders, and osteomalacia when used in combination with phenytoin or phenobarbital [195]. Adverse events that occur during the DT are described in the supplementary materials to this article and on the journal's website.

Drug interactions of diuretics

Drug interaction is a change in the effects of a drug caused by its concomitant administration with another drug. Adverse drug interactions of diuretics

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1427

are associated with the development of electrolyte imbalance, which increases the risk of developing heart rate disorders and sudden cardiac death if used in combination with drugs that prolong the QT interval (macrolide antibiotics, anti-arrhythmic drugs, antidepressants, etc.), the toxicity of cardiac glycosides, and the toxicity of lithium drugs.

It should be kept in mind that the risk of hypokalemia increases when diuretics are combined with corticosteroids, β2 agonists and theophylline, and the risk of hyponatremia increases when used with carbamazepine. Concomitant use of furosemide and risperidone increases death risk in elderly patients with dementia [196]. Moreover, furosemide can reduce vancomycin levels in plasma by 50% [196]. Aliskiren, phenytoin, and indomethacin (possibly other NSAIDs) may reduce the efficacy of diuretics, which may require increasing the doses. Nephrotoxicity occurs when diuretics are combined with other potentially nephrotoxic drugs, e.g. NSAIDs, and the ototoxic effect occurs in combination with aminoglycoside and vancomycin. However, patients with CHF did not have adverse effects on pharmacodynamics and pharmacokinetics of concomitant administration of meloxicam (NSAIDs) and furosemide [197] Most patients taking torasemide do not require correction of warfarin doses [198]. The main adverse drug interactions of diuretics are described in the supplementary materials to this article and on the journal's website.

Diuretic treatment in specific clinical situations

Gender- and age-related characteristics of the diuretic therapy

There are no sex-specific peculiarities of using diuretics in patients with CHF. At the same time, it is known that female patients develop hyponatremia faster during the DT, which is explained by the higher activity of natrium-glucose cotransporter in comparison with males [199], and acute kidney injury (AKI) occurs more frequently [200]. The general incidence of side effects of diuretics in female patients is higher than in male patients [201].

The mechanisms of homeostasis regulation weaken with age, which is why elderly and senile patients are more likely to have adverse shifts in water-salt metabolism and acid-base balance during the use of diuretics. If elderly and senile patients develop DR, elevating the dose usually does not increase the diuretic effect, but aggravate electrolyte disorders and enlarge shifts in the acid-base balance. For elderly and senile patients with CHF, it is recommended to administer diuretics with extended diuretic effect in minimally effective doses, continuous evaluation of the clinical effect, and careful control of electrolyte levels in the blood [202].

Table 9. Dosing of diuretics in acute and chronic heart failure

Drug	Initial dose (mg/day)	Normal dose (mg/day)
Furosemide	20–40	40–240
Bumetanide	0,5–1,0	1–5
Torasemide	5–10	10–20
Hydrochlorothiazide	25	12,5–100
Indapamide	2,5	2,5–5
Spironolac tone/ eplerenone	12,5–25/50	50/100–200
Triamterene	25/50	100/200

Diabetes mellitus

Diabetes mellitus is a factor of diuretic resistance. CHF and ADHF patients with DM need higher doses of furosemide than those without DM [203]. The main cause of reducing the doses of diuretics out of necessity in patients with concomitant CHF and DM, is renal dysfunction due to diabetic nephropathy.

Disorder of purine metabolism

Given the adverse effect of diuretics on purine metabolism, MCRAs should be used if possible, rather than thiazide and loop diuretics to reduce the severity of congestion in patients with CHF, concomitant hyperuricemia and gout. When thiazide/loop diuretics are required, the use of xanthine oxidase inhibitor allopurinol, which prevents uric acid formation should be considered, with the blood levels of xanthine oxidase being monitored. Renal dysfunction due to chronic interstitial nephritis is an important factor affecting the choice and dosage of diuretics in patients with concomitant CHF and gout.

It should be noted that the withdrawal of DT in patients with CHF and signs of congestion is not acceptable, even in the presence of hyperuricemia and acute gouty arthritis.

Hyperuricemia should be corrected in patients with CHF to maintain the blood levels of uric acid less than 357 umol/L (less than 6 mg/dL) only in the presence of gout [53]; otherwise, gout should be treated according to the current relevant guidelines. Hyperuricemia does not require drug correction with allopurinol in patients with CHF without gout regardless of the presence of DT [53].

Pregnancy and lactation

CHF is treated during pregnancy and lactation according to the general principles, except for RAAS blockers contraindicated in this category of patients [204]. Diuretics are administered in the presence of signs of pulmonary circulation congestion, which persist despite the use of beta-blockers. Diuretics should be used with care, given the possible reduction in placental blood flow. In the Food and Drug Administration (FDA) classification, the following categories of risks of using diuretics in pregnant women are established:

- A amiloride, torasemide, indapamide;
- B (animal studies did not identify risks of adverse fetal exposure, there were no adequate trials in pregnant women), bumetanide, furosemide, triamterene;
- C (animal studies demonstrated adverse fetal exposure, no adequate trials in pregnant women, but the potential benefit of a drug in pregnant women may justify its use despite the risk), spironolactone; and
- D (there is evidence of the risk of adverse fetal exposure, but the potential benefit of the drug in pregnant women may justify its use despite the risk). Using diuretics is the most dangerous in the first trimester of pregnancy.

Drug entry into milk and the baby's safety during breastfeeding are not known for all diuretics. All diuretics are known to reduce lactation. If a nursing mother requires DT, especially in high-dose diuretics, it is reasonable to stop breastfeeding before they are used.

Thyroid disorders

Both thyroid hyperfunction and hypofunction can impair myocardial contractility, tachycardia or bradycardia, heart rate disorders, which cause CHF and edema syndrome. The main treatment for this category of patients is the correction of thyroid function, which can resolve congestion events without the use of diuretics. The main mechanism of developing peripheral edema in hypothyroidism is an increase in oncotic pressure in tissues due to the accumulation of albumins and mucin, which is why diuretics are not used in myxedema.

Liver failure and cirrhosis

Spironolactone is a first-line diuretic used to treat edema syndrome in patients with liver cirrhosis. Spironolactone can be combined with both thiazide and loop diuretics. Torasemide is the loop diuretic mostly chosen for patients with cirrhosis [205, 206]. In patients with liver cirrhosis DT begins with minimal drug doses. Up-titration is slow: it is recommended to increase the dose no more than once every 3–4 days under liver function control. Severe hepatic insufficiency is a contraindication to the use of diuretics.

Hypoalbuminemia

Decreased blood protein levels in patients with CHF is an independent cause of edema syndrome and a predictor of adverse outcomes [207]. Protein malabsorption, insufficient dietary intake, increased excretion, and disturbance of synthesis are mechanisms of hypoalbuminemia development. Renal failure and liver cirrhosis are additional (often major) factors contributing to hypoalbuminemia in patients with CHF. Low plasma oncotic pressure is the main cause of edema syndrome in patients with hypoalbuminemia. Edema usually appears when the albumin levels in the blood decrease <35 g/L. The anti-edema effect of diuretics is significantly reduced if a CHF patient has hypoalbuminemia. The levels of albumin in the blood plasma should be corrected to restore the effect of diuretics.

Arterial hypertension

Decreased systolic blood pressure <90 mm Hg is accompanied by a reduced blood supply to the kidneys, which significantly diminishes the effect of diuretics. If patients with CHF in need of the DT develop arterial hypotension, then the cause of low blood pressure should be identified and, if possible, eliminated. Dose reduction and even temporary withdrawal of drugs with antihypertensive effects (ACE inhibitors, ARBs, MCRAs, beta-beta-blockers, angiotensin receptor antagonists and neprilysin inhibitors) are possible. If this is not enough, drugs with a positive inotropic effect (dobutamine, dopamine) are used. The plasma levels of albumin should be evaluated and normalized if necessary, in patients with arterial hypotension and edema syndrome.

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1427

Chronic kidney disease

Chronic kidney disease worsens the prognosis and makes it difficult to carry out drug treatment of CHF. Impaired kidney function limits the use of ACE inhibitors, MCRAs, and other drugs, including diuretics. The national guidelines on cardio-nephroprotective management include the rules on the use of diuretics in patients with concomitant CHF and CKD [208]. The diuretic dose depends on the initial functional state of the kidneys (GFR and levels of serum potassium). Treatment should begin with minimal doses of diuretics (Table 9). The serum levels of urea, creatinine, uric acid, and potassium should be monitored in 1–2 weeks after the beginning of the treatment and after the diuretic dose has been increased.

Dose correction of the loop diuretics is not required if GFR decreases. Thiazide diuretics and indapamide are ineffective when GFR is <30 mL/min/1.73 m^2 and < 10 mL/min/1.73 m^2, respectively. Combining the loop and thiazide diuretics in patients with CKD significantly increases the risk of hypovolemia, hypotension, hypokalemia, and aggravated renal dysfunction. If renal function deteriorates during the combination DT, the thiazide diuretic should be disregarded. It is recommended to use MCRAs with extreme caution in the most exceptional cases when the levels of serum potassium are >5 mmol/L, serum creatinine >221 mmol/L (>2.5 mg/dL), and GFR <30 mL/min/1.73 m^2.

If necessary, up-titration dosage should begin in 4 to 8 weeks after the beginning of the therapy. In patients with CKD who take MCRAs, the serum levels of creatinine and potassium should be monitored at 1 and 4 weeks after the beginning of the therapy or up-titration dosage, then at 8 and 12 weeks, 6, 9, and 12 months, and once every 4 months. If potassium levels are >5.5 mmol/L, creatinine levels >221 mmol/L (>2.5 mg/dL), or GFR <30 mL/min/1.73 m^2, the dosage should be reduced twice, and potassium and creatinine levels should be controlled. If the levels of potassium are increased to 6.0 mmol/L, creatinine to 310 mmol/L (3.5 mg/dL), GFR is reduced to <20 mL/min/1.73 m^2, the drug should be withdrawn, and the patient should be referred to a nephrologist. It is recommended to avoid using MCRA in combination with potassium-containing and potassium-saving diuretics (amiloride, triamterene), nephrotoxic drugs (NSAIDs), and some salt substitutes, as they contain significant amounts of potassium.

Types of kidney dysfunction and a strategy of diuretic therapy in decompensated heart failure

Periodic changes in creatinine levels during the active DT occur in 30–65% of patients with decompensated HF [209–211].

Given different pathophysiological mechanisms and effects on outcomes, there is true AKI and functional kidney injury (functional decrease in glomerular filtration or pseudo-renal failure) during the treatment of patients with decompensated HF [212–214]. The latter can be associated with both the effects of known hemodynamic factors and directly with the treatment, including aggressive therapy aimed at resolving congestion. The functional decrease in GFR more often develops some time later during hospital stay (usually more than 3 days after admission) and, unlike true AKI, is accompanied by the improved clinical condition with no significant increase in kidney injury biomarkers. It is characterized by relatively rapid regression and is not associated with adverse outcomes if euvolemia is achieved. Conversely, a significant increase in creatinine and kidney injury markers, especially associated with hyperkalemia and metabolic acidosis, should suggest true AKI [27, 209]. Thus, changes in the creatinine levels and/or GFR should be interpreted in view of the clinical status of a particular patient [213].

When DT is ordered to patients with decompensated HF, established protocol should be followed [27, 209]:

- with a careful monitoring of kidney function (creatinine, electrolytes). The onset of kidney function impairment should be interpreted in view of the clinical status and overall response to DT.
- the diuretic response and severity of congestion should be assessed early and daily. If the response to diuretics is good, every effort should be made to achieve euvolemia.
- using RAAS blockers, subject to titration, should be considered in all patients with reduced ejection fraction.
- diuretic dose reduction should only be considered if euvolemia is achieved.

Thus, when kidney function is impaired during the treatment of decompensated HF, it is necessary to assess the timing of its onset, the patient's clinical status, the degree of creatinine increase and decrease in GFR, the presence of acid-base and electrolyte imbalances, and the intensity of the response to diuretics therapy. Only a global assessment allows

avoiding early withdrawal of the required therapy if functional kidney injury develops.

Diuretic treatment in patients with heart failure with preserved left ventricular ejection fraction

The use of loop diuretics (furosemide, torasemide) in patients with HFpEF and HFrEF is aimed at eliminating symptoms and signs of fluid retention in the pulmonary and/or systemic circulatory systems and improving the quality of life, i.e., reducing shortness of breath and edema, and increasing the exercise tolerance. Diuretics should be used in patients with HFpEF with more care than in patients with HFrEF due to a higher risk of developing fixed cardiac output syndrome [1]. The main cause of this syndrome in HFpEF is an excessive decrease in the filling pressure of the poorly compliant left ventricle in increased diuresis, due to which the ventricle cannot adequately increase its stroke volume during stress. The left ventricular compliance is reduced in HFpEF due to fibrosis (excess formation of connective tissue) and increased diastolic tension of cardiomyocytes.

Loop diuretics can be used sometimes in patients with HFpEF if they have no clinical signs of fluid retention, which is the case when they are indicated in the increased left ventricular filling pressure at rest, which is diagnosed in diastolic dysfunction grade II-III and/or high ratio E/e′ (>14), pulmonary hypertension (tricuspid regurgitation rate >2.8 m/s), and left atrial enlargement (maximum volume index >34 mL/m^2) [215]. Diuretics should be initiated in such euvolemic patients with minimal doses (torasemide 2.5–5 mg and furosemide 10 mg) followed by a slow up-titration (not more often than once every 2 weeks) under the clinical control and the monitoring of blood pressure, heart rate, and blood electrolytes. Diuretic titration dosage discontinues when diastolic dysfunction improves, particularly to grade I (indicative of a decrease/normalization of filling pressure), decrease in HF FC (by two units or up to FC I), and onset of initial signs of cardiac output fixation (weakness, rapid fatigue, tachycardia) [216].

The positive effect of diuretics usually becomes evident at the beginning of the treatment. It manifests as a better exercise tolerance, which is associated with the normalization of blood flow to the heart and the decrease in the left ventricular filling pressure. However, following 1 to 2 months from the beginning of the treatment, the diuretic effect of the drugs can decrease. In the case of furosemide, the achieved improvement in the patient's state can be reduced as a result of partial restoration of the filling pressure. In contrast, the positive clinical and hemodynamic effect of torasemide usually does not decrease with time [216], which is explained by the antifibrotic effect of the drug [217]. The antifibrotic effect of torasemide occurs later than the diuretic effect and consists in an increase in the left ventricular compliance, resulting in maintaining the adequate left ventricular filling without the concomitant increase in its filling pressure.

Thus, loop diuretics are indicated to patients with HFpEF if they have symptoms and signs of fluid retention. They can also be used in patients without congestive events, but with the increased filling pressure at rest [1]. In any case, the clinical condition, heart rate, blood pressure, and blood electrolytes should be carefully monitored. Diuretic therapy should be carried out by gradual up-titration, which avoids fixed cardiac output syndrome. Torasemide is a diuretic of choice in HFpEF (especially if there are no clinical signs of fluid retention) due to its high safety, long-lasting effect, minimal influence on the blood electrolytes, and the antifibrotic effect. The latter fact is essential precisely for patients with HFpEF, in which case myocardial fibrosis is the main cause of progressing left ventricular diastolic dysfunction and increasing filling pressure [218].

Noncardiac edema syndrome

Diuretic therapy in ascites

Ascites occurs due to liver diseases (liver cirrhosis, acute alcoholic hepatitis, and liver cancer) in 81.5% of cases, malignant tumors in 10%, HF in 3%, tuberculous peritonitis in 1.7%, pancreatitis, and other diseases in 1% [219].

The management of ascites consists in treating the underlying disease and its complications, which were shown to cause the development of ascites [220]. Approaches to the DT in ascites do not depend on the underlying disease, but are associated with the grade of ascites. For example, diuretics and/or a low-sodium diet are not recommended in ascites grade I. In ascites grade II, moderate sodium restriction (4.6–6.9 g of NaCl per day) is recommended, and MCRA is administered at an

[1] Fixed cardiac output syndrome is manifested by fatigue, apathy, hypotension, and tachycardia. Moreover, if the left ventricular filling pressure is too low, kidney hypoperfusion can occur with prerenal azotemia, RAAS activation, and water and sodium retention.

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1427

initial dose of 100 mg/day and a gradual up-titration by 100 mg/day every 72 hours until a maximum of 400 mg/day is reached if there is no effect on weight loss by 2 kg per week. If weight is not lost by 2 kg a week on the maximum dose of MCRA, or if hyperkalemia develops, during the use of MCRA, it is recommended to add furosemide at a minimal dose of 40 mg/day, with a gradual up-titration by 40 mg every 7 days to the maximum of 160 mg/ay. The decrease in the serum levels of sodium < 120 mmol/L and the progression of CKD to the terminal stage require the urgent withdrawal of diuretics. If serum potassium levels decrease <3 mmol/L, the patient should stop taking furosemide; if potassium levels rise >6 mmol/L, spironolactone should be withdrawn. DT is not recommended in patients with persistent overt hepatic encephalopathy. High-volume paracentesis is recommended as the first line for patients with severe ascites.

Chronic venous insufficiency with edema syndrome

Chronic venous diseases are common and highly prevalent worldwide [221]. For example, the prevalence of chronic venous diseases in the adult populations of different countries varies widely from 2 to 60%.

The typical symptoms of chronic venous diseases are feeling of fullness in the lower legs, feet, and leg edema, as well as feeling of heaviness and pain in the lower legs (calves), and fatigue of the legs [222].

A differential diagnostic search for the causes of leg edema should include ultrasound angiography of the lower extremities, to identify or rule out chronic venous diseases as an etiological factor of edema syndrome [223].

Physicians note that the DT is often used in chronic venous diseases in the presence of edema syndrome, but it is not indicated and may even increase the risk of thrombotic complications [224, 225]. The main treatment of chronic venous diseases is compression therapy, which can be used independently or additionally to invasive interventions [226]. Phlebotropic drugs are the basic drugs used to treat chronic venous diseases [227].

Chronic lymphatic edema of the lower extremities (peripheral lymphedema)

According to epidemiological studies, 90 to 250 million people suffer lymphedema worldwide, up to 90% of them being of working age [228].

Lymphedema is classified as primary and secondary based on the etiology. Primary lymphedema is due to genetic defects of the lymphatic system; secondary lymphedema is associated with injuries, inflammatory diseases (lymphadenites, lymphangitis), surgeries for malignant tumors, and iatrogenic injuries of the lymphatic vessels.

Scintigraphy of lymphatic vessels is recommended in peripheral lymphedema to diagnose lymphatic system abnormalities [229].

Diuretic therapy is not recommended to treat peripheral lymphedema, due to the lack of effect and potential complications associated with fluid and electrolyte imbalance [230].

The therapy of peripheral lymphedema is based on conservative non-drug approaches, such as a comprehensive physical or physiotherapeutic approach, intermittent pneumatic compression, kinesiology taping, etc., and microsurgeries aimed at increasing the return of lymph to the lymphatic system [230].

Lifestyle optimization and possibilities of self-control during the diuretic therapy

Regular training for HF patients is fundamental to maintain compliance to the DT and effectively control signs of the progression of congestion or excessive diuresis.

To reduce the risk of adverse events and prevent patients from abandoning the DT due to reduced quality of life, the following issues should be discussed with the patient and repeated at each visit, if necessary:

- Rules of taking diuretics
- Changes in daily routine as may be required
- Consumption of table salt
- Fluid intake regimen
- Possible side effects of diuretics
- Importance of weighing and keeping records
- Recommendations for the period of congestion
- Motor and drinking regimen in case of progressing congestion

The daily routine should be planned, considering that the patient may need to stay at home in the morning after taking diuretics. Physical training should also be scheduled considering the use of diuretics. If training takes place in the morning, diuretics can be taken at noon. However, it is not acceptable to miss the dose.

Due to the acquired tastes of national cuisine, salt consumption is very high in the Russian Federation and exceeds the recommended levels of the World Health Organization (WHO) by 2.3 to 4.2 times. Patients should be informed on reasonable

salt consumption levels not exceeding the WHO recommended norms of 2.5–3 g sodium or 5–6 g of table salt. It should be made clear that this means the total intake of salt from all food consumed, and therefore a list of the products with the highest salt content, such as sausages, canned foods, etc. should be given.

According to some authors, limiting sodium chloride consumption to less than 3 mg/day may be useful for patients with HF FC III-IV [231].

Limited fluid consumption is relevant only in extreme situations, e.g., in severe decompensated CHF requiring intravenous administration of diuretics. Normally, it is not recommended to consume more than 2 L/day of fluid (minimum 1.5 L/day during the active phase of diuretic therapy) [232, 233].

Side effects of diuretics in most cases are due to impaired water-electrolyte imbalance caused by these drugs.

Symptoms of water-electrolyte disorders requiring medical attention

Dry mouth, thirst, gastrointestinal disorders (including nausea and vomiting), weakness, drowsiness, mental confusion, muscle aches or cramps, hypotension (including postural hypotension), oliguria, and arrhythmia.

Weight monitoring

Weight records are the main method of self-monitoring in patients with HF. Dose correction of diuretics based on weight changes is also often recommended, as part of self- monitoring in HF to reduce the likel ihood of congestion and prevent exacerbation of HF. It was shown that clinically significant increases in body weight could occur, at least 1 week before the hospitalization due to HF. Moreover, the risks of hospitalization for HF increases constantly proportional to weight gain during this period [50].

There is also evidence that the presence of feet edema, in the first week after discharge from the hospital, increases almost 3-fold the risk of re-hospitalization within one year [234]. The efficacy of weight control was significantly higher where patients kept records of their weight rather than just reporting it [235].

No conflict of interest is reported.

The article was received on 26/10/2020

Appendices to the expert opinion on the use of diuretics in chronic heart failure

Appendix I. Normal values of cardiac chamber pressures

Indicator	Reference
Right atrial pressure	1–6 mm Hg (mean 3 mm Hg)
Right ventricular systolic pressure	20–30 mm Hg (mean 25 mm Hg)
Mean right ventricular diastolic pressure	2 mm Hg
Pulmonary artery systolic pressure	20–30 mm Hg
Pulmonary artery diastolic pressure	10–15 mm Hg
Mean pulmonary artery pressure	less than 20 mm Hg
Pulmonary arterial wedge pressure	6–12 mm Hg
Mean left atrial pressure	8–9 mm Hg
Mean left ventricular systolic pressure	120 mm Hg
Mean left ventricular diastolic pressure	4 mm Hg

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1427

Appendix II. Adverse events (AEs) occurring during the use of diuretics

Hemodynamic effects	Metabolic disorders	Hematologic and allergic AEs
Common AEs of LD and TD		
Thick blood, hypovolemia, hypotension, dehydration, re-nal dysfunction (creatinine accumulation), postural hypo-tension, prerenal azotemia, dizziness, and fainting	Hyponatremia, hypokalemia, hypochlo-remic alkalosis, hypomagnesemia, hyper-glycemia, hypertriglyceridemia, hypercholesterolemia, hyperuricemia, onset and exacerbation of podagric arthritis, im-paired protein metabolism. Rare symp-toms: headache, skin photosensitization, kidney interstitial fibrosis, myalgia, ab-dominal spasms, anorexia, diarrhea, con-stipation, jaundice, pancreatitis, hepatic encephalopathy, fever, necrotizing angiitis, blurred vision, reduced potency, increased hepatic enzymes, xanthopsia (furosemide)	Thrombocytopenia, leukopenia, anemia, agranulocytosis, aplastic and hemolytic anemia, allergic manifestations (sulfona-mide intolerance), urticaria, anaphylactic shock, multiform erythema, exfoliative dermatitis, Steven-Johnson syndrome, toxic epidermal necrosis, DRESS syn-drome – a drug reaction in the form of eo-sinophilia and systemic symptoms
AEs specific to individual types of DT		
PD-specific AEs		**TD-specific AEs**
Hypocalcemia; deafness (etacrynic acid has the greatest toxicity, the risk is lower during the use of torasemide versus furosemide*); tinnitus; consti-pation or diarrhea; furosemide-dependent kidney; osteoporosis, fractures of flat bones		Hypercalcemia, hydrochlorothiazide in-creases the risk of vertebral fractures in females when combined with allopurinol: increased risk of DRESS syndrome
AEs specific to potassium-saving diuretics (amiloride and triamterene)		
Hyperkalemia in combination with ACE inhibitors/ARBs, potassium-containing drugs and food additives, hyponatremia (in combination with ACE inhibitors/ARBs), nephrolithiasis (triamterene), kidney failure in combination with NSAIDs.		

* DiNicolantonio JJ. Should Torsemide Be Loop Diuretic of Choice in Systolic HF? [Internet] Available at: http://www.medscape.com/viewarticle/771976_5

Appendix III. Main adverse drug interactions of diuretics

Diuretic	Drug/interactions	Possible reactions
Furosemide	Digoxin	Increased risk of glycoside intoxication, hypomagnesemia, hypokalemia, and consequently arrhythmia
	Warfarin, vitamin K antagonists	Increased anticoagulant effect
	GCs	Increased risk of hypokalemia
	Aminoglycosides	Increased ototoxicity and nephrotoxicity
	Cephalosporins	Increased risk of kidney injury, especially when highdose cephalosporins are used, which are excreted mainly by the kid-neys
	NSAIDs	Reduced diuretic effect. Increased risk of acute renal failure in patients with hypovolemia and dehydration during the use of furosemide
	Insulin and other antidiabetic drugs	Reduced hypoglycemic effect caused by hypokalemia
	Cisplatin	Increased risk of kidney injury
	Amphotericin B	Increased risk of kidney injury
	High-dose salicylates	Increased risk of salicylism (competitive renal excretion)
	Tubocurarine (curare-like muscle relaxants)	Reduced muscle relaxant effect
	Lithium	Reduced renal clearance of lithium-containing drugs (increased risk of intoxication)
	Radiopaque agents	Patients at high risk of nephropathy treated with furosemide were more likely to experience kidney dysfunction when radiopaque agents were administered than patients at high risk of nephropathy who received radiopaque agents after intrave-nous hydration
Torasemide	Digoxin	Increased risk of glycoside intoxication, hypomagnesemia, hypokalemia, and consequently arrhythmia
	Warfarin, vitamin K antagonists	Increased anticoagulant effect
	Glucocorticoids	Increased risk of hypokalemia
	Aminoglycosides	Increased ototoxicity and nephrotoxicity
	Cephalosporins	Increased ototoxicity and nephrotoxicity
	NSAIDs	Reduced diuretic effect
	Insulin and other antidiabetic drugs	Reduced hypoglycemic effect caused by hypokalemia
	Cisplatin	Increased risk of kidney injury
	Amphotericin B	Increased risk of kidney injury
	High-dose salicylates	Increased risk of salicylism (competitive renal excretion)
	Methotrexate	Reduced efficacy of torasemide (the same secretion pathway). Decreased renal elimination of methotrexate
	Probenecid	Reduced efficacy of torasemide (the same secretion pathway). Decreased renal elimination of probenecid
	Lithium	Reduced renal clearance of lithium-containing drugs (increased risk of intoxication)
	Radiopaque agents	Patients at high risk of nephropathy taking oral torasemide were more likely to experience kidney dysfunction when radio-paque agents were administered than patients at high risk of nephropathy who received radiopaque agents after intrave-nous hydration
Hydro-chlorothiazide	Digoxin	Increased risk of glycoside intoxication, hypomagnesemia, hypokalemia, and consequently arrhythmia
	Amiodarone	Increased risk of arrhythmias associated with hypokalemia
	Beta-blockers	Increased fatigue, lethargy, elevated glucose levels
	NSAIDs	Reduced diuretic effect

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1427

Appendix III. Continued . Main adverse drug interactions of diuretics

Diuretic	Drug/interactions	Possible reactions
Hydro-chlorothiazide	Anti-diabetic drugs	Reduced hypoglycemic effect
	Glucocorticoids	Increased risk of hypokalemia
	Lithium	Reduced renal clearance of lithium-containing drugs (increased risk of intoxication)
Indapamide	Digoxin	Increased risk of glycoside intoxication, hypomagnesemia, hypokalemia, and consequently arrhythmia
	Beta-blockers	Increased fatigue, lethargy, elevated glucose levels
	NSAIDs	Reduced diuretic effect
	GCs	Increased risk of hypokalemia, reduced diuretic effect
	Tricyclic antidepressants, antipsy-chotics	Increased risk of orthostatic hypotension (additive effect)
	Insulin	Reduced hypoglycemic effect
	Lithium	Reduced renal clearance of lithium-containing drugs (increased risk of intoxication)
Spironolactone	Heparin, coumarin/ indandione deriv-atives	Decreased efficacy of anticoagulants
	Digoxin	Increased risk of glycoside intoxication due to the increased digoxin half-life
	Norepinephrine	Decreased vascular sensitivity to norepinephrine, which re-quires careful anesthesia
	Lithium	Increased lithium toxicity
	Glucocorticoids	Enhancement and acceleration of the diuretic and natriuretic effects
	Potassium drugs, potassium-saving diuretics, angiotensin-converting en-zyme inhibitors, angiotensin II an-tagonists, aldosterone blockers, in-domethacin, cyclosporine, ammoni-um chloride, colestyramine	Increased risk of hyperkalemia

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