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E. V. Reznik*, I. G. Nikitin

2nd Department of Internal Medicine, Advanced Course, General Medicine Department, Federal State Budgetary Educational Institution of Higher Education Pirogov Russian National Research Medical University under the Ministry of Health of the Russian Federation, Moscow, Russia

CARDIORENAL SYNDROME IN PATIENTS WITH HEART FAILURE AS A STAGE OF THE CARDIORENAL CONTINUUM (PART 2): PROGNOSIS, PREVENTION AND TREATMENT

Abstract

Cardiorenal syndrome in patients with heart failure is a regular link of cardiorenal continuum. Doctors of various specialties may encounter patients with cardiorenal syndrome: general practitioners, cardiologists, nephrologists, resuscitators, anesthetists, cardiac surgeons, etc. The currently definition, classification, pathogenesis, diagnosis and epidemiology of cardiorenal syndrome in patients with heart failure were presented in the first part of our review. In the second part, prognosis, approaches to the prevention and treatment of cardiorenal syndrome in patients with heart failure are discussed. They include treatment of cardiovascular pathology and heart failure in accordance with current guidelines for the prevention of episodes of acute and decompensated chronic heart failure; diet; quitting smoking and drinking alcohol, weaning off nephrotoxic drug administration; body weight, blood pressure and glycemia control; use of angiotensin converting enzyme inhibitors, angiotensin receptor antagonists or angiotensin receptors and neprilisin inhibitors (ARNI), statins; reducing of the abdominal pressure, and others. It is necessary to develop and introduce new approaches to nephroprotection in patients with cardiorenal syndrome, which is possible with the joint work of a multidisciplinary team.

Key words: *cardiorenal continuum, cardiorenal syndrome, chronic heart failure, acute heart failure, chronic kidney disease, acute kidney injury, glomerular filtration rate, albuminuria, prognosis, mortality, survival, diagnosis, nephroprotection, prevention, treatment, angiotensin converting enzyme inhibitor, angiotensin receptor antagonist, angiotensin receptor and neprilisin inhibitor (ARNI)*

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ASA — acetylsalicylic acid, BMI — body mass index, CRS — cardiorenal syndrome, NUPs — natriuretic peptides, ADHF — acute decompensated chronic heart failure, AKI — acute kidney injury, AHF — acute heart failure, RF — renal failure, RCS — randomized clinical studies, GFR — glomerular filtration rate, HF — heart failure, CRT — cardiac resynchronization therapy, LVEF — left ventricular ejection fraction, FC (NYHA) — functional class, CKD — chronic kidney disease, CHF — chronic heart failure

Cardiorenal syndrome (CRS) is a typical link in cardiorenal continuum. It is a condition when a patient has heart failure (HF) and renal failure (RF) at the same time. CRS is reported in 32-90.3 % of HF patients. There are acute and chronic types of CRS in HF. Acute CRS is acute kidney injury (AKI) in acute heart failure (AHF) or decompensated chronic HF (ADHF) [17, 25, 73, 78, 116].

* Contacts. E-mail: elenaresnik@gmail.com

Chronic CRS is the development of chronic kidney disease (CKD) in chronic heart failure (CHF) [81]. The prognostic significance of CRS, approaches to CRS and kidney injury progression prevention in HF patients are discussed in this part of the review.

Prognostic significance of impaired renal function, albuminuria and renal hemodynamics in HF patients

The importance of renal function as a prognostic factor in HF has been underestimated or ignored for a long time. In randomized clinical studies (RCS), emphasis was placed on cardiovascular events and mortality, while renal outcomes were either reported as safety endpoints or were not evaluated at all [39].

The prognostic significance of serum concentrations of creatinine in patients with CHF was demonstrated for the first time in the middle 1990s [50, 92]. In 2000, Hillege et al. calculated glomerular filtration rate (GFR) in patients with CHF NYHA III–IV and left ventricular ejection fraction (LVEF) of less than 35 % enrolled in PRIME-II study [66]. They showed that GFR is an independent predictor of the total and cardiovascular mortality, even more potent than NYHA FC and LVEF [53, 71, 72]. This was confirmed by numerous international and Russian studies [9, 11, 18, 19, 49].

It was found that both baseline serum creatinine and its increase during hospitalization (deterioration of renal function) were associated with longer hospitalization duration, frequency of hospitalization, and mortality [54, 89, 111]. Gottlieb et al. showed that it is observed even in case of increase in creatinine concentration by 0.1 mg/dL (8.8 μmol/L). Smith et al. demonstrated that increase in serum concentration of creatinine by 0.2 mg/dL (17.7 μmol/L) or more during hospitalization is associated with the increase of risk of death within 6 months by 67 % and rehospitalization probability by 33 % [127]. Its increase by ≥0.3 mg/dL (or 26.5 μmol/L), which is currently a criterion for AKI diagnosis when it occurs within 48 hours, made it possible to predict in-hospital mortality at 81 % sensitivity and 62 % specificity, and hospitalization duration of more than 10 days at 64 % sensitivity and 65 % specificity [62]. Moreover, the increase in creatinine concentration during hospitalization was a more potent mortality predictor as compared to its baseline level [127].

In the meta-analysis of 7 studies involving CHF patients (n=16,106) and 2 studies involving AHF patients (n=54,305), Smith et al. revealed an increase in risk of long-term mortality in severe kidney injury (GFR<53 mL/min/1.73 m^2) by 56 %. Furthermore, deterioration of renal function was associated with an increase in mortality within 6 months by 47 % [126]. The meta-analysis conducted by Damman et al. (n=18,634) showed that the deterioration of renal function leads to the increase in mortality risk by 61 % and rehospitalization risk by 30 % within 2–6 months of follow-up [41].

In their meta-analysis of 20 prospective studies, 5 subanalyses of clinical studies and 17 retrospective observational studies involving patients with acute HF (n=275,832, with the observation period of 1 month to 8 years, in most cases — 6 months to 1 year), Butler et al. confirmed that kidney injury and deterioration of renal function (in most studies, creatinine concentration increased by ≥0.3 mg/dL (26.5 μmol/L) during hospitalization) are related to in-hospital, long-term mortality, rehospitalization frequency, combined hospitalization/death endpoint, and length of stay in hospital [22, 30, 37, 52, 54, 83, 84, 89, 91, 103, 106–108, 127, 140]. Heywood et al. demonstrated that worsening of renal dysfunction is associated with higher necessity for cardiopulmonary resuscitation, mechanical ventilation and ultrafiltration [70]. Forman et al. found that worsening of renal function led to a twofold increase in the likelihood of major complications, such as cardiogenic shock, myocardial infarction, stroke, sepsis, significant hypotension and atrial fibrillation [54].

Predictors of deterioration of renal function during hospitalization in CHF are male gender, baseline serum creatinine >1.5 mg/dL (132.6 μmol/L), uncontrolled hypertension (systolic BP>200 mm Hg), HR>100 beats/min, crackles appearing outside basal areas of lungs [89], atrial fibrillation [37], age, and concomitant diabetes mellitus [54, 62]. Predictors of reduced renal function in HF within 6 months following examination are vascular pathology (acute cerebrovascular accidents and transient ischemic attacks, peripheral

vascular diseases, renal artery stenosis, abdominal aortic aneurysm diagnosed at the time of enrollment to the study), treatment with thiazide diuretics and baseline serum urea over 9 mmol/L [42]. There were no significant differences in percentages of the maximum recommended dose of ACE inhibitors, which was administered at the baseline and during observation, in patients with decreased and increased GFR [43]. Initially prescribed doses of diuretics did not differ in patients with increased and decreased GFR, although 6 months later, the doses of diuretics were significantly higher in patients with deterioration of renal function as compared to patients without it [42].

Valente MA et al. conducted a study involving 120 patients having clinically stable CHF with LVEF <45 % and mainly NYHA FC II and III, the follow-up period was 3 years, the combined endpoint included all-cause mortality, heart transplantation and hospitalization for decompensated HF. This study demonstrated the equal prognostic significance of the following GFR determination methods: based on ^{125}I-iothalamate clearance, calculation using the formula of MDRD, CKD-EPI serum cystatin C, CKD-EPI creatinine and serum cystatin C, and the Cockcroft-Gault formula [7]. The study conducted earlier by Zamora E. et al. (2011), which involved 925 patients with CHF, also compared the predictive significance of the CKD-EPI, MDRD and Cockcroft-Gault formulae. However, the prediction of risk of death proved to be the most exact for the Cockcroft-Gault formula, while the CKD-EPI and MDRD formulae demonstrated similar predictive efficacy [7]. The meta-analysis of 25 prospective studies for risk stratification in HF patients based on GFR (irrespective of LVEF) has shown that the CKD-EPI formula provides the best risk stratification as compared to the MDRD [7].

In addition to blood creatinine and GFR, poor prognosis in CHF patients is associated with albuminuria irrespective of their levels. The CHARM sub-study (n=2,310) showed accurate independent worsening of prognosis for the combined endpoint (total mortality, cardiovascular mortality and hospitalization for ADHF) in HF patients and microalbuminuria or macroalbuminuria (RR: 1.43 (1.21–1.69); p<0.0001 and 1.75 (1.39–2.20); p<0.0001, respectively) [22][7]. The GISSI-HF sub-study (n=2,131) also confirmed the role of micro- and macroalbuminuria as a predictor of total mortality in CHF patients with LVEF 33±9 % (RR = 1.42 (1.11–1.81); p=0.005 and RR=1.70 (1.16–2.50); p=0.006) [7]. In the Russian population, micro- and macroalbuminuria (A2 and A3) also negatively affected prognosis in patients with CHF: mortality of patients with albuminuria was significantly higher as compared to patients without it [65, 129].

Renal blood flow figures are also related to with prognosis. Ennezat PV et al. were the first to demonstrate the negative prognostic value of renal resistance indices in patients with CHF. This was confirmed in other foreign and domestic studies [7]. Moreover, the prognostic significance of reduced volumetric renal blood flow in CHF was demonstrated in the Russian population [9, 12].

Thus, the prognosis in HF patients is associated with impaired renal function, albuminuria and renal hemodynamics. This may be due to that the existence of renal dysfunction reflects the severity of HF. Moreover, renal dysfunction is related to insufficient elimination of toxic substances, such as oxidized catecholamines, uremic factors and uric acid, increased cardiac pre- and afterload, anemia, disturbed calcium-phosphorus metabolism and other metabolic processes, which may also contribute to the worsening of prognosis in this patient population [42, 126].

Cardiorenal syndrome prevention and treatment in HF patients

In accordance with pathogenetic mechanisms for the development of cardiorenal syndrome, and current guidelines for management of patients with HF, CKD, AKI, the following approaches can be used to prevent the development and progression of cardiorenal syndrome in HF patients.

1. HF therapy in accordance with current guidelines [1, 5, 114]. Since ADHF episodes predispose to the development of AKI, subsequent development and progression of CKD [39], it is crucial, with the aim of nephroprotection, to prescribe adequate therapy of HF according to current guidelines in order to prevent and reduce incidence of decompensations [38]. In most patients, it should include

ACE inhibitors / angiotensin receptor antagonists, beta-blocking agents, diuretics, mineralocorticoid receptor antagonists. If the above combination is ineffective, ACE inhibitors / angiotensin receptor antagonists may be replaced with sacubitril/valsartan in systolic blood pressure >100 mm Hg, ivabradine may be added in sinus rhythm with HR ≥70, and cardiac resynchronization therapy (CRT) may be considered at QRS ≥130 msec. In this case, to prevent episodes of hypovolemia and hypotension, which promote the development of AKI, it is necessary to start the drug therapy with minimum doses, and slowly titrate and adjust doses in accordance with GFR values [5, 6, 8, 13].

2. Diet. Low-salt diet (salt <6 g/day, sodium <2.4 g/day), low-protein diet (1 g/kg/day in CKD Stages 1–2, and 0.6–0.8 g/kg/day in CKD Stages 3a–4), replacement of animal proteins with plant proteins, which put lesser stress on kidneys (soy proteins have lesser negative impact on renal hemodynamics, and also effect nephro-, cardioprotective and antisclerotic action), low-potassium diet (>4 g/day in CKD Stages 1–2, and 2–4 g/day in CKD Stages 3a–4), and low-phosphate diet (1.7 g/day in CKD Stages 1–2, and 0.8–1.0 g/day in CKD Stages 3a–4) have proved to be effective in preventing the progression of CKD [10, 14, 15].

3. Smoking cessation, because smoking is a dose-dependent risk factor for the reduction of GFR and the development of microalbuminuria [110, 136].

4. Limitation of alcohol consumption [15, 16, 90].

5. Elimination or minimization of modifiable risk factors for the development and progression of CKD. Nephrotoxic drugs, including non-steroidal anti-inflammatory drugs (NSAIDs), nephrotoxic antibiotics, contrast agents, food supplements (including Thai Herbs, Fat Burners, weight-gainer shakes), which may negatively affect the renal function, should be avoided.

The administration of even small doses of acetylsalicylic acid (ASA), as well as other NSAIDs, in CHF patients is associated with worsening of outcome, as these drugs block the synthesis of prostaglandins, which prevent the negative impact of neurohumoral activation, and weaken the effect of drugs for CHF treatment — ACE inhibitors, diuretics, spironolactone, carvedilol [3, 23, 55]. Prescription of ASA is associated with the higher frequency of hospitalization for worsening CHF [98]. This indicates that NSAIDs should be avoided in CHF (except for prescribing ASA at the early stage to 8 weeks after suffering myocardial infarction), particularly when there is renal dysfunction [4]. If antiplatelet therapy is required, ASA may be indicated to be replaced with clopidogrel [48].

It should be borne in mind that, starting from CKD Stage 3b, the effectiveness of thiazide diuretics is reduced and the risk of their side effects grows, therefore, loop diuretics should be preferred [8]. Moreover, aldosterone antagonists are strictly contraindicated in GFR <30 mL/min/1.73 m^2 due to the risk of aggravated renal dysfunction and hyperkalemia, and in GFR 30–60 mL/min/1.73 m^2 they should be used with caution at a dose of no more than 25 mg/day, with close monitoring of on-treatment blood potassium and creatinine 7 days following the beginning of therapy or dose change, subsequently on a weekly basis for up to 1.5 months, and then once every 4 months [8, 16, 123].

Cardiac glycosides in CRS patients should be prescribed with great caution, only when there is atrial fibrillation [8]. GFR should be taken into account when prescribing digoxin, since the elimination of digoxin decreases with reduced GFR, and serum concentration of digoxin should be maintained at <0.8 ng/mL [104]. For safety purposes, it is not recommended to start treatment in CRS patients with loading doses, and low doses should be used as maintenance doses, i. e., 0.125 mg, probably every other day [123].

6. Maintaining the body mass index (BMI) within the range of 20–25 kg/m^2 through adjusted dietary calories and sufficient physical activity (30 min aerobic activities at least 4–5 times a week), since the increase of BMI >25 kg/m^2 even in young healthy individuals is associated with a higher risk of end-stage chronic renal failure [74].

7. Close blood pressure monitoring. The target BP is <140/90 mm Hg at optimal EAM <10 mg/g (A0), and <130/80 mm Hg at higher albuminuria (A1–A4). In this case, it is very important to avoid the reduction in systolic BP <120 mm Hg in order to prevent the decrease of renal blood flow [15, 79, 95, 138, 139].

8. Close glycemia monitoring. The target glycated hemoglobin (HbA1c) level depends on age and existing complications (Table 1); in most patients, it is <7 % [8].

Table 1. *The target level of glycated hemoglobin in patients with cardiorenal syndrome [8]*

HbA1c target, %	Age, years		
	Young adults <45	Middle age ≥45<70	Elderly (≥70) or life expectancy <5 years
Absence of macrovascular complications and/or hypoglycemia risk	<6.5 %	<7.0 %	<7.5 %
Presence of macrovascular complications and/or hypoglycemia risk	<7.0 %	<7.5 %	<8.0 %

9. Prescribing ACE inhibitors/ARBs/ARNIs [20]. Nephroprotective action of ACE inhibitors and ARBs is due to the fact that they increase renal blood flow through the dilation of afferent arterioles and increase in cardiac output, and block negative renal effects of angiotensin II, including proliferation and hypertrophy of mesangial cells [118]. In case of long-term administration of ACE inhibitors/ARBs, the dilation of efferent arterioles prevents hyperfiltration and reduces albuminuria [69]. All this leads to slower progression of CKD and reduced risk of end-stage CRF.

ACE inhibitors were contraindicated for a long time with blood potassium over 5 mmol/L and creatinine over 220 μmol/L (2.5 mg/dL). In the analysis of 20902 Medicare participants over 65 years of age with systolic dysfunction (LVEF < 40%), the reduction in mortality within 1 year in the course of treatment with ACE inhibitor was more significant in patients with serum creatinine >265 μmol/L (3mg/dL) as compared to patients with creatinine concentration ≤265mg/dL (37% and 16%, respectively) [55]. In light of this, "there is no specific level of creatinine, at which ACE inhibitors are contraindicated" [69, 75-77, 80]. According to most experts, ACE inhibitors or angiotensin II receptor antagonists may be prescribed in serum creatinine <6 mg/dL (528 μmol/L) and GFR≥20 mL/min. However, renal artery stenosis should be excluded before starting treatment. In patients with GFR<30 mL/min/1.73 m², treatment should be started in a hospital, where creatinine and potassium can be analyzed on a daily basis and agents for treating acute RF are available [44, 94, 100]. Patients with GFR ≥30 mL/min/1.73m² should be analyzed for serum creatinine and potassium and GFR 7 days following the first administration and dose increase, subsequently once a week for up to 1.5 months, and then once every 4 months [16]. If, in the course of treatment, creatinine concentration has increased by less than 50% and remains below 266 μmol/L, GFR — above 25 mL/min/1.73m², potassium — below or equal to 5.5 mmol/L, no changes in the therapy with ACE inhibitors or ARBs are required. In case of more pronounced changes in blood concentrations of creatinine and/or potassium, ACE inhibitor/ARB doses should be reduced twice, and creatinine and potassium should be controlled in 1 week. When blood concentration of potassium increases to >5.5 mmol/L, creatinine increases by over 100% or above 310 μmol/L, GFR decreases to <20 mL/min/1.73m², RAAS blockers should be discontinued and nephrologist consultation is required (Table 2). ACE inhibitors and ARBs should be interrupted in case of scheduled administration of contrast agents, preparation to colonoscopy, or before major surgical interventions [2, 8].

The combination of ACE inhibitor and ARB reduces EAM and BP better than isolated use of any of these groups of medications, but does not

Table 2. *Management of patients with changes in serum creatinine concentration / glomerular filtration rate on the background of angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) [8]*

Increasing of serum creatinine, %	Serum creatinine, μmol/l	Glomerular filtration rate, ml/min/1,73 m²	Serum potassium, mmol/l	Changes in the dose of ACEI / ARB
<50 %	<266	>25	<5,5	Not required
50-100 %	266-310	20-25	-	Decreasing of the dose 2 times, control after 1 week
>100 %	>310	<20	>5,5	Drug's withdrawal

prevent the combined endpoint: doubling of creatinine, dialysis dependence or death [96]. In light of this, the combination of ACE inhibitor and ARB is not recommended at present.

Sacubitril/valsartan, a drug of the new ARNI class, includes ARB and neprilysin inhibitor. Neprilysin is a neutral endopeptidase that cleaves natriuretic peptides (NUPs), bradykinin, and other peptides. Inhibition of neprilysin leads to increased blood levels of NUPs, increased urine output, natriuresis, improved myocardial relaxation, and decreased secretion of renin and aldosterone [64, 117]. In PARADIGM-HF study, sacubitril/valsartan reduced cardiovascular mortality and frequency of hospitalizations for HF 20%, and all-cause mortality 15% better than enalapril [13, 88].

Subanalysis of findings from the PARADIGM-HF study (n=1,872) has shown that GFR decreased significantly less in the course of treatment of CHF patients with impaired LVEF with sacubitril/valsartan as compared to enalapril: by 1.61 and 2.04 mL/min/1.73m^2/year, respectively ($p<0.001$). However, the increase in albumin/creatinine ratio was higher with sacubitril/valsartan as compared to enalapril: by 1.2 mg/mmol and 0.9 mg/mmol, respectively ($p<0.001$) [40]. Similar data were obtained during the PARAMOUNT study in patients with preserved LVEF [134]. Moreover, in the PARADIGM-HF study, hyperkalemia was rarer among patients who received mineralocorticoid receptor antagonists in the course of treatment with sacubitril/valsartan as compared to enalapril [46].

10. Lipid-lowering therapy. To slow down atherosclerosis and renal fibrosis, which promote the development of CKD, statins are indicated. According to the meta-analysis of 50 studies (n=30,144), at various stages of CKD, statins significantly reduced daily proteinuria, although they had no considerable effect on GFR. Positive effects of statins did not depend on the stage of CKD [128]. The GREACE study showed improved renal filterability in CHF patients who received atorvastatin. Nevertheless, in accordance with the current guidelines, since statins do not affect the selected (solid) endpoints, it is not recommended at present to initiate therapy with statins in CHF, although such therapy may be continued in patients with CHF of ischemic etiology [7]. Perhaps, it is particularly important to continue treatment with statins in patients with CRS.

11. Reducing abdominal pressure. Paracentesis with fluid evacuation to relieve the symptoms can be considered for patients with ascites. By reducing abdominal pressure, this procedure can partially increase renal filtration pressure and GFR [1, 10, 105, 114, 133].

Potential approaches to nephroprotection in CRS

In addition to the above, a number of other approaches to nephroprotection in CRS were and are still being intensively studied.

Nesiritide

Nesiritide is a synthetic form of brain natriuretic peptide (BNP). Experimental studies have shown its favorable effect on kidneys [124]. However, its diuretic action was less pronounced in CHF patients as compared to healthy individuals. Effects of nesiritide on renal plasma flow, urine output and sodium excretion were comparable to the placebo [135]. Under its influence, GFR did not increase even in patients in whom this drug produced natriuretic and diuretic effect [97, 135]. In the FUSION II study, nesiritide (infusions 1-2 times a week for 12 weeks) caused an increase in serum creatinine by 0.5 mg/dL (44 μmol/L) [94, 141]. In their meta-analysis, Sackner-Bernstein et al. found that the risk of death within 30 days was higher in patients receiving nesiritide as compared to the placebo group. The study conducted by Peacock et al. showed that, as compared to placebo, the probability of rehospitalization within 30 days was 57% lower in the patients receiving nesiritide, and the duration of rehospitalization was 2.6 times shorter. The meta-analysis of seven large randomized controlled studies performed by Arora et al. demonstrated that the relative risk of death within 30 and 180 days was not significantly different in the nesiritide and placebo groups [112]. The ROSE study, which involved 360 patients with decompensated HF and GFR of 15 to 60 mL/min/1.73m^2, did not reveal any advantages of nesiritide (0.005 mcg/kg/min) as compared to placebo in regard to congestion and GFR [33]. Tachycardia and hypotension were reported in many patients. In light of this, the use of nesiritide in patients with CRS is limited [114, 133].

Vasopeptidase inhibitors

In theory, vasopeptidase inhibitors may have a clinical advantage over ACE inhibitor in patients with CHF. The first drug of the group, omapatrilat, blocked 3 enzymes: ACE, aminopeptidase P and neprilysin [109]. However, it often led to allergic reactions, therefore, is not recommended for administration [88]. The drug of the ARNI class, which contains neprilysin inhibitor, is described above.

Vasopressin receptor antagonists

Antagonists of renal (V2) vasopressin receptors increase urine output and aquaresis (excretion of water without electrolyte loss), and allow resolving hyponatremia either in the presence or absence of HF [51, 59]. A number of studies showed the potent aquaretic effect of tolvaptan without damage to the kidneys in patients with ADHF [56]. The SALT study demonstrated that this drug is effective and safe in patients with HF and hyponatremia. In the EVEREST study (n=4,133), reduction in body weight and intensity of clinical symptoms was higher in the patients hospitalized for HF, who received tolvaptan, as compared to the control group; however, there was no favorable effect on mortality, including cardiovascular mortality, and frequency of hospitalization for HF [57, 85, 88, 112]. Other studies showed no advantages of vasopressin antagonists (tolvaptan, conivaptan) for renal function as compared to furosemide in patients with CHF [21, 36, 87, 104, 121]. The meta-analysis performed by Sen J. et al. based on data obtained in 17 studies (n=1,597) did not find any differences concerning changes in GFR and serum creatinine among control groups and tolvaptan group [122]. There is no justification to prescribe these drugs for nephroprotection in patients without hyponatremia [114].

Adenosine A1 receptor blockers

As noted above, increased plasma adenosine is observed in HF patients, which reduces cortical blood flow in kidneys and sodium excretion. Selective adenosine A1 receptor blockers (BG9719, KW3902 — rolofylline) increase urine output and natriuresis. Gottieb et al. demonstrated that BG9719 in combination with furosemide increased urine excretion and caused no changes in GFR as compared to the placebo [60-62]. In another study, rolofylline led to significant increase in GFR by 32% and in renal plasma flow by 48% [47, 58]. However, in the PROTECT placebo-controlled randomized study (n=2,033), rolofylline did not improve clinical outcomes and serum creatinine in patients hospitalized for ADHF, having GFR 20-80 mL/min/1.73 m^2, as compared to the placebo. Moreover, neurological complications were more common in the rolofylline group [99, 103, 113, 137]. Another pilot study also confirmed the neutral effect of rolofylline on renal function [63]. Administration of rolofylline for nephroprotection in CHF is not justified at present.

Endothelin receptor blockers

In two VERITAS studies, intravenous infusion of endothelin receptor blocker tezosentan, despite its more favorable hemodynamic effect, failed to improve acute HF symptoms, change short- and long-term disease prognosis, or prove the nephroprotective action of the drug as compared to the placebo [102, 131].

Guanylate cyclase activators and stimulators

It has been shown that soluble guanylate cyclase activators and stimulators (BAY 58-2667, cinaciguat; HMR1766, ataciguat; BAY 1021189/MK-1242, vericiguat; BAY 63-2521, riociguat; BAY60-4552, nelociguat) also reduce pre- and afterload and increase cardiac output in HF animals, increase sodium excretion, with preservation of glomerular filtration[87, 120]. These drugs, including their nephroprotective action, are currently being studied in HF patients [86].

Iron and erythropoietin preparations

Correction of anemia in CHF leads to increased exercise tolerance, reduced intensity of clinical symptoms, but has no effect on survival [17, 24, 88, 101]. In some studies, erythropoietin preparations had cardioprotective effect through suppression of apoptosis, oxidative stress and inflammation, reduced infarction area, increased angiogenesis and prevented

arrhythmias [29]. Nephroprotective effect of erythropoetin and its analogues was proven [32], but they led to hypertension , which negatively affected the overall outcome. Darbepoetin alfa, a stimulator of erythropoietin synthesis, does not improve prognosis in HF patients with reduced LVEF and mild to moderate anemia, but results in thromboembolic complications. Therefore, it is not recommended [1, 5, 114]. In some studies, correction of anemia with iron preparations increased oxidative stress [27, 82]. The nephroprotective effect of iron and erythropoietin preparations in patients with CRS has not been proven, and their administration for nephroprotection is not recommended at present [1].

Relaxin

Relaxin 2, a natural peptide that participates in adaptation of the female body to pregnancy, is a potent renal vasodilator [35]. The RELAX-AHF study showed significantly reduced dyspnea (primary endpoint), improved GFR and decreased total mortality within 180 days (secondary endpoints) in patients with decompensated HF who received serelaxin (human recombinant relaxin 2) as compared to the placebo [130]. Moreover, administration of serelaxin reduced intensity of congestion and the need for intravenous diuretics [93]. The subsequent RELAX-AHF-EU study did not confirm the drug effect on the primary endpoint (death + HF worsening), for which reason further studies and the manufacture of the drug, which is potentially prospective for CRS treatment, were suspended.

Cardiac resynchronization therapy

Perfusion in CHF can be improved using cardiac resynchronization therapy (CRT). In one study, CRT increased GFR by 2.7 mL/min/1.73m^2 in the subgroup of patients with GFR of 30–60 mL/min/1.73m^2 [28]. This issue needs thorough examination.

TNF-α inhibitors

Given the role of inflammation in the genesis of HF and kidney injury, there was an idea to use TNF-inhibitors (infliximab and etanercept) for the treatment of heart failure, but the ATTACH, RECOVER and RENASSAINCE (RENEWAL) studies had disappointing results. Despite the reduced plasma concentrations of the highly sensitive C-reactive protein and IL-6, the lack of effect on prognosis or increased mortality were reported in the course of treatment with these drugs [34, 96]. However, there is no sufficient information on renal function in these studies [39].

Effect on oxidative stress

Despite the fact that the role of oxidative stress in the development of CRS has been proven, the potential therapeutic effect on this component of pathogenesis remains understudied. Clinical studies did not demonstrate any effect of treatment with antioxidants (vitamins E, C), which can be explained by the lack of specificity in their mechanism of action. Currently, animal studies are conducted for selective blockers of different oxidative stress pathways: NADPH oxidase inhibitors (S17834, gp91ds-tat) and mitochondrial antioxidant (MitoQ) [7].

Denervation of renal arteries

Given the role of sympathoadrenal system activation in the genesis of kidney injury in HF, sympathetic denervation of renal arteries was assumed as one of potential approaches to the management of CRS patients. However, given that the SYMPLICITY HTN-3 study identified no advantages of renal artery denervation as compared to a sham procedure, the importance of this treatment method is rather doubtful [26].

Compression therapy for lymphatic drainage

In lower limb swelling resistant to diuretic therapy, compression therapy may be appropriate to provide for lymphatic drainage and fluid return from intercellular spaces to blood streams [132]. The renal effect of that has not been studied.

Mechanical circulatory support

In most HF patients with reduced LVEF and CRS, renal function improved after implanting mechanical circulatory support (MCS) devices [67, 119]. The worst renal function before the devices were implanted was associated with the poor

prognosis [31]. Moreover, in patients who received MCS as a bridge to kidney transplantation, post-transplantation renal function correlated to that observed following the initiation of MCS [45, 125]. However, the use of MCS is associated with future complications, such as infection, bleeding and thrombosis, and may not be considered as treatment of CRS [133].

The existing approaches to nephroprotection in patients with CHF are summarized in Table 3. Areas for further studies on the issue are as follows: 1) epidemiological data, including data on AKI in HF; 2) understanding of CRS pathogenesis; 3) feasibility of using a biomarker panel for diagnosis and management of CRS; and 4) development of new approaches to nephroprotection [115].

Table 3. *Approaches to nephroprotection in patients with HF (with changes as per [38, 68, 133])*

The purpose of the treatment	Existing approaches	Possible/future approaches
Modification of risk factors for renal dysfunction	Prevention of CH decompensation Careful titration of doses of the drug, depending on renal function Diet Quitting smoking, drinking alcohol Limitation of nephrotoxic effects, incl. drugs Control of hypertension Avoidance of hypotension Glycemia control Maintain optimal BMI Careful monitoring of fluid balance, urine excretion	Allopurinol SGLT2 Physical exercise
Hemodynamic disorders	Adequate diuretic therapy ACE inhibitors / ARB / ARNI Cardiac resynchronization therapy Mechanical circulatory support Heart and / or kidney transplantation	Vasopressin V2 Receptor Antagonists Calcium Sensitizers Endothelin receptor antagonists Luso-inotropic agents (istaroxime) Heart myosin activators Relaxin-2
Neurohumoral activation	ACE inhibitors / ARB / ARNI β-blockers	FGF-23 Receptor Blockers Adenosine A1 receptor antagonists Direct renin inhibitors Physical exercise Renal artery denervation
Atherosclerosis, endothelial dysfunction, coagulation and vascular&platelet hemostasis disorders, thromboembolic complications	Statins Antiplatelet therapy Anticoagulants	Nitrogen oxide Physical exercise Endothelin receptor antagonists
Malnutrition, inflammation, oxidative stress, cachexia	Nutritional support Physical exercise	Ghrelin Antioxidants Anti-inflammatory drugs
Uremia	Peritoneal dialysis / hemodialysis	Removal of toxins by high-flow hemofiltration and / or new absorbents
Anemia, iron deficiency	Iron	Diet Anti-hepcidin therapy Carnitine Erythropoietin preparations
Mineral and bone disorders [14]	Diet Preparations of the active form of vitamin D Selective Vitamin D Receptor Activators Phosphate binding agents Calcimimetics	FGF-23 Receptor Blockers Antibodies to FGF-23

Note: ARB — angiotensin receptor blocker, ARNI — angiotensin receptor and neprilysin antagonist, ACE — angiotensin converting enzyme, BMI — body mass index, FGF — fibroblast growth factor, SGLT2 — type 2 sodium-glucose transporter inhibitors

Thus, cardiorenal syndrome is a regular component of cardiorenal continuum [115]. It is reported in most patients with CHF. Doctors of various specialties may encounter patients with cardiorenal syndrome: general practitioners, cardiologists, nephrologists, resuscitators, anesthetists, cardiac surgeons, etc. In order to prevent and slow down progression of kidney injury, treatment according to the current guidelines for HF, CKD and AKI should be recommended for patients with CHF. There is need to develop and introduce new approaches to nephroprotection, which is possible with the collaborative work of a multidisciplinary team.

Conflict of interests

The authors declare no conflict of interests.

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