Medicinska istraživanja 2026 | DOI: 10.5937/medi0-64542

OPEN ACCESS

Medical Research | Published by Faculty of Medicine University of Belgrade

REVIEW ARTICLE

Cardiorenal syndrome type 1 in the cardiology intensive care unit

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Submitted: 01 February 2026

Revised: 10 March 2026

Accepted: 12 March 2026

Online First: 18 March 2026

Check for updates

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Summary

The kidneys and the heart are closely connected, and the dysfunction or failure of one organ often leads to the dysfunction or failure of the other. This condition is known as cardiorenal syndrome. There are five types of cardiorenal syndrome (CRS), categorized by the primarily failing organ (kidneys or heart) and whether the failure is acute or chronic. CRS type 1 (CRS-1) is defined as acute kidney injury (AKI) caused by acute heart failure (AHF). CRS-1 develops in more than 30% of patients hospitalized in the cardiology intensive care unit (CICU). This narrative review aims to present the pathophysiological mechanisms, therapeutic implications, and prognostic significance of CRS-1 in patients hospitalized in the CICU. The mechanisms of CRS-1 development are complex. They include low cardiac output and venous congestion, leading to subsequent neurohumoral activation and inflammation. Since the hallmark of CRS-1 is diuretic resistance, the development of CRS-1 complicates the treatment strategy in acutely decompensated patients, and strongly and negatively affects patients' short- and long-term outcomes. For clinicians, early identification of patients at risk of developing CRS-1 is essential, along with timely adjustment of the therapeutic approach to achieve optimal decongestion, prevent CRS-1 progression, and improve both short- and long-term prognosis.

Keywords: cardiorenal syndrome, acute heart failure, acute kidney injury, treatment strategy, prognosis

INTRODUCTION

The kidneys and the heart are closely connected, and the dysfunction or failure of one organ leads to the dysfunction or failure of the other. Combined disorders of the heart and kidneys are known as cardiorenal syndrome (CRS) (1-4). Although the close interplay between the heart and the kidneys has been recognized since the nineteenth century, the term *cardiorenal syndrome* first appeared in the literature in the 1940s and has been recognized as a particularly important medical problem in the past two decades (1,5).

The primary failing organ categorizes CRS into five types and indicates whether the failure is acute or chronic. CRS types 1 and 3 are considered acute conditions, indicating acute deterioration of heart or kidney function. In contrast, CRS types 2 and 4 are considered chronic conditions, as they are caused by chronic heart or kidney failure **(Figure 1)**.

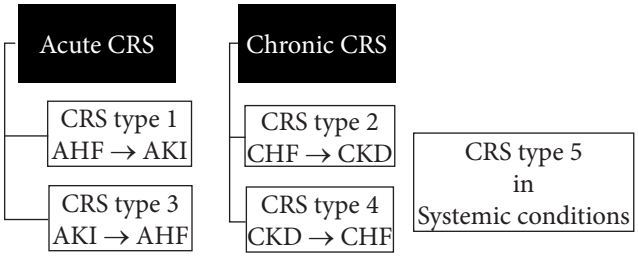

Figure 1. Acute and chronic CRS
Abbreviations: CRS=cardiorenal syndrome; AHF=acute heart failure; AKI=acute kidney injury; CHF=chronic heart failure; CKD=chronic kidney injury

Finally, CRS type 5 integrates all cardiac and kidney involvements induced by systemic disease (2,6,7,8). The five types of CRS are presented in **Table 1** (6).

In addition to classifying CRS into five types, the American Heart Association has introduced the term *cardiovascular-kidney-metabolic syndrome* (CKM), which encompasses not only renal and cardiac dysfunction/failure but also the presence of metabolic syndrome in the setting of concomitant chronic heart and kidney failure (5,9). The literature also refers to *cardiorenal-anemia syndrome* (CRAS) due to the frequent presence of anemia in patients with CKD (10). Both terms refer to more detailed descriptions of CRS types, specifically types 2 and 4.

For patients hospitalized in the cardiology intensive care unit (CICU), the development of cardiorenal syndrome type 1 (CRS-1) is very significant. CRS-1 is defined as acute kidney injury (AKI) caused by acute heart failure (AHF) (1,11-15). It affects more than 50% of patients hospitalized for AHF. This means that the first step in developing CRS-1 is the occurrence of AHF, which is one of the most common indications for hospitalization in the CICU. CRS-1 can develop in any patient with AHF, regardless of the underlying cause and regardless of whether the patient has heart failure with reduced or preserved left ventricular ejection fraction (HFrEF; HFpEF).

AKI is defined as a rise of 0,3-0,5mg/dl in serum creatinine value or a decrease in glomerular filtration rate (GFR) of 9-15ml/min within 24-48 hours, or rise of creatinine value to ≥1.5 times within 7 days as compared to basal value (8,12,16-20). Another parameter indicating the development of AKI is a reduction in urine output. This parameter is used to determine the stage/severity of AKI, with oliguria progressing to anuria indicating severe AKI (13).

There are four subtypes of CRS-1: 1) *de novo* AHF leading to *de novo* AKI; 2) *de novo* AHF leading to AKI in patients with preexisting chronic kidney disease (CKD); 3) acute decompensated chronic heart failure (CHF) leading to *de novo* AKI; and 4) acute decompensated CHF leading to AKI in patients with preexisting CKD (20). Regardless of the subtype, the development of CRS-1 significantly complicates the clinical course, therapeutic options, and patient prognosis. Therefore, early identification of CRS-1 and implementation of measures to stop its progression are of great clinical significance (2,13).

This narrative review aims to present the pathophysiological mechanisms, therapeutic implications, and prognostic significance of CRS-1 in patients hospitalized in the CICU.

METHODS

A comprehensive literature search was conducted in PubMed using keywords to identify relevant articles written in English. The following key words were used: "cardiorenal syndrome", "acute heart failure", "acute kidney injury", "prognosis", "therapy". Relevant data were

Table 1. Classification of cardiorenal syndrome (CRS)

CRS type	Name	Etiology/primarily failing organ
1	Acute cardiorenal syndrome	Acute heart failure (AHF)/cardiogenic shock (different causes), including acute decompensated heart failure, acute myocardial infarction (AMI), acute myocarditis, etc.
2	Chronic cardiorenal syndrome	Chronic heart failure (CHF) leading to chronic kidney disease (CKD)
3	Acute renocardiac syndrome	Acute kidney injury (AKI) - different causes of HF
4	Chronic renocardiac syndrome	Chronic kidney disease (CKD) leading to CKD-associated cardiomyopathy and HF
5	Secondary CRS	Systemic condition/disease leading to simultaneous kidney and heart dysfunction/failure (e.g., amyloidosis, sepsis, cirrhosis)

extracted from selected articles, and their quality was evaluated using established criteria (which included study design, methodology, control of bias and confounding, validity and reliability of measurements, statistical analysis, and generalizability of findings). The reference lists of the selected studies were also reviewed to identify additional relevant publications.

THE INCIDENCE, RISK FACTORS, PATHOPHYSIOLOGY, AND DIAGNOSIS OF CRS TYPE 1

According to data from the literature, approximately 30% of patients with AHF hospitalized in the CICU develop CRS-1. In addition, CRS-1 develops in about 25% of patients with acute myocardial infarction (AMI) complicated by AHF. Although in theory, CRS-1 can develop in all patients with AHF, factors that increase the risk of its occurrence include diabetes mellitus (DM), arterial hypertension (HTA), and preexisting chronic kidney disease (CKD) (1,13,15,22-24). Elevated blood pressure at the patient's initial evaluation has been associated with the development of CRS-1, probably reflecting neurohumoral activation and sodium and water retention (21).

Furthermore, the literature reports that approximately 60% of patients who develop CRS-1 have preexisting CKD, whereas AKI in patients with previously preserved renal function is observed in about 40% of cases (6). Body weight has also been mentioned as a possible risk factor for the development of CRS-1. However, its impact is complex, and data from existing analyses are contradictory. Some data suggest an association between the development of CRS-1 and low body weight, although this hypothesis has not been confirmed in epidemiological studies. On the other hand, obesity is a risk factor for heart failure with preserved ejection fraction (HFpEF), as well as for DM, HTA, and CKD. In obese patients, the increased number of adipocytes secreting proinflammatory cytokines may facilitate the development of AKI in the setting of AHF (13, 21, 25-27).

Therapy for AHF can also affect CRS-1 development in hospitalized patients; high (loop) diuretic doses may be associated with CRS-1 development, probably due to activation of the renin-angiotensin-aldosterone system (RAAS) (13). Other drugs used for the treatment of DM (such as metformin), some antibiotics, and iodine contrast administration may also affect the delicate balance between the heart and contribute to the occurrence of AKI, especially when glomerular filtration is already compromised due to low cardiac output and RAAS activation (21).

Finally, there is also evidence that some individuals experience repeated episodes of subclinical or clinically unrecognized AKI in their lifetime. These episodes may occur during periods of dehydration, exposure to nephrotoxic therapies for other diseases, and similar conditions. With each episode of AKI, a certain number of nephrons are injured. Although the kidneys can adapt their blood flow, thereby usually returning filtration, creatinine, and eGFR values to normal, the total number of remaining nephrons gradually declines. This may explain why some patients without baseline CKD and without other recognized risk factors easily develop CRS-1 in the setting of AHF (21).

The pathophysiology of CRS-1 development is complex and involves changes in hemodynamic parameters and the (over)activation of multiple neurohumoral mechanisms, leading to oxidative stress, inflammation, and other effects. Additionally, low cardiac output and venous congestion directly induce a hypoxic state in the renal parenchyma, which significantly impairs kidney function (14,23,28,29,30). All these mechanisms trigger a vicious cycle between the heart and kidneys (1,17).

In AHF, hemodynamic-driven changes in renal blood flow are primarily responsible for GFR changes. Low cardiac output and elevated left-sided and right-sided filling pressures with venous congestion cause kidney hypoperfusion. Kidney hypoperfusion stimulates renin release and the activation of the renin-angiotensin-aldosterone system (RAAS) (14). At the same time, sympathetic nervous system activation occurs. Sympathetic activity dominantly affects renal vasculature, but also the proximal tubular segment of the nephron and juxtaglomerular cells. Sympathetic activation directly leads to renal vasoconstriction and stimulation of the RAAS. Enhanced RAAS activation (stimulated by kidney hypoperfusion and sympathetic activity) is a maladaptive process in patients with AHF. It causes vasoconstriction of the afferent and efferent arterioles, decreases GFR, and enhances sodium and water reabsorption to preserve kidney perfusion and filtration. Additionally, the stimulation of adrenergic receptors in proximal tubular cells enhances sodium reabsorption (21).

In patients with AHF, renal tubular function is also important for alleviating congestion, but elevated angiotensin II levels increase renal venous pressure and contribute to kidney venous congestion. Venous congestion causes renal interstitial pressure to rise, and the lumen of the tubules can be obliterated. Finally, increased intra-abdominal pressure in patients with advanced heart failure increases central venous pressure and directly compresses the kidneys and their blood vessels, causing hypoperfusion (3,16).

The second important step in CRS-1 development is inflammation, the formation of oxidative stress mediators, and endothelial cell dysfunction (6,16). Angiotensin II (AT II) upregulates cytokines, such as transforming growth factor beta, tumor-necrosis factor alpha (TNF-alpha), nuclear factor kappa B, and interleukin-6 (IL-6). Inflammation stimulates the apoptosis of tubular epithelial cells (1). Endothelial stretch induced by peripheral

venous congestion confers proinflammatory properties on the vascular endothelium, underscoring the importance of decongestion in patients with CRS-1 beyond its hemodynamic effects (8).

Underperfusion of the gastrointestinal system and hematogenous release of bacterial endotoxins in patients with AHF can be an important mechanism in the development of CRS-1, especially in cachectic patients (21). Also, translocation of gram-negative bacteria due to intestinal dysfunction can activate proinflammatory cytokines, affecting heart and kidney function (21). Superimposed infection (most often pneumonia) in patients with AHF further stimulates cytokine activation.

Emerging data suggest the existence of "crosstalk" between cardiac and renal dendritic cells, which plays a central role in innate and adaptive immune responses in the context of CRS (8).

Finally, decreased uremic toxin clearance due to AKI development and hyponatremia are believed to mediate further progression of CRS-1. The accumulation of uremic toxins, including indoxyl sulphate, p-cresyl sulfate, and fibroblast growth factor, has been linked to endothelial dysfunction, stimulation of fibrosis in the renal interstitium, and further exacerbation of inflammation (17).

Hyponatremia results from elevated arginine vasopressin, caused by insufficient systemic and tubular blood flow, and is often seen in congestive states. Both uremic toxins and hyponatremia are associated with an increased risk of adverse events in patients with congestion (16). Pathophysiological mechanisms for CRS-1 development are presented in **Figure 2**.

The CRS-1 diagnosis is established when AHF and AKI coexist, with the requirement that AHF be the initial disorder (1,31). However, diagnosis of AKI in patients with AHF can be complex, because small fluctuations in the serum creatinine level (and urine output) are often observed in patients with AHF and do not represent true kidney injury. The cornerstone of distinguishing AKI from transitory worsening of renal function (WRF) lies in a combination of clinical assessment of perfusion status and relevant hemodynamic parameters, detection of markers of intrinsic kidney injury (such as urine microscopy), and investigation of alternative explanations for WRF (8).

Noninvasive imaging modalities, such as echocardiography, may help diagnose congestive heart failure and the development of CRS-1. In addition to a detailed analysis of cardiac function, echocardiography can be used for assessing central venous pressure, systolic pulmonary artery pressure, and pulmonary capillary pressure. Renal ultrasonography of intrarenal venous flow patterns is an emerging tool in diagnosing renal venous congestion. Also, renal ultrasonography provides information on the chronicity of renal disease, including renal size, echogenicity, cortical thickness, and an abnormal corticomedullary ratio, which are important for diagnosing AKI and demonstrating the presence of preexisting CKD (8).

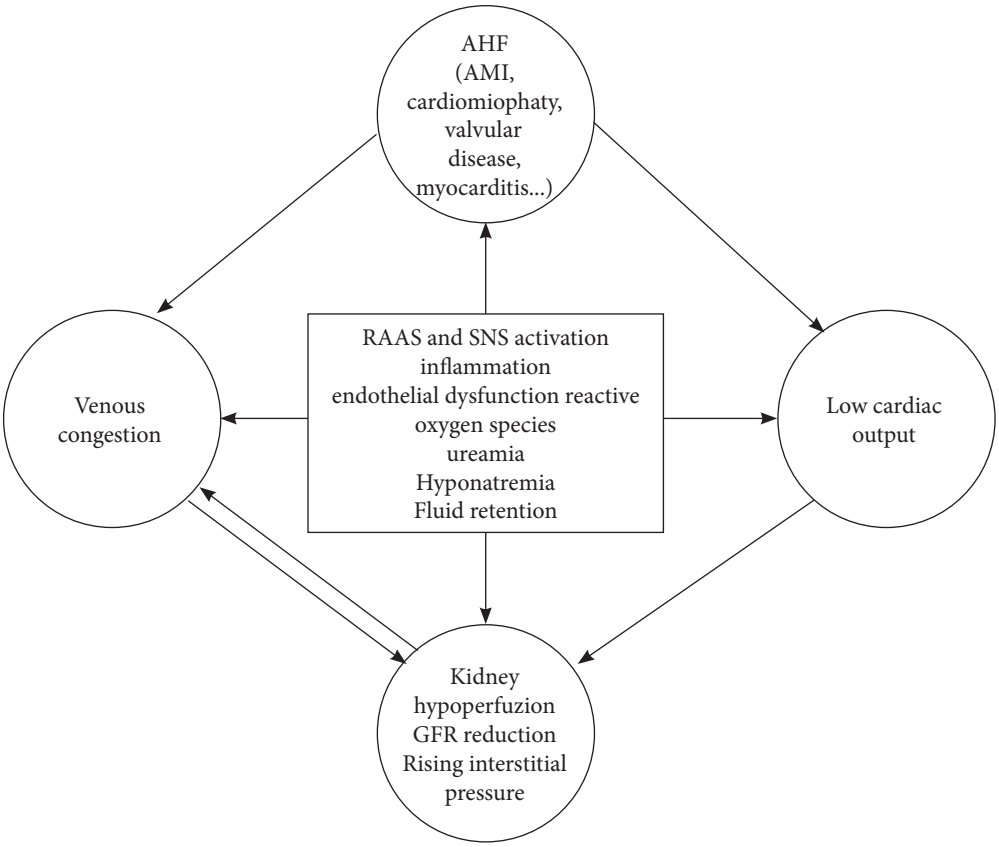

Figure 2. Pathophysiological mechanisms leading to CRS-1
Abbreviations: CRS-1= cardiorenal syndrome type 1; RAAS=renin-angiotensin-aldosteron system; SNS=sympathetic nervous system; GFR=glomerular filtration rate

There are many proposed biochemical markers for diagnosing AKI, even before a rise in serum creatinine (such as kidney injury molecules (KIMs), neutrophil gelatinase-associated lipocalin (NGAL), etc.). Unfortunately, none of these tubular injury markers seems suitable for early AKI diagnosis and kidney function follow-up, as they depend on volume status, renal inflammation, neurohumoral activation, etc. NGAL (siderocalin) is a biomarker that is detectable in blood and urine in patients with AKI. Its elevated levels can be detected in serum even before creatinine levels begin to rise. One study found that NGAL had a sensitivity of 90% and a specificity of 99% in detecting AKI. (8,29,30).

Despite this, at this time, the role of novel renal biomarkers for the diagnosis and/or prognosis of CRS-1 needs further validation. Until such a time, serum creatinine-based definitions remain a strong tool in diagnosing AKI in everyday clinical practice (1,31).

THERAPEUTIC OPTIONS IN PATIENTS WITH CRS-1

Starting with hospital admission, clinicians should use all available therapeutic strategies to prevent the development of CRS-1 in patients with AHF. In patients with established CRS-1, it is very important to break the vicious cycle between the heart and kidneys. Fluid overload represents a core target for treatment. Management of CRS-1 should focus on rapid and effective decongestion and the early introduction of therapy with proven benefits for both cardiovascular and kidney outcomes (3,8). Therapeutic options include careful titration and combination of diuretic therapy, neurohumoral system-targeted therapy, therapy to increase cardiac output, and mechanical circulatory support to maintain adequate renal perfusion (17). Possible therapeutic options are presented in **Table 2** (2, 3, 8).

An appropriate and desirable response to diuretics in patients with AHF is achieving an initial diuresis of more than 150 mL/h, i.e., more than 3 liters over 24 hours (32). Loop diuretics are the cornerstone treatment for congestion. However, they are also a double-edged sword, as they alleviate congestion but worsen kidney perfusion and enhance activation of the RAAS and the sympathetic system (21). Fast and effective decongestion can be achieved with careful titration of loop diuretics, a combination of loop diuretics with acetazolamide or thiazides, or an aldosterone antagonist, especially finerenon (the so-called sequential nephron blockade) (2, 3,16).

It is very important to bear in mind that, in clinical practice, the development of CRS usually limits the efficacy of diuretic therapy due to a decline in kidney function, and often coincides with resistance to loop diuretics, which is considered one of the hallmarks of CRS-1 (16,17). The literature describes, and clinical practice applies, various approaches to overcoming diuretic resistance, aiming to achieve the fastest and most effective possible decongestion of patients, thereby significantly reducing the occurrence and progression of CRS-1.

The Combination of Loop with Thiazide Diuretics in Patients with Decompensated Heart Failure (CLOROTIC) trial treatment, with thiazides in addition to loop diuretics, showed greater weight loss in the combined group. However, in the thiazide group, a somewhat higher percentage of patients with registered WRF was recorded, compared with the group treated with loop diuretics alone (17).

In the Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial, treatment with acetazolamide improved diuresis and decongestion compared with loop diuretics alone, but there was no difference in all-cause mortality or heart failure hospitalization (3).

Mineralocorticoid receptor antagonists (MRAs) are effective as part of sequential nephron blockade but also

Table 2. Therapeutic options in patients with CRS-1

Therapy	Comments
Loop diuretics	The mainstay of therapy for decongestion. Ideally, it should be combined with ACEi/ARB/ARNI and MRAs.
ACEi inhibitors/ARB/ARNI	Cornerstone therapy in patients with heart failure; transitory WRF when starting therapy has no adverse prognostic impact. Cautions: hypotension may further cause a decline in kidney function.
Mineralocorticosteroid receptor antagonists (MRAs)	Successful in combination with loop diuretics Caution: hyperkalemia
SGLT2 inhibitors	Improve prognosis in patients with HFrEF and HFpEF. Initial WRF is transitory; it is followed by kidney function recovery and has no adverse prognostic impact.
Dopamin	According to some authors, so-called diuretic doses may improve decongestion, while others found no effect on decongestion (15).
Inotropic agents	Can improve renal perfusion in advanced AHF and/or cardiogenic shock.
MCS	Improve cardiac output and renal perfusion in severe HFrEF/cardiogenic shock.

CRS=cardiorenal syndrome; ACEi=angiotensin converting enzyme inhibitors; ARB=angiotensin receptor blocker; ARNI=angiotensin receptor blocker, nephrylisin inhibitor; SGLT-2= sodium-glucose cotransporter; HFrEF=heart failure with reduced ejection fraction; HFpEF=heart failure with preserved ejection fraction; MCS=mechanical circulatory support

completely block aldosterone receptors; they can prevent myocardial fibrosis and remodeling, and their long-term benefits have been demonstrated in numerous previous studies. They have the same effect on the kidneys, which is why these drugs are not only diuretics but also an important part of neurohumoral blockade. MRA antagonists are weak diuretics, but are very important for preventing hypokalaemia; they also target the neurohumoral system. The Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ANTHENA–HF) trial included 360 patients with AHF who were randomized into two groups: the group treated with a high dose of spironolactone (100 mg) and the group treated with placebo or low-dose spironolactone (25 mg), in addition to loop diuretics. The results showed no difference in diuresis, weight loss, in-hospital mortality, or 60-day rehospitalization between the two analyzed groups, indicating that small doses of spironolactone are as effective as large doses (17). In patients with CRS-1, careful titration of MRA inhibitors is necessary, with close monitoring of kidney function and electrolyte levels (3).

Tolvaptan, a direct vasopressin V2 receptor antagonist, has been associated with greater urine output and weight loss when added to standard diuretic therapy; however, it has not been demonstrated to improve outcomes or reduce rehospitalization (17). Currently, tolvaptan is used for treating significant hypervolemia and euvolemic hyponatremia. Tolvaptan is not approved for the treatment of AHF, even in patients with diuretic resistance. However, it is reasonable to use it in patients with AHF and hyponatremia despite treatment with ACEi.

Vasodilation with direct vasodilators such as nitrates, in combination with hydralazine, can affect central hemodynamics and, indirectly, enhance diuresis. However, this therapy is reserved only for hypertensive and potentially normotensive patients, with careful blood pressure monitoring (33-35).

The infusion of recombinant human brain natriuretic peptide (rhBNP) was examined, with the hypothesis that vasodilation and natriuresis would facilitate renal blood flow and decongestion. Studies did not show differences in diuresis, kidney hemodynamics, or mortality (17). At present, sequential nephron blockade is the most effective method for achieving faster, more efficient decongestion, particularly when adequate diuresis is not achieved with loop diuretics. However, it should be noted that the therapeutic approach should be tailored to the individual patient, i.e., based on the treating physician's decision and assessment.

Differential renal replacement therapy (RRT) is recommended only when, despite all previous measures, there is no effective decongestion. This is because RRT has many adverse events, including further WRF to the terminal stage (3). Studies have not demonstrated the superiority of renal replacement therapy (RRT) over diuretic therapy, either for decongestion or for prognosis.

The Diuretic Optimization Strategies Evaluation (DOSE) trial (34), the Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial (35), and the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial compared the different decongestion strategies in patients with volume overload, but without AKI. WRF was reported more often in patients treated with high doses of loop diuretics than in those treated with ultrafiltration (UF) in the DOSE trial, and more often in patients treated with UF than in those treated with diuretic therapy in the CARRESS-HF trial. Also, UF led to a greater increase in plasma-renin activity than stepwise pharmacological care (8). On the other hand, there was no difference in WRF prevalence between the treatment groups (diuretics *vs* UF) in the UNLOAD trial. Although decongestion was better in patients treated with UF, there was no difference in prognosis between the two analyzed groups (35). However, the results of the CARRESS-HF trial provided a strong argument against the use of UF as primary treatment in patients with CRS-1 (8).

The next, very important step in treatment is to start or continue with cardio- and nephroprotective drugs as soon as possible, together with a decongestion strategy (2).

The benefits of RAAS hormonal pathway blockade with ACEi/ARB/sacubitril-valsartan (ARNI) have been demonstrated in many landmark trials and in patients with HFrEF (of different etiologies) (3,36-38). Although the results of these studies are related to patients with chronic HF (36-38), introducing or continuing treatment with RAAS blocking drugs, if hemodynamically tolerated, is indicated in patients with AHF, with kidney function monitoring. In the PARADIGM trial, which included over 8,000 patients with HfrEF, the sacubitril/valsartan group showed a significant reduction in cardiovascular death and rehospitalization. There was a slight decrease in eGFR during follow-up in the sacubitril/valsartan group compared with the enalapril group, but this difference did not reach statistical significance (36). In the PARAGON trial, patients with HFpEF treated with sacubitril/valsartan had a 50% reduction in the incidence of the kidney composite outcome, including kidney-related death, development of kidney failure, or a >50% decline in eGFR. Similar conclusions were drawn after recent analysis of the pooled PARAGON and PRADIGM trials examining these composite kidney outcomes (37, 38).

The CIBIS-II and MERIT-HF (16, 39) trials clearly demonstrated the advantage of beta-blockers in patients with HF and renal dysfunction. Although sympathetic overstimulation is an important step in CRS-1 development, beta blockers are often discontinued in many acutely congested patients. These drugs should be reintroduced as soon as the patient is decongested (3).

Sodium-glucose cotransporter 2 (SGLT2) inhibitors activate sirtuin-1, which reduces fibrosis and

inflammation in renal cells and reduces hypoxic injury in cardiomyocytes. These effects are protective for both the heart and the kidneys, especially in the long term (1,3,40). Data demonstrate that introducing SGLT-2 inhibitors in patients with AHF is safe and has led to greater weight loss/decongestion (40).

Persistently elevated intra-abdominal pressure after treatment has been associated with worsening of renal function regardless of central hemodynamic measures (41). Reduction in intra-abdominal pressure (IAP) following intensive medical therapy is associated with improved renal function. Prompt reduction in IAP has been observed with mechanical fluid removal, either by paracentesis (in the presence of ascites) or by ultrafiltration. This reduction is also associated with improvement of renal function (42).

Cardiogenic shock (CS) is especially significant in the development of CRS-1. Cardiogenic shock (CS) is associated with high mortality, and patients with cardiogenic shock (CS) require a specific therapeutic approach. Detailed therapeutic options in patients with CS are beyond the scope of this review. In brief, an observational study of patients with cardiogenic shock showed a mortality benefit of invasive hemodynamic monitoring with a pulmonary artery catheter (43,44), which has not been shown in patients with AHF without hypotension or shock (8). The main therapeutic strategy in patients with CS is to treat the underlying cause (such as revascularization in patients with AMI). If this is not possible, inotropic agents and mechanical circulatory support are used to improve cardiac output and renal perfusion. Inotropes are also used in patients with low cardiac output and cardiogenic shock, but they do not have any influence on decongestion or patient outcome (8). Currently, randomized controlled data on head-to-head comparisons of various short-term mechanical circulatory support devices regarding kidney function, CRS-1 development, and treatment are lacking (8). Some data indicate that reduced pulsatile circulation may activate the RAAS (8). A single-center study has shown a reduction in the AKI rate with Impella 2.5 support during high-risk percutaneous coronary intervention (8). What is important to know is that each form of mechanical circulatory support poses a particular risk regarding kidney function, including the positioning of the device, e.g., the position of the balloon in patients with an intraaortic balloon pump (it mustn't block the renal arteries) or hemolysis-related pigment-induced AKI in patients with Impella. All patients with CS are extremely ill and remain at an increased risk of multiorgan failure, including the progression of AKI (17).

PROGNOSTIC SIGNIFICANCE OF CRS-1 FOR PATIENTS HOSPITALIZED IN THE CICU

It is well known that reduced renal function (acute or chronic) represents one of the most significant predictors of mortality and complications in patients with cardiovascular diseases, particularly those with acute myocardial infarction (AMI) and/or acute heart failure (AHF) (4,11,12). The development of CRS-1 is also among the strongest predictors of adverse cardiovascular and nephrological events in both short- and long-term follow-up.

In patients with AHF, transient worsening of renal function (WRF) is often observed and should not be confused with true AKI, i.e., with the development of CRS-1. Transitory WRF observed in AHF patients with good decongestion and high diuresis is consistently associated with adverse outcomes but not with CRS-1 development, as already mentioned. This is because a transitory WRF can occur after diuretic and ACEi/ARB/ARNI administration, and the cardiovascular benefits of these medications and enhanced diuresis outweigh the risk of adverse events associated with transitory WRF (3). This has been confirmed in many previous trials. For example, in the SOLVD trial, the initial transient decline in eGFR after initiating enalapril in patients with acute decompensated HFrEF showed no adverse impact on patient prognosis (3). Post-hoc analysis of the ESCAPE trial showed that a transient acute decline in eGFR as a consequence of diuretic therapy and signs of successful decongestion were not associated with higher mortality or hospitalization rates (16,45). On the other hand, AKI development in patients with ongoing congestion has been associated with CRS-1 development and higher short- and long-term mortality and rehospitalization for heart failure (46). However, in patients with previous CKD and acute WRF in the settings of AMI or AHF, any (even transitory) WRF is associated with adverse short- and long-term outcomes (3).

The occurrence of AKI in patients with AHF and ongoing congestion is an indicator of CRS-1 development, which is an independent risk factor for both short- and long-term mortality and the occurrence of major adverse cardiovascular events (7,13,15,47,48). Also, CRS-1 was associated with longer hospital stay, increased various hospital complications (including infection/sepsis), new onset atrial fibrillation, as well as higher in-hospital cost (11,13).

Mortality and the risk of other adverse events increase with the severity of AKI and are the highest in patients in whom AKI progresses to end-stage renal disease (ESRD) (22,49). The negative prognostic effect of CRS-1 is complex. It might be the result of an associated acceleration of cardiovascular disorder (disease) due to kidney dysfunction through the activation of neurohumoral, cell-signaling, oxidative stress, or fibrosis pathways (21).

In a large retrospective study involving 20,000 patients from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, 17.8% of patients had AKI, and 65% had a one-year survival after hospitalization. AKI (defined as a discharge serum creatinine increase>0.3mg/dL) was independently associated with 1-year mortality (56).

In another study, CRS-1 developed in 38% of hospitalized patients with AHF. There was a stepwise association with a combined primary outcome that included death, rehospitalization, and dialysis with progressive AKI stages (57). Similar results were also found in other studies involving patients with acute heart failure (AHF), as well as in a meta-analysis including eight studies (58,59).

Patients with acute myocardial infarction are a particular category when it comes to treatment in the CICU. AKI in patients with AMI is a well-known predictor of poor short-term and long-term prognosis. According to literature data, in patients with AMI and AKI, the long-term mortality rate is as high as 57.5%, which is significantly higher than that of AMI patients with no AKI (50). Some studies have shown that the prognosis in AMI patients with AKI depends on the time when AKI occurs. Patients who develop AKI in the early phase (in the first three days) have a higher risk of mortality and the occurrence of other complications than patients in whom AKI develops later during hospitalization (four to seven days after AMI). Later AKI development might be caused by contrast-induced nephropathy (in patients treated with percutaneous coronary intervention – PCI) and is not a part of CRS-1 development (51,52). In a study by Lazaros et al., patients with early AKI were found to have higher CRP levels, suggesting that an inflammatory response in the cardiorenal axis may be a significant cause of CRS-1 development in these patients (53). On the other hand, data show that iodine contrast used for PCI in AMI patients is not as toxic to the kidney as initially believed (54). These findings suggest that in AMI patients with diagnosed AKI, clinicians should first think about inadequate renal perfusion caused by low cardiac output until proven otherwise (2,21,55).

In addition, the development of CRS-1 may also have a lasting effect on renal function – AKI as part of CRS-1 may be a transient dysfunction with recovery of renal function, partial recovery of renal function with the development of chronic kidney disease (CKD), or further deterioration to end-stage renal disease (ESRD) requiring renal replacement therapy (RRT). Results of a retrospective study from Sweden showed that AHF leads, in the majority of patients, to an accelerated decline in eGFR values, particularly in those with an initial eGFR >60 ml/min/m^2. The same authors also demonstrated in a subsequent analysis that the development of AHF is the most important risk factor for progression of renal dysfunction to ESRD; the incidence of ESRD among patients with heart failure was 10% at five years and 15% at ten years (60, 61). Permanent impairment of renal function that may persist after AKI places the patient at a high risk of cardiovascular and overall mortality in both short-term and long-term follow-up (60, 61).

FUTURE DIRECTIONS

There are many studies investigating novel agents for preventing and treating CRS-1. Some of the most promising agents are monoclonal antibodies that target inflammatory cytokines and augment the innate and humoral immune system to combat inflammation and improve endothelial function. Other areas of investigation include treating diuretic resistance and device-based therapy, which help increase kidney perfusion by either propelling blood from the renal vein or decompressing renal intracapsular pressure (17).

CONCLUSION

The development of CRS-1 in patients hospitalized in the CICU is registered in more than 30% of patients. The mechanisms for CRS-1 development are complex. Development of CRS-1 can complicate treatment strategy and significantly and negatively affect short- and long-term outcomes in patients. Understanding the mechanisms that lead to the development of CRS-1 is necessary to prevent its occurrence and break the vicious circle it represents. Earlier identification of patients at risk of developing CRS-1 and earlier initiation of therapies shown to provide prognostic benefit are important to improve patients' prognosis.

Acknowledgement: N/A

Funding information: N/A

Conflicts of interest: No conflicts of interest to report

Author Contributions: Each author contributed significantly to the submitted work. All authors have read and approved the manuscript. The paper is not under consideration elsewhere. None of the paper's contents has been previously published. All authors have read and agreed to the published version of the manuscript.

Ethical approval: N/A

Informed consent: N/A

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KARDIORENALNI SINDROM TIP 1 U KARDIOLOŠKOJ INTENZIVNOJ NEZI

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Sažetak

Bubrezi i srce su usko povezani i disfunkcija ili insuficijencija jednog organa dovodi do disfunkcije ili insuficijencije drugog organa. Ovo stanje je poznato kao kardiorenalni sindrom. Postoji pet vrsta kardiorenalnog sindroma (KRS) kategorisanih prema primarnom poremećenom organu (bubreg ili srce) i da li je otkazivanje bilo akutno ili hronično. KRS tip 1 (KRS-1) je definisan kao akutna povreda bubrega (ABI) uzrokovana akutnom srčanom insuficijencijom (ASI). Razvoj KRS-1 je registrovan kod više od 30% pacijenata hospitalizovanih na odeljenju intenzivne nege kardiologije (KIN). Cilj ovog narativnog pregleda je da predstavi patofiziološke mehanizme, terapijske implikacije i prognostički značaj CRS-1 kod pacijenata hospitalizovanih na odeljenju intenzivne kardiološke nege. Mehanizmi za razvoj KRS-1 su složeni i uključuju udarni volumen i vensku kongestiju, sa naknadnom neurohumoralnom aktivacijom i pojavom inflamacije. Pošto je obeležje KRS-1 rezistencija na diuretike, razvoj KRS-1 komplikuje strategiju lečenja kod akutno dekompenzovanih pacijenata i snažno i negativno utiče na kratkoročnu i dugoročnu prognozu bolesnika. Za klinicare je važno da što ranije prepoznaju bolesnike koji su u riziku za razvoj KRS-1 i da modifikuju terapijski pristup u cilju postizanja što efikasnije dekongestije, prevencije progresije KRS-1 i poboljšanja kratkoročne i dugoročne prognoze.

Ključne reči: kardiorenalni sindrom, akutna srčana insuficijencija, akutna povreda bubrega, terapijski pristup, prognoza

Primljen: 01. 02. 2026. I **Revidiran**: 10. 03. 2026. I **Prihvać**en: 12. 03. 2026. I **Online First:** 18. 03. 2026.

Medicinska istraživanja 2026