hearts

MDPI

Review

Strategies for the Management of Cardiorenal Syndrome in the Acute Hospital Setting

Deepak Chandramohan [1], Prathap Kumar Simhadri [2], Nihar Jena [3] and Sujith Kumar Palleti [4,*]

[1] Department of Internal Medicine/Nephrology, University of Alabama at Birmingham, Birmingham, AL 35233, USA; deepakchandramohan@uabmc.edu
[2] Department of Nephrology, Advent Health/FSU College of Medicine, Daytona Beach, FL 32117, USA; prathap.simhadri@gmail.com
[3] Department of Internal Medicine/Cardiovascular Medicine, Trinity Health Oakland/Wayne State University, Pontiac, MI 48341, USA; niharjmd@gmail.com
[4] Department of Internal Medicine/Nephrology, LSU Health Shreveport, Shreveport, LA 71103, USA
* Correspondence: sujithpes@gmail.com

Abstract: Cardiorenal syndrome (CRS) is a life-threatening disorder that involves a complex interplay between the two organs. Managing this multifaceted syndrome is challenging in the hospital and requires a multidisciplinary approach to tackle the many manifestations and complications. There is no universally accepted algorithm to treat patients, and therapeutic options vary from one patient to another. The mainstays of therapy involve the stabilization of hemodynamics, decongestion using diuretics or renal replacement therapy, improvement of cardiac output with inotropes, and goal-directed medical treatment with renin–angiotensin–aldosterone system inhibitors, beta-blockers, and other medications. Mechanical circulatory support is another viable option in the armamentarium of agents that improve symptoms in select patients.

Keywords: cardiorenal syndrome; heart disease; congestive heart failure; kidney disease

Citation: Chandramohan, D.; Simhadri, P.K.; Jena, N.; Palleti, S.K. Strategies for the Management of Cardiorenal Syndrome in the Acute Hospital Setting. *Hearts* **2024**, *5*, 329–348. https://doi.org/10.3390/hearts5030024

Academic Editor: Matthias Thielmann

Received: 25 June 2024
Revised: 29 July 2024
Accepted: 30 July 2024
Published: 1 August 2024

1. Introduction

The number of people suffering from heart failure and kidney disease has increased over the past decade. The mortality and morbidity of the diseases, along with the high economic burden, have made effective treatment imperative [1–3]. Cardiorenal syndrome (CRS) represents a convoluted and intricate dysfunction of the heart and the kidneys, where one organ's impairment triggers the deterioration of the other. A vicious cycle starts, culminating in a multitude of downstream effects that are deleterious to the body [4]. CRS can manifest as an acute or chronic dysfunction of either the heart or kidneys, leading to the failure of the other. Since these two organs have complex and vital roles, the effective management of patients is essential to avoiding adverse outcomes [5]. It is known that the acute kidney injury that occurs as a result of congestive heart failure (CHF) carries an unfavorable prognosis [6]. Moreover, patients with pre-existing CKD experience a rapid decline in glomerular filtration rate (GFR) in the presence of CHF [7]. The widely accepted classification of CRS has five types based on the acuity of the disease process and whether the inciting event is a primary or secondary organ failure [8]. Other classifications consider the hemodynamic, neurohumoral, vascular disturbances along with other pathologies, such as anemia and mineral metabolism [9]. The complex pathophysiology makes the management of CRS challenging, especially in the hospital setting. This comprehensive review summarizes the therapeutic management of patients with acute type 1 CRS in the hospital. Type 1 CRS is defined as the onset of acute kidney injury (AKI) due to CHF in those who have no pre-existing kidney disease or those with non-dialysis chronic kidney disease (CKD). This review explores the current evidence in disease management, while drawing attention to their deficiencies, and will guide providers to make better clinical decisions.

2. Discussion

2.1. Monitoring Hemodynamics

The first step in managing CRS involves a careful physical examination, which can provide clues to the perfusion status. The presence of cold extremities, the classical finding of poor perfusion, is seen in acute CRS. In addition, recognizing other hemodynamic profiles is important as they can help guide therapy. The presence of "warm and dry" extremities indicates preserved perfusion but may have reduced renal blood flow. Conversely, "cold and wet" patients will likely have systemic congestion and reduced perfusion associated with decreased renal perfusion. "Warm and wet" patients denote the presence of adequate systemic perfusion but have renal congestion due to volume overload. Lastly, "cold and dry" patients face both poor systemic circulation due to low cardiac output and decreased renal perfusion [10].

This should be followed by methods to precisely assess hemodynamic parameters by continuous monitoring. Of many techniques, two commonly employed to investigate the patient's hemodynamic status are echocardiography and Swan–Ganz catheterization (SGC). Early and precise assessment helps identify the degree of cardiac and renal insufficiency, which guides further therapeutic interventions [11]. Prioritizing prevention is necessary, given the absence of a single definitive treatment for CRS. Symptoms such as early satiety or, in worse cases, anorexia may indicate the presence of splanchnic congestion and increased intra-abdominal pressure. Therefore, careful history taking and swift recognition of these symptoms will prevent the deterioration of CRS [12].

Pulmonary capillary wedge pressure (PCWP) and left atrial pressure (LAP) measurements can be obtained non-invasively using echocardiography. Filling pressures are considered high when PCWP exceeds 12 mmhg. The Doppler velocity (E/e') can be used to gather more information as it has been shown to correlate with PCWP and LAP. A ratio of E/e' under eight indicates normal filling pressures, whereas an E/e' greater than 15 indicates high filling pressures [13].

Type 1 CRS seen in acute decompensated heart failure results in renal congestion and reduced renal perfusion. Hemodynamically guided interventions using mean arterial pressure (MAP) and central venous pressure (CVP) are also critical indicators. Increased CVP more often causes renal dysfunction than reduced cardiac output (CO) in CRS. The renal perfusion pressure is determined by both the MAP and the CVP. The transrenal perfusion pressure gradient, calculated by subtracting the central venous pressure (CVP) from the mean arterial pressure (MAP), determines the renal perfusion pressure necessary for optimal organ function. However, invasive CVP monitoring using SGC is unreliable as it also depends on the venous tone, which is frequently altered based on the amount of neurohormonal activation [1]. The ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) study did not show any decrease in AKI when hemodynamic monitoring using a pulmonary artery catheter was employed [14].

Renal venous pressure can be assessed using renal Doppler ultrasonography. With increasing right atrial pressures (RAP), the intrarenal waveform becomes more pulsatile with flow reversal during systole due to pressure transmission from the RAP to the renal veins. This congested venous pattern has been associated with poorer prognosis [15]. The renal function could also worsen with concomitant increased intra-abdominal pressure (IAP), which has been demonstrated in patients with low ejection fraction (EF) and preexisting CKD [16]. Commonly seen in hepatorenal syndrome and surgical patients, elevated IAP $\geq$ 8 mm Hg in congestive heart failure (CHF) requires further interventions, such as paracentesis and monitoring [17,18].

Similarly, IVC dilation is a marker for individuals likely to experience a decline in kidney function. A diameter above 2.1 cm characterizes a dilated inferior vena cava (IVC). This can be easily assessed at the bedside and has been linked to adverse renal events [1].

The occurrence of acute kidney injury (AKI) in type-1 CRS is significantly high [19,20]. Pre-existing CKD also increases mortality and hospitalizations in CHF [14]. Hypotension management generally includes maintaining adequate perfusion pressure with inotropes

and vasopressors. Balancing the fluid status is a sine qua non in preventing volume overload or depletion, which is the main contributor to the development of renal dysfunction [21]. Using mechanical circulatory support devices is another therapeutic option [2]. The kidneys regulate the GFR by afferent and efferent arteriole constriction as a response to alterations in arterial pressures. It is, therefore, also essential to avoid potential nephrotoxins that cause vasoconstriction to the renal vasculature to avoid AKI [22,23]. Ultimately, the main focus of this critical step is to reach hemodynamic stability for effective cardiac and renal function improvement without further organ injury.

2.2. Diuretics

Diuretics remain the cornerstone in treating patients with CRS. Exacerbations of heart failure may affect gastrointestinal absorption, thus hampering adequate diuresis and require intravenous administration of these medications [23]. Loop diuretics, such as furosemide, have been commonly used for their greater efficiency [24]. The administration and dosage of diuretics should be regulated depending on the volume status and fluid removal goal. For example, the initial dose depends on the severity of fluid overload and renal function, while titration is based on the patient's response and symptom burden. Meanwhile, electrolytes should be monitored regularly to avert adverse effects [25].

Patients with renal failure, especially those with glomerular filtration rates (GFR) of <15 mL/min/1.73 m^2, usually require a larger dose of loop or thiazide diuretics due to the presence of uremic toxins. For example, these patients frequently require spot furosemide doses close to 160–200 mg [26]. Continuous diuretic infusions are generally well tolerated and may decrease the risk of ototoxicity compared to bolus infusions. Dosages commonly used are 10 to 20 mg/h, and dosages as high as 200 mg/h have been described. Other loop diuretics, such as bumetanide, can also be used [27]. The DOSE (Diuretic Optimization Strategies Evaluation) trial compared bolus vs. continuous infusion of loop diuretics and found no differences in symptoms or renal function between the two strategies. Continuous infusion of loop diuretics was, however, attributed to an increased risk of hyponatremia, vasopressor requirements, and readmissions [28].

Chronic diuretic therapy sometimes renders patients resistant to these treatments, thereby increasing the risk of rehospitalization and mortality. Therefore, diuretic resistance demands an alternative strategy with either a combination of diuretic therapy or ultrafiltration to manage fluid overload effectively [29]. When natriuresis is stalled, two or more classes of diuretics can be combined to obtain the desired effect by blocking different segments of the nephron, depending on the severity of CHF. Loop diuretics and thiazides are frequently combined to address this problem [26]. Thiazide diuretics have the added benefit of having a longer half-life [27]. Moreover, examination of the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) showed that the risk of heart failure reduced with chlorthalidone when compared to amlodipine at the end of 1 year [30]. Patients with decompensated CHF have poor outcomes if they remain congested upon discharge; hence, treatment to ensure euvolemia is of importance [31].

Diuretic use, particularly high doses of loop diuretics and combination diuretics, has been attributed to worsening renal function. This could be due to increased renin–angiotensin–aldosterone system (RAAS) and sympathetic activity [32]. A decrease in the glomerular filtration rate (GFR) could result from renal afferent artery vasoconstriction in response to sodium loss. Decongestion due to the effect of diuretics could also directly lead to increased serum creatinine by hemoconcentration. Analysis of two large trials, RELAX-AHF-2 (Relaxin in Acute Heart Failure 2) and PROTECT (Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function), however, showed that worsening renal function in the first 96 h was not associated with poor outcomes [33]. The ROSE-AHF (Renal Optimization Strategies Evaluation–Acute Heart Failure) trial utilized high doses of diuretics to rapidly decongest patients with CHF and found no increases in urinary neutrophil gelatinase-associated lipocalin (NGAL), *N*-acetyl-β-D-glucosaminidase (NAG), and kidney

injury molecule 1 (KIM-1), demonstrating that aggressive diuresis is not linked to renal tubular injury [34]. While the risk of AKI exists, diuretics should be continued in CRS till euvolemia is achieved. Care should be taken to titrate the dose of diuretics based on clinical response and delineate patients who develop worsening renal function due to concomitant administration of RAAS inhibitors [33].

Similarly, loop diuretics and carbonic hydrase inhibitors can be combined for their augmented effect [26]. The ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial examined the association of acetazolamide in addition to loop diuretics in CHF. Volume optimization was obtained sooner in these patients, and there was also an associated reduction in hospitalized days. However, there was no associated decrease in hospital readmissions. But, it was noted that the rehospitalization rate was lower compared to that of the DOSE and the CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) trials [35].

The TACTICS-HF (Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure), EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan), and SECRET of CHF (Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure) trials assessed the use of tolvaptan and showed no improvements in mortality [36,37]. Thus, the commonly utilized diuretics in the in-patient setting have shown good efficacy, and their early administration mitigates volume overload. Early recognition of diuretic resistance is also needed to prevent further worsening of CRS [26].

A decrease in dietary sodium also plays an essential role in mitigating fluid overload. Restricting sodium to 2.3 g/day can also impact improved blood pressure and prevent worsening edema [38]. A positive in-hospital sodium balance has been shown to increase the risk of death [3]. The studies are listed in Table 1.

Table 1. Clinical studies on the efficacy of diuretics in the management of cardiorenal syndrome.

Study, Year	Study Design; Patients and Controls	Total, *n*	Inclusion and Exclusion Criteria	Outcomes Measured	Main Findings
DOSE [28], 2011	Design: randomized control trial Patients and controls: 1:1:1:1 randomization into low-dose vs. high-dose furosemide as a bolus or continuous infusions	308	Inclusion criteria: history of CHF and prior use of an oral loop diuretic Exclusion criteria: systolic BP < 90 mmhg, serum creatinine >3 mg/dL	Primary: improvement in symptoms, creatinine change in 72 h Secondary: changes in body weight, treatment failure, death, readmissions	No significant changes were noted to the patient's symptoms or renal function between bolus vs. continuous infusions or low-dose vs. high-dose groups. High-dose strategy was associated with more diuresis but also had transient worsening of creatinine.
ALLHAT [30], 2002	Design: randomized control trial Patients and controls: randomized to receive chlorthalidone, amlodipine, or lisinopril	42,418	Inclusion criteria: ≥55 years Exclusion criteria: EF < 35%, serum creatinine > 2 mg/dL	Primary: fatal acute coronary syndrome Secondary: all-cause mortality, stroke, heart failure, and end-stage renal disease	Treatment with chlorthalidone prevented cardiovascular events as effective as amlodipine and lisinopril. Chlorthalidone was superior to amlodipine or lisinopril in preventing CHF.
ADVOR [35], 2022	Design: multicenter randomized control trial Patients and controls: 1:1 randomization to receive intravenous acetazolamide or placebo	519	Inclusion criteria: acute CHF and elevated natriuretic peptide levels Exclusion criteria: use of other proximal tubular diuretics, SGLT2i	Primary: absence of fluid overload Secondary: all-cause mortality, readmissions in 3 months	The addition of acetazolamide increased the chances of decongestion compared to placebo.
TACTICS-HF [36], 2017	Design: multicenter randomized control trial Patients and controls: 1:1 randomization to receive tolvaptan or placebo	257	Inclusion criteria: acute decompensated CHF, BNP > 400 pg/mL or NT-proBNP > 2000 pg/mL Exclusion criteria: systolic BP < 90 mmhg, serum creatinine >3.5 mg/dL	Primary: decreased mortality, improvement of dyspnea Secondary: change in body weight, worsening renal function, total length of hospital stays	Adding tolvaptan to standard diuretic therapy did not lead to significantly improved outcomes.

Abbreviations: BNP, B-type natriuretic peptide; BP, blood pressure; CHF, congestive heart failure; EF, ejection fraction; NT-proBNP, N-terminal pro b-type natriuretic peptide; SGLT2i, sodium–glucose cotransporter-2 inhibitor.

2.3. Management of Diuretic Resistance

The mortality in CRS, especially in Type 1 CRS, is high. Therefore, rapid improvements in hemodynamics and decongestion are required [39]. Loop diuretic agents are organic

anions with a strong affinity for albumin, with a binding capacity above 90%. Therefore, their distribution quantities become large in cases of severe hypoalbuminemia. However, there is limited evidence to support the use of albumin infusions with loop diuretics to enhance natriuresis. The efficacy of loop diuretics seems to be preserved in serum albumin levels over 2 g/dL [23]. As mentioned previously, diuretics are often prescribed to deal with fluid retention in patients with CRS. But in some cases where patients develop a strong resistance to conventional diuretic therapy, alternative therapy becomes necessary to effectively control fluid overload and avoid further progression of organ damage [25,40].

Ultrafiltration is recommended in refractory volume overload and in patients with severe renal dysfunction or in instances where there is insufficient urine output due to AKI [41]. Among the methods for ultrafiltration, continuous renal replacement therapy (CRRT) is frequently preferred over intermittent hemodialysis [42]. However, while there is an adequate response to diuretics, ultrafiltration is not beneficial. The CARRESS-HF showed that ultrafiltration was inferior to diuretic therapy and was, in fact, associated with adverse effects. In the randomized trial, patients in the ultrafiltration arm had a larger increase in serum creatinine at 96 h, with no significant change in the patient's weight when compared to the pharmacologic therapy arm. One criticism of the study is that they used a set ultrafiltration rate of 200 mL/h, but the diuretic arm used a stepping-up strategy for diuretic dosing [43]. The AVOID-HF (Aquapheresis versus Intravenous Diuretics and Hospitalization for Heart Failure) study used a protocol that allowed for adjustable ultrafiltration rates. There were no differences in mortality compared to the diuretic arm, and more adverse effects were noted with ultrafiltration. There were also no differences in the renal function [44].

Other studies like the UNLOAD (Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure) trial also showed no improvements in renal function, although there was an increased removal of fluid with ultrafiltration [45]. Renal replacement therapy (RRT) is also linked to myocardial stunning in both chronic and acute situations. Hence, caution must be taken while utilizing renal replacement therapies in patients with cardiac dysfunction. The reduction in myocardial perfusion depends on the dose of RRT administered and causes microcirculatory injury and the resultant stunning could be seen in CRRT. This phenomenon of myocardial stunning during CRRT was shown in a small retrospective study, but further studies are needed to establish this [46].

The continuous monitoring of patient response and adjustment of therapy based on clinical signs are crucial in managing diuretic resistance [29]. Currently, there is insufficient evidence to suggest that ultrafiltration should be employed earlier in the management of CRS [15]. The studies discussed are listed in Table 2.

Table 2. Clinical studies on the management of diuretic resistance in cardiorenal syndrome.

Study, Year	Study Design; Patients and Controls	Total, *n*	Inclusion and Exclusion Criteria	Outcomes Measured	Main Findings
CARRESS-HF [43], 2012	Design: randomized control trial Patients and controls: randomized to ultrafiltration or stepped-up pharmacological diuretic therapy	188	Inclusion criteria: acute decompensated CHF, an increase in serum creatinine of at least 0.3 mg/dL within 12 weeks before admission Exclusion criteria: serum creatinine level > 3.5 mg/dL, intravenous vasodilators or inotropes	Primary: change in serum creatinine and body weight Secondary: rapidity of decongestion	Ultrafiltration was associated with a significant worsening of renal function compared to pharmacologic therapy but showed no significant difference in weight loss. Ultrafiltration also led to higher rates of serious adverse events.

Table 2. *Cont.*

Study, Year	Study Design; Patients and Controls	Total, *n*	Inclusion and Exclusion Criteria	Outcomes Measured	Main Findings
UNLOAD [45], 2007	Design: multicenter, randomized control trial Patients and controls: 1:1 randomized to early ultrafiltration or. diuretics	200	Inclusion criteria: acute decompensated CHF, EF $\leq$ 40% Exclusion criteria: serum creatinine > 3.0 mg/dL, systolic BP < 90 mm Hg	Primary: change in body weight and dyspnea Secondary: net volume removal at 48 h, readmissions, electrolytes	Ultrafiltration resulted in greater weight and net volume removal at 48 h than diuretics. There were fewer readmissions within 90 days. The incidence of adverse events was similar between the groups, with no significant difference in serum creatinine levels
AVOID-HF [44], 2016	Design: randomized, unblinded control trial Patients and controls: 1:1 randomized to adjustable ultrafiltration or adjustable loop diuretics	224	Inclusion criteria: acute decompensated CHF Exclusion criteria: contraindications to ultrafiltration	Primary: recurrence of heart failure within 90 days of discharge Secondary: clinical improvement at 30 and 90 days, adverse effects	There were no significant differences in the recurrence of heart failure between the groups. More adverse events were noted in the ultrafiltration group

Abbreviations: BP, blood pressure; CHF, congestive heart failure; EF, ejection fraction.

2.4. Inotropes

Inotropes play an important role in managing CRS; by increasing myocardial contractility, they improve hemodynamic stability [47]. Inotropes are indicated in low cardiac output states when the other therapeutic measures are insufficient. An improvement in renal perfusion could, in turn, result in increased diuresis [26]. Dobutamine and milrinone are commonly used to augment CO and improve renal perfusion [6]. Studies have not established that inotropes have a direct effect on GFR. The ROSE AHF failed to show any renal function improvement with low-dose dopamine or low-dose nesiritide [3]. This lack of renal function improvement was also reproduced in other studies [6]. A post hoc analysis of the ALARM-HF (AHF global survey of standard treatment) assessed the effects of intravenous catecholamine use, such as dopamine, dopamine, norepinephrine, and epinephrine. The study found that the use of dopamine and dobutamine was associated with an elevated risk of mortality. Although this risk was less compared to catecholamines, the risk of death due to tachyarrhythmias remained. The same study also reported that using nitrates as vasodilators, when added to diuretics, had lower in-hospital mortality [48]. Patients with chronic CHF treated with beta-blockers (β-blockers) could have a blunted effect with dobutamine and, in those cases, alternate inotropes should be used [49].

Milrinone is a phosphodiesterase III inhibitor that causes vasodilation and improves trans-renal perfusion pressure but, much like dopamine, it has not been shown to have significant changes in GFR [26]. The OPTIME-CHF (outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure) study did not show any significant improvements in mortality or readmissions, and only a small improvement in renal function was demonstrated [50].

Levosimendan, a calcium-sensitizing inotrope, improves cardiac function and promotes pre-glomerular vasodilation, thereby optimizing renal blood flow. It was shown to have a renoprotective effect among patients with acute decompensated CHF with an EF < 40% and GFR of between 30 and 60 mL/min per 1.73 m^2 [51]. This protective effect was also seen among patients with chronic CHF and CKD stages 2–3 when compared to dobutamine [52]. Also, in a large meta-analysis, levosimendan decreased mortality compared to other inotropes. It is currently not approved for use by the United States (U.S.) Food and Drug Administration [6,53]. Although inotropes stabilize hemodynamics, prolonged use may have negative effects, such as arrhythmias and increased mortality. Hence, they should be administered under close observation [54].

Vasodilators may be appropriate in patients with elevated blood pressure or anginal symptoms, but their role is generally limited in CRS. Their use may decrease dyspnea symptoms, but they do not affect mortality or hospitalizations. Intravenous nitroglycerin is preferred when choosing a vasodilator, but prolonged use could result in tachyphylaxis. The use of intravenous nitroprusside is not recommended in patients with CKD or hepatic dysfunction due to the possibility of cyanide toxicity [55]. The studies on inotropes discussed are listed in Table 3.

Table 3. Clinical studies on the efficacy of inotropes in the management of cardiorenal syndrome.

Study, Year	Study Design; Patients and Controls	Total, *n*	Inclusion and Exclusion Criteria	Outcomes Measured	Main Findings
ROSE-AHF [3], 2016	Design: multicenter randomized control trial Patients and controls: randomized to low-dose dopamine vs. low-dose nesiritide vs. placebo	360	Inclusion criteria: acute CHF Exclusion criteria: systolic BP < 90 mmhg, serum creatinine >3 mg/dL, use of intravenous vasodilators or inotropes	Primary: urine output over 72 h, changes to renal renal function determined by cystatin-C Secondary: change in body weight, changes in NT-proBNP levels	Significant improvements in CHF and renal function were not seen in both dopamine and nesiritide groups. Adverse effects were similar in both groups
Post hoc analysis of ALARM-HF study, 2011 [48]	Design: multicenter retrospective study Patients and controls: propensity-based groups were created to compare groups receiving inotropes along with diuretics	4953	Inclusion criteria: acute decompensated CHF	Primary: all-cause mortality, length of hospital stays Secondary:	Dopamine, dobutamine, norepinephrine, and epinephrine were associated with increased in-hospital mortality.
OPTIME-CHF [50], 2003	Design: randomized control trial Patients and controls: randomized to receive milrinone or placebo	949	Inclusion criteria: acute decompensated CHF Exclusion criteria: systolic BP < 80 mm Hg, serum creatinine >3.0 mg/d, arrhythmias	Primary: length of hospitalized days Secondary: mortality at 60 days, ability to reach maximum dosing of ACEi	Patients treated with milrinone had longer hospitalizations. Patients with ischemic heart failure had worse outcomes, but patients with non-ischemic heart failure had good outcomes
LIDO [53], 2002	Design: randomized control trial Patients and controls: Randomized to receive levosimendan or dobutamine	203	Inclusion criteria: EF < 35%, cardiac index < 2.5 L/min/m^2 Exclusion criteria: severe renal or hepatic failure, restrictive or hypertrophic cardiomyopathy	Primary: hemodynamic improvement in 24 h Secondary: improvement of heart failure symptoms, time to development of worsening heart failure or death	Treatment with levosimendan improved hemodynamics when compared to dobutamine. The levosimendan group had less mortality at 180 days.

Abbreviations: ACEi, angiotensin-converting enzyme Inhibitor; BP, blood pressure; CHF, congestive heart failure; NT-proBNP, N-terminal pro b-type natriuretic peptide.

2.5. Pharmacological Therapy in CRS

The activation of the RAAS has unfavorable effects on the heart and the kidneys. Therefore, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) are integral to goal-directed medical therapy (GDMT) in managing CRS. They work by the inhibitory effects they have on the levels of angiotensin II, which prevents glomerular hyperfiltration and maintains renal function. They have been shown to decrease mortality and hospitalizations and are particularly beneficial in patients with concurrent hypertension and heart failure [24,56]. An initial reduction in GFR after RAAS inhibitor initiation is due to the hemodynamic effects of the medications and should not be considered as AKI. In a post hoc analysis of the SOLVD (studies of left ventricular dysfunction) trial, it was demonstrated that up to a 35% reduction in GFR was still associated with decreased hospitalization risk in CHF [57]. Adding RAAS inhibitors to conventional therapy has

been proven to decrease the occurrence of decompensated CHF hospitalizations among patients with reduced ejection fraction [12]. The combined use of ACEi and ARBs in CRS should be avoided due to the potential for worsening renal function and exacerbating hyperkalemia [26]. In the management of acute CRS, there is no evidence that stopping ACEi and ARB is beneficial. Their discontinuation is recommended only in cases of hyperkalemia or AKI, and they must be resumed once the condition resolves [31].

The novel agent sacubitril, which is a neprilysin inhibitor (ARNi) combined with the ARB, valsartan, was evaluated in the PARADIGM-HF (Prospective Comparison of ARNi with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial. There was a decrease in all-cause mortality and hospitalization compared to enalapril. However, it should be noted that the study excluded patients with an estimated GFR (eGFR) < 30 mL/min/1.73 m^2 or a decrease in GFR > 25% after initiating the drug [58]. There was a lower risk of hyperkalemia with sacubitril/valsartan when compared to enalapril [59]. Similar results were also found in the PIONEER-HF (Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) study. The study showed that among hospitalized patients with acute decompensated CHF and EF $\leq$ 40%, treatment with sacubitril–valsartan showed a higher reduction in N-terminal pro–B-type natriuretic peptides (NT-proBNP) when compared to enalapril. Moreover, the rates of worsening renal function and hyperkalemia were similar to enalapril [60].

Because β-blockers reduce the heart rate and the myocardial oxygen demand, they lead to global enhancement of cardiac function with a low risk of arrhythmias. Therefore, they are among the first-line drugs in the long-term management of heart failure [29,61]. The combined use of RAAS inhibitors along with β-blockers does improve outcomes among patients with CRS but should be managed with caution because there is much potential for causing adverse effects, like hypotension and hyperkalemia [62,63]. The pathophysiology of CRS and the common therapies used are shown in Figure 1.

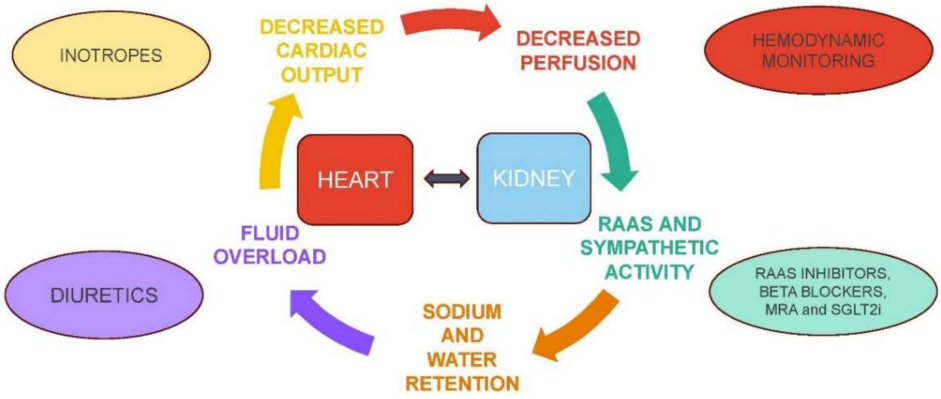

Figure 1. Pathophysiological mechanisms in cardiorenal syndrome and targets for medical therapies. Abbreviations: MRA, mineralocorticoid receptor antagonist; RAAS, renin–angiotensin–aldosterone system; SGLT2i, sodium–glucose-linked transporter type 2 inhibitors.

Similarly, higher levels of aldosterone are commonly observed in aging, diabetes mellitus, and hypertension, can potentially raise the risk of cardiovascular disease-related renal disease. This is due to a sequence of events that involve inflammation- and oxidative stress-induced dysfunction of the endothelium [64]. The existing evidence supporting the use of mineralocorticoid receptor antagonist (MRA) showing a mortality benefit and decreased hospitalization is from the RALES (Randomized Aldactone Evaluation Study) trial. Mineralocorticoid receptor antagonists (MRA) such as spironolactone reduced the risk of all-cause mortality by 30% in patients with severe CHF compared to placebo, according to the RALES trial [65]. However, this was not seen in other trials. There were no significant improvements in symptom relief or N-Terminal Pro-B-Type Natriuretic Peptide

(NT-proBNP) with high-dose spironolactone, as evidenced by the ATHENA-HF (Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure) study [66]. While RALEs evaluated spironolactone, the EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) and the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) studies evaluated eplerenone, a more selective MRA [67,68]. The difference in these trials was that the cohort in EPHESUS had moderate to severe CHF, while EMPHASIS-HF included a cohort with NYHA class II symptoms [68].

However, RALES and the EMPHASIS-HF excluded patients with severe CKD and there are limited data on their outcomes while on Mineralocorticoid Receptor Antagonists (MRA) [69]. Care should be taken to monitor for hyperkalemia when prescribing MRA and RAAS inhibitors together [31]. It was again noted in the clinical trials, that using combination therapy with RAAS inhibitors, β-blockers, and MRA revealed decreased morbidity and mortality among the patients [70,71]. The combined use of these medications in advanced CKD is lacking in data [72].

Sodium–glucose-linked transporter type 2 inhibitors (SGLT2i) are promising adjuncts to loop diuretics because they reduce proximal tubular sodium reabsorption and synergize with loop diuretics to enhance natriuresis eventually [73]. SGLT2i has also been shown to decrease the cumulative dose of loop diuretics in some studies of patients with acute CHF and diabetes mellitus [74]. Although a post hoc assessment of the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in *Heart Failure*) did not show this phenomenon, the study did not show any escalating requirement of baseline diuretics [75]. Empagliflozin was shown to improve overall functional status and decrease the risk of cardiovascular mortality and subsequent hospitalizations [76]. In addition to these, they also exert an anti-hypertensive effect [74]. The EMPEROR (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction) trial showed that there was a decrease in mortality and rehospitalizations. The added benefit of a decline in the progression of CKD is beneficial in patients with pre-existing renal disease [7]. Cardiovascular benefits were also seen with the use of canagliflozin in the CANVAS (Canagliflozin Cardiovascular Assessment Study) and the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trials [77,78]. SGLT2i also prevents the worsening of heart failure and thus plays an important role in disease prevention [79]. Therefore, there is a clear benefit to adding SGLT2i in CHF.

Very few studies have evaluated SGLT2i in the acute setting. The EMPULSE trial (Empagliflozin in Patients Hospitalized with Acute Heart Failure Who Have Been Stabilized) demonstrated improvements in symptoms and quality of life that were seen as early as 15 days from when SGLT2i was started in patients with acute decompensated CHF [80]. The ongoing EMPA-AHF (Early treatment with a sodium–glucose co-transporter 2 inhibitor in high-risk patients with acute heart failure) has completed enrollment and will provide further information about the safety and efficacy of Empagliflozin started in acute CHF [81].

SGLT2i are generally well tolerated, but caution should be taken when prescribing them in patients with frequent urinary tract infections or who are at risk for fungal genital infections [82]. A large cross-trial analysis that analyzed the effects of ARNI, β-blockers, MRA, and SGLT2i demonstrated decreased mortality and heart failure hospitalizations thus supporting the use of these four GDMT agents. Using the cohort from the trials, EMPHASIS-HF, PARADIGM-HF, and DAPA-HF, it was estimated that a 55-year-old would be free of cardiovascular-related death or hospitalizations for about 8.3 years [83].

The use of hydralazine and isosorbide dinitrate was assessed in the A-HeFT (African American Heart Failure Trial), and it showed survival benefits in blacks, but this benefit may not be present in other ethnicities. Hydralazine and isosorbide dinitrate are especially useful for patients who cannot tolerate ARNI, ACEi, or ARB [84]. Medications that can be considered in pregnant women include furosemide, β-blockers, hydralazine, and nitrates.

However, shared decision-making is recommended before instituting them [55]. The studies discussed are listed in Table 4.

Table 4. Clinical studies on the efficacy of pharmacological therapy in the management of cardiorenal syndrome.

Study, Year	Study Design; Patients and Controls	Total, *n*	Inclusion and Exclusion Criteria	Outcomes Measured	Main Findings
Analysis of data from SOLVD [57], 2019	Design: multicenter randomized control trial Patients and controls: randomized to receive enalapril or placebo	6245	Inclusion criteria: symptomatic or asymptomatic CHF Exclusion criteria: serum creatinine level of >2.5 mg/dL, age > 80 years, uncontrolled HTN	Primary: all-cause mortality over 3 to 5 years Secondary: cardiovascular-related deaths and CHF readmissions	Patients with HFrEF treated with enalapril had a decreased risk of mortality and CHF hospitalizations. After initiating enalapril, a moderate decrease in eGFR was noted and was acceptable.
PARADIGM-HF [58], 2014	Design: multicenter randomized control trial Patients and controls: 1:1 randomization to receive LCZ696 or enalapril	10,521	Inclusion criteria: NYHA class II-IV symptoms, EF $\leq$ 35%, and elevated BNP or NT-proBNP levels Exclusion criteria: systolic BP < 100 mmhg, eGFR <30 mL/min/1.73 m^2, serum potassium > 5.4 mmol/L	Primary: death due to cardiovascular causes, CHF hospitalization Secondary: time to death from all causes, new onset of atrial fibrillation, worsening renal function	ARNi reduced deaths due to cardiovascular causes and CHF hospitalizations by 20% compared to enalapril. The risk of death from all causes was also decreased.
PIONEER-HF [60], 2019	Design: multicenter randomized control trial Patients and controls: 1:1 randomization to receive sacubitril–valsartan or enalapril	887	Inclusion criteria: EF $\leq$ 40%, elevated BNP or NT-proBNP levels Exclusion criteria: severe renal impairment, symptomatic hypotension	Primary: change in NT-proBNP concentration Secondary: worsening renal function, hyperkalemia, symptomatic hypotension	Treatment with sacubitril–valsartan caused a higher reduction in the NT-proBNP concentration. The rates of hyperkalemia or worsening renal function did not differ significantly between the groups.
RALES [65], 1999	Design: randomized control trial Patients and controls: 1:1 randomization to receive spironolactone or placebo	1663	Inclusion criteria: NYHA class III or IV symptoms, EF $\leq$ 35% Exclusion criteria: serum creatinine > 2.5 mg/dL, serum potassium > 5 mmol/L	Primary: all-cause mortality Secondary: death due to cardiovascular causes, CHF hospitalizations	Treatment with spironolactone significantly reduced the risk of all-cause mortality who were receiving standard therapy, which included an ACEi.
ATHENA-HF [66], 2020	Design: multicenter randomized control trial Patients and controls: randomized to receive high dose (100 mg of spironolactone or low dose spironolactone (25 mg) or placebo	112	Inclusion criteria: acute decompensated CHF, elevated BNP or NT-proBNP levels	Primary: change in NT-proBNP concentration at 96 h Secondary: change in body weight, net urine volume, dyspnea relief	Treatment with high-dose spironolactone did not significantly improve NT-proBNP concentrations or the other secondary endpoints compared to low-dose spironolactone or placebo.
EPHESUS [67], 2003	Design: multicenter randomized control trial Patients and controls: 1:1 randomization to receive eplerenone or placebo	6642	Inclusion criteria: patients with myocardial infarction, EF $\leq$ 40%, symptomatic CHF Exclusion criteria: serum creatinine > 2.5 mg/dL, serum potassium > 5 mmol/L	Primary: All-cause mortality Secondary: death due to cardiovascular causes	Treatment with eplerenone significantly reduced all-cause mortality, other cardiovascular events, and CHF hospitalizations. The risk of hyperkalemia was higher in the eplerenone group.

Table 4. *Cont.*

Study, Year	Study Design; Patients and Controls	Total, *n*	Inclusion and Exclusion Criteria	Outcomes Measured	Main Findings
EMPEROR [7], 2020	Design: randomized control trial Patients and controls: 1:1 randomization to receive empagliflozin or placebo	3730	Inclusion criteria: NYHA class III or IV symptoms, EF $\leq$ 40%	Primary: death due to cardiovascular causes, worsening CHF Secondary: CHF hospitalizations, worsening of eGFR	Treatment with empagliflozin significantly reduced death due to cardiovascular causes, CHF hospitalizations and rate of eGFR decline.
Analysis of data from CREDENCE [77], 2021	Design: randomized control trial Patients and controls: 1:1 randomization to receive canagliflozin or placebo	4401	Inclusion criteria: HbA1c levels between 6.5% and 12.0%, and chronic kidney disease with eGFR of 30 to less than 90 mL/min/1.73 m^2 and albuminuria between 300 to 5000 mg/g	Primary: death due to renal or cardiovascular causes, doubling of serum creatinine Secondary: death due to cardiovascular causes and CHF hospitalizations	Canagliflozin significantly reduced the risk of end-stage kidney disease, doubling serum creatinine, and renal or cardiovascular death. It also reduced the risk of heart failure hospitalizations and cardiovascular death by 31%.
EMPULSE [80], 2022	Design: multicenter randomized control trial Patients and controls: 1:1 randomization to receive empagliflozin or placebo	530	Inclusion criteria: Acute decompensated CHF Exclusion criteria: cardiogenic shock, eGFR of 20 mL/min/1.73 m^2	Primary: all-cause mortality, number and time to first heart failure event Secondary: death due to cardiovascular cause, CHF hospitalizations, change in NT-proBNP concentrations	Empagliflozin showed a significant clinical benefit over a placebo when started in patients with acute CHF. Empagliflozin had fewer adverse effects than placebo.

Abbreviations: ACEi, angiotensin-converting enzyme Inhibitor; ARB, Angiotensin Receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; BNP, B-type natriuretic peptide; BP, blood pressure; CHF, congestive heart failure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HTN, hypertension; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium–glucose cotransporter-2 inhibitor.

2.6. Management of Electrolyte Abnormalities

Patients with CRS are often found to have electrolyte imbalances of sodium, potassium, magnesium, and calcium. Clinical assessment and serial blood work are required. Any signs and symptoms linked to electrolyte imbalances must be taken care to avoid serious complications [85]. The LYTE-VT Study found that among CHF patients with severe hypokalemia who experienced ventricular tachycardia (VT) or ventricular fibrillation (VF), almost one-third reported gastrointestinal symptoms before the event, while another third had recently increased their diuretic dosage. Hypokalemia occurred in these patients while on an ACEi/ARB or MRA, and a higher proportion of patients were taking diuretics. In addition to hypokalemia, hypomagnesemia was found in about 7.8 of these patients as well [86].

Hyperkalemia occurs frequently in the late stages of CKD, and the common medications attributed to this are the RAAS inhibitors. The occurrence of hyperkalemia also prompts the discontinuation of RAAS inhibitors, and restarting is generally avoided, which may have disadvantages [87]. Hyperkalemia concerns are also the main reason for the discontinuation of MRAs. Greater than 75% of the patients do not get restarted on MRAs after discontinuation, and this increases the risk for future cardiovascular events [5]. The concomitant use of potassium binders, such as a patiromer, can decrease the risk of hyperkalemia while using RAASi with MRAs, which has been demonstrated in the DIAMOND trial [88]. Similarly, sodium zirconium cyclosilicate can reduce serum potassium and maintain normokalaemia in patients with hyperkalemia while on ACEi [89].

Hyponatremia could occur due to hypervolemia or the activation of arginine–vasopressin (AVP) release in response to low intra-arterial volume. Hyponatremia is associated with increased mortality and the requirement of short-term RRT. It was found that a higher percentage of patients with diabetes mellitus are prone to developing hyponatremia in CRS [90]. Fluid restriction only has a modest improvement in most cases, and careful assessment to detect the underlying cause is required for proper management [91]. The use of 3% sodium chloride may be required in severe hyponatremia or symptomatic cases. The correction rate for patients at low risk of osmotic demyelination is 8 mEq/L in 24 h, while for individuals at high risk, it is 6 mEq/L [92].

The management plan for electrolyte disturbances includes dietary changes, appropriate medication and supplements, removal of culprit medications, and medication alterations [55]. Emphasis should be placed on identifying the root cause of the electrolyte imbalance and preventing further reoccurrence.

2.7. Implantable Devices and Mechanical Circulatory Support

Cardiac resynchronization therapy (CRT) in patients with NYHA class II or III heart failure and reduced ejection fraction of <30% has been shown to decrease mortality and hospitalizations [93]. It is also known that patients with CKD have left ventricular dysfunction and early onset of fibrosis than the general population [94]. The use of implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death in patients with CKD was assessed in a meta-analysis. It was concluded that there was a survival benefit in patients with eGFR $\geq$ 60 mL/min/1.73 m^2, but this benefit was not seen in patients with eGFR <60 mL/min/1.73 m^2. It should also be noted that only about 36% of the patients in the meta-analysis had an eGFR < 60 mL/min/1.73 m^2 [95].

Mechanical circulatory support (MCS) in acute CHF and cardiogenic shock are being increasingly employed and can improve hemodynamics [2]. Intra-aortic balloon pump (IABP), impella, and left ventricular assist devices (LVAD) are the MCS types discussed here. The European Society of Cardiology (ESC), in their 2020 guidelines, recommended that IABP should be considered in patients with hemodynamic instability, but routine use in all patients was not recommended. The American Heart Association (AHA)/American College of Cardiology (ACC) recommended considering their use in non-ST elevation myocardial infarction when other therapies have failed [96]. Studies such as the IABP-SHOCK II (The Intra-aortic Balloon Pump in Cardiogenic Shock II) trial showed no difference in mortality, hospitalization, or AKI events compared to fibrinolytics alone in patients with myocardial infarction [97]. Similarly, a mortality benefit has also not been shown in other trials [2].

Flaherty et al. assessed the rates of AKI in patients with CKD who underwent impella placement and high-risk percutaneous coronary intervention (PCI). It was shown that AKI post-PCI was reduced even in patients with severe reductions in LVEF. The requirements of dialysis were also less in the impella group [98]. Similar findings of reduced rates of AKI were also seen in another study that included CKD patients with a median eGFR of around 48 mL/min/1.73 m^2 who underwent impella placement and high-risk PCI [99]. The current literature lacks data if impella offers any mortality advantages over IABP [20]. Pre-existing renal dysfunction is not a contraindication for MCS utilization, but post-procedural AKI after MCS is associated with poor prognosis [100].

The utilization of LVAD in advanced heart failure as a bridge to heart transplantation or as a standalone destination therapy has recently increased [9]. Brisco et al. analyzed the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) data that included patients with a mean eGFR of 60 mL/min/1.73 m^2. The analysis showed an improvement in the renal function after the left ventricular assist device (LVAD), and the renal function was maintained for a few weeks to months. About 11% of the cohort had an eGFR < 60 mL/min/1.73 m^2 [101]. The requirement of dialysis after LVAD placement portends a poor prognosis. A predictive model by the ADHERE (Acute Decompensated Heart Failure National Registry) takes into account blood urea nitrogen (BUN) and creatinine to

prognosticate patients. A BUN of ≥43 mg/dL and serum creatinine ≥ 2.75 mg/dL are considered high risk. While renal dysfunction is not a contraindication for LVAD implantation, placement in patients who may require long-term dialysis is not recommended [100]. If dialysis is required post hospitalization, particularly when heart transplantation is considered, peritoneal dialysis (PD) may be a suitable choice for individuals with heart failure, especially those with relatively low blood pressure (BP), as PD can offer volume optimization, but without the concerns for hemodynamic stress seen in thrice-weekly hemodialysis [102].

2.8. Treatment of Associated Conditions

Acute CHF patients with hyperglycemia have been found to have increased in-hospital mortality and, in addition, have an increased mortality of 1 year. Therefore, hyperglycemia management is crucial in addition to other therapies [41]. History should emphasize the recent usage of nephrotoxic medications such as nonsteroidal anti-inflammatory medicines, antibiotics, and aggressive diuretic therapy [12]. Avoidance of nephrotoxic medications during hospitalization is paramount to avoid further insult to the hemodynamically compromised kidneys [103]. Contrast-induced AKI can exacerbate renal dysfunction in patients with CHF or those who undergo a coronary artery bypass graft [19,22].

Anemia is a common problem in CHF that occurs either due to a decreased transferrin saturation or a functional iron deficiency. Iron deficiency states are common and can coexist with anemia of chronic disease. Anemia in the presence of iron overload states have also been described. Derangements of iron metabolism strongly correlate with the severity of CHF. Iron deficiency needs to be identified and treated as it is related to increased mortality compared to the degree of anemia [104]. The risk of mortality over 3 months in iron deficiency anemia was close to 46% in patients with severe CHF in a study by Nanas et al. The mean EF in the cohort was 22.5%, and the eGFR was 51 mL/min/1.73 m^2 [105]. Similar outcomes were noted in the studies, DEFINE-HF (Definition of Iron Deficiency in Chronic Heart Failure) and BIOSTAT-CHF (Biology Study to Tailored Treatment in Chronic Heart Failure) [106,107]. It was also found that patients with low iron storage had increased mortality and hospitalizations compared to patients with defective iron utilization. The study used a ferritin cut-off value of 128 ng/mL, but, in practice, a cut-off value of 100 ng/mL is used to diagnose iron deficiency anemia and low transferrin saturation levels in patients with CKD [108]. Patients with thalassemia have high rates of dilated cardiomyopathy and develop CRS. Iron overload is frequently encountered in these patients. Thalassemia also causes intrinsic glomerular injury due to tubular atrophy [109]. SGLT2i has been shown to increase hematocrit levels and could be added if other criteria for their use are present. While the exact mechanism is unclear, the increase erythropoiesis by inhibiting hepcidin and efficiently utilizing iron stores [74]. Figure 2 shows the various conditions that need to be addressed and the therapy options available.

Management of mineral bone disease is also essential in patients with chronic CHF. In a meta-analysis, the severity of loss of bone mineralization was closely associated with the severity of CHF. While vitamin D deficiency is common and easily treatable, there may be other factors, such as elevated levels of osteoprotegerin and lower levels of nuclear factor-κ B ligand (RANKL) stimulators. Patients with CKD may have secondary hyperparathyroidism, and dietary restriction of phosphorus may be required to improve bone mineralization [110].

Treating metabolic acidosis in chronic kidney disease (CKD) will slow down the decline in GFR and this is typically achieved by the addition of sodium bicarbonate (NaHCO3). Acidosis also affects myocardial contractility. The goal is to keep plasma bicarbonate >22 meQ/L [38]. While dietary changes and oral sodium bicarbonate are recommended in CKD, current research does not provide sufficient evidence to recommend intravenous sodium bicarbonate for high anion gap metabolic acidosis, especially due to lactic acidosis. Sodium bicarbonate infusion may have a potential function only in treating severe metabolic acidosis. Untoward adverse effects such as hypercapnia and respiratory depression have been observed [111].

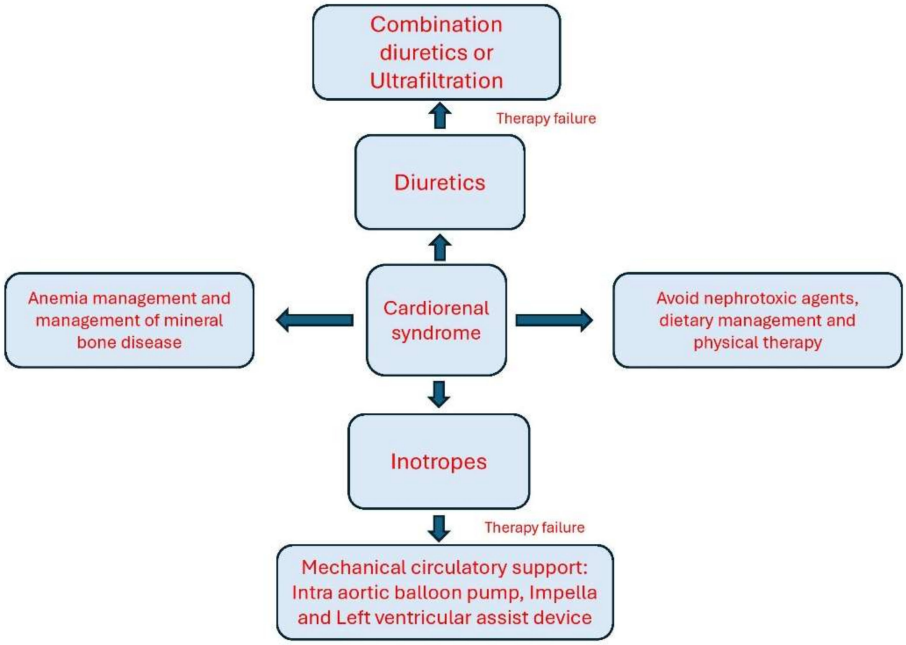

Figure 2. Therapy options available in the management of cardiorenal syndrome.

Physical therapy is an essential part of the management of CRS. When patients are stable enough to participate in physical therapy, a gradually stepped-up physical activity regimen must be incorporated, as insufficient physical activity levels are linked to increased mortality and reduced 11-month event-free survival. The American Physical Therapy Association recommends inspiratory muscle, aerobic exercise, resistance training, and neuromuscular electrical stimulation (NMES) to improve the mobility and quality of life in patients with heart failure. Simple interventions such as an educational program that covers topics of heart failure, medications, diet, exercise recommendations, symptom tracking, and self-care can decrease hospital readmissions by up to 13% [112].

2.9. Palliative Care

In patients with advanced CHF and in patients with limited therapeutic options or approaching end of life, discussions about quality of life and treatment goals should be established. In such patients, prioritizing symptom management becomes more important than pursuing treatments, and the deterioration of renal function should not limit diuretic use if the patient remains in volume overload [31]. The INTrEPID (Investigation of Nontransplant-Eligible Patients Who Are Inotrope Dependent) trial found that transplant-ineligible patients with severe CHF and inotrope dependent had a mortality rate of around 90% in the first year. Those on optimal medical therapy also had similar mortality rates. [113].

The significance of advanced care planning has been acknowledged by the AHA. In their statement in 2012, they recommended shared decision-making in patients with advanced CHF. Patients with type 1 CRS have inferior renal outcomes, and the requirement of CRRT has been related to increased mortality in these patients, especially those >70 years of age [42]. RAAS inhibitors are recommended to be stopped for end-of-life care management [31]. Patients with advanced heart failure have poor health-related quality of life (HRQOL) due to various factors such as symptom burden, physical disability, and depression. Therefore, addressing these issues is recommended [114].

3. Future Directions and Conclusions

Machine learning models using the least absolute shrinkage and selection operator (LASSO) logistic regression have been created to predict the mortality of patients with CHF and CKD [41,115]. The normograms generated by these models can be used to stratify

high-risk patients. These models have been validated in an acute setting and can aid management [41]. Various biomarkers are gaining interest as possible methods to detect early AKI. Although many require validation and need to become easily accessible, they could be valuable tools in the care of these patients [9]. Novel urinary biomarkers are also being developed to detect AKI and tubular injury. At present, NGAL, NAG, and KIM-1 are available, but their use is limited [34].

The management of CRS requires the individualization of therapy to address the underlying cause. Understanding and detecting overlap in the comorbidities helps construct effective management strategies. There are a lack of data on patients with advanced CKD, such as stages 4 and 5. The overall management of CRS mandates stabilization of hemodynamics, use of inotropic and diuretic agents, mitigating diuretic resistance, GDMT, and electrolyte derangements. Mechanical circulatory support offers additional advantages in select patients. These strategies address the complex interplay between the cardiac and renal functions to enhance patient outcomes and reduce the burden of this challenging condition.

Author Contributions: Conceptualization, D.C. Data Curation, D.C. and P.K.S.; Writing—Original Draft Preparation, D.C.; Writing—Review and Editing, P.K.S., N.J. and S.K.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Cortesi, C.; Ibrahim, M.; Rivera, F.C.; Hernandez, G.A. Cardiorenal syndrome, hemodynamics, and noninvasive evaluation. *Clin. Med. Insights Ther.* **2017**, *9*. [CrossRef]
2. Ergle, K.; Parto, P.; Krim, S.R. Percutaneous Ventricular Assist Devices: A Novel Approach in the Management of Patients with Acute Cardiogenic Shock. *Ochsner J.* **2016**, *16*, 243–249. [PubMed]
3. Wan, S.H.; Stevens, S.R.; Borlaug, B.A.; Anstrom, K.J.; Deswal, A.; Felker, G.M.; Givertz, M.M.; Bart, B.A.; Tang, W.H.; Redfield, M.M.; et al. Differential Response to Low-Dose Dopamine or Low-Dose Nesiritide in Acute Heart Failure with Reduced or Preserved Ejection Fraction: Results from the ROSE AHF Trial (Renal Optimization Strategies Evaluation in Acute Heart Failure). *Circ. Heart Fail.* **2016**, *9*, e002593. [CrossRef] [PubMed]
4. Yogasundaram, H.; Chappell, M.C.; Braam, B.; Oudit, G.Y. Cardiorenal Syndrome and Heart Failure—Challenges and Opportunities. *Can. J. Cardiol.* **2019**, *35*, 1208–1219. [CrossRef] [PubMed]
5. Kobayashi, M.; Girerd, N.; Zannad, F. When to use either spironolactone, eplerenone or finerenone in the spectrum of cardiorenal diseases. *Nephrol. Dial. Transplant.* **2024**, *39*, 1063–1072. [CrossRef] [PubMed]
6. Chen, W.-C.; Lin, M.-H.; Chen, C.-L.; Lai, Y.-C.; Chen, C.-Y.; Lin, Y.-C.; Hung, C.-C. Comprehensive comparison of the effect of inotropes on cardiorenal syndrome in patients with advanced heart failure: A network meta-analysis of randomized controlled trials. *J. Clin. Med.* **2021**, *10*, 4120. [CrossRef] [PubMed]
7. Packer, M.; Anker, S.D.; Butler, J.; Filippatos, G.; Pocock, S.J.; Carson, P.; Januzzi, J.; Verma, S.; Tsutsui, H.; Brueckmann, M.; et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N. Engl. J. Med.* **2020**, *383*, 1413–1424. [CrossRef]
8. Ronco, C.; Haapio, M.; House, A.A.; Anavekar, N.; Bellomo, R. Cardiorenal syndrome. *J. Am. Coll. Cardiol.* **2008**, *52*, 1527–1539. [CrossRef] [PubMed]
9. Hatamizadeh, P.; Fonarow, G.C.; Budoff, M.J.; Darabian, S.; Kovesdy, C.P.; Kalantar-Zadeh, K. Cardiorenal syndrome: Pathophysiology and potential targets for clinical management. *Nat. Rev. Nephrol.* **2013**, *9*, 99–111. [CrossRef]
10. Haase, M.; Müller, C.; Damman, K.; Murray, P.T.; Kellum, J.A.; Ronco, C.; McCullough, P.A. Pathogenesis of cardiorenal syndrome type 1 in acute decompensated heart failure: Workgroup statements from the eleventh consensus conference of the Acute Dialysis Quality Initiative (ADQI). *Contrib. Nephrol.* **2013**, *182*, 99–116. [CrossRef]
11. Grodin, J.L.; Stevens, S.R.; De Las Fuentes, L.; Kiernan, M.; Birati, E.Y.; Gupta, D.; Bart, B.A.; Felker, G.M.; Chen, H.H.; Butler, J.; et al. Intensification of Medication Therapy for Cardiorenal Syndrome in Acute Decompensated Heart Failure. *J. Card. Fail.* **2016**, *22*, 26–32. [CrossRef]
12. Gnanaraj, J.; Radhakrishnan, J. Cardio-renal syndrome. *F1000Research* **2016**, *5*, 2123. [CrossRef]
13. Cowie, B.; Kluger, R.; Rex, S.; Missant, C. Noninvasive estimation of left atrial pressure with transesophageal echocardiography. *Ann. Card. Anaesth.* **2015**, *18*, 312–316. [CrossRef] [PubMed]
14. Nohria, A.; Hasselblad, V.; Stebbins, A.; Pauly, D.F.; Fonarow, G.C.; Shah, M.; Yancy, C.W.; Califf, R.M.; Stevenson, L.W.; Hill, J.A. Cardiorenal interactions: Insights from the ESCAPE trial. *J. Am. Coll. Cardiol.* **2008**, *51*, 1268–1274. [CrossRef] [PubMed]
15. Lim, S.Y.; Kim, S. Pathophysiology of Cardiorenal Syndrome and Use of Diuretics and Ultrafiltration as volume control. *Korean Circ. J.* **2021**, *51*, 656. [CrossRef] [PubMed]

16. Mullens, W.; Abrahams, Z.; Skouri, H.N.; Francis, G.S.; Taylor, D.O.; Starling, R.C.; Paganini, E.; Tang, W.H. Elevated intra-abdominal pressure in acute decompensated heart failure: A potential contributor to worsening renal function? *J. Am. Coll. Cardiol.* **2008**, *51*, 300–306. [CrossRef]
17. Chandramohan, D.; Konda, R.; Pujari, A.; Avula, S.; Palleti, S.K.; Jena, N.; Naik, R.; Bali, A. Acute kidney injury after robot-assisted laparoscopic prostatectomy: A meta-analysis. *Int. J. Med. Robot. Comput. Assist. Surg.* **2024**, *20*, e2630. [CrossRef] [PubMed]
18. Naik, R.; Bali, A.; Shaik, B.F.; Kata, M.; Arora, H.; Chandramohan, D.; Ramachandran, R. Hepatorenal Syndrome. In *Advances in Renal Diseases and Dialysis*; BP International (a Part of SCIENCEDOMAIN International): London, UK, 2023; pp. 19–34.
19. Chandramohan, D.; Simhadri, P.K.; Palleti, S.K. Risk Factors for Acute Kidney Injury in Surgical Patients—A Review. *J. Urol. Ren. Dis.* **2024**, *9*, 1385. [CrossRef]
20. Ghionzoli, N.; Sciaccaluga, C.; Mandoli, G.E.; Vergaro, G.; Gentile, F.; D'ascenzi, F.; Mondillo, S.; Emdin, M.; Valente, S.; Cameli, M. Cardiogenic shock and acute kidney injury: The rule rather than the exception. *Heart Fail. Rev.* **2021**, *26*, 487–496. [CrossRef]
21. Caetano, F.; Barra, S.; Faustino, A.; Botelho, A.; Mota, P.; Costa, M.; Leitão Marques, A. Cardiorenal syndrome in acute heart failure: A vicious cycle? *Rev. Port. Cardiol. (Engl. Ed.)* **2014**, *33*, 139–146. [CrossRef]
22. Chandramohan, D.; García, J.J.C.; Kata, M.; Naik, R.; Bali, A.; Shaik, B.F.; Arora, H.; Avula, S. Acute Kidney Injury. In *Advances in Renal Diseases and Dialysis*; BP International (a Part of SCIENCEDOMAIN International): London, UK, 2023; pp. 2–18.
23. Felker, G.M.; Ellison, D.H.; Mullens, W.; Cox, Z.L.; Testani, J.M. Diuretic therapy for patients with heart failure: JACC state-of-the-art review. *J. Am. Coll. Cardiol.* **2020**, *75*, 1178–1195. [CrossRef]
24. Heywood, J.T. The Cardiorenal Syndrome: Lessons from the ADHERE Database and Treatment Options. *Heart Fail. Rev.* **2005**, *9*, 195–201. [CrossRef] [PubMed]
25. Aundhakar, S.C.; Mahajan, S.K.; Mane, M.B.; Lakhotia, A.N.; Mahajani, V.V. Cardiorenal syndrome: Resistant to diuretics, sensitive to ultraflitration. *J. Cardiovasc. Dis. Res.* **2012**, *3*, 173–175. [CrossRef] [PubMed]
26. Thind, G.S.; Loehrke, M.; Wilt, J.L. Acute cardiorenal syndrome: Mechanisms and clinical implications. *Clevel. Clin. J. Med.* **2018**, *85*, 231–239. [CrossRef]
27. Shah, N.; Madanieh, R.; Alkan, M.; Dogar, M.U.; Kosmas, C.E.; Vittorio, T.J. A perspective on diuretic resistance in chronic congestive heart failure. *Ther. Adv. Cardiovasc. Dis.* **2017**, *11*, 271–278. [CrossRef]
28. Felker, G.M.; Lee, K.L.; Bull, D.A.; Redfield, M.M.; Stevenson, L.W.; Goldsmith, S.R.; LeWinter, M.M.; Deswal, A.; Rouleau, J.L.; Ofili, E.O.; et al. Diuretic strategies in patients with acute decompensated heart failure. *N. Engl. J. Med.* **2011**, *364*, 797–805. [CrossRef] [PubMed]
29. Marques, M.; Cobo, M.; López-Sánchez, P.; García-Magallón, B.; Salazar, M.L.S.; López-Ibor, J.V.; Janeiro, D.; García, E.; Briales, P.S.; Montero, E.; et al. Multidisciplinary approach to patients with heart failure and kidney disease: Preliminary experience of an integrated cardiorenal unit. *Clin. Kidney J.* **2023**, *16*, 2100–2107. [CrossRef]
30. Davis, B.R.; Piller, L.B.; Cutler, J.A.; Furberg, C.; Dunn, K.; Franklin, S.; Goff, D.; Leenen, F.; Mohiuddin, S.; Papademetriou, V.; et al. Role of diuretics in the prevention of heart failure: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Circulation* **2006**, *113*, 2201–2210. [CrossRef] [PubMed]
31. Clark, A.L.; Kalra, P.R.; Petrie, M.C.; Mark, P.B.; Tomlinson, L.A.; Tomson, C.R. Change in renal function associated with drug treatment in heart failure: National guidance. *Heart* **2019**, *105*, 904–910. [CrossRef]
32. Palazzuoli, A.; Ruocco, G.; Ronco, C.; McCullough, P.A. Loop diuretics in acute heart failure: Beyond the decongestive relief for the kidney. *Crit. Care* **2015**, *19*, 296. [CrossRef]
33. Emmens, J.E.; Ter Maaten, J.M.; Matsue, Y.; Figarska, S.M.; Sama, I.E.; Cotter, G.; Cleland, J.G.F.; Davison, B.A.; Felker, G.M.; Givertz, M.M.; et al. Worsening renal function in acute heart failure in the context of diuretic response. *Eur. J. Heart Fail.* **2022**, *24*, 365–374. [CrossRef] [PubMed]
34. Ahmad, T.; Jackson, K.; Rao, V.S.; Tang, W.H.W.; Brisco-Bacik, M.A.; Chen, H.H.; Felker, G.M.; Hernandez, A.F.; O'Connor, C.M.; Sabbisetti, V.S.; et al. Worsening Renal Function in Patients with Acute Heart Failure Undergoing Aggressive Diuresis Is Not Associated with Tubular Injury. *Circulation* **2018**, *137*, 2016–2028. [CrossRef] [PubMed]
35. Mullens, W.; Dauw, J.; Martens, P.; Verbrugge, F.H.; Nijst, P.; Meekers, E.; Tartaglia, K.; Chenot, F.; Moubayed, S.; Dierckx, R. Acetazolamide in acute decompensated heart failure with volume overload. *N. Engl. J. Med.* **2022**, *387*, 1185–1195. [CrossRef] [PubMed]
36. Felker, G.M.; Mentz, R.J.; Cole, R.T.; Adams, K.F.; Egnaczyk, G.F.; Fiuzat, M.; Patel, C.B.; Echols, M.; Khouri, M.G.; Tauras, J.M.; et al. Efficacy and Safety of Tolvaptan in Patients Hospitalized with Acute Heart Failure. *J. Am. Coll. Cardiol.* **2017**, *69*, 1399–1406. [CrossRef] [PubMed]
37. Konstam, M.A.; Gheorghiade, M.; Burnett, J.C., Jr.; Grinfeld, L.; Maggioni, A.P.; Swedberg, K.; Udelson, J.E.; Zannad, F.; Cook, T.; Ouyang, J.; et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: The EVEREST Outcome Trial. *JAMA* **2007**, *297*, 1319–1331. [CrossRef] [PubMed]
38. Goraya, N.; Wesson, D.E. Dietary interventions to improve outcomes in chronic kidney disease. *Curr. Opin. Nephrol. Hypertens.* **2015**, *24*, 505–510. [CrossRef] [PubMed]
39. Seckinger, D.; Ritter, O.; Patschan, D. Risk factors and outcome variables of cardiorenal syndrome type 1 from the nephrologist's perspective. *Int. Urol. Nephrol.* **2022**, *54*, 1591–1601. [CrossRef] [PubMed]
40. Kher, V.; Srisawat, N.; Noiri, E.; Benghanem Gharbi, M.; Shetty, M.S.; Yang, L.; Bagga, A.; Chakravarthi, R.; Mehta, R. Prevention and Therapy of Acute Kidney Injury in the Developing World. *Kidney Int. Rep.* **2017**, *2*, 544–558. [CrossRef]

41. Gao, L.; Bian, Y.; Cao, S.; Sang, W.; Zhang, Q.; Yuan, Q.; Xu, F.; Chen, Y. Development and validation of a simple-to-use nomogram for predicting in-hospital mortality in patients with acute heart failure undergoing continuous renal replacement therapy. *Front. Med.* **2021**, *8*, 678252. [CrossRef]
42. Watanabe, Y.; Inoue, T.; Nakano, S.; Okada, H. Prognosis of Patients with Acute Kidney Injury due to Type 1 Cardiorenal Syndrome Receiving Continuous Renal Replacement Therapy. *Cardiorenal Med.* **2023**, *13*, 158–166. [CrossRef]
43. Bart, B.A.; Goldsmith, S.R.; Lee, K.L.; Givertz, M.M.; O'Connor, C.M.; Bull, D.A.; Redfield, M.M.; Deswal, A.; Rouleau, J.L.; LeWinter, M.M.; et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N. Engl. J. Med.* **2012**, *367*, 2296–2304. [CrossRef] [PubMed]
44. Costanzo, M.R.; Negoianu, D.; Jaski, B.E.; Bart, B.A.; Heywood, J.T.; Anand, I.S.; Smelser, J.M.; Kaneshige, A.M.; Chomsky, D.B.; Adler, E.D. Aquapheresis versus intravenous diuretics and hospitalizations for heart failure. *JACC Heart Fail.* **2016**, *4*, 95–105. [CrossRef] [PubMed]
45. Costanzo, M.R.; Guglin, M.E.; Saltzberg, M.T.; Jessup, M.L.; Bart, B.A.; Teerlink, J.R.; Jaski, B.E.; Fang, J.C.; Feller, E.D.; Haas, G.J.; et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J. Am. Coll. Cardiol.* **2007**, *49*, 675–683. [CrossRef] [PubMed]
46. Slessarev, M.; Salerno, F.; Ball, I.M.; McIntyre, C.W. Continuous renal replacement therapy is associated with acute cardiac stunning in critically ill patients. *Hemodial. Int.* **2019**, *23*, 325–332. [CrossRef] [PubMed]
47. Tariq, S.; Aronow, W.S. Use of inotropic agents in treatment of systolic heart failure. *Int. J. Mol. Sci.* **2015**, *16*, 29060–29068. [CrossRef] [PubMed]
48. Mebazaa, A.; Parissis, J.; Porcher, R.; Gayat, E.; Nikolaou, M.; Boas, F.V.; Delgado, J.F.; Follath, F. Short-term survival by treatment among patients hospitalized with acute heart failure: The global ALARM-HF registry using propensity scoring methods. *Intensive Care Med.* **2011**, *37*, 290–301. [CrossRef]
49. Triposkiadis, F.; Dalampiras, P.; Kelepeshis, G.; Skoularigis, J.; Sitafidis, G. Hemodynamic effects of dobutamine in patients with an exacerbation of chronic systolic heart failure treated with low doses of carvedilol. *Int. J. Clin. Pharmacol. Ther.* **2008**, *46*, 136–139. [CrossRef]
50. Felker, G.M.; Benza, R.L.; Chandler, A.B.; Leimberger, J.D.; Cuffe, M.S.; Califf, R.M.; Gheorghiade, M.; O'Connor, C.M. Heart failure etiology and response to milrinone in decompensated heart failure: Results from the OPTIME-CHF study. *J. Am. Coll. Cardiol.* **2003**, *41*, 997–1003. [CrossRef] [PubMed]
51. Fedele, F.; Bruno, N.; Brasolin, B.; Caira, C.; D'Ambrosi, A.; Mancone, M. Levosimendan improves renal function in acute decompensated heart failure: Possible underlying mechanisms. *Eur. J. Heart Fail.* **2014**, *16*, 281–288. [CrossRef]
52. Lannemyr, L.; Ricksten, S.E.; Rundqvist, B.; Andersson, B.; Bartfay, S.E.; Ljungman, C.; Dahlberg, P.; Bergh, N.; Hjalmarsson, C.; Gilljam, T.; et al. Differential Effects of Levosimendan and Dobutamine on Glomerular Filtration Rate in Patients with Heart Failure and Renal Impairment: A Randomized Double-Blind Controlled Trial. *J. Am. Heart Assoc.* **2018**, *7*, e008455. [CrossRef]
53. Follath, F.; Cleland, J.G.; Just, H.; Papp, J.; Scholz, H.; Peuhkurinen, K.; Harjola, V.; Mitrovic, V.; Abdalla, M.; Sandell, E. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): A randomised double-blind trial. *Lancet* **2002**, *360*, 196–202. [CrossRef]
54. Sankaranarayanan, R.; Douglas, H.; Wong, C. Cardio-nephrology MDT meetings play an important role in the management of cardiorenal syndrome. *Br. J. Cardiol.* **2020**, *27*, 26. [CrossRef] [PubMed]
55. Heidenreich, P.A.; Bozkurt, B.; Aguilar, D.; Allen, L.A.; Byun, J.J.; Colvin, M.M.; Deswal, A.; Drazner, M.H.; Dunlay, S.M.; Evers, L.R.; et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* **2022**, *145*, e895–e1032. [CrossRef] [PubMed]
56. Yancy, C.W.; Jessup, M.; Bozkurt, B.; Butler, J.; Casey, D.E., Jr.; Colvin, M.M.; Drazner, M.H.; Filippatos, G.S.; Fonarow, G.C.; Givertz, M.M.; et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J. Am. Coll. Cardiol.* **2017**, *70*, 776–803. [CrossRef]
57. McCallum, W.; Tighiouart, H.; Ku, E.; Salem, D.; Sarnak, M.J. Acute declines in estimated glomerular filtration rate on enalapril and mortality and cardiovascular outcomes in patients with heart failure with reduced ejection fraction. *Kidney Int.* **2019**, *96*, 1185–1194. [CrossRef] [PubMed]
58. McMurray, J.J.; Packer, M.; Desai, A.S.; Gong, J.; Lefkowitz, M.P.; Rizkala, A.R.; Rouleau, J.L.; Shi, V.C.; Solomon, S.D.; Swedberg, K.; et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N. Engl. J. Med.* **2014**, *371*, 993–1004. [CrossRef] [PubMed]
59. Desai, A.S.; Vardeny, O.; Claggett, B.; McMurray, J.J.; Packer, M.; Swedberg, K.; Rouleau, J.L.; Zile, M.R.; Lefkowitz, M.; Shi, V.; et al. Reduced Risk of Hyperkalemia During Treatment of Heart Failure with Mineralocorticoid Receptor Antagonists by Use of Sacubitril/Valsartan Compared with Enalapril: A Secondary Analysis of the PARADIGM-HF Trial. *JAMA Cardiol.* **2017**, *2*, 79–85. [CrossRef] [PubMed]
60. Velazquez, E.J.; Morrow, D.A.; DeVore, A.D.; Duffy, C.I.; Ambrosy, A.P.; McCague, K.; Rocha, R.; Braunwald, E. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. *N. Engl. J. Med.* **2019**, *380*, 539–548. [CrossRef] [PubMed]
61. Bristow, M.R. Treatment of chronic heart failure with β-adrenergic receptor antagonists: A convergence of receptor pharmacology and clinical cardiology. *Circ. Res.* **2011**, *109*, 1176–1194. [CrossRef]

62. Ferrario, C.M. Addressing the theoretical and clinical advantages of combination therapy with inhibitors of the renin-angiotensin-aldosterone system: Antihypertensive effects and benefits beyond BP control. *Life Sci.* **2010**, *86*, 289–299. [CrossRef]
63. Ziff, O.J.; Covic, A.; Goldsmith, D. Calibrating the impact of dual RAAS blockade on the heart and the kidney—Balancing risks and benefits. *Int. J. Clin. Pract.* **2016**, *70*, 537–553. [CrossRef] [PubMed]
64. Ferreira, N.S.; Tostes, R.C.; Paradis, P.; Schiffrin, E.L. Aldosterone, Inflammation, Immune System, and Hypertension. *Am. J. Hypertens.* **2021**, *34*, 15–27. [CrossRef] [PubMed]
65. Pitt, B.; Zannad, F.; Remme, W.J.; Cody, R.; Castaigne, A.; Perez, A.; Palensky, J.; Wittes, J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N. Engl. J. Med.* **1999**, *341*, 709–717. [CrossRef] [PubMed]
66. de Denus, S.; Leclair, G.; Dubé, M.P.; St-Jean, I.; Zada, Y.F.; Oussaïd, E.; Jutras, M.; Givertz, M.M.; Mentz, R.J.; Tang, W.H.W.; et al. Spironolactone metabolite concentrations in decompensated heart failure: Insights from the ATHENA-HF trial. *Eur. J. Heart. Fail.* **2020**, *22*, 1451–1461. [CrossRef] [PubMed]
67. Pitt, B.; Remme, W.; Zannad, F.; Neaton, J.; Martinez, F.; Roniker, B.; Bittman, R.; Hurley, S.; Kleiman, J.; Gatlin, M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N. Engl. J. Med.* **2003**, *348*, 1309–1321. [CrossRef] [PubMed]
68. Zannad, F.; McMurray, J.J.; Krum, H.; van Veldhuisen, D.J.; Swedberg, K.; Shi, H.; Vincent, J.; Pocock, S.J.; Pitt, B. Eplerenone in patients with systolic heart failure and mild symptoms. *N. Engl. J. Med.* **2011**, *364*, 11–21. [CrossRef] [PubMed]
69. Rangaswami, J.; Bhalla, V.; Blair, J.E.A.; Chang, T.I.; Costa, S.; Lentine, K.L.; Lerma, E.V.; Mezue, K.; Molitch, M.; Mullens, W.; et al. Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement from the American Heart Association. *Circulation* **2019**, *139*, E840–E878. [CrossRef] [PubMed]
70. Miura, M.; Sugimura, K.; Sakata, Y.; Miyata, S.; Tadaki, S.; Yamauchi, T.; Onose, T.; Tsuji, K.; Abe, R.; Oikawa, T.; et al. Prognostic impact of loop diuretics in patients with chronic heart failure—Effects of addition of renin-angiotensin-aldosterone system inhibitors and β-blockers. *Circ. J.* **2016**, *80*, 1396–1403. [CrossRef] [PubMed]
71. Shlipak, M.G.; Browner, W.S.; Noguchi, H.; Massie, B.; Frances, C.D.; McClellan, M. Comparison of the Effects of Angiotensin Converting-enzyme Inhibitors and Beta Blockers on Survival in Elderly Patients with Reduced Left Ventricular Function after Myocardial Infarction. *Am. J. Med.* **2001**, *110*, 425–433. [CrossRef]
72. Banerjee, D.; Rosano, G.; Herzog, C.A. Management of Heart Failure Patient with CKD. *Clin. J. Am. Soc. Nephrol.* **2021**, *16*, 1131–1139. [CrossRef]
73. Tang, J.; Ye, L.; Yan, Q.; Zhang, X.; Wang, L. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Water and Sodium Metabolism. *Front. Pharmacol.* **2022**, *13*, 800490. [CrossRef] [PubMed]
74. Kambara, T.; Shibata, R.; Osanai, H.; Nakashima, Y.; Asano, H.; Murohara, T.; Ajioka, M. Importance of sodium-glucose cotransporter 2 inhibitor use in diabetic patients with acute heart failure. *Ther. Adv. Cardiovasc. Dis.* **2019**, *13*, 1753944719894509. [CrossRef]
75. Jackson, A.M.; Dewan, P.; Anand, I.S.; Bělohlávek, J.; Bengtsson, O.; de Boer, R.A.; Böhm, M.; Boulton, D.W.; Chopra, V.K.; DeMets, D.L.; et al. Dapagliflozin and Diuretic Use in Patients with Heart Failure and Reduced Ejection Fraction in DAPA-HF. *Circulation* **2020**, *142*, 1040–1054. [CrossRef] [PubMed]
76. Packer, M.; Anker, S.D.; Butler, J.; Filippatos, G.; Ferreira, J.P.; Pocock, S.J.; Sattar, N.; Brueckmann, M.; Jamal, W.; Cotton, D.; et al. Empagliflozin in Patients with Heart Failure, Reduced Ejection Fraction, and Volume Overload: EMPEROR-Reduced Trial. *J. Am. Coll. Cardiol.* **2021**, *77*, 1381–1392. [CrossRef] [PubMed]
77. Arnott, C.; Li, J.W.; Cannon, C.P.; de Zeeuw, D.; Neuen, B.L.; Heerspink, H.J.L.; Charytan, D.M.; Agarwal, A.; Huffman, M.D.; Figtree, G.A.; et al. The effects of canagliflozin on heart failure and cardiovascular death by baseline participant characteristics: Analysis of the CREDENCE trial. *Diabetes Obes. Metab.* **2021**, *23*, 1652–1659. [CrossRef] [PubMed]
78. Neal, B.; Perkovic, V.; Mahaffey, K.W.; de Zeeuw, D.; Fulcher, G.; Erondu, N.; Shaw, W.; Law, G.; Desai, M.; Matthews, D.R. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N. Engl. J. Med.* **2017**, *377*, 644–657. [CrossRef] [PubMed]
79. Iguchi, M.; Wada, H.; Martínez, F.; Hasegawa, K. When Should We Start Sodium-Glucose Co-transporter Inhibitors in Patients with Heart Failure? The Importance of Early Intervention. *Eur. Cardiol.* **2023**, *18*, e41. [CrossRef] [PubMed]
80. Voors, A.A.; Angermann, C.E.; Teerlink, J.R.; Collins, S.P.; Kosiborod, M.; Biegus, J.; Ferreira, J.P.; Nassif, M.E.; Psotka, M.A.; Tromp, J.; et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: A multinational randomized trial. *Nat. Med.* **2022**, *28*, 568–574. [CrossRef] [PubMed]
81. Horiuchi, Y.; Matsue, Y.; Nogi, K.; Onitsuka, K.; Okumura, T.; Hoshino, M.; Shibata, T.; Nitta, D.; Yoshida, K.; Sato, S.; et al. Early treatment with a sodium-glucose co-transporter 2 inhibitor in high-risk patients with acute heart failure: Rationale for and design of the EMPA-AHF trial. *Am. Heart. J.* **2023**, *257*, 85–92. [CrossRef]
82. Simhadri, P.K.; Vaitla, P.; Sriperumbuduri, S.; Chandramohan, D.; Singh, P.; Murari, U. Sodium-glucose Co-transporter-2 Inhibitors Causing Candida tropicalis Fungemia and Renal Abscess. *JCEM Case Rep.* **2024**, *2*, luae010. [CrossRef]
83. Vaduganathan, M.; Claggett, B.L.; Jhund, P.S.; Cunningham, J.W.; Pedro Ferreira, J.; Zannad, F.; Packer, M.; Fonarow, G.C.; McMurray, J.J.V.; Solomon, S.D. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: A comparative analysis of three randomised controlled trials. *Lancet* **2020**, *396*, 121–128. [CrossRef] [PubMed]

84. Taylor, A.L.; Ziesche, S.; Yancy, C.; Carson, P.; D'Agostino, R., Jr.; Ferdinand, K.; Taylor, M.; Adams, K.; Sabolinski, M.; Worcel, M.; et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N. Engl. J. Med.* **2004**, *351*, 2049–2057. [CrossRef]
85. Raina, R.; Nair, N.; Chakraborty, R.; Nemer, L.; Dasgupta, R.; Varian, K. An Update on the Pathophysiology and Treatment of Cardiorenal Syndrome. *Cardiol. Res.* **2020**, *11*, 76–88. [CrossRef] [PubMed]
86. Laslett, D.B.; Cooper, J.M.; Greenberg, R.M.; Yesenosky, G.A.; Basil, A.; Gangireddy, C.; Whitman, I.R. Electrolyte abnormalities in patients presenting with ventricular arrhythmia (from the LYTE-VT Study). *Am. J. Cardiol.* **2020**, *129*, 36–41. [CrossRef] [PubMed]
87. Chang, A.R.; Sang, Y.; Leddy, J.; Yahya, T.; Kirchner, H.L.; Inker, L.A.; Matsushita, K.; Ballew, S.H.; Coresh, J.; Grams, M.E. Antihypertensive Medications and the Prevalence of Hyperkalemia in a Large Health System. *Hypertension* **2016**, *67*, 1181–1188. [CrossRef] [PubMed]
88. Butler, J.; Anker, S.D.; Lund, L.H.; Coats, A.J.S.; Filippatos, G.; Siddiqi, T.J.; Friede, T.; Fabien, V.; Kosiborod, M.; Metra, M.; et al. Patiromer for the management of hyperkalemia in heart failure with reduced ejection fraction: The DIAMOND trial. *Eur. Heart J.* **2022**, *43*, 4362–4373. [CrossRef] [PubMed]
89. Spinowitz, B.S.; Fishbane, S.; Pergola, P.E.; Roger, S.D.; Lerma, E.V.; Butler, J.; von Haehling, S.; Adler, S.H.; Zhao, J.; Singh, B.; et al. Sodium Zirconium Cyclosilicate among Individuals with Hyperkalemia: A 12-Month Phase 3 Study. *Clin. J. Am. Soc. Nephrol.* **2019**, *14*, 798–809. [CrossRef] [PubMed]
90. Pliquett, R.U.; Schlump, K.; Wienke, A.; Bartling, B.; Noutsias, M.; Tamm, A.; Girndt, M. Diabetes prevalence and outcomes in hospitalized cardiorenal-syndrome patients with and without hyponatremia. *BMC Nephrol.* **2020**, *21*, 393. [CrossRef]
91. Dunlap, M.E.; Hauptman, P.J.; Amin, A.N.; Chase, S.L.; Chiodo, J.A., 3rd; Chiong, J.R.; Dasta, J.F. Current Management of Hyponatremia in Acute Heart Failure: A Report from the Hyponatremia Registry for Patients with Euvolemic and Hypervolemic Hyponatremia (HN Registry). *J. Am. Heart Assoc.* **2017**, *6*, e005261. [CrossRef] [PubMed]
92. Adrogué, H.J.; Tucker, B.M.; Madias, N.E. Diagnosis and Management of Hyponatremia: A Review. *JAMA* **2022**, *328*, 280–291. [CrossRef]
93. Tang, A.S.; Wells, G.A.; Talajic, M.; Arnold, M.O.; Sheldon, R.; Connolly, S.; Hohnloser, S.H.; Nichol, G.; Birnie, D.H.; Sapp, J.L. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N. Engl. J. Med.* **2010**, *363*, 2385–2395. [CrossRef]
94. Chandramohan, D.; Rajasekaran, R.; Konda, R.; Pujari, A.; Avula, S.; Bell, M.; Palleti, S.K.; Deotare, A.; Naik, R.; Bali, A.; et al. Cardiac Magnetic Resonance Imaging Findings in Patients with Chronic Kidney Disease and End-Stage Kidney Disease: A Systematic Review and Meta-Analysis. *Cureus* **2024**, *16*, e51672. [CrossRef] [PubMed]
95. Pun, P.H.; Al-Khatib, S.M.; Han, J.Y.; Edwards, R.; Bardy, G.H.; Bigger, J.T.; Buxton, A.E.; Moss, A.J.; Lee, K.L.; Steinman, R. Implantable cardioverter-defibrillators for primary prevention of sudden cardiac death in CKD: A meta-analysis of patient-level data from 3 randomized trials. *Am. J. Kidney Dis.* **2014**, *64*, 32–39. [CrossRef]
96. Baldetti, L.; Pagnesi, M.; Gramegna, M.; Belletti, A.; Beneduce, A.; Pazzanese, V.; Calvo, F.; Sacchi, S.; Van Mieghem, N.M.; den Uil, C.A. Intra-aortic balloon pumping in acute decompensated heart failure with hypoperfusion: From pathophysiology to clinical practice. *Circ. Heart Fail.* **2021**, *14*, e008527. [CrossRef] [PubMed]
97. Thiele, H.; Zeymer, U.; Neumann, F.J.; Ferenc, M.; Olbrich, H.G.; Hausleiter, J.; Richardt, G.; Hennersdorf, M.; Empen, K.; Fuernau, G.; et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N. Engl. J. Med.* **2012**, *367*, 1287–1296. [CrossRef]
98. Flaherty, M.P.; Pant, S.; Patel, S.V.; Kilgore, T.; Dassanayaka, S.; Loughran, J.H.; Rawasia, W.; Dawn, B.; Cheng, A.; Bartoli, C.R. Hemodynamic support with a microaxial percutaneous left ventricular assist device (Impella) protects against acute kidney injury in patients undergoing high-risk percutaneous coronary intervention. *Circ. Res.* **2017**, *120*, 692–700. [CrossRef] [PubMed]
99. O'NEILL, W.W.; Schreiber, T.; Wohns, D.H.; Rihal, C.; Naidu, S.S.; Civitello, A.B.; Dixon, S.R.; Massaro, J.M.; Maini, B.; Ohman, E.M. The current use of Impella 2.5 in acute myocardial infarction complicated by cardiogenic shock: Results from the USpella Registry. *J. Interv. Cardiol.* **2014**, *27*, 1–11. [CrossRef]
100. Peura, J.L.; Colvin-Adams, M.; Francis, G.S.; Grady, K.L.; Hoffman, T.M.; Jessup, M.; John, R.; Kiernan, M.S.; Mitchell, J.E.; O'Connell, J.B.; et al. Recommendations for the use of mechanical circulatory support: Device strategies and patient selection: A scientific statement from the American Heart Association. *Circulation* **2012**, *126*, 2648–2667. [CrossRef]
101. Brisco, M.A.; Kimmel, S.E.; Coca, S.G.; Putt, M.E.; Jessup, M.; Tang, W.W.; Parikh, C.R.; Testani, J.M. Prevalence and prognostic importance of changes in renal function after mechanical circulatory support. *Circ. Heart Fail.* **2014**, *7*, 68–75. [CrossRef]
102. Sarnak, M.J.; Auguste, B.L.; Brown, E.; Chang, A.R.; Chertow, G.M.; Hannan, M.; Herzog, C.A.; Nadeau-Fredette, A.-C.; Tang, W.H.W.; Wang, A.Y.-M. Cardiovascular effects of home dialysis therapies: A scientific statement from the American Heart Association. *Circulation* **2022**, *146*, e146–e164. [CrossRef]
103. Chandramohan, D.; Lapsiwala, B.; Simhadri, P.K.; Patel, D.; Singh, P.; Avula, S.; Jena, N.; Chandramohan, D. Outcomes of Acute Kidney Injury among Hospitalized Patients with Infective Endocarditis: A National Inpatient Sample Analysis. *J. Clin. Med.* **2024**, *13*, 4262. [CrossRef] [PubMed]
104. Okonko, D.O.; Mandal, A.K.; Missouris, C.G.; Poole-Wilson, P.A. Disordered iron homeostasis in chronic heart failure: Prevalence, predictors, and relation to anemia, exercise capacity, and survival. *J. Am. Coll. Cardiol.* **2011**, *58*, 1241–1251. [CrossRef] [PubMed]
105. Nanas, J.N.; Matsouka, C.; Karageorgopoulos, D.; Leonti, A.; Tsolakis, E.; Drakos, S.G.; Tsagalou, E.P.; Maroulidis, G.D.; Alexopoulos, G.P.; Kanakakis, J.E. Etiology of anemia in patients with advanced heart failure. *J. Am. Coll. Cardiol.* **2006**, *48*, 2485–2489. [CrossRef] [PubMed]

106. Gale, E.; Torrance, J.; Bothwell, T. The quantitative estimation of total iron stores in human bone marrow. *J. Clin. Investig.* **1963**, *42*, 1076–1082. [CrossRef] [PubMed]
107. Voors, A.A.; Anker, S.D.; Cleland, J.G.; Dickstein, K.; Filippatos, G.; van der Harst, P.; Hillege, H.L.; Lang, C.C.; Ter Maaten, J.M.; Ng, L.; et al. A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure: Rationale, design, and baseline characteristics of BIOSTAT-CHF. *Eur. J. Heart Fail.* **2016**, *18*, 716–726. [CrossRef] [PubMed]
108. Grote Beverborg, N.; van der Wal, H.H.; Klip, I.T.; Anker, S.D.; Cleland, J.; Dickstein, K.; van Veldhuisen, D.J.; Voors, A.A.; van der Meer, P. Differences in Clinical Profile and Outcomes of Low Iron Storage vs. Defective Iron Utilization in Patients with Heart Failure: Results From the DEFINE-HF and BIOSTAT-CHF Studies. *JAMA Cardiol.* **2019**, *4*, 696–701. [CrossRef] [PubMed]
109. Makmettakul, S.; Tantiworawit, A.; Phrommintikul, A.; Piriyakhuntorn, P.; Rattanathammethee, T.; Hantrakool, S.; Chai-Adisaksopha, C.; Rattarittamrong, E.; Norasetthada, L.; Fanhchaksai, K.; et al. Cardiorenal syndrome in thalassemia patients. *BMC Nephrol.* **2020**, *21*, 325. [CrossRef] [PubMed]
110. Xing, W.; Lv, X.; Gao, W.; Wang, J.; Yang, Z.; Wang, S.; Zhang, J.; Yan, J. Bone mineral density in patients with chronic heart failure: A meta-analysis. *Clin. Interv. Aging* **2018**, *13*, 343–353. [CrossRef]
111. Lo, K.B.; Garvia, V.; Stempel, J.M.; Ram, P.; Rangaswami, J. Bicarbonate use and mortality outcome among critically ill patients with metabolic acidosis: A meta analysis. *Heart Lung* **2020**, *49*, 167–174. [CrossRef]
112. Shoemaker, M.J.; Dias, K.J.; Lefebvre, K.M.; Heick, J.D.; Collins, S.M. Physical therapist clinical practice guideline for the management of individuals with heart failure. *Phys. Ther.* **2020**, *100*, 14–43. [CrossRef]
113. Rogers, J.G.; Butler, J.; Lansman, S.L.; Gass, A.; Portner, P.M.; Pasque, M.K.; Pierson, R.N., 3rd. Chronic mechanical circulatory support for inotrope-dependent heart failure patients who are not transplant candidates: Results of the INTrEPID Trial. *J. Am. Coll. Cardiol.* **2007**, *50*, 741–747. [CrossRef] [PubMed]
114. Braun, L.T.; Grady, K.L.; Kutner, J.S.; Adler, E.; Berlinger, N.; Boss, R.; Butler, J.; Enguidanos, S.; Friebert, S.; Gardner, T.J.; et al. Palliative Care and Cardiovascular Disease and Stroke: A Policy Statement from the American Heart Association/American Stroke Association. *Circulation* **2016**, *134*, e198–e225. [CrossRef] [PubMed]
115. Chen, J.; Li, Y.; Liu, P.; Wu, H.; Su, G. A nomogram to predict the in-hospital mortality of patients with congestive heart failure and chronic kidney disease. *ESC Heart Fail.* **2022**, *9*, 3167–3176. [CrossRef] [PubMed]