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Cardiorenal Syndrome: Diagnostic Approaches, Imaging Modalities, and Contemporary Therapeutic Strategies. A Comprehensive Review of the Literature up to 2025

Síndrome cardiorrenal: Enfoques diagnósticos, técnicas de imagen y estrategias terapéuticas contemporáneas. Una revisión exhaustiva de la literatura hasta 2025.

Síndrome cardiorrenal: abordagens diagnósticas, modalidades de imagem e estratégias terapêuticas contemporâneas. Uma revisão abrangente da literatura até 2025.

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Abstract

Cardiorenal Syndrome (CRS) is a clinical concept that describes the bidirectional and pathological interaction between the heart and the kidney. It is defined as a disorder in which acute or chronic dysfunction of one organ precipitates the dysfunction of the other, underscoring the interconnected nature of the cardiovascular and renal systems. This systematic review (based on 28 studies and following the PRISMA 2020 protocol for literature from 2015 to 2025) concludes that the management of Cardiorenal Syndrome (CRS) has radically evolved, identifying venous congestion (congestive nephropathy) as the main driver of acute renal deterioration. Therapeutically, SGLT2 Inhibitors (SGLT2i) have been consolidated as the cornerstone due to their dual effect (cardiac and renal) that reduces mortality and hospitalizations, and slows the decline of renal function. In diagnosis, the key lies in a multimodal approach that integrates fluid overload biomarkers (CA-125), tubular injury markers (NGAL/KIM-1), and the non-invasive, real-time hemodynamic quantification of organ congestion using the VExUS protocol (POCUS). Despite the robustness of these findings, the biggest clinical challenge is the persistent absence of consensus guidelines for CRS, which propels the future towards precision medicine facilitated by Artificial Intelligence (AI) to improve risk stratification.

Keywords: Cardiorenal Syndrome, SGLT2 Inhibitors, Venous Congestion, Congestive Nephropathy, VExUS, Biomarkers, Heart Failure.

Resumen

El Síndrome Cardiorrenal (SCR) es un concepto clínico que describe la interacción bidireccional y patológica entre el corazón y el riñón. Se define como un trastorno en el cual la disfunción aguda o crónica de un órgano precipita la disfunción del otro, lo que subraya la naturaleza interconectada del sistema cardiovascular y renal. Esta revisión sistemática (basada en 28 estudios y siguiendo el protocolo PRISMA 2020 para la literatura de 2015 a 2025) concluye que el manejo del Síndrome Cardiorrenal (SCR) ha evolucionado radicalmente, identificando a la congestión venosa (nefropatía congestiva) como el principal impulsor del deterioro renal agudo. Terapéuticamente, los Inhibidores SGLT2 (SGLT2i) se han consolidado como la piedra angular por su efecto dual (cardíaco y renal) que reduce la mortalidad y hospitalizaciones, y retrasa el declive de la función renal. En el diagnóstico, la clave reside en un enfoque multimodal que integra biomarcadores de

sobrecarga hídrica (CA-125), marcadores de lesión tubular (NGAL/KIM-1), y la cuantificación hemodinámica no invasiva y en tiempo real de la congestión orgánica mediante el protocolo VExUS (POCUS). A pesar de la solidez de estos hallazgos, el mayor desafío clínico es la persistente ausencia de guías consensuadas para el SCR, lo que impulsa el futuro hacia la medicina de precisión facilitada por la Inteligencia Artificial (IA) para mejorar la estratificación de riesgo.
Palabras Clave: Síndrome Cardiorrenal, Inhibidores SGLT2, Congestión Venosa, Nefropatía Congestiva, VExUS, Biomarcadores, Insuficiencia Cardíaca

Resumo

A síndrome cardiorrenal (SCR) é um conceito clínico que descreve a interação bidirecional e patológica entre o coração e os rins. É definida como uma desordem em que a disfunção aguda ou crónica de um órgão precipita a disfunção do outro, realçando a natureza interligada dos sistemas cardiovascular e renal. Esta revisão sistemática (baseada em 28 estudos e seguindo o protocolo PRISMA 2020 para literatura de 2015 a 2025) conclui que a gestão da síndrome cardiorrenal (SCR) evoluiu radicalmente, identificando a congestão venosa (doença renal congestiva) como o principal fator desencadeante da lesão renal aguda. Do ponto de vista terapêutico, os inibidores do SGLT2 (iSGLT2) tornaram-se a base do tratamento devido ao seu duplo efeito (cardíaco e renal) na redução da mortalidade e das hospitalizações, além de retardar a deterioração da função renal. No diagnóstico, a chave reside numa abordagem multimodal que integra biomarcadores de sobrecarga hídrica (CA-125), marcadores de lesão tubular (NGAL/KIM-1) e quantificação hemodinâmica não invasiva e em tempo real da congestão orgânica utilizando o protocolo VExUS (POCUS). Apesar da robustez destes achados, o maior desafio clínico é a persistente falta de diretrizes consensuais para a síndrome cardiorrenal (SCR), o que impulsiona o futuro para a medicina de precisão facilitada pela inteligência artificial (IA) para melhorar a estratificação de risco.
Palavras-chave: Síndrome Cardiorrenal, Inibidores do SGLT2, Congestão Venosa, Nefropatia Congestiva, VExUS, Biomarcadores, Insuficiência Cardíaca

Introduction

Definition and Functional Classification of Cardiorenal Syndrome (CRS)

Cardiorenal Syndrome (CRS) is a clinical concept that describes the bidirectional and pathological interaction between the heart and the kidney. It is defined as a disorder in which the acute or chronic dysfunction of one organ precipitates the dysfunction of the other, underscoring the interconnected nature of the cardiovascular and renal systems. This phenomenon should not be interpreted simply as a comorbidity, but as a dynamic syndrome that significantly accelerates patient morbidity and mortality (1).

To facilitate study and clinical management, the Ronco classification is used, which divides CRS into five functional subtypes. Types 1 and 2 refer to renal dysfunction induced by an acute or chronic cardiac event (respectively). Types 3 and 4 describe cardiac dysfunction secondary to acute kidney injury or chronic kidney disease (CKD). Finally, Type 5 encompasses systemic conditions, such as sepsis or amyloidosis, that cause concurrent dysfunction in both organs (2). The critical importance of CRS lies in the demonstrated correlation between the co-existence of cardiac and renal disease and a worse long-term prognosis, evidenced by an increased risk of hospital readmissions and an elevated mortality rate.

Justification of the Review and Period of Analysis (2015–2025)

The management of CRS has undergone a paradigmatic revolution, especially during the period between 2015 and 2025. This decade has witnessed disruptive advances that have modified international clinical practice guidelines (1). The fundamental change is found in therapeutic strategies, particularly with the introduction of agents that modify the disease trajectory, such as sodium-glucose cotransporter 2 inhibitors (SGLT2i) and angiotensin receptor-neprilysin inhibitors (ARNIs) (1, 3).

Simultaneously, diagnostic capacity has expanded through the validation of new biomarkers of tubular injury and fibrosis (e.g., NGAL, sST2) (4, 5), and the consolidation of non-invasive imaging techniques. Specifically, Point-of-Care Ultrasound (POCUS) and the Venous Excess Ultrasound Grading (VExUS) protocol have transformed the assessment of congestion (6, 7). An updated synthesis of this evidence is imperative so that clinicians can apply the most contemporary strategies, distinguishing between the diagnostic and therapeutic approaches that have been replaced or improved by recent evidence.

Methodology

Search Strategy and Data Sources

This literature review adhered to the methodological principles established by the PRISMA 2020 framework, in order to ensure the transparency, structure, and reproducibility of the evidence selection process. The search period was delimited to articles published between 2015 and 2025, a crucial span that captures the most significant therapeutic and diagnostic advances in the area.

The search was conducted in high-impact academic and clinical databases, including PubMed, Cochrane Library, ClinicalTrials, and Google Scholar. To optimize the retrieval of pertinent information, standardized MESH terms and keywords in English and Spanish were used, such as: "Cardio-renal Syndrome/Biomarkers," "Cardio-renal Syndrome/physiopathology," "SGLT2 Inhibitors," "POCUS," "VExUS," and "Artificial Intelligence."

Inclusion and Exclusion Criteria

The literature selection was based on rigorous criteria. Systematic reviews, meta-analyses, randomized controlled trials (RCTs), and clinical practice guidelines published by key organizations (AHA, ESC, KDIGO) were considered for inclusion. Preference was given to studies offering quantifiable clinical outcomes relevant to the contemporary diagnosis and treatment of CRS.

In contrast, exclusion criteria were established to maintain a clinical and high-evidence focus. Isolated case reports, purely observational studies without relevant clinical outcomes, *in vitro* or animal research models, and literature published outside the 2015–2025 period were excluded.

Selection and Data Extraction Process

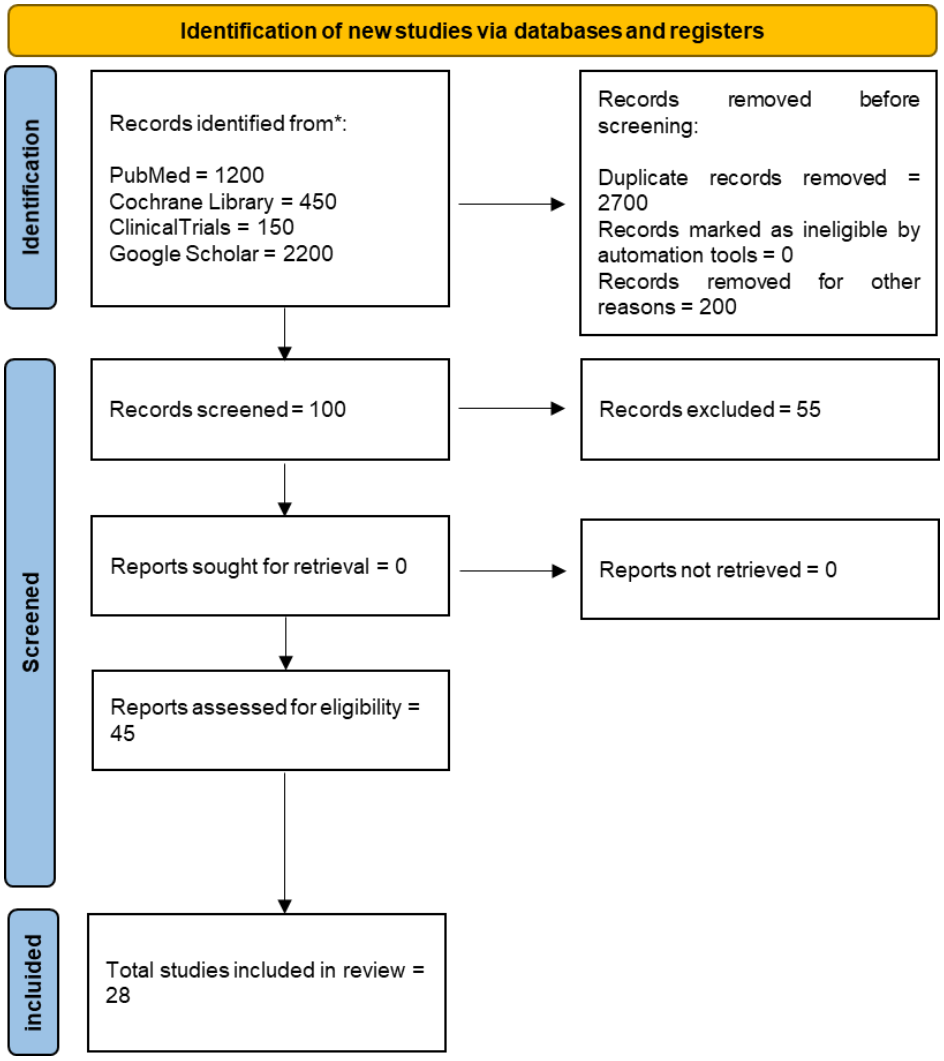
The article selection process was executed in two sequential phases. The first phase consisted of an initial screening based on reading the title and abstract. The preselected articles moved to the second phase, where the full text was evaluated to verify its eligibility and strict compliance with the inclusion criteria.

Subsequently, data extraction was performed from the included studies, compiling essential metadata such as the author, year of publication, study design, sample size, main findings, and reported methodological limitations. This information was organized and qualitatively analyzed, grouping the findings according to the thematic areas defined in the objectives of this review.

Table 1. *Selection of Articles by Database*

Database	Articles Initially Identified	Articles Selected for Full Review	Articles Selected
PubMed	1200	45	10
Cochrane Library	450	15	3
ClinicalTrials	150	5	3
Google Scholar	2200	35	12
Total (After duplicate elimination)	**3000**	**100**	**28**

Figure 1. *PRISMA Flow Diagram and Representation*



Results

Detailed Pathophysiology of Cardiorenal Syndrome (Types 1–5)

CRS Type 1 and 2: The Central Role of Venous Congestion

The understanding of CRS pathophysiology, especially in the acute (Type 1) and chronic (Type 2) types, has evolved significantly. Classically, renal deterioration was predominantly attributed to low cardiac output and hypoperfusion. However, recent evidence underscores that venous congestion is a primary driver, known as congestive nephropathy. Increased Central Venous Pressure (CVP), characteristic of decompensated heart failure, is transmitted retrogradely to the renal venous system (8).

This increase in intrarenal pressure drastically reduces the effective pressure gradient for glomerular filtration (difference between mean arterial pressure and renal venous pressure), which lowers the Glomerular Filtration Rate (GFR) and promotes tubular reabsorption of sodium and water (8). The recognition of this mechanism has implied a fundamental therapeutic shift: managing congestion is an absolute priority over simply pursuing a cardiac output goal. If venous pressure is the dominant mechanism of kidney injury, effective decongestion of the abdomen and kidney becomes the most critical therapeutic intervention.

Inflammation, Neurohormonal Activation, and Mixed Pathophysiology

Beyond hemodynamics, acute and chronic heart failure are characterized by a persistent proinflammatory state. Elevated circulating levels of cytokines, such as Tumor Necrosis Factor alpha (TNF-α), contribute to vascular dysfunction and have been associated with a negative prognostic value. This inflammatory activation plays a role in volume overload and can lead to inflammatory and ischemic damage to the renal tubule (9).

Regarding neurohormonal activation, the chronic activation of the Renin-Angiotensin-Aldosterone System (RAAS) and the sympathetic nervous system seeks to maintain cardiac output. However, in situations of severe congestion, pharmacological inhibition of these compensatory responses can be counterproductive, as curbing this response may precipitate cardiogenic shock, so the dosing of RAAS blockers must be progressive and carefully monitored (9).

CRS Type 3 and 4: Molecular Dysregulation in CKD

CRS Type 4, where Chronic Kidney Disease (CKD) causes cardiac dysfunction, is extremely common, often driven by diabetes mellitus and hypertension (9). The pathology in this phenotype

is strongly mediated by uremic toxins and mineral metabolism alterations. Hyperphosphatemia and hyperparathyroidism are established as independent risk factors that increase cardiovascular mortality in advanced stages of CKD. These imbalances are related to accelerated vascular calcifications and increased cardiac fibrosis (10).

An emerging molecular factor of great interest is Fibroblast Growth Factor 23 (FGF23). FGF23, which regulates phosphorus homeostasis, has been identified as a potent factor that correlates with the development of cardiovascular disease and myocardial fibrosis in patients with CKD (10). This implies that therapy for CRS Type 4 must be directed not only at volume overload but also at the correction of these molecular factors.

Diagnostic Evaluation: Clinical, Biomarkers, and Functional Tests

Biomarkers for Risk Stratification and Monitoring

Biomarkers have moved from being research tools to integral components of the personalized diagnosis and management of CRS (1). The combination of markers allows for a multimodal assessment of myocardial stress, systemic congestion, and structural kidney damage.

- **Natriuretic Peptides and Congestion Markers:** Although NT-proBNP is standard for HF, its utility may be limited in the context of severe renal dysfunction, as reduced renal clearance falsely elevates its levels. Given this, Carbohydrate Antigen 125 (CA-125) has emerged as a robust marker of systemic fluid overload and serositis (1). CA-125 is increasingly used for the dynamic adjustment of diuretic treatment, offering a decongestion metric less dependent on GFR than NT-proBNP (11, 12).

- **Biomarkers of Acute Kidney Injury (AKI):** The distinction between functional azotemia (prerenal, hemodynamic) and structural acute tubular injury (ATI) is crucial in CRS Type 1. **NGAL** (Neutrophil Gelatinase-Associated Lipocalin) and KIM-1 (Kidney Injury Molecule 1) are early biomarkers of tubular injury. The elevation of these markers in a patient with decompensated heart failure and elevated creatinine suggests structural cellular damage in the kidney, indicating a need for intervention different from if the creatinine elevation were purely functional (5).

- **Biomarkers of Fibrosis and Immune Stress: Galectin 3** and **sST2** (soluble ST2 signaling regulatory protein) are emerging markers of myocardial fibrosis and immune dysfunction. These biomarkers have significant prognostic value in heart failure and kidney disease (4).

Functional Tests and Guided Decongestion

The functional evaluation of the patient with CRS requires a global assessment that transcends the monitoring of diuresis and clinical symptoms, which can be misleading (13). A multimodal strategy is required, where the combination of biochemical markers (such as CA-125) and bedside imaging are fundamental. The integration of CA-125 and POCUS to evaluate systemic and pulmonary congestion is a promising strategy for effectively guiding the escalation of diuretic therapy (12).

Imaging Modalities: POCUS, VExUS, MRI, and AI

- **Echocardiography and Cardiac Magnetic Resonance (CMR):** Echocardiography remains the fundamental tool for initial assessment. However, Cardiac Magnetic Resonance (CMR) has been established as the reference standard for several entities. MRI offers superior precision for the quantification of ventricular volumes and Ejection Fraction (LVEF), in addition to being unsurpassed in tissue characterization (detection of fibrosis, myocarditis, and cardiomyopathies) (14). In the context of CRS, MRI has demonstrated added value over echocardiography in the evaluation of Functional Mitral Regurgitation (15), an important predictor of poor prognosis.

- **Point-of-Care Ultrasound (POCUS) and VExUS Protocol:** POCUS, due to its portability and real-time capability, has become the tool of choice for the dynamic and non-invasive assessment of renal and systemic congestion (13). The VExUS Protocol (Venous Excess Ultrasound grading system) systematizes this assessment, examining venous flow in the Inferior Vena Cava (IVC), hepatic veins, portal vein, and renal veins (16). This protocol provides a semi-quantitative quantification of venous excess that correlates with Right Atrial Pressure (RAP) (17). The clinical and prognostic value of VExUS is significant. Recent studies indicate that the presence of moderate to severe congestion (VExUS Grade 2−3) in patients with Acute Heart Failure (AHF) is associated with increased mortality and rehospitalization rates. Furthermore, VExUS is fundamental for identifying congestive nephropathy, a condition present in approximately one-third of AHF patients, whose identification directly influences decongestion strategies (6). VExUS allows for the transformation of congestion assessment from a binary measure to a graduated physiological evaluation of organ venous pressure. Despite its promise, the routine integration of VExUS into clinical practice faces challenges. The accuracy of the

method depends significantly on operator experience and skill. There is still a need for greater methodological consensus to standardize its use across different patient populations (7, 17).

- **Artificial Intelligence (AI) in Imaging and Prediction: Artificial Intelligence (AI)**, through Machine Learning (ML) methods, represents the frontier in the application of new technologies in nephrology and cardiology (18, 19). AI has the capacity to analyze large volumes of clinical, biochemical, and imaging data in a multimodal manner. In CRS, AI offers the potential to overcome the limitations of traditional markers by processing complex information to **more accurately predict** the probability of developing AKI or the response to diuretic therapy, long before changes are observed in creatinine or conventional imaging parameters (1). For example, it could automate the segmentation of MRI images or classify subtle patterns in VExUS, thereby improving objectivity and allowing for earlier and more personalized therapeutic intervention.

Contemporary Therapeutic Strategies (2020–2025)

Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i)

SGLT2i (Empagliflozin, Dapagliflozin) are the therapy with the greatest impact on the cardiorenal continuum in the last decade. Evidence from large randomized clinical trials has consolidated their role as the cornerstone of modern treatment for heart failure and chronic kidney disease (20).

International clinical practice guidelines have converged on their recommendation for cardiorenal protection. Both the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (21) and the American Diabetes Association (ADA) guidelines (22) establish a Strong Recommendation (1A) for the use of SGLT2i in patients with type 2 diabetes and Chronic Kidney Disease (CKD) with an eGFR≥20 mL/min/1.73 m2, prioritizing agents with documented renal or cardiovascular benefit.

Furthermore, the Canadian Cardiovascular Society (CCS) (23) strongly recommends the use of SGLT2i both in patients with Heart Failure with reduced LVEF (LVEF≤40%) to reduce mortality and hospitalization for HF, and in patients with CKD (UACR>20 mg/mmol and eGFR≥25 mL/min/1.73 m2) to reduce the risk of composite cardiorenal events.

Contemporary Therapeutic Strategies (Continued)

The integration of SGLT2i requires specific precautions in the context of CRS, especially in volume management. KDIGO suggests that if a patient is at risk of hypovolemia, loop or thiazide diuretic doses should be considered for reduction before initiating SGLT2i treatment, and volume status should be monitored after initiation. This reflects the understanding that the drug's dual effects may require adjustments in decongestive management.

- **Cardiovascular Protection:** In patients with Heart Failure with Reduced Ejection Fraction (HFrEF), the EMPEROR-Reduced (Empagliflozin) and DAPA-HF (Dapagliflozin) trials demonstrated a significant reduction in the combined primary endpoint (cardiovascular death or hospitalization for HF). Specifically, EMPEROR-Reduced showed a 24% reduction in this endpoint (HR 0.76, 95% CI [0.67–0.87]; P<0.0001). This benefit was consistently observed in diabetic and non-diabetic patients, confirming a class effect (3).
- **Renal Protection:** These drugs provide robust renal protection by delaying the rate of GFR decline. The DAPA-CKD and other meta-analyses have confirmed their efficacy in reducing the risk of incident diabetes in patients with cardiovascular disease or CKD, highlighting their cardiovascular, renal, and metabolic benefits (20, 24). The strength of these results suggests that the primary mechanism of action of SGLT2i goes beyond glucoregulation, involving an improvement in renal hemodynamics (reduction of hyperfiltration) and an improvement in cardiac bioenergetics.

Angiotensin Receptor-Neprilysin Inhibitors (ARNIs)

ARNIs (Sacubitril/Valsartan) are essential in the treatment of HFrEF. Their application in Heart Failure with Preserved Ejection Fraction (HFpEF), relevant for CRS Type 2, was explored in the PARAGON-HF trial. Although the trial did not meet its primary endpoint in the overall HFpEF population, subgroup analysis suggested a possible benefit in patients with specific characteristics, such as a lower LVEF (close to 50%), female sex, and those with a history of declining renal function. Given that renal deterioration is an intrinsic component of CRS, these subgroups are particularly important for treatment stratification. Monitoring of renal function, blood pressure, and electrolytes is mandatory when initiating and titrating the dose (25).

Advanced Volume Management and Ultrafiltration

Advanced management of volume overload must be personalized and guided by functional assessment. While loop diuretics are the standard, it is crucial to avoid excessive volume depletion, as this can induce renal hypoperfusion and precipitate functional Acute Kidney Injury, thus worsening the prognosis (9).

Modern strategies propose that diuretic dose titration be modified according to clinical evolution and incorporate biomarkers like CA-125 and imaging (POCUS/VExUS) to ensure effective decongestion without compromising renal perfusion (12, 26). Ultrafiltration is generally reserved for cases of volume overload refractory to maximum diuretic doses, although evidence from clinical trials on its superiority is still under debate.

Critical Discussion

A. Synthesis and Impact of New Tools

The evidence gathered between 2015 and 2025 underscores a radical transformation in CRS management, moving from a supportive approach to a disease-modifying strategy. This transition is driven by the pathophysiological understanding that venous congestion is the primary engine of renal damage in heart failure, and by the introduction of drugs with dual cardiac and renal protection (3).

Diagnostic success lies in the integration of real-time hemodynamic information (VExUS) with evidence of structural cellular damage (NGAL/KIM-1) and the measurement of systemic congestion (CA-125). This multimodal approach allows for a more accurate classification of heart-induced renal deterioration and ensures that decongestion is not only effective but also safe, avoiding iatrogenic injury due to hypovolemia.

B. Knowledge Gaps and Limitations

Despite the advances, the main limitation in clinical practice is the absence of consensual international clinical practice guidelines exclusively addressing the diagnosis and management of CRS. Currently, practitioners must extrapolate recommendations from heart failure (AHA/ESC) and kidney disease (KDIGO) guidelines, which can generate inconsistencies in the management of patients with complex dual pathology.

From a technical perspective, the utility of the VExUS protocol is limited by the high dependence on operator experience for the acquisition and interpretation of Doppler images (7, 17). The lack

of universal methodological consensus hinders its integration as a standard tool, despite its potential to guide decongestion in congestive nephropathy.

C. Future Perspectives and Emerging Strategies

1. Artificial Intelligence (AI) and Machine Learning

The future of CRS management is projected toward precision medicine, with Artificial Intelligence (AI) as a catalyst (18). Machine Learning has the capacity to analyze heterogeneous datasets (clinical, biochemical, imaging, and genomic) to create robust predictive models. In CRS, AI will allow for finer risk stratification, identifying patients with a high probability of developing AKI or diuretic refractoriness much earlier than clinical manifestation (1, 18). This will facilitate early intervention and algorithmic adaptation of treatments.

2. Regenerative Therapies and Gene Editing

Gene therapies and gene editing (CRISPR) represent the farthest frontier of research (27). Advances in the delivery of genetic material using lipid nanoparticles (LNP) have reduced the immune response, opening the door to repeated dosing and in vivo correction of defective genes (28). These strategies are expected to expand beyond monogenic diseases to treat complex and prevalent conditions such as heart failure and CKD (CRS Type 4), offering the possibility of modifying the disease at a molecular level (27).

D. Summary Tables of Evidence

The results of the review are synthesized in the following tables, which compare the diagnostic modalities and fundamental therapeutic strategies, highlighting the most relevant evidence from the 2015–2025 period.

Table 1. *Comparison of Emerging Diagnostic Modalities in Cardiorenal Syndrome*

Modality	Assessment Objective	Key Advantages	Limitations	Prognostic/Clinical Impact
Natriuretic Peptides (NT-proBNP)	Myocardial Stress	High sensitivity for HF	Complex interpretation in AKI/CKD (elevation due to reduced clearance)	Standard of care, prognosis guidance
CA-125	Systemic Congestion/Serositis	Correlates with systemic volume overload, less GFR-dependent	Non-specific (can be elevated by other causes)	Useful for guiding diuretic titration in AHF
ATI Biomarkers (NGAL, KIM-1)	Early Structural Tubular Injury	Differentiates structural injury from functional azotemia	Requires standardization in routine clinical practice	Early detection and differentiation of kidney damage in CRS Type 1
VExUS Protocol (POCUS)	Venous Congestion and Intrarenal Pressure	Non-invasive, real-time, at the bedside	Operator-dependent, lack of consensus	Grade 2-3 associated with higher mortality and congestive nephropathy
Artificial Intelligence (AI)	Risk Prediction and Stratification	Multimodal analysis of big data for early prediction	Need for rigorous validation in clinical settings	Potential for personalized therapy and AKI prediction

Source: Ayala Briseño et al; Campos-Sáenz de Santamaría et al; Campos Sáenz de Santamaría et al; García-Blas et al; Latoch et al; Quiroga et al; Velastegui Guerrero et al (1,5–7,11,12,17).

Table 2. *Summary of Clinical Evidence for Fundamental Therapies in Cardiorenal Syndrome*

Therapeutic Class	Representative Drug	Key Clinical Trial	Relevant CRS Population	Specific Cardiorenal Benefits
SGLT2 Inhibitors	Empagliflozin, Dapagliflozin	EMPEROR-Reduced, DAPA-CKD	HF with reduced LVEF, CKD (with and without T2DM)	24% reduction in CV Death/HF Hosp.; Delay in CKD progression; class effect
ARNIs	Sacubitril/Valsartan	PARADIGM-HF, PARAGON-HF	HF with reduced LVEF / HFpEF subgroups	Reduction in mortality/hospitalizations in HFrEF. Possible benefit in HFpEF with lower LVEF and renal impairment
Volume Management	Diuretics (Furosemide)	CA-125 Guided Strategy	CRS Type 1 (AHF)	Optimization of decongestion by guiding titration and avoiding excessive depletion

Source: Ayala Briseño et al; Chávez-Iñiguez et al; García-Blas et al; Montejo Hernández et al; Wagdy (2,3,11,12,20).

Conclusions

The decade 2015-2025 has rewritten the understanding and the management of the Cardiorenal Syndrome. Now the pathophysiology centers now on the congestive nephropathy, where the increase of the intrarenal venous pressure, more than the hypoperfusion, is identified as the principal driver of the acute renal deterioration.

In the therapeutic scope, the SGLT2 Inhibitors have consolidated as the pharmacological intervention of greatest impact, offering dual cardiac and renal protection with a robust class effect, even in populations without diabetes. This is backed by strong recommendations from key guidelines like KDIGO (1A), ADA (1A) and CCS.

From the diagnostic point of view, the key for a safe management resides in the adoption of a multimodal approach that integrates the evaluation of early tubular injury biomarkers (NGAL/KIM-1) and systemic congestion markers (CA-125) with the dynamic hemodynamic evaluation at the foot of the bed provided by the VExUS protocol.

This combination permits differentiation between the structural renal injury and the hemodynamic dysfunction, guiding the diuretic titration towards an effective and safe euvolemia.

Facing the future, the investigation must center on the standardization of tools like VExUS and on the urgent development of specific clinical guidelines for the CRS. In parallel, the application of Artificial Intelligence and the progress in gene therapies promise to offer personalized predictive and therapeutic methods that will overcome the current limitations of cardiovascular and renal medicine.

Bibliography

1. Quiroga B, Santamaría Olomo R, Gorostidi M. Síndrome Cardiorrenal. Sociedad Española Nefrol. 2023;
2. Wagdy K. The EMPEROR-Reduced trial: SGLT2 inhibitors for heart failure get more support. Glob Cardiol Sci Pract [Internet]. 2020 Dec 30;2020(3). Available from: https://globalcardiologyscienceandpractice.com/index.php/gcsp/article/view/448
3. Chávez-Iñiguez JS, Sánchez-Villaseca SJ, García-Macías LA, Chávez-Iñiguez JS, Sánchez-Villaseca SJ, García-Macías LA. Síndrome cardiorrenal: clasificación, fisiopatología,

diagnóstico y tratamiento. Una revisión de las publicaciones médicas. Arch Cardiol México [Internet]. 2021 Nov 23;92(2). Available from: https://www.archivoscardiologia.com/frame_esp.php?id=384

4. Escalona-González SO, Pavón-Rojas AJ, Cisnero-Reyes L, González-Milán ZC. Síndrome cardiorrenal, revisión de la literatura. Rev científica Estud 2 Diciembre [Internet]. 2020 Sep 8;3(3 SE-Artículos de Revisión):e77. Available from: https://revdosdic.sld.cu/index.php/revdosdic/article/view/77

5. Velastegui Guerrero AM, Remache Catota GP, Adriano Cuvi AF, Caisatoa Cabrera ED, Silva Sampedro KA. Utilidad clínica de los biomarcadores en el diagnóstico y pronóstico del síndrome cardiorrenal. Multidiscip Collab J [Internet]. 2025 Sep 13;3(3):131–42. Available from: https://mcjournal.editorialdoso.com/index.php/home/article/view/76

6. Latoch E, Konończuk K, Muszyńska-Rosłan K, Taranta-Janusz K, Wasilewska A, Szymczak E, et al. Urine NGAL and KIM-1—Tubular Injury Biomarkers in Long-Term Survivors of Childhood Solid Tumors: A Cross-Sectional Study. J Clin Med [Internet]. 2021 Jan 21;10(3):399. Available from: https://www.mdpi.com/2077-0383/10/3/399

7. Campos Sáenz de Santamaría A, Alcaine Otín A, Crespo Aznarez S, Josa Laorden C, Esterellas Sánchez L, Sánchez Marteles M, et al. Análisis multimodal de la congestión y utilidad pronóstica del protocolo VExUS en pacientes hospitalizados por insuficiencia cardiaca en un hospital terciario. Rev Clínica Española [Internet]. 2025;225(7). Available from: https://www.revclinesp.es/es-analisis-multimodal-congestion-utilidad-pronostica-articulo-S0014256525000955

8. Sánchez Baena AH. Plan de cuidados estandarizado en el abordaje del paciente con síndrome cardio-renal. [Internet]. UNIVERSIDAD AUTÓNOMA DE SAN LUIS POTOSÍ; 2025. Available from: https://ninive.uaslp.mx/xmlui/bitstream/handle/i/9401/TesinaE.FEPZM.2025.Plan.Sánchez.pdf?sequence=1&isAllowed=y

9. BARCIA ANDRADE A. Sistema renina angiotensina, riesgo cardiovascular y de infecciones, actualización [Internet]. UNIVERSIDAD ESTATAL DEL SUR DE MANABI;

2022. Available from: https://repositorio.unesum.edu.ec/bitstream/53000/3752/1/Barcia.A_Sistema renina angiotensina%2C riesgo cardiovascular y de infeciones%2C actualizacion.pdf

10. Cargua Ríos JN. Systematic analysis of recent scientific literature on edentulism using the PRISMA 2020 methodology. Salud, Cienc y Tecnol [Internet]. 2024 Dec 4;4. Available from: https://sct.ageditor.ar/index.php/sct/article/view/1251

11. García-Blas S, Bonanad C, Llàcer P, Ventura S, Núñez JM, Sánchez R, et al. Estrategias diuréticas en insuficiencia cardiaca aguda con disfunción renal: terapia convencional frente a guiada por el antígeno carbohidrato 125. Diseño de ensayo clínico. Rev Española Cardiol [Internet]. 2017 Dec;70(12):1067–73. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0300893217301239

12. Ayala Briseño A, Medina Estrada JL, Salgado Barrera DL, Arteaga Bruno LA, Bustos Luna KA. Uso de Biomarcadores en el Manejo de la Congestión en Pacientes con Insuficiencia Cardíaca Aguda. Cienc Lat Rev Científica Multidiscip [Internet]. 2025 Nov 12;9(5):12815–33. Available from: https://ciencialatina.org/index.php/cienciala/article/view/20514

13. Moncho Francés F, Montomoli M, González Rico M. Síndrome cardiorrenal: Nuevas herramientas diagnósticas. Soc Española Nefrol. 2022;

14. Aguilar-Torres R, Gómez de Diego JJ, Forteza-Albert JF, Vivancos-Delgado R. Actualización en técnicas de imagen cardiaca: ecocardiografía, cardiorresonancia y tomografía computarizada. Rev Española Cardiol [Internet]. 2010 Jan;63:116–31. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0300893210701457

15. Chango-Azanza DX, Rosales-Uvera S, Vásquez Z, Munín MA, Obregón R. El valor añadido emergente de la resonancia magnética cardiaca sobre la ecocardiografía en la evaluación de la insuficiencia mitral funcional. Cardiovasc Metab Sci [Internet]. 2021;32(4):188–96. Available from: https://www.medigraphic.com/cgi-bin/new/resumen.cgi?IDARTICULO=102770

16. Lara García A. VExUS, valoración ecográfica de la congestión [Internet]. 2024. Available from: https://www.cardioteca.com/infografias-cardiovasculares/5524-vexus-valoracion-ecografica-de-la-congestion.html

17. Campos-Sáenz de Santamaría A, Albines Fiestas ZS, Crespo-Aznarez S, Esterellas-Sánchez LK, Sánchez-Marteles M, Garcés-Horna V, et al. VExUS Protocol Along Cardiorenal Syndrome: An Updated Review. J Clin Med [Internet]. 2025 Feb 17;14(4):1334. Available from: https://www.mdpi.com/2077-0383/14/4/1334

18. Martín de Francisco AL. ARTIFICIAL: La Nueva Inteligencia y su Aplicación en Nefrología. Soc Española Nefrol. 2024;

19. Mayo Clinic. Inteligencia artificial en la medicina cardiovascular [Internet]. 2025. Available from: https://www.mayoclinic.org/es/departments-centers/ai-cardiology/overview/ovc-20486648

20. Montejo Hernández JD, Lopera JM, Rosselli C, Ronderos I, Daza R, Yama-Mosquera E, et al. Consenso colombiano basado en evidencia y en la opinión de expertos para la utilización de los inhibidores del cotransportador sodio-glucosa tipo 2 (iSGLT-2) en el continuo cardiorrenal de pacientes con enfermedad renal crónica. Rev Colomb Nefrol [Internet]. 2025 May 27;12(2). Available from: https://revistanefrologia.org/index.php/rcn/article/view/938

21. KDIGO. KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION AND MANAGEMENT OF CHRONIC KIDNEY DISEASE [Internet]. 2024. Available from: https://kdigo.org/wp-content/uploads/2024/03/KDIGO-2024-CKD-Guideline.pdf

22. American Diabetes Association. The American Diabetes Association's Standards of Care in Diabetes—2025 [Internet]. 2025. Available from: https://professional-diabetes-org.translate.goog/sites/dpro/files/2024-12/2025-ADA-SOC-Slide-Deck-all-recommendations-FINAL-12-9-24.pptx?_x_tr_sl=en&_x_tr_tl=es&_x_tr_hl=es&_x_tr_pto=tc

23. Toquica AR, Pérez S OA. Actualización 2021 de las Guías Canadienses de Insuficiencia Cardíaca-CCS/CHFS: Definición de un nuevo estándar farmacológico para la insuficiencia cardíaca con fracción de eyección reducid [Internet]. Sociedad Colombiana de Cardiología

y Cirugía Cardiovascular; 2021. Available from: https://scc.org.co/wp-content/uploads/2018/10/PAD-162-GUIAS-2021-ICFER-CANADIENSES-.pdf

24. Ostrominski JW, Højbjerg Lassen MC, Claggett BL, Miao ZM, Inzucchi SE, Docherty KF, et al. Sodium-glucose co-transporter 2 inhibitors and new-onset diabetes in cardiovascular or kidney disease. Eur Heart J [Internet]. 2024 Nov 21; Available from: https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehae780/7905901

25. Dr oracle. What are the indications for using Angiotensin Receptor-Neprilysin Inhibitor (ARNI) in Heart Failure with preserved Ejection Fraction (HFpEF)? [Internet]. Available from: https://www.droracle.ai/articles/273893/what-are-the-indications-for-using-angiotensin-receptor-neprilysin-inhibitor

26. Ortiz Cortés C. Manejo de la congestión y uso de diuréticos en la IC (y II) [Internet]. 2019. Available from: https://secardiologia.es/blog/10369-manejo-de-la-congestion-y-uso-de-diureticos-en-la-ic-parte-ii

27. Continental Hospitals. Avances en la terapia génica en 2025 [Internet]. 2025. Available from: https://continentalhospitals.com/es/blog/gene-therapy-breakthroughs-in-2025/

28. Henderson H. Ensayos clínicos CRISPR: una actualización en 2025 [Internet]. 2025. Available from: https://innovativegenomics.org/es/noticias/ensayos-clínicos-crispr-2025/

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