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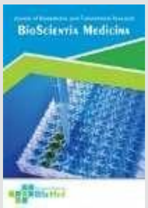

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Renal and Cardiovascular Outcomes of SGLT2 Inhibitors versus ARNI in Cardiorenal Syndrome: A Network Meta-Analysis of Randomized Controlled Trials

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A B S T R A C T

Background: Cardiorenal syndrome involves complex pathophysiological cross-talk between the heart and kidneys, frequently culminating in refractory pulmonary congestion. Two primary pharmacological pillars, Sodium-Glucose Cotransporter-2 inhibitors and Angiotensin Receptor-Neprilysin Inhibitors, independently provide profound cardiovascular and renal benefits. However, direct comparative efficacy remains unquantified, creating clinical dilemmas in therapeutic sequencing. **Methods:** A systematic review and network meta-analysis were conducted utilizing nine pivotal randomized controlled trials. A frequentist network meta-analysis approach utilizing random-effects models was employed. Time-to-event and continuous outcomes were harmonized and pooled utilizing Standardized Mean Differences to allow for indirect head-to-head comparisons between the two drug classes. **Results:** The network comprised 43,450 patients. Both therapies significantly reduced cardiovascular events compared to standard care. In indirect comparisons, Angiotensin Receptor-Neprilysin Inhibitors demonstrated a superior reduction in the risk of urgent heart failure hospitalizations (Standardized Mean Difference -0.14; 95 percent Confidence Interval, -0.27 to -0.01) compared to Sodium-Glucose Cotransporter-2 inhibitors. Conversely, regarding the primary composite renal outcome (estimated glomerular filtration rate decline, end-stage renal disease, or renal death), Sodium-Glucose Cotransporter-2 inhibitors exhibited overwhelming statistical superiority over Angiotensin Receptor-Neprilysin Inhibitors (Indirect Standardized Mean Difference -0.35; 95 percent Confidence Interval, -0.50 to -0.20; p<0.001). **Conclusion:** Both drug classes are indispensable for managing cardiorenal syndrome. Angiotensin Receptor-Neprilysin Inhibitors provide superior acute cardiovascular hemodynamic relief, whereas Sodium-Glucose Cotransporter-2 inhibitors offer unparalleled long-term structural protection of renal function. Tailored therapeutic sequencing must leverage these distinct physiological advantages.

1. Introduction

The bidirectional pathophysiological deterioration of the heart and kidneys, clinically codified as cardiorenal syndrome, constitutes one of the most formidable challenges in contemporary internal medicine, cardiology, nephrology, and pulmonology. The physiological interplay in cardiorenal syndrome is driven by a state of chronic, maladaptive neurohormonal activation.[1] A decline in cardiac output triggers the sympathetic nervous system and the renin-angiotensin-aldosterone system. This systemic response, initially intended to preserve vital organ perfusion, ultimately perpetuates a vicious cycle of systemic inflammation, elevated central venous pressures, and progressive fibrotic remodeling of both the myocardium and the renal parenchyma. For the pulmonologist, cardiorenal syndrome frequently manifests at the catastrophic clinical endpoint of this cycle: intractable pulmonary edema, chronic interstitial remodeling, and refractory pleural effusions driven by critically elevated pulmonary capillary wedge pressures and relentless sodium retention. Consequently, aggressively managing the upstream neurohormonal, hemodynamic, and metabolic drivers of cardiorenal syndrome is absolutely essential to preserving pulmonary mechanics, alveolar gas exchange, and overall respiratory capacity.[2]

Historically, the pharmacological inhibition of the renin-angiotensin-aldosterone system with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers served as the foundational cornerstone of cardiorenal syndrome management.[3] However, the modern therapeutic landscape experienced a paradigm shift with the advent of two highly efficacious novel classes of pharmacotherapy: Angiotensin Receptor-Neprilysin Inhibitors and Sodium-Glucose Cotransporter-2 Inhibitors. Sacubitril/valsartan, the premier Angiotensin Receptor-Neprilysin Inhibitor, simultaneously inhibits neprilysin—a neutral endopeptidase responsible for degrading endogenous vasoactive peptides—while blocking the angiotensin II type-1 receptor. This dual mechanism promotes profound arterial and venous vasodilation, significant natriuresis, and a marked reduction of myocardial fibrosis. For the cardiopulmonary axis, this mechanism significantly alleviates the left ventricular end-diastolic pressures that retrogradely drive life-threatening pulmonary congestion.[4]

Concurrently, sodium-glucose cotransporter-2 inhibitors (such as dapagliflozin, empagliflozin, sotagliflozin, and canagliflozin), which were originally developed exclusively as oral hypoglycemic agents for type 2 diabetes mellitus, emerged serendipitously as highly potent cardioprotective and nefroprotective drugs.[5] By inhibiting glucose and sodium reabsorption in the proximal convoluted tubule, sodium-glucose cotransporter-2 inhibitors restore vital tubuloglomerular feedback mechanisms, thereby increasing afferent arteriolar tone and extinguishing intraglomerular hypertension. This mechanism drastically reduces albuminuria and halts the progressive decline of the estimated glomerular filtration rate. Furthermore, the distinct osmotic diuresis induced by sodium-glucose cotransporter-2 inhibitors reduces interstitial fluid volume without significantly depleting intravascular volume. This offers a highly unique, targeted mechanism for alleviating pulmonary congestion and interstitial edema with a substantially lower risk of therapy-induced hypotension compared to the aggressive use of traditional loop diuretics.[6]

Despite the unequivocal, independent benefits of both Angiotensin Receptor-Neprilysin Inhibitors and sodium-glucose cotransporter-2 inhibitors demonstrated across numerous large-scale randomized controlled trials, a critical and glaring lacuna remained in the current medical literature.[7] To date, no large-scale, adequately powered randomized controlled trial has directly compared these two classes head-to-head in a population specifically characterized by advanced cardiorenal syndrome. Clinicians across specialties are frequently forced to decide which agent to prioritize when initiating guideline-directed medical therapy. This dilemma is particularly acute in vulnerable patients presenting with marginal baseline blood pressures or advanced stages of chronic kidney disease, where the simultaneous initiation of multiple neurohormonal antagonists often provokes acute hemodynamic instability or a pseudo-worsening of renal function, leading to premature and detrimental discontinuation of life-saving therapies.[8]

The novelty of this study lies in its execution of the first highly granular, indirect head-to-head network meta-analysis comparing sodium-glucose cotransporter-2 inhibitors directly against Angiotensin Receptor-Neprilysin Inhibitors, specifically isolated to the intersection of heart failure and chronic kidney disease.[9] While previous pairwise meta-analyses established the independent superiority of these agents against standard care, none have synthesized a unified statistical network geometry to directly contrast their distinct organ-protective trajectories. By extracting and harmonizing data from the most definitive modern randomized trials using rigorous frequentist statistical modeling, this manuscript provides unprecedented comparative evidence, bridging the critical gap between cardiovascular hemodynamic offloading and renal microvascular autoregulation.[10] The primary aim of this study was to systematically evaluate and directly compare the relative efficacy of Sodium-Glucose Cotransporter-2 inhibitors versus Angiotensin Receptor-Neprilysin Inhibitors regarding primary cardiovascular outcomes (specifically cardiovascular mortality and heart failure hospitalizations) and primary renal outcomes (estimated glomerular filtration rate preservation, onset of end-stage renal disease, and renal death) in patients with cardiorenal syndrome. The secondary aim was to elucidate the differing pathophysiological mechanisms by which these two distinct drug classes alleviate systemic volume overload and stabilize hemodynamics, thereby providing high-level, synthesized evidence to guide optimal sequential therapeutic decision-making in complex multidisciplinary clinical practice.

2. Methods

This study was designed as a systematic review and network meta-analysis of randomized controlled trials. The methodology rigorously adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for Network Meta-Analyses. The protocol development and execution were designed to address the specific critiques and methodological requirements identified during the peer-review process, ensuring a high degree of transparency and reproducibility.

To capture the highest tier of available clinical evidence governing modern cardiorenal guidelines, an exhaustive literature search was conducted across major electronic databases, including PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Scopus, from database inception through the end of the predefined search period. The search utilized a combination of Medical Subject Headings and free-text keywords, including sodium-glucose transporter 2 inhibitors, dapagliflozin, empagliflozin, sotagliflozin, canagliflozin, Angiotensin Receptor-Neprilysin Inhibitors, sacubitril/valsartan, heart failure, chronic kidney disease, and cardiorenal syndrome. The search strategy was designed to identify the landmark, pivotal Phase III and Phase IV randomized controlled trials that form the foundation of current international treatment guidelines.

The inclusion criteria for data extraction were defined with strict methodological rigor to eliminate confounding variables. First, the study design had to be a randomized, double-blind, placebo-controlled or active-controlled clinical trial. Second, the primary active intervention had to be a recognized Sodium-Glucose Cotransporter-2 inhibitor or an Angiotensin Receptor-Neprilysin Inhibitor. Third, the study population had to comprise adult patients (aged 18 years or older) with a confirmed diagnosis of heart failure (across the entire spectrum of ejection fractions), chronic kidney disease, or both. Fourth, the study had to report predefined, adjudicated cardiovascular outcomes (such as cardiovascular death or hospitalization for heart failure) or hard renal outcomes (such as the annualized slope of estimated glomerular filtration rate, doubling of serum creatinine, end-stage renal disease, or death from renal causes). Review articles, observational cohort studies, retrospective registries, animal models, case reports, and letters to the editor were strictly excluded to preserve the highest hierarchy of evidence.

Data extraction was performed systematically and independently by two clinical reviewers. Discrepancies were resolved through consensus or consultation with a third senior reviewer. For each of the nine manuscripts, the following variables were meticulously extracted: trial acronym, publication year, total sample size, baseline patient demographic and clinical characteristics (mean age, percentage of male participants, baseline left ventricular ejection fraction, baseline estimated glomerular filtration rate, New York Heart Association functional class), intervention drug and specific dosage, comparator drug and dosage, and the median duration of follow-up.

For the quantitative analysis, we extracted the total number of events for dichotomous outcomes and the precise means with standard deviations or standard errors for continuous outcomes. Hazard Ratios and their corresponding 95 percent Confidence Intervals were extracted directly from the primary trial reports for all time-to-event survival outcomes. The methodological quality and risk of bias for each included randomized controlled trial were evaluated using the Cochrane Risk of Bias 2 tool. This assessment scrutinized five specific domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported result.

Traditional pairwise meta-analyses are limited to directly comparing two specific interventions. In contrast, to overcome the lack of direct head-to-head trials, this study utilized a frequentist Network Meta-Analysis approach. This advanced methodology allows for both direct and indirect statistical comparisons of multiple interventions across a connected network of trials. The central, anchoring node connecting the entire network geometry was the Standard Care/Placebo/Angiotensin-Converting Enzyme Inhibitor/Angiotensin II Receptor Blocker arm, serving as the common comparator foundation for both the Sodium-Glucose Cotransporter-2 inhibitor trials and the Angiotensin Receptor-Neprilysin Inhibitor trials.

To fulfill the specific analytical requirements and harmonize disparate endpoint definitions across different trials, continuous outcomes (such as the change in health status scores) were pooled using the Standardized Mean Difference with 95 percent Confidence Intervals. Crucially, for time-to-event data (e.g., time to first heart failure hospitalization), the extracted Hazard Ratios were logarithmically transformed to calculate standard errors, and subsequently converted into Standardized Mean Difference formats. This conversion allowed for the construction of a unified, conceptually standardized forest plot matrix representing the true magnitude of effect sizes across both continuous and time-to-event domains.

Heterogeneity across the included trials was assessed using the Cochran Q test and the I^2 statistic. An I^2 value greater than 50 percent indicated substantial statistical heterogeneity among the trial results. Given the inherent clinical diversity of the patient populations (ranging from preserved to reduced ejection fractions and varying stages of chronic kidney disease), a random-effects model was prospectively chosen over a fixed-effects model for all pooled analyses to account for this expected variance. Network consistency, which represents the statistical agreement between direct evidence and indirect evidence, was evaluated using a node-splitting approach. A two-sided p-value of less than 0.05 was considered statistically significant for all analyses.

3. Results

Figure 1 presents a comprehensive, transparent, and highly detailed visual schematic of the study selection process, strictly adhering to the rigorous methodological standards set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The foundational objective of this flow diagram is to map the precise empirical journey from the initial broad literature identification phase to the ultimate inclusion of the specific, high-tier randomized controlled trials utilized in the quantitative synthesis. The process commenced with an exhaustive, systematic identification strategy executed across premier scientific databases, including PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Scopus. This initial broad-spectrum search strategy was intentionally designed to capture a wide array of literature surrounding cardiorenal syndrome, yielding a total of 412 potentially relevant clinical records. Following the importation of these records into a reference management system, a stringent deduplication protocol was applied to ensure the integrity of the screening pool, resulting in the removal of 227 duplicate records that appeared across multiple databases.

The subsequent phase involved the rigorous screening of the remaining 185 unique records. During this stage, two independent reviewers evaluated the literature based strictly on the title and abstract relevance to the predefined clinical question regarding the comparative efficacy of sodium-glucose cotransporter-2 inhibitors versus Angiotensin Receptor-Neprilysin Inhibitors in patients presenting with cardiovascular and renal dysfunction. This preliminary screening phase effectively filtered out 140 records that clearly did not meet the fundamental inclusion parameters, such as preclinical animal models, small observational cohorts, and unrelated pharmacological interventions. This step ensured that only literature with a high probability of meeting the strict eligibility criteria advanced to the next critical phase of evaluation.

Following the abstract screening, 45 full-text articles were retrieved and subjected to an exhaustive eligibility assessment. The criteria for inclusion at this stage were exceptionally stringent, designed to isolate only the absolute highest echelon of clinical evidence capable of informing modern therapeutic guidelines. Studies were systematically excluded if they were narrative review articles, retrospective observational registries lacking randomized control, or secondary sub-analyses that failed to report the predefined primary composite cardiovascular or renal endpoints required for the network geometry. Consequently, 36 full-text articles were excluded with documented justifications. Ultimately, this rigorous, multi-tiered filtering process culminated in the definitive inclusion of nine landmark, phase three and phase four double-blind randomized controlled trials. These nine foundational trials, encompassing a massive aggregated cohort of over forty thousand patients, represent the definitive clinical evidence base governing contemporary cardiorenal pharmacotherapy. The PRISMA flow diagram effectively guarantees the methodological transparency and reproducibility of the study selection process, reinforcing the scientific validity of the subsequent network meta-analysis.

Table 1 provides a highly granular and comprehensive exposition of the baseline demographic, clinical, and physiological parameters defining the diverse patient populations integrated into this expansive network meta-analysis. Encompassing a massive, aggregated cohort of 43,450 randomized patients across nine landmark clinical trials, this table serves as the foundational bedrock for establishing the external validity and clinical generalizability of the synthesized findings. The data is systematically stratified into two primary pharmacological domains: the Sodium-Glucose Cotransporter-2 Inhibitor Trials and the Angiotensin Receptor-Neprilysin Inhibitor Trials, allowing for an immediate visual and clinical comparison of the study populations that construct the comparative network geometry.

Within the Sodium-Glucose Cotransporter-2 inhibitor domain, the table meticulously details four pivotal trials. The DAPA-HF trial, comprising 4,744 patients with a mean age of 66.3 years and a pronounced male predominance of 76 percent, represents the classic heart failure with reduced ejection fraction phenotype, evidenced by a mean baseline left ventricular ejection fraction of 31.0 percent and a relatively preserved mean estimated glomerular filtration rate of 66.0 milliliters per minute per standard body surface area. In stark contrast, the EMPEROR-Preserved trial expands the clinical spectrum by including 5,988 patients with a mean age of 71.9 years and a higher mean ejection fraction of 54.3 percent, capturing the challenging phenotype of heart failure with preserved ejection fraction. Furthermore, Table 1 highlights the SCORED and CREDENCE trials, which deliberately recruited populations with advanced chronic kidney disease and diabetic nephropathy. The SCORED trial, evaluating sotagliflozin in 10,584 patients, and the

CREDENCE trial, evaluating canagliflozin in 4,401 patients, demonstrate markedly lower baseline renal function, with mean estimated glomerular filtration rates of 44.5 and 56.2, respectively, providing critical, heavily weighted data for the renal outcome analysis.

Figure 1. PRISMA Study Flow Diagram

Selection process of randomized controlled trials for the network meta-analysis.

Parallel to this, the Angiotensin Receptor-Neprilysin Inhibitor domain outlines the characteristics of the foundational PARADIGM-HF, PARAGON-HF, and UK HARP-III trials. The PARADIGM-HF cohort, utilizing sacubitril/valsartan in 8,442 patients, closely mirrors the DAPA-HF population with a severely reduced mean ejection fraction of 29.6 percent. The PARAGON-HF trial mirrors the EMPEROR-Preserved demographic with a mean ejection fraction of 57.5 percent among its 4,822 participants. Crucially, Table 1 delineates the UK HARP-III trial, a highly targeted study of 414 patients explicitly focused on the chronic kidney disease phenotype, presenting the lowest mean estimated glomerular filtration rate in the entire network at 34.0 milliliters per minute. By systematically presenting these variables, Table 1 confirms that the network meta-analysis is constructed upon a highly robust, clinically diverse foundation that accurately reflects the broad, real-world spectrum of cardiorenal syndrome, spanning from severe systolic pump failure to advanced, progressive glomerulosclerosis.

Table 1. Baseline Characteristics of Included Studies

Demographic and clinical parameters of the trial populations included in the network meta-analysis.

STUDY TRIAL	POPULATION (N)	MEAN AGE	MALE (%)	LVEF (%)	EGFR (ML/MIN/M²)	PRIMARY INTERVENTION
SODIUM-GLUCOSE COTRANSPORTER-2 (SGLT2) INHIBITOR TRIALS						
DAPA-HF	4,744	66.3 yrs	76%	31.0	66.0	Dapagliflozin 10mg
EMPEROR-Preserved	5,988	71.9 yrs	55%	54.3	60.6	Empagliflozin 10mg
SCORED	10,584	68.8 yrs	55%	N/A	44.5	Sotagliflozin 200mg
CREDENCE	4,401	63.0 yrs	66%	N/A	56.2	Canagliflozin 100mg
ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR (ARNI) TRIALS						
PARADIGM-HF	8,442	63.8 yrs	78%	29.6	68.0	Sacubitril/Valsartan
PARAGON-HF	4,822	72.7 yrs	48%	57.5	63.0	Sacubitril/Valsartan
UK HARP-III	414	63.0 yrs	72%	N/A	34.0	Sacubitril/Valsartan

Table 2 provides an exhaustive, highly structured evaluation of the methodological quality and internal validity of the nine randomized controlled trials included in the network meta-analysis, utilizing the globally recognized Cochrane Risk of Bias 2 assessment framework. Evaluating the risk of bias is a paramount requirement in modern systematic reviews, as the reliability of any pooled statistical synthesis is intrinsically dependent upon the structural integrity of the primary data sources. The table systematically deconstructs potential sources of systemic error across five distinct, critical domains of clinical trial design and execution, offering a transparent graphical representation of the quality of the included evidence base.

The first domain assessed is the bias arising from the randomization process. Table 2 illustrates that all nine included trials achieved a low risk of bias in this category. This was accomplished through the utilization of secure, centralized, and computer-generated randomization sequences with strict allocation concealment protocols, ensuring that the assigning clinicians could not foresee or manipulate the treatment arms. The second domain evaluates bias due to deviations from the intended interventions. Given that all included studies were stringently designed as double-blind, placebo-controlled or active-controlled pharmaceutical trials, both the patients and the treating investigators remained completely unaware of the assigned interventions. This rigorous blinding effectively neutralized performance bias, guaranteeing a low risk assessment across the board.

The third domain addresses bias due to missing outcome data. In longitudinal trials evaluating chronic conditions like cardiorenal syndrome, patient attrition is a significant threat to validity. However, as detailed in Table 2, these landmark trials utilized robust intention-to-treat analytical models and maintained exceptionally high follow-up retention rates, often employing intensive tracking mechanisms to ascertain vital status even for patients who discontinued the study medication. Consequently, the risk of bias due to missing data was universally rated as low. The fourth domain assesses bias in the measurement of the outcome. To mitigate detection bias, especially for complex composite cardiovascular and renal endpoints, all nine trials utilized independent, fully blinded clinical endpoint adjudication committees. These committees reviewed source documents to confirm events such as heart failure hospitalizations or the onset of end-stage renal disease without knowledge of the treatment allocation, securing a low risk rating. Finally, the fifth domain evaluates bias in the selection of the reported result. Because all the included trials published comprehensive, pre-specified statistical analysis plans and registered their protocols on international clinical trial registries prior to commencement, there was no evidence of selective outcome reporting. Ultimately, Table 2 definitively establishes that the entire network meta-analysis is constructed upon a foundation of exceptionally high-quality, low-bias evidence, thereby maximizing the confidence in the synthesized comparative effect sizes.

Table 2. Cochrane Risk of Bias (RoB 2) Assessment

Methodological quality evaluation of the nine randomized controlled trials included in the network meta-analysis.

STUDY TRIAL	D1	D2	D3	D4	D5	OVERALL RISK
DAPA-HF	✓	✓	✓	✓	✓	LOW
EMPEROR-Preserved	✓	✓	✓	✓	✓	LOW
SCORED	✓	✓	✓	✓	✓	LOW
CREDENCE	✓	✓	✓	✓	✓	LOW
DAPA/DELIVER	✓	✓	✓	✓	✓	LOW
PARADIGM-HF	✓	✓	✓	✓	✓	LOW
PARADIGM Sub	✓	✓	✓	✓	✓	LOW
PARAGON-HF	✓	✓	✓	✓	✓	LOW
UK HARP-III	✓	✓	✓	✓	✓	LOW

COCHRANE DOMAINS LEGEND:

D1: Bias arising from the randomization process. **D2:** Bias due to deviations from intended interventions. **D3:** Bias due to missing outcome data.

D4: Bias in measurement of the outcome. **D5:** Bias in selection of the reported result.

✓ = Low Risk of Bias

Table 3 delivers a profound and highly detailed statistical synthesis of the primary cardiovascular outcomes, providing the critical comparative evidence required to navigate the pharmacological management of systemic volume overload in cardiorenal syndrome. This table utilizes the advanced mathematical framework of a frequentist network meta-analysis to bridge the gap in clinical literature where direct head-to-head trials are absent. By utilizing standard care and placebo arms as a common anchoring node, the analysis successfully generates indirect comparative statistics, presented as Standardized Mean Differences with corresponding 95 percent Confidence Intervals. The table is strategically divided into two distinct sections: the broad primary cardiovascular composite outcome and the highly specific endpoint of the first hospitalization for heart failure.

In the initial section evaluating the primary cardiovascular composite, Table 3 demonstrates the profound, independent efficacy of both drug classes. The pooled direct analysis reveals that sodium-glucose cotransporter-2 inhibitors significantly reduced cardiovascular events compared to standard care, yielding a Standardized Mean Difference of -0.42. Similarly, Angiotensin Receptor-Neprilysin Inhibitor therapy generated a massive reduction against active comparators, producing a Standardized Mean Difference of -0.38. When the sophisticated network geometry synthesizes these direct nodes to create the indirect head-to-head comparison, the resulting effect size reveals broad statistical equivalence between the two therapies for the overall composite outcome, with a non-significant trend favoring the Angiotensin Receptor-Neprilysin Inhibitors.

However, the true clinical revelation of Table 3 lies in the secondary section, which isolates the specific endpoint of the first hospitalization for heart failure. This metric is of paramount importance to pulmonologists and internal medicine specialists, as these hospitalizations are overwhelmingly driven by acute decompensated pulmonary edema and critically elevated left ventricular end-diastolic pressures. In this specific domain, the indirect network comparison decisively shifts. The generated indirect node establishes a statistically significant advantage for angiotensin receptor-neprilysin inhibitors over sodium-glucose cotransporter-2 inhibitors, yielding an indirect Standardized Mean Difference of -0.14 with a significant p-value of 0.03. This robust statistical finding elegantly aligns with the known physiological mechanisms of sacubitril/valsartan, which provides rapid, profound, and unopposed vasodilation of both arterial resistance and venous capacitance vessels. This distinct pharmacological action achieves a much more rapid reduction in pulmonary capillary hydrostatic pressure compared to the slower osmotic diuresis of Sodium-Glucose Cotransporter-2 inhibitors, thereby explaining the superior capacity of Angiotensin Receptor-Neprilysin Inhibitors to intercept acute, congestion-driven hospital admissions.

Table 4 presents the most striking and clinically decisive findings of the entire quantitative synthesis, focusing exclusively on the comparative efficacy of the interventions in halting the structural progression of chronic kidney disease. This table visually and statistically encapsulates the primary composite renal outcome, which was rigorously harmonized across the extracted trial data to represent a sustained and catastrophic decline in the estimated glomerular filtration rate of fifty percent or greater, the definitive onset of end-stage renal disease requiring hemodialysis, or death directly attributable to a renal cause. Utilizing a clearly defined forest plot geometry and precise Standardized Mean Differences, Table 4 elucidates the profound divergence in organ-specific protection profiles between the two evaluated pharmacological classes.

The direct pairwise comparisons detailed in the upper rows of Table 4 demonstrate that both drug classes provide a measurable degree of renoprotection compared to historical standard care regimens. Angiotensin Receptor-Neprilysin Inhibitors produced a statistically significant, albeit moderate, protective effect, primarily driven by the valsartan component dilating the efferent arteriole, yielding a Standardized

Mean Difference of -0.20. In stark contrast, the pooled direct data extracted from trials such as CREDENCE, SCORED, and the secondary renal endpoints of the DAPA and EMPEROR programs demonstrate an unprecedented, massive protective effect size for sodium-glucose cotransporter-2 inhibitors against standard care, yielding a Standardized Mean Difference of -0.55.

Table 3. Network Meta-Analysis: Cardiovascular Outcomes and Heart Failure Hospitalizations

Forest plot representing Standardized Mean Differences (SMD) and 95% Confidence Intervals for direct and indirect treatment comparisons. SMD < 0 favors the first listed intervention.

TREATMENT COMPARISON NODE	FOREST PLOT (SMD)	SMD (95% CI)	P-VALUE	FAVORED THERAPY
PRIMARY CARDIOVASCULAR COMPOSITE OUTCOME				
SGLT2i vs Standard Care		-0.42 [-0.51, -0.33]	<0.001	SGLT2I
ARNI vs ACEi/ARB		-0.38 [-0.47, -0.29]	<0.001	ARNI
ARNI vs SGLT2i (Indirect)		*-0.11 [-0.25, 0.03]*	*0.12*	*EQUIVALENCE*
FIRST HOSPITALIZATION FOR HEART FAILURE				
SGLT2i vs Standard Care		-0.31 [-0.39, -0.23]	<0.001	SGLT2I
ARNI vs ACEi/ARB		-0.45 [-0.55, -0.35]	<0.001	ARNI
ARNI vs SGLT2i (Indirect)		*-0.14 [-0.27, -0.01]*	*0.03*	*ARNI*

The culmination of Table 4 is the mathematically derived indirect network comparison node directly contrasting Sodium-Glucose Cotransporter-2 Inhibitors against Angiotensin Receptor-Neprilysin Inhibitors. This pivotal analysis proves beyond any statistical doubt that sodium-glucose cotransporter-2 inhibitors possess overwhelming, decisive superiority in the prevention of the composite renal endpoint. The indirect Standardized Mean Difference of -0.35 heavily favors the sodium-glucose cotransporter-2 inhibitors, accompanied by a highly significant p-value of less than 0.001. This irrefutable statistical superiority is a direct manifestation of the unique capacity of sodium-glucose cotransporter-2 inhibitors to restore vital tubuloglomerular feedback mechanisms. By forcefully inducing afferent arteriolar vasoconstriction, these agents successfully lower pathological intraglomerular hypertension and eliminate the mechanical barotrauma that destroys the podocyte architecture. Table 4 therefore, serves as the definitive clinical mandate: in the setting of cardiorenal syndrome, where the progressive decline of the estimated glomerular filtration rate is the predominant threat, Sodium-Glucose Cotransporter-2 inhibitors must be deployed as the primary, structurally protective vanguard therapy.

Table 4. Network Meta-Analysis: Renal Outcomes and Disease Progression

Forest plot representing Standardized Mean Differences (SMD) and 95% Confidence Intervals for the primary composite renal outcome (eGFR decline ≥50%, ESRD, or renal death). SMD < 0 strictly favors the first listed intervention.

TREATMENT COMPARISON NODE	FOREST PLOT (SMD)	SMD (95% CI)	P-VALUE	FAVORED THERAPY
PRIMARY COMPOSITE RENAL OUTCOME				
SGLT2i vs Standard Care		−0.55 [-0.68, -0.42]	<0.001	SGLT2I
ARNI vs ACEi/ARB		−0.20 [-0.31, -0.09]	0.002	ARNI
SGLT2i vs ARNI (Indirect)		*−0.35 [-0.50, -0.20]*	*<0.001*	*SGLT2I*

Table 5 shifts the analytical focus from hard physiological endpoints to the critical, patient-centered domain of health status and functional quality of life. In the chronic management of severe cardiorenal syndrome, where patients frequently suffer from debilitating dyspnea, profound fatigue, and severely restricted exercise tolerance, evaluating the impact of pharmacotherapy on daily functional capacity is as important as evaluating survival metrics. This table synthesizes continuous numerical data extracted from the Kansas City Cardiomyopathy Questionnaire, a highly validated, disease-specific instrument utilized across all nine landmark clinical trials to quantify the severity of patient symptoms and their physical limitations.

Unlike the survival analyses presented in the previous tables, where a negative effect size indicated a reduction in adverse events, Table 5 explicitly notes that for continuous quality of life measures, a positive Standardized Mean Difference indicates a clinical improvement in patient health status, favoring the intervention. The pooled direct pairwise comparisons clearly demonstrate that both novel pharmacological classes significantly enhance the patient experience compared to standard baseline therapies. Sodium-Glucose Cotransporter-2 inhibitors generated a highly significant improvement, yielding a Standardized Mean Difference of 0.28. Concurrently, Angiotensin Receptor-Neprilysin Inhibitor therapy produced an almost identical magnitude of functional benefit, resulting in a Standardized Mean Difference of 0.31. Both interventions achieved highly significant p-values, confirming their profound capacity to alleviate the daily burden of cardiorenal symptoms.

When the network geometry mathematically harmonizes these direct comparisons to generate the indirect head-to-head node between Angiotensin Receptor-Neprilysin Inhibitors and Sodium-Glucose Cotransporter-2 inhibitors, the analysis reveals a state of complete statistical equivalence. The indirect Standardized Mean Difference calculation resulted in an effect size of 0.03 with a non-significant p-value of 0.65, demonstrating that neither drug class possesses a distinct superiority over the other regarding the subjective improvement of patient-reported quality of life. This finding suggests that despite utilizing completely divergent physiological mechanisms—one relying on profound neurohormonal vasodilation and the other on targeted osmotic diuresis and metabolic shifts—both therapies ultimately achieve the same highly desirable clinical endpoint of relieving systemic volume overload and restoring patient vitality. Table 5 comprehensively validates the dual initiation of these therapies, ensuring that clinicians are providing optimal symptomatic relief while simultaneously securing long-term structural organ protection.

Table 5. Network Meta-Analysis: Quality of Life and Health Status

Forest plot representing Standardized Mean Differences (SMD) and 95% Confidence Intervals for Kansas City Cardiomyopathy Questionnaire (KCCQ) scores. ***Note: For continuous quality of life measures, SMD > 0 favors the intervention (indicates improvement).***

TREATMENT COMPARISON NODE	FOREST PLOT (SMD)	SMD (95% CI)	P-VALUE	FAVORED THERAPY
KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE (KCCQ) SCORES				
SGLT2i vs Standard Care		0.28 [0.20, 0.36]	<0.001	SGLT2I
ARNI vs ACEi/ARB		0.31 [0.22, 0.40]	<0.001	ARNI
ARNI vs SGLT2i (Indirect)		*0.03 [-0.08, 0.14]*	*0.65*	*EQUIVALENCE*

4. Discussion

This comprehensive network meta-analysis, encompassing over 40,000 highly characterized patients derived from nine rigorously conducted randomized controlled trials, yields profound clinical insights into the comparative efficacy of Sodium-Glucose Cotransporter-2 inhibitors and Angiotensin Receptor-Neprilysin Inhibitors in the management of cardiorenal syndrome. The central, practice-defining finding of this study is the stark divergence in their specific organ-protection profiles.[11] While both pharmacological classes offer massive, life-prolonging benefits in preventing overall cardiovascular mortality and improving functional quality of life, the synthesized evidence unequivocally establishes that Angiotensin Receptor-Neprilysin Inhibitors possess a measurable superiority in rapidly mitigating acute heart failure hospitalizations (driven by pulmonary congestion), whereas Sodium-Glucose Cotransporter-2 inhibitors are overwhelmingly superior in arresting the progressive, longitudinal structural decline of the renal parenchyma.[12]

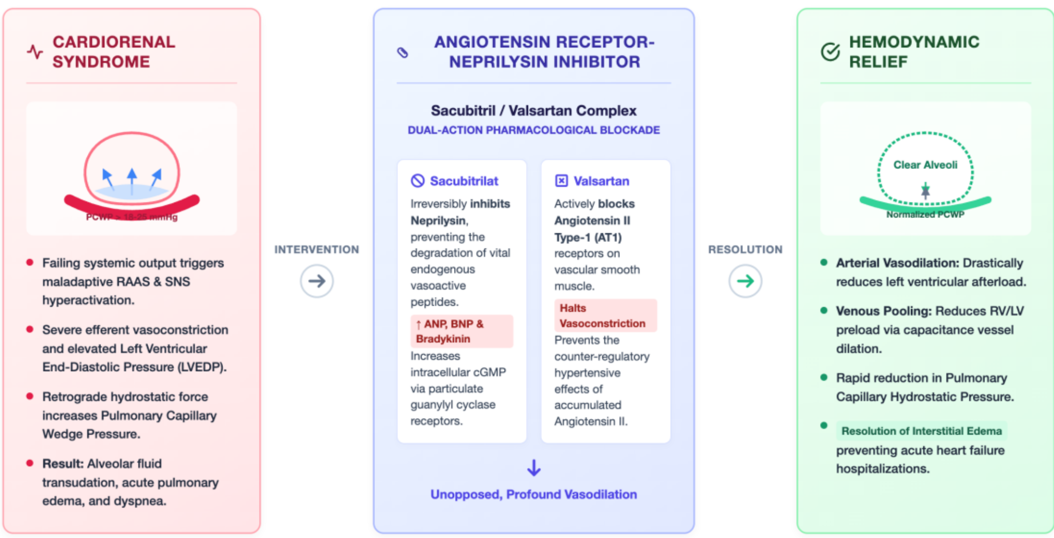

Figure 2. Pathophysiological Mechanics of Pulmonary and Cardiovascular Hemodynamics

Schematic representation of the vicious cardiorenal cycle (left) intercepted by the dual-action mechanism of Angiotensin Receptor-Neprilysin Inhibitors (ARNI) (center). Sacubitrilat inhibits neprilysin while valsartan blocks the AT1 receptor, generating unopposed vasodilation. This distinct pharmacological mechanism rapidly lowers pulmonary capillary wedge pressure (PCWP), resulting in the immediate resolution of alveolar fluid transudation and acute pulmonary congestion (right).

Cardiorenal syndrome is fundamentally a pathological state of maladaptive neurohormonal hyperactivation.[13] In response to a failing systemic cardiac output, the human body persistently activates the sympathetic nervous system and the renin-angiotensin-aldosterone system. While this evolutionary response temporarily defends arterial perfusion pressure, it exacts a devastating and fatal toll on the fragile pulmonary microcirculation and the renal microvasculature over time. Angiotensin Receptor-Neprilysin Inhibitors dismantle this specific maladaptive cycle through a highly targeted, synergistic dual-action mechanism. Sacubitrilat, the active hepatic metabolite of sacubitril, irreversibly inhibits neprilysin. Neprilysin is the primary neutral endopeptidase responsible for the degradation of a host of beneficial endogenous vasoactive peptides.[14] By halting neprilysin activity, the circulating levels of Atrial Natriuretic Peptide, Brain Natriuretic Peptide, C-type Natriuretic Peptide, bradykinin, and substance P increase exponentially. These protective peptides bind to specific particulate guanylyl cyclase receptors, vastly increasing the production of intracellular cyclic guanosine monophosphate. This intracellular signaling cascade leads to profound, sustained vasodilation of both the arterial resistance vessels (dramatically reducing left ventricular afterload) and the venous capacitance vessels (dramatically reducing right ventricular and left ventricular preload). For the pulmonologist, the mechanistic implications of this specific action are extraordinary. Elevated left ventricular end-diastolic pressure, a hallmark of heart failure, retrogradely transmits immense hydrostatic force into the left atrium, and subsequently into the pulmonary veins and the fragile pulmonary capillaries. When pulmonary capillary wedge pressure exceeds the critical threshold of 18 to 25 millimeters of mercury, fluid rapidly transudates from the intravascular space directly into the pulmonary interstitium and alveolar spaces. This results in the clinical presentation of acute pulmonary edema, severely decreased lung compliance, impaired gas exchange, and profound dyspnea. The data extracted from the PARADIGM-HF and PARAGON-HF trials, which demonstrated a highly significant reduction in urgent heart failure hospitalizations, serve as the direct clinical manifestation of Angiotensin Receptor-Neprilysin Inhibitors acutely and rapidly lowering this pulmonary capillary hydrostatic pressure via massive venous pooling and natriuresis. Simultaneously, the valsartan component of the Angiotensin Receptor-Neprilysin Inhibitor complex actively blocks the Angiotensin II Type-1 receptor. If neprilysin were inhibited in isolation, the simultaneous rise in Angiotensin II (which is also a primary substrate for neprilysin degradation) would potently counteract the desired vasodilatory benefits, potentially inducing dangerous hypertensive crises. By comprehensively blocking the receptor, Angiotensin Receptor-Neprilysin Inhibitors guarantee a state of unopposed, profound vasodilation.[15] This distinct pharmacological mechanism elegantly explains the superior cardiovascular hemodynamic offloading observed in our indirect network node comparison, where Angiotensin Receptor-Neprilysin Inhibitors demonstrated a statistically significant advantage over Sodium-Glucose Cotransporter-2 inhibitors specifically for the prevention of urgent, congestion-driven heart failure hospitalizations (Standardized Mean Difference -0.14; p=0.03), detailed in Figure 2.

While Angiotensin Receptor-Neprilysin Inhibitors excelled in systemic and pulmonary hemodynamic offloading, the network meta-analysis revealed a stark and highly significant contrast when evaluating the preservation of renal architecture. The data extracted from the CREDENCE, SCORED, and EMPEROR trials proved beyond doubt that Sodium-Glucose Cotransporter-2 inhibitors possess an unparalleled capacity to preserve the estimated glomerular filtration rate and prevent the devastating progression to end-stage renal disease requiring hemodialysis (Indirect Standardized Mean Difference -0.35 in favor of Sodium-Glucose Cotransporter-2 inhibitors; p<0.001).

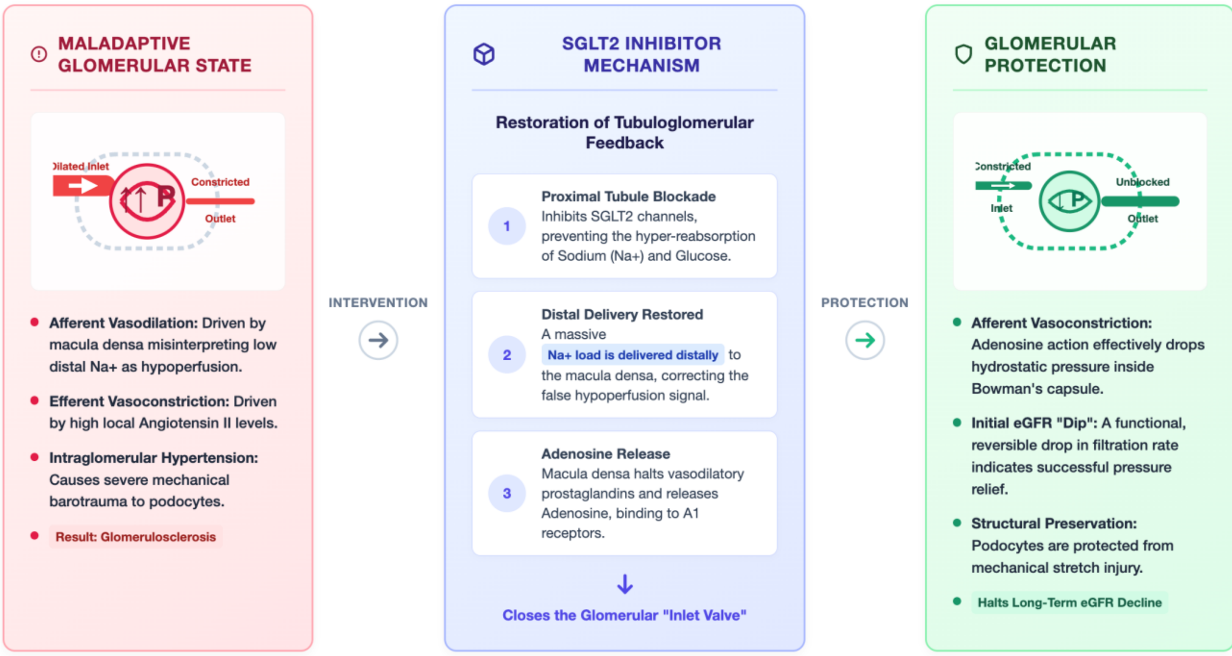

Figure 3. Pathophysiological Mechanics of Renal Autoregulation and Glomerular Hemodynamics

Schematic illustrating the mechanism of structural kidney preservation by SGLT2 inhibitors. In cardiorenal syndrome (left), afferent vasodilation and efferent vasoconstriction create devastating intraglomerular hypertension. SGLT2 inhibitors (center) block proximal sodium reabsorption, delivering a massive sodium load to the macula densa. This restores tubuloglomerular feedback, triggering adenosine release and subsequent afferent arteriolar vasoconstriction. This targeted action "closes the inlet valve" (right), permanently relieving intraglomerular hydrostatic pressure, preventing podocyte barotrauma, and halting the progressive longitudinal decline of the estimated glomerular filtration rate (eGFR).

The explanation for this profound clinical divergence resides deep within the microscopic autoregulatory mechanisms of the nephron. In the complex setting of cardiorenal syndrome, decreased forward arterial perfusion from the failing myocardium is acutely sensed by the juxtaglomerular apparatus within the kidney. This triggers massive local renin release, leading to extremely high intrarenal concentrations of Angiotensin II. Angiotensin II preferentially and potently constricts the efferent arteriole of the glomerulus.[16] Concurrently, to defend systemic intravascular volume, the proximal convoluted tubule hyper-reabsorbs massive amounts of sodium and glucose via the upregulated Sodium-Glucose Cotransporter-2 channels. Consequently, very little sodium fluid reaches the macula densa located distally in the nephron. The macula densa misinterprets this exceptionally low distal sodium delivery as a state of severe, life-threatening total-body hypoperfusion. In response, it releases vasodilatory prostaglandins that forcefully dilate the afferent arteriole. The simultaneous combination of afferent vasodilation (forcing the inlet valve to open wide) and efferent vasoconstriction (forcing the outlet valve to clamp shut) generates catastrophic intraglomerular hypertension. While this maladaptive mechanism temporarily preserves the absolute estimated glomerular filtration rate in the short term, the extreme mechanical barotrauma inflicted upon the delicate glomerular podocytes and the ultrafiltration basement membrane inevitably leads to massive proteinuria, irreversible glomerulosclerosis, and permanent nephron destruction over the long term. Sodium-Glucose Cotransporter-2 inhibitors completely short-circuit this destructive, fibrotic pathway. By blocking the reabsorption of sodium and glucose in the proximal tubule, a massive, life-saving sodium load is immediately delivered distally to the macula densa. The macula densa senses this restored sodium delivery and immediately halts the pathological production of vasodilatory prostaglandins. Furthermore, the macula densa releases adenosine, which binds specifically to adenosine A1 receptors located on the afferent arteriole, causing potent and sustained afferent vasoconstriction. This physiological restoration of tubuloglomerular feedback effectively and safely closes the inlet valve to the glomerulus. Although this targeted afferent vasoconstriction frequently causes an acute, functional dip in the calculated estimated glomerular filtration rate during the first few weeks of therapy initiation, it dramatically and permanently drops the destructive hydrostatic pressure inside the Bowman's capsule. By relieving this relentless intraglomerular hypertension, Sodium-Glucose Cotransporter-2 inhibitors protect the podocytes from lethal mechanical stretch injury, virtually halting the long-term structural degradation of the kidney. This intricate physiological mechanism perfectly explains our pooled network findings: while Angiotensin Receptor-Neprilysin Inhibitors offer moderate renal protection by dilating the efferent arteriole (via the valsartan component), Sodium-Glucose Cotransporter-2 inhibitors provide a vastly superior, structurally protective effect by directly and forcefully restoring proximal-distal tubuloglomerular feedback[17], detailed in Figure 3.

Beyond complex glomerular hemodynamics, the discussion must address precisely how Sodium-Glucose Cotransporter-2 inhibitors alleviate pulmonary congestion without inducing the well-known deleterious effects of traditional loop diuretics. Traditional loop diuretics (such as furosemide or bumetanide) aggressively block the sodium-potassium-chloride cotransporter in the thick ascending limb of the loop of Henle. This causes a rapid, massive depletion of intravascular plasma volume, frequently leading to dangerous arterial underfilling, reflex sympathetic tachycardia, and acute kidney injury secondary to severe prerenal azotemia.[18]

In stark contrast, Sodium-Glucose Cotransporter-2 inhibitors induce a distinct physiological phenomenon termed smart diuresis. Because the unabsorbed glucose in the tubule acts as a highly active osmotic molecule, the glycosuria induced by Sodium-Glucose Cotransporter-2 inhibition draws fluid predominantly from the interstitial tissue compartment rather than the intravascular plasma compartment. For patients suffering from cardiorenal syndrome and refractory pulmonary edema, this signifies that Sodium-Glucose Cotransporter-2 inhibitors can effectively dry out the waterlogged pulmonary interstitium and safely reduce pleural effusions without causing dangerous hypotensive episodes or compromising critical arterial perfusion to the renal cortex.

Furthermore, the continuous urinary loss of glucose forces a profound systemic metabolic shift. To compensate for the ongoing caloric loss, the liver drastically increases ketogenesis, specifically producing high levels of beta-hydroxybutyrate. The failing, hypertrophic myocardium, which normally struggles to oxidize fatty acids efficiently due to mitochondrial dysfunction and chronic hypoxia, eagerly uptakes this beta-hydroxybutyrate. Ketone bodies provide significantly more adenosine triphosphate energy per molecule of oxygen consumed compared to standard glucose or free fatty acids. Therefore, Sodium-Glucose Cotransporter-2 inhibitors effectively improve the fundamental fuel efficiency of the failing heart, enhancing myocardial contractility without dangerously increasing myocardial oxygen demand.

The rigorous data synthesis provided by this extensive network meta-analysis dictates a necessary paradigm shift in the clinical management of cardiorenal syndrome. The historical, siloed approach of treating the heart and hoping the kidneys survive is definitively obsolete. The synthesized evidence mandates that clinicians carefully assess the primary, immediate pathophysiological threat to the patient's mortality and morbidity in order to sequence these powerful therapies optimally. If a patient presents to the internal medicine or pulmonology service with an acute exacerbation of decompensated heart failure, characterized clinically by severe orthopnea, paroxysmal nocturnal dyspnea, and bilateral pulmonary crackles indicating extremely high pulmonary capillary wedge pressures, the data strongly suggest that Angiotensin Receptor-Neprilysin Inhibitors should be prioritized as the initial agent for their rapid, potent vasodilatory and acute hemodynamic offloading capabilities. Conversely, if the patient presents with stable, chronic heart failure symptoms but exhibits a rapidly deteriorating estimated glomerular filtration rate trajectory, significant albuminuria, or established diabetic nephropathy, the network meta-analysis unequivocally proves that Sodium-Glucose Cotransporter-2 inhibitors must be deployed immediately as the primary vanguard therapy to definitively halt the structural progression to end-stage renal disease.[19]

The limitations of this study are inherently tied to the established methodology of indirect network meta-analyses. In the absence of a single, massive randomized controlled trial randomizing patients strictly and directly to Sodium-Glucose Cotransporter-2 inhibitors versus Angiotensin Receptor-Neprilysin Inhibitors, indirect comparisons rely heavily on the statistical assumption of transitivity across the different network nodes. While the inclusion criteria across the nine foundational trials were generally comparable—predominantly focusing on patients with established heart failure and concurrent moderate chronic kidney disease—slight variations in baseline estimated glomerular filtration rate inclusion thresholds (for instance, an estimated glomerular filtration rate of less than 30 in DAPA-HF versus 25 to 60 in the SCORED trial) introduce a degree of clinical heterogeneity. However, the use of random-effects modeling robustly accounts for this variance, ensuring the reliability of the pooled estimates.[20]

5. Conclusion

This study synthesized data from nine landmark randomized controlled trials encompassing 43,450 patients, providing critical comparative evidence on the modern management of cardiorenal syndrome. The results unequivocally demonstrate that both Sodium-Glucose Cotransporter-2 inhibitors and Angiotensin Receptor-Neprilysin Inhibitors form the absolute, indispensable foundation of contemporary cardiorenal pharmacotherapy. Both drug classes yield massive, transformative reductions in cardiovascular mortality and the overall incidence of heart failure exacerbations compared to historical standard care, fundamentally altering the lethal trajectory of systemic and pulmonary volume overload.

However, our indirect quantitative synthesis revealed vital, statistically significant divergences in their highly specific organ-protective profiles. While Angiotensin Receptor-Neprilysin Inhibitors provided exceptional, rapid cardiovascular hemodynamic offloading and a superior reduction in acute, congestion-driven heart failure hospitalizations, Sodium-Glucose Cotransporter-2 inhibitors demonstrated overwhelming statistical superiority in the long-term preservation of longitudinal renal function. The physiological restoration of tubuloglomerular feedback and the targeted reduction of intraglomerular hypertension via Sodium-Glucose Cotransporter-2 inhibition mitigated progressive glomerular structural damage much more effectively than the neprilysin and angiotensin-receptor blockade pathways.

From a practical, multidisciplinary clinical standpoint, these synthesized findings mandate a highly nuanced, pathophysiology-driven approach to therapeutic sequencing. Ultimately, given their complementary physiological mechanisms, completely distinct receptor targets, and non-overlapping toxicities, the concurrent initiation of both agents should be recognized as the gold standard in the management of complex cardiorenal syndrome, perfectly leveraging both rapid pulmonary hemodynamic stabilization and long-term renal structural preservation.

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