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CARDIOPROTECTIVE EFFECTS OF SGLT INHIBITORS IN ADULTS WITH ADVANCED CHRONIC KIDNEY DISEASE (EGFR <30 ML/MIN/1.73M²)

A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS, META-ANALYSES, AND REAL-WORLD EVIDENCE

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Abstract

Background. *SGLT inhibitors have transformed the treatment of heart failure and chronic kidney disease (CKD), yet their role in patients with severely reduced kidney function–eGFR below 30 ml/min/1.73m²–remains poorly defined. Most landmark trials either excluded these patients or enrolled too few to draw firm cardiovascular conclusions. This evidence gap matters because cardiovascular disease causes roughly half of all deaths in CKD Stage 4–5, and clinicians lack robust evidence precisely where it is most needed.*

Methods. *We conducted a systematic review (PROSPERO: CRD420261377175) following PRISMA 2020 guidance. PubMed, EMBASE, and Cochrane CENTRAL were searched from January 2015 through March 2026, supplemented by ClinicalTrials.gov and manual reference mining. We included randomised controlled trials (RCTs) and their prespecified subgroup analyses reporting eGFR <30 outcomes, individual patient data and aggregate meta-analyses, and propensity score matched cohort studies with at least 12 weeks of follow-up. Two reviewers independently screened studies and extracted data. Risk of bias was assessed using the Cochrane RoB 2.0 tool, and certainty of evidence was rated using GRADE. The primary outcomes were hospitalisation for heart failure (HHF) and major adverse cardiovascular events (MACE).*

Results. *Twenty-two publications met the inclusion criteria: 9 landmark RCTs (~31,900 patients), 5 meta-analyses (pooling up to 97,412), 4 RCT subgroup analyses, and 4 real-world cohort studies. More than 17,000 patients with eGFR <30 or CKD Stage 4–5 contributed direct outcome data. Hazard ratios for HHF/CV death ranged from 0.69 to 0.84 across individual RCTs, converging on a pooled estimate near 0.74. No trial or meta-analysis demonstrated a significant interaction between baseline eGFR and treatment effect (P-trend = 0.16 in SMART-C; P >0.10 in DAPA-CKD subgroups). The Spiazzi 2024 meta-analysis showed that MACE reduction was largest in KDIGO Very High Risk patients (HR 0.72; P-interaction = 0.038). DAPA-CKD was the only individual trial to demonstrate a significant mortality reduction (HR 0.69; P = 0.004); pooled estimates from adequately powered analyses also reached significance (RR 0.87; 95% CI 0.80–0.95). Sotagliflozin demonstrated unique reductions in MI (HR 0.68) and stroke (HR 0.66), likely reflecting dual*

SGLT1/2 inhibition. Safety was reassuring overall: no DKA events occurred with dapagliflozin in DAPA-CKD, and AKI was consistently lower with SGLT inhibitors (RR 0.77–0.82). Evidence certainty was Moderate for HHF/CV death and mortality, and High for kidney progression.

Conclusions. *Available evidence consistently points toward meaningful cardioprotection with SGLT inhibitors in patients with eGFR <30, with no attenuation of benefit at lower eGFR. These findings argue for extending guideline recommendations into CKD Stage 4–5 and highlight the need for adequately powered RCTs enrolling this population.*

1. INTRODUCTION

The burden of chronic kidney disease is staggering—roughly 850 million people worldwide are affected, and projections place CKD among the top five causes of global mortality by 2040. What makes CKD especially lethal is not the kidney disease itself, at least not directly. It is the cardiovascular toll. Patients with Stage 4–5 CKD (eGFR <30 ml/min/1.73m²) face cardiovascular death rates 20 to 30 times higher than age-matched controls [21]. In our clinical practice, we see this daily: patients referred to nephrology with advanced CKD who already carry diagnoses of heart failure, ischaemic heart disease, or both. More than half of patients reaching eGFR <15 have some form of heart failure, often unrecognised [21].

The reasons for this excess risk extend well beyond traditional atherosclerotic factors. Advanced CKD creates a hostile cardiovascular milieu—uremic toxin accumulation, deranged calcium-phosphate metabolism with elevated FGF-23, chronic volume overload, accelerated arterial stiffening, and persistent low-grade inflammation that conventional risk factor modification cannot fully address [21]. Heart failure in this context is both a downstream consequence of CKD and a driver of further renal decline, establishing the well-described cardio-renal syndrome.

Against this background, the emergence of SGLT2 inhibitors over the past decade has been transformative. Beginning with the EMPA-REG OUTCOME results in 2015, a series of landmark trials established these agents as pillars of therapy in type 2 diabetes with cardiovascular disease, heart failure (across the ejection fraction spectrum), and CKD. The evidence base is now extensive: DAPA-CKD [6], EMPA-KIDNEY [3], CREDENCE [7], and the heart failure megatrials (DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DELIVER) collectively enrolled tens of thousands of patients. The 2024 KDIGO guideline responded by recommending SGLT2 inhibitors for CKD patients with type 2 diabetes or heart failure down to eGFR 20 ml/min/1.73m² [19].

However, while the overall evidence for SGLT2 inhibitors is robust, data from patients with eGFR <30 remain comparatively thin. CREDENCE imposed a hard exclusion at eGFR 30. DAPA-CKD enrolled patients down to eGFR 25, but only 14.5% (n = 624) fell below 30. EMPA-KIDNEY enrolled 2,282 patients with eGFR <30, fully 34.5% of its cohort, yet its cardiovascular outcomes were non-significant for reasons we discuss in detail below. The result is a clinical paradox: the patients who stand to benefit the most are those for whom we have the weakest direct evidence.

Several recent developments prompted us to revisit this question systematically. In January 2026, the SMART-C Consortium published two companion individual patient data meta-analyses in JAMA, pooling 10 RCTs with over 70,000 patients and providing dedicated eGFR subgroup analyses extending below eGFR 20 [10, 11]. Spiazzi and colleagues completed KDIGO risk-stratified meta-analyses across 14 RCTs (nearly 100,000 patients), with a striking finding: MACE benefit was actually greatest in the highest KDIGO risk category [12]. Two large real-world studies from the TriNetX platform pushed observational evidence into CKD Stage 5 and end-stage kidney disease [13, 15]. Together, these publications have substantially changed the evidence landscape, and a comprehensive synthesis was overdue.

This review was also motivated by practical considerations relevant to low- and middle-income country (LMIC) populations. In Pakistan, where CKD prevalence is estimated at 15–20% of the adult population and access to renal replacement therapy is limited, preventing cardiovascular events in advanced CKD has enormous public health implications. Generic dapagliflozin is now available locally at a fraction of branded cost, making implementation feasible if the evidence supports it. We therefore set out to systematically evaluate whether SGLT inhibitors reduce hospitalisation for heart failure, MACE, and all-cause mortality in adults with eGFR <30 ml/min/1.73m².

2. METHODS

2.1 Study Design and Protocol Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD420261377175), available at https://www.crd.york.ac.uk/PROSPERO/view/CRD420261377175. The full PICO framework, search strategy, and eligibility criteria were finalised prior to article screening.

2.2 PICO Framework

Population. Adults aged ≥18 years with eGFR <30 ml/min/1.73m² (CKD Stage 4–5), pre-dialysis only. Renal transplant recipients were excluded, as their pharmacokinetic and comorbidity profiles differ substantially from native kidney CKD populations.

Intervention. Any SGLT inhibitor at any approved dose: dapagliflozin 10 mg once daily, empagliflozin 10 mg once daily, canagliflozin 100 mg once daily, or sotagliflozin 200–400 mg once daily. Sotagliflozin was included despite its dual SGLT1/SGLT2 mechanism because it is the only agent with mandatory eGFR 25–60 enrolment and exhibits unique cardiovascular signals; it was analysed separately in sensitivity analyses.

Comparator. Placebo plus standard of care, with optimised renin-angiotensin system blockade (ACE inhibitor or ARB) where tolerated.

Primary outcomes. (1) Hospitalisation for heart failure; (2) MACE, defined as the composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

Secondary outcomes. All-cause mortality, cardiac arrhythmias, rate of eGFR decline, diabetic ketoacidosis (DKA), and acute kidney injury (AKI).

2.3 Eligibility Criteria

Eligible study designs included RCTs, prespecified or post-hoc subgroup analyses of RCTs reporting eGFR <30 outcome data, individual patient data meta-analyses, aggregate meta-analyses with KDIGO-stratified or eGFR-stratified results, and propensity score matched cohort studies. Minimum follow-up was 12 weeks. The search was limited to publications from January 2015 onward, given that EMPA-REG OUTCOME—the first SGLT2 inhibitor cardiovascular outcomes trial—was published in that year. Editorials, narrative reviews, case reports, animal studies, and conference abstracts without full-text publications were excluded, although editorials and reviews were used for contextual framing where relevant.

2.4 Search Strategy and Information Sources

MEDLINE (via PubMed), EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched. The Boolean search combined three concept blocks: SGLT inhibitor terms (including all four drug names), CKD/eGFR terms (including "stage 4," "stage 5," "eGFR <30," and "advanced chronic kidney disease"), and cardiovascular outcome terms (heart failure hospitalisation, MACE, cardiovascular death, myocardial infarction, atrial fibrillation). The full search string is provided in Supplementary Appendix 1. The database search was supplemented by a ClinicalTrials.gov search for ongoing and recently completed trials, a Google Scholar search for grey literature, and

manual backward and forward reference mining of all included articles and recent meta-analyses.

2.5 Study Selection and Data Extraction

Two reviewers independently screened titles and abstracts against pre-defined inclusion criteria. Articles deemed potentially eligible were retrieved in full text and assessed independently by both reviewers; disagreements were resolved by discussion. Data extraction was performed in duplicate using a standardised form capturing study design, sample size, drug and dose, eGFR range and the proportion with eGFR <30, follow-up duration, hazard ratios (or risk ratios) with 95% confidence intervals for primary and secondary outcomes, safety event rates, and—critically—interaction P-values for eGFR subgroups where reported. These interaction tests are central to the review question, as they indicate whether the treatment effect changes at lower eGFR.

2.6 Risk of Bias and Quality Assessment

Risk of bias for RCTs was assessed using the Cochrane RoB 2.0 tool across five domains: randomisation, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. For observational studies, the assessment focused on propensity score methodology quality, handling of unmeasured confounders, and whether outcomes were adjudicated. Meta-analyses were assessed for trial selection, statistical approach, and heterogeneity handling. Risk of bias was assessed independently by both reviewers, with disagreements resolved by discussion.

2.7 Certainty of Evidence

The GRADE framework was applied to rate evidence certainty for each key outcome domain. Factors considered included risk of bias, inconsistency across studies, indirectness (a particular concern, given that much of the eGFR <30 data comes from subgroup analyses rather than dedicated trials), imprecision, and publication bias.

2.8 Approach to Synthesis

A de novo meta-analysis was not performed, for two principal reasons. First, the included studies vary considerably in design—mixing RCTs with their own subgroup analyses, published meta-analyses, and observational data—and pooling across these layers would risk double-counting the same patients (for example, DAPA-CKD participants appear in the main trial, the Wheeler subgroup paper, the Waijer post-hoc analysis, and all five meta-analyses). Second, multiple high-quality published meta-analyses already exist, including the SMART-C IPD analyses with over 70,000 patients; replication with aggregate data would be methodologically inferior. Instead, a narrative synthesis with forest plot visualisation of hazard ratios from individual studies and available published meta-analytic pooled estimates is presented. This approach is more transparent and avoids the pitfalls of layered pooling.

3. RESULTS

3.1 Study Selection

The database search returned 847 records, with an additional 63 identified through reference mining, ClinicalTrials.gov, and Google Scholar. After removal of 198 duplicates, 712 titles and abstracts were screened. The majority (n = 594) were excluded at this stage, mostly because they addressed SGLT2 inhibitors in populations without CKD or did not report cardiovascular outcomes. Full-text assessment was performed on 118 articles; 96 were excluded (41 had no eGFR <30 subgroup data; 18 involved overlapping patient cohorts already captured by a parent publication; 14 were review articles or editorials without original data; 8 had follow-up shorter than 12 weeks; and 15 did not report relevant cardiovascular endpoints). Twenty-two articles met all inclusion criteria (Figure 1).

Figure 1. PRISMA 2020 Flow Diagram

3.2 Characteristics of Included Studies

The 22 articles fell naturally into tiers. Nine were landmark RCTs or their prespecified subgroup analyses (Articles 1–9): the DAPA-CKD diabetes/non-diabetes subgroup analysis [1], the

DAPA-CKD heart failure subgroup [2], EMPA-KIDNEY [3], SCORED [4], SOLOIST-WHF [5], the main DAPA-CKD trial [6], CREDENCE [7], the Waijer KDIGO-stratified post-hoc of DAPA-CKD [8], and the Aggarwal/Bhatt SCORED MACE analysis [9]. Five were meta-analyses pooling between 70,000 and 97,000 patients [10–14]. The remaining eight comprised high-priority RCT subgroup analyses [15–18] and contextual articles, including the KDIGO 2024 guideline, two editorials/reviews, and two real-world cohort studies [19–22].

The total unique patient base exceeded 130,000. Specific eGFR <30 evidence came from several sources: EMPA-KIDNEY contributed the largest single RCT cohort at this threshold (n = 2,282; 34.5% of trial); DAPA-CKD contributed 624 patients (14.5%); SCORED contributed approximately 813 (7.7%); and the Waijer analysis added 1,170 KDIGO Very High Risk patients enriched for eGFR <30. The SMART-C IPD meta-analysis pooled over 3,895 patients with eGFR <30 across 10 RCTs. Real-world studies added approximately 9,500 patients at CKD Stage 5 or ESKD. In total, direct outcome data were available for more than 17,000 patients in the target population.

Follow-up ranged from 9 months in SOLOIST-WHF to 2.62 years in CREDENCE. Four agents were represented. Dapagliflozin had the most CKD-specific trial data and the most favourable safety profile. Empagliflozin contributed the largest eGFR <30 cohort through EMPA-KIDNEY. Canagliflozin, through CREDENCE, provided robust heart failure data but excluded eGFR <30 entirely. Sotagliflozin, a dual SGLT1/2 inhibitor, was the only agent tested in a population with mandatory eGFR 25–60 at baseline (SCORED) and generated a unique ischaemic signal addressed separately below.

3.3 Hospitalisation for Heart Failure and Cardiovascular Death

This composite was the most consistently reported cardiovascular endpoint, and findings were remarkably uniform across studies. In DAPA-CKD, dapagliflozin reduced CV death/HHF by 29% (HR 0.71; 95% CI 0.55–0.92; P = 0.009) [6]. Benefit held regardless of diabetes status (P-interaction = 0.27) [1], baseline heart failure (P-interaction not significant) [2], or established cardiovascular disease (P-interaction = 0.97) [18]. In the eGFR <30 subgroup, the interaction P-value exceeded 0.10, indicating that the treatment effect was statistically indistinguishable from the overall result [1].

EMPA-KIDNEY presents a more nuanced picture. Despite enrolling the largest eGFR <30 cohort in any RCT (n = 2,282), the composite of HHF/CV death did not reach statistical significance (HR 0.84; 95% CI 0.67–1.07; P = 0.15) [3]. At first glance, this resembles a negative result. It is not. EMPA-KIDNEY enrolled a population with low baseline cardiovascular risk: the majority were non-diabetic (54%), median albuminuria was modest (UACR 329 mg/g), and the cardiovascular event rate in the placebo arm was below 1.2 per 100 patient-years. By comparison, rates in DAPA-CKD were three to four times higher. The trial simply did not have sufficient events to detect a CV benefit. The kidney primary composite, in contrast, was highly significant (HR 0.72; P < 0.001), and the eGFR <30 subgroup result (HR 0.73; 95% CI 0.62–0.86) confirmed biological activity. This distinction is widely misunderstood and is addressed in the Discussion.

SCORED demonstrated robust HHF reduction with sotagliflozin (HR 0.67; 95% CI 0.55–0.82), as did CREDENCE with canagliflozin (HR 0.61; 95% CI 0.47–0.80), although CREDENCE excluded eGFR <30 [4, 7]. The CREDENCE eGFR 30–45 subgroup (HR 0.75) provides bridging evidence toward the lower range [7].

Meta-analytic data solidified the picture further. Mavrakanas et al. found that HHF reduction was amplified in CKD compared with non-CKD patients (RR 0.67 vs 0.78; P-interaction = 0.08)—a borderline significant interaction in the direction of greater benefit at lower eGFR [14]. The SMART-C analysis by Staplin et al. stratified by diabetes status: HHF was reduced in both diabetic (HR 0.68; 95% CI 0.62–0.74) and non-diabetic patients (HR 0.75; 95% CI 0.63–0.88), with no interaction by albuminuria level [11]. This last point is clinically important, given that current KDIGO guidelines restrict SGLT2 inhibitor use in

non-diabetic CKD to patients with UACR ≥200 mg/g; the meta-analytic data suggest this restriction may be unnecessary.

Figure 2. Forest Plot: HHF / Cardiovascular Death

3.4 Evidence Specifically at eGFR <30

The central question of this review is whether benefit persists when kidney function falls below eGFR 30. Across every study and analysis examined, the answer was the same: no significant attenuation was found. In DAPA-CKD, the eGFR <30 subgroup (n = 624) showed a treatment effect consistent with the overall trial (P-interaction >0.10) [1]. EMPA-KIDNEY's eGFR <30 subgroup (n = 2,282) yielded HR 0.73 (95% CI 0.62–0.86) for the primary kidney composite [3]. In SCORED, the eGFR <60 subgroup—which by design included patients down to eGFR 25—showed enhanced benefit (HR 0.59; 95% CI 0.44–0.79) [4].

The SMART-C IPD meta-analysis by Neuen et al. [10] was arguably the single most informative analysis for this review. Pooling 10 RCTs and 70,361 patients, it showed kidney progression HR of 0.71 (95% CI 0.60–0.83) at eGFR <30, with a P-for-trend across eGFR categories of 0.16—no significant interaction. In exploratory analyses, the point estimate at eGFR <20 was similar to that at eGFR 20–30, suggesting that benefit may extend below the current KDIGO threshold.

Waijer et al. [8] added another dimension by stratifying DAPA-CKD by KDIGO risk categories rather than eGFR alone. In the Very High Risk group (enriched for eGFR <30), all-cause mortality was reduced by 37% (HR 0.63; 95% CI 0.46–0.87). The absolute risk reduction was 5.8% in the highest-risk group compared with 2.2% in those with eGFR ≥45, reflecting the substantially higher baseline event rate (14.9 vs 5.1 per 100 patient-years). The number needed to treat was correspondingly lower.

Perhaps the most striking finding came from Spiazzi et al. [12], whose meta-analysis of 14 RCTs (n = 97,412) showed that MACE reduction was significantly greater in KDIGO Very High Risk patients (HR 0.72; 95% CI 0.61–0.86) than in lower-risk groups (P-interaction = 0.038). This is the opposite of what many clinicians assume—that drug efficacy diminishes as CKD worsens. Higher baseline risk appears to amplify absolute benefit.

Figure 3. Forest Plot: Outcomes in eGFR <30 / CKD Stage 4–5

3.5 MACE

Three-point MACE was reported in CREDENCE (HR 0.80; P = 0.01) [7], SCORED (HR 0.77; P = 0.002) [4], and in the Spiazzi and Mavrakanas meta-analyses (HR 0.89 and RR 0.84, respectively) [12, 14]. The most novel finding came from the Aggarwal/Bhatt prespecified analysis of SCORED [9], in which sotagliflozin was associated with reductions in total MI (HR 0.68; 95% CI 0.52–0.89; P = 0.004) and total stroke (HR 0.66; 95% CI 0.48–0.91; P = 0.012). These are the first statistically significant individual MACE component reductions reported for any SGLT inhibitor, with benefit onset at 94 days—remarkably early.

Caution is warranted in interpreting these results. Sotagliflozin inhibits both SGLT1 (in the gut) and SGLT2 (in the kidney). The proposed mechanism for the ischaemic benefit involves delayed intestinal glucose absorption via SGLT1 inhibition, which reduces postprandial glycaemic excursions and may attenuate oxidative stress and platelet activation. While biologically plausible, this means the MI and stroke reductions cannot be attributed to SGLT2 inhibition alone. SCORED also had methodological concerns: the primary endpoint was modified mid-trial, events were not fully adjudicated, and the trial was terminated early due to loss of funding. These were flagged in the risk of bias assessment, and sotagliflozin data are presented separately in the forest plots.

Figure 5. Forest Plot: MACE

3.6 All-Cause Mortality

DAPA-CKD is the only individual trial to demonstrate a significant reduction in all-cause death (HR 0.69; 95% CI 0.53–0.88; P = 0.004) [6]. EMPA-KIDNEY showed a non-significant trend

(HR 0.87) [3], as did CREDENCE (HR 0.83) [7]. SCORED showed no signal (HR 0.99) [4]. The question is whether DAPA-CKD is an outlier or whether the other trials were simply underpowered for mortality.

The meta-analytic evidence supports the latter interpretation. Mavrakanas et al. [14] pooled mortality across 12 RCTs in CKD patients and found a significant reduction (RR 0.87; 95% CI 0.80–0.95). The SMART-C analysis confirmed this for diabetic patients (HR 0.86; 95% CI 0.80–0.91), although the non-diabetic estimate did not reach significance (HR 0.91; 95% CI 0.78–1.05) [11]. In the Waijer KDIGO analysis, the mortality reduction was most pronounced in Very High Risk patients (HR 0.63; 95% CI 0.46–0.87) [8], again consistent with greater absolute benefit at higher baseline risk.

A particularly illuminating analysis was performed by Heerspink et al. [17], who dissected causes of death in DAPA-CKD. The all-cause mortality benefit was driven not by cardiovascular or kidney-related deaths—which were numerically but not significantly lower—but by non-CV, non-kidney causes (HR 0.52; 95% CI 0.33–0.83), including deaths from infection and malignancy. The implication is that dapagliflozin may exert pleiotropic effects beyond known haemodynamic and renal actions—possibly through anti-inflammatory or immunomodulatory pathways. While speculative, this finding has biological plausibility given emerging data on SGLT2 inhibitor effects on NLRP3 inflammasome activation, autophagy, and erythropoietin production.

Figure 4. Forest Plot: All-Cause Mortality

3.7 Real-World Evidence

While RCTs provide the highest level of evidence, they necessarily exclude many patients seen in clinical practice. Real-world data become valuable here, not as a substitute but as a complement. Anuforo et al. [13] used the TriNetX platform to identify 4,470 propensity score matched patients with CKD Stage 5 (eGFR <15) who received SGLT2 inhibitors. The composite of mortality, ESRD, and heart failure was reduced by 36%, with a number needed to treat of 9 over 5 years. All-cause mortality was reduced by 34% (RR 0.66). These are large effects, and this study is the only one specifically addressing eGFR <15.

Wu et al. [15], published in early 2026, extended this further by enrolling 5,016 patients per arm from the TriNetX database with both heart failure and ESKD, including patients on dialysis. The mortality reduction was striking (HR 0.69; 95% CI 0.63–0.76) and held across HFrEF and HFpEF, diabetic and non-diabetic subgroups, and all three SGLT2 inhibitors. This study also reported a modest but significant increase in DKA (HR 1.33; 95% CI 1.03–1.72)—an important safety signal in the ESKD population that warrants vigilance.

Chen et al. [22] provided data from the Taiwan National Health Insurance database—a smaller study (248 SGLT2 inhibitor users) but valuable for demonstrating benefit in an Asian population with CKD Stage 5 and diabetes. All three observational studies pointed in the same direction as the RCT evidence, adding to overall confidence, although these results must be interpreted with the usual caveats about channelling bias, residual confounding, and non-adjudicated endpoints.

3.8 Safety

The safety profile in advanced CKD was more favourable than anticipated. Diabetic ketoacidosis, the most widely feared adverse effect, was entirely absent in the dapagliflozin arm of DAPA-CKD—zero events among 2,152 treated patients [6]. Empagliflozin showed similarly low rates in EMPA-KIDNEY (6 vs 1 event) [3]. Risk was higher with canagliflozin (2.2 vs 0.2 per 1,000 patient-years in CREDENCE) [7] and with sotagliflozin (0.6% vs 0.3%; P = 0.02 in SCORED) [4], suggesting a drug-specific rather than class-wide concern. In the ESKD population, the Wu et al. [15] study flagged a significant DKA increase (HR 1.33), reinforcing the need for vigilant sick-day education in very advanced CKD.

Acute kidney injury, which one might expect to increase with SGLT inhibitors in patients with minimal renal reserve, was actually lower in every trial and meta-analysis reviewed. The range of risk ratios across studies was 0.77 to 0.82, confirmed at

the meta-analytic level by both Mavrakanas (RR 0.82) [14] and Staplin/SMART-C (AKI protection regardless of diabetes status) [11]. This consistent nephroprotective signal is clinically important, given how often AKI concerns are cited as a reason not to prescribe SGLT2 inhibitors in advanced CKD. Hyperkalaemia was numerically lower with empagliflozin (HR 0.83; NS) [3], volume depletion was manageable, and there was no signal for excess amputation or fracture risk in any included study.

3.9 Risk of Bias and GRADE Assessment

Overall, the quality of evidence was good. All landmark RCTs received low risk of bias ratings. Some concerns were noted with SCORED and SOLOIST-WHF, both of which had mid-trial endpoint modifications, incomplete event adjudication, and were stopped early for non-efficacy reasons (loss of funding). The Waijer post-hoc analysis was not prespecified, which was documented. Observational studies had inherent design limitations but used rigorous propensity score matching on numerous covariates.

GRADE certainty was High for CKD progression and AKI safety, reflecting the large body of RCT evidence with consistent results. For HHF/CV death and all-cause mortality at eGFR <30, certainty was rated Moderate. The downgrade from High was driven primarily by indirectness (data come from subgroup analyses rather than dedicated trials) and some imprecision in the eGFR <30 confidence intervals. MACE was rated Moderate, partly because the strongest signal comes from sotagliflozin, a pharmacologically distinct agent.

4. DISCUSSION

4.1 What This Review Shows

The evidence, taken as a whole, tells a clear story: SGLT inhibitors offer meaningful cardiovascular protection to patients with eGFR <30, and the treatment effect does not fade as kidney function worsens. If anything, absolute benefit increases in higher-risk groups, because these patients have more events to prevent. The pooled HHF reduction is in the range of 23–33%; kidney progression is slowed by 27–39%; and mortality—when studies are adequately powered—is reduced by 13–31%. These effects are consistent across agents, across diabetic and non-diabetic populations, and across observational and experimental designs.

Perhaps the most important clinical implication of this review is the absence of any eGFR interaction. Not a single trial, not a single meta-analysis, found that the treatment effect was significantly attenuated at eGFR <30. The SMART-C P-trend was 0.16. DAPA-CKD interaction P-values exceeded 0.10. The Spiazzi interaction for MACE actually went in the opposite direction—greater benefit at worse kidney function (P = 0.038). This should change clinical thinking about these drugs in advanced CKD. The prevailing hesitancy—"the kidneys are too far gone for this drug to work"—is not supported by the data.

4.2 Understanding the EMPA-KIDNEY Cardiovascular Results

EMPA-KIDNEY has occasionally been cited as evidence that SGLT2 inhibitors lack CV benefit in advanced CKD. This interpretation is incorrect, and it is worth explaining why. The trial enrolled a deliberately broad population: low albuminuria was permitted (median UACR 329 mg/g, compared with ~900 in DAPA-CKD and ~927 in CREDENCE), and 54% of patients had no diabetes. These are lower-risk patients who experience fewer cardiovascular events per unit time. The placebo arm cardiovascular event rate was below 1.2 per 100 patient-years; at that rate, even a 6,609-patient trial stopped at median 2 years is underpowered for HHF or MACE.

The kidney data from EMPA-KIDNEY, in contrast, were unequivocal. The primary composite was reduced with HR 0.72. The eGFR <30 subgroup showed HR 0.73. The eGFR slope benefit was 1.37 ml/min/1.73m² per year. There is no reasonable interpretation of EMPA-KIDNEY indicating that the drug fails to work at low eGFR; it simply did not have enough cardiovascular events to prove a CV benefit in isolation. When pooled with other trials in meta-analyses, the CV benefit in CKD patients emerges clearly (Mavrakanas: RR 0.79 for CV death/HHF; Spiazzi: HR 0.78).

4.3 How Do These Drugs Work When Glucosuria Is Minimal?

This is the question colleagues most often raise. At eGFR <30, filtered glucose is so low that SGLT2 inhibition produces negligible glucosuria, raising the question of how the drugs continue to confer benefit. The answer almost certainly lies in glucose-independent mechanisms, of which several have been proposed. Tubuloglomerular feedback restoration—reducing intraglomerular pressure by increasing sodium delivery to the macula densa—may persist at low GFR, even if magnitude is reduced. Direct anti-fibrotic effects on the heart and kidney have been demonstrated in preclinical models independent of glucose. Myocardial energetics may improve through a shift toward ketone body oxidation, a more oxygen-efficient fuel. AMPK/mTOR-mediated autophagy enhancement and sirtuin-1/HIF-2α pathways leading to erythropoietin stimulation have been proposed, particularly by the Wu et al. [15] group. The Heerspink mortality analysis [17], showing that the survival benefit in DAPA-CKD was driven by non-cardiovascular, non-renal deaths, adds another layer. If these drugs reduce infection-related and possibly cancer-related mortality, the mechanism must extend beyond haemodynamics and involve systemic anti-inflammatory or immunomodulatory effects. This is one of the more provocative findings in the literature and warrants dedicated mechanistic investigation.

4.4 The Sotagliflozin Question

Sotagliflozin's MI and stroke reductions [9] are notable but require careful handling. No selective SGLT2 inhibitor has demonstrated these benefits, and the proposed mechanism—postprandial glucose smoothing via intestinal SGLT1 blockade reducing platelet activation—is specific to dual SGLT1/2 inhibition in diabetic patients. Excluding sotagliflozin from this review would have omitted the only agent with mandatory enrolment at eGFR 25–60 and a prespecified MACE analysis. The compromise was to include it but analyse it separately, flag the dual mechanism explicitly, and avoid generalising the MI/stroke findings to the SGLT2 inhibitor class as a whole.

4.5 The Risk-Treatment Paradox in Advanced CKD

A frustrating pattern emerges from clinical practice, one that Gregg et al. [20] have termed the "risk-treatment paradox": patients at the highest cardiovascular risk are the least likely to receive evidence-based therapy. In LMIC settings, including Pakistan, this is compounded by limited nephrology workforce, fragmented care pathways, and—until recently—high drug costs. An eGFR below 30 often triggers reflexive drug discontinuation rather than treatment intensification. The data reviewed here suggest this instinct is misguided. When the Spiazzi meta-analysis shows that MACE benefit is largest in KDIGO Very High Risk patients (HR 0.72; P-interaction = 0.038) [12], and Waijer shows that absolute risk reduction is nearly three times greater in the sickest quartile [8], the case for treating rather than withholding is strong.

The timing may be favourable for implementation. Generic dapagliflozin is now available in Pakistan at approximately PKR 30–50 per day (roughly USD 0.10–0.18), compared with branded pricing that was prohibitive for most patients only two years ago. If this review provides the evidence rationale and generic availability provides the economic feasibility, the remaining barrier is physician awareness and confidence.

4.6 Implications for Guidelines

The 2024 KDIGO guideline recommends SGLT2 inhibitors down to eGFR 20 for patients with diabetes or heart failure and requires UACR ≥200 mg/g for non-diabetic, non-heart-failure CKD [19]. Based on these findings, three modifications are warranted. First, the cardiovascular protection indication should be explicitly extended to CKD Stage 4 regardless of diabetes status, given consistent benefit in non-diabetic subgroups (Staplin et al.: HR 0.75 for HHF) [11]. Second, the albuminuria threshold should be reconsidered, since the SMART-C data show benefit at UACR <30 and no UACR interaction for cardiovascular outcomes [10, 11]. Third, continuation through CKD Stage 5 until dialysis should be supported, given real-world evidence from Anuforo [13] and Wu [15] and the established safety profile. These

recommendations align with positions taken by Gregg et al. in their recent JAMA editorial [20].

4.7 Strengths and Limitations

The principal strength of this review is its comprehensiveness. By including RCTs, their subgroup analyses, IPD and aggregate meta-analyses, and real-world data—spanning publications through March 2026—the full scope of available evidence has been captured. The systematic GRADE assessment adds rigour, and the focused PICO on eGFR <30 addresses a specific and unresolved clinical question.

Limitations should be stated plainly. First, the eGFR <30 evidence comes overwhelmingly from subgroup analyses of trials that were not designed or powered for this population. While the consistency of results across multiple independent trials and meta-analyses is reassuring, definitive proof requires a dedicated trial, such as the ongoing RENAL LIFECYCLE study (NCT05374291). Second, no de novo meta-analysis was performed; the rationale for this decision is sound (risk of double-counting; availability of high-quality published meta-analyses), but it remains a limitation. Third, sotagliflozin is pharmacologically distinct, and its inclusion complicates class-level conclusions. Fourth, real-world studies, while valuable for extending evidence into Stage 5 and ESKD, carry the inherent biases of observational research—channelling bias is a particular concern, as clinicians who prescribe SGLT2 inhibitors at very low eGFR may be more proactive in general care. Fifth, language restriction to English may have excluded relevant non-English publications, although given the dominance of English-language journals in this field the impact is likely small.

5. CONCLUSIONS

On the basis of evidence from over 17,000 patients with eGFR <30 or CKD Stage 4–5 drawn from nine RCTs, five large meta-analyses, and four real-world studies, SGLT inhibitors reduce heart failure hospitalisation by approximately 23–33%, slow kidney disease progression by 27–39%, and—when evidence is adequately pooled—reduce all-cause mortality by 13–31% in this population. No study has shown attenuation of benefit at lower eGFR, and the largest meta-analysis to examine this question (SMART-C; n = 70,361) found no eGFR-treatment interaction. MACE benefit, in fact, appears greatest in the highest-risk patients. The safety profile is acceptable, with dapagliflozin showing the most favourable signal (zero DKA; reduced AKI) and modest DKA excess seen mainly with canagliflozin, sotagliflozin, and in ESKD populations.

These findings have direct clinical relevance for the millions of patients worldwide with advanced CKD who currently do not receive these drugs. The risk-treatment paradox in advanced CKD—withholding effective therapy from those who need it most—should be challenged at the guideline level and in daily practice. In resource-limited settings where generic formulations are now available, the opportunity for impact is enormous. The forthcoming results of the RENAL LIFECYCLE and DAPA-DIALYSIS trials will provide the dedicated evidence needed to move from "probably beneficial" to "proven" in this population.

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Conflicts of Interest

The authors declare no conflicts of interest relevant to this work.

Author Contributions

Both authors contributed to study conception, protocol development, literature search, study selection, data extraction, risk of bias assessment, evidence synthesis, and manuscript drafting. Both authors reviewed and approved the final manuscript and accept full responsibility for its content.

Data Availability

All data presented in this review were extracted from published sources cited in the reference list.

No individual patient data were accessed. The data extraction sheets and risk of bias assessments are available from the corresponding author upon reasonable request.

Use of Artificial Intelligence

In accordance with International Committee of Medical Journal Editors (ICMJE) guidance, the authors disclose that artificial intelligence (AI) language model assistance (Claude, Anthropic) was used during the preparation of this manuscript. AI assistance was limited to organising the evidence extraction summary, formatting tables, generating the PRISMA flow diagram and forest plot figures (using Python/matplotlib), and drafting initial prose for subsequent author revision. AI tools were not used for study selection, data extraction decisions, risk of bias judgement, or interpretation of clinical findings. All AI-generated content was critically reviewed, verified against original sources, and edited by the authors. The authors take full responsibility for the accuracy, integrity, and clinical interpretation of the entire manuscript, including all citations and data presented.

PROSPERO Registration

This systematic review was prospectively registered with PROSPERO (registration number CRD420261377175; registered 24 April 2026). The full record is available at https://www.crd.york.ac.uk/PROSPERO/view/CRD420261377175.

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SUPPLEMENTARY TABLE 1. GRADE Evidence Summary

Outcome	N Studies	RoB	Inconsistency	Indirectness	GRADE	Pooled Estimate
HHF / CV death	5 RCTs + 3 MAs	Low	None	Some	MODERATE	HR 0.71–0.77
CKD progression	6 RCTs + 4 MAs	Low	None	Minor	HIGH	HR 0.61–0.73
All-cause mortality	4 RCTs + 2 MAs	Low	Some	Some	MODERATE	HR/RR 0.69–0.87
MACE (3-point)	3 RCTs + 2 MAs	Low/Mod	Some	Some	MODERATE	HR 0.77–0.89
AKI (safety)	6 RCTs + 2 MAs	Low	None	Minor	HIGH	RR 0.77–0.82 (protective)
DKA (safety)	6 RCTs	Low	Moderate	Low	MODERATE	0–2× risk (drug-dependent)

GRADE: Grading of Recommendations, Assessment, Development and Evaluation. RoB: Risk of Bias. HHF: Hospitalisation for Heart Failure. MA: Meta-analysis. RCT: Randomised Controlled Trial. AKI: Acute Kidney Injury. DKA: Diabetic Ketoacidosis.

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