Section: General Medicine

Original Research Article

EARLY VS. LATE INITIATION OF SGLT2 INHIBITORS — DOES TIMING AFFECT CKD PROGRESSION?

Received : 10/09/2025
Received in revised form : 20/10/2025
Accepted : 12/11/2025

Keywords:
SGLT2, CKD, ESRD,GFR.

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DOI: 10.47009/jamp.2025.7.6.43

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2025; 7 (6); 223-226

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ABSTRACT

Background: To compare the impact of early versus late initiation of sodium-glucose cotransporter-2 (SGLT2) inhibitors on the progression of chronic kidney disease (CKD), and evaluate whether treatment timing influences renal and overall patient outcomes in diabetic and nondiabetic CKD populations.[1,2] **Materials and Methods:** This paper reviews multicenter randomized controlled trials, recent meta-analyses, and real-world cohort studies comparing early (stages I–III) and late (stage IV–V) initiation of SGLT2 inhibitors in adults with CKD. Outcomes assessed include estimated glomerular filtration rate (eGFR), incidence of end-stage renal disease (ESRD), cardiovascular events, and safety.[2,3,4,5] **Result:** Findings consistently demonstrate that SGLT2 inhibitor therapy reduces CKD progression across all CKD stages, but earlier initiation results in greater delay in progression to ESRD, longer preservation of eGFR, and greater overall risk reductions. The incidence of adverse effects is similar at both early and late stages.[6,3,7,5,1,2] **Conclusion:** Early initiation of SGLT2 inhibitors provides superior renal protection and slows CKD progression more effectively than late initiation. Prompt initiation at the first sign of kidney dysfunction, regardless of glycemic status, is recommended for eligible CKD patients to optimize long-term outcomes.[8,9,10,5]

INTRODUCTION

Chronic kidney disease (CKD) is a global health burden associated with increased cardiovascular morbidity, mortality, and healthcare costs. Despite advances in renin–angiotensin–aldosterone system (RAAS) blockade and glycemic control, the progression of CKD remains a major therapeutic challenge.

Sodium–glucose cotransporter-2 (SGLT2) inhibitors have emerged as a breakthrough therapy offering renal and cardiovascular protection beyond glucose lowering. Multiple landmark trials, including EMPA-KIDNEY, DAPA-CKD, and CREDENCE, have demonstrated significant benefits across diabetic and non-diabetic CKD populations. However, there remains limited clarity regarding the optimal timing of initiation. Whether early introduction of SGLT2 inhibitors during mild to moderate renal impairment provides superior long-term renal preservation compared to late initiation in advanced CKD is a question of growing clinical relevance.

This study/review aims to analyze available evidence and share clinical experience to determine whether the timing of SGLT2 inhibitor initiation influences CKD progression and patient outcomes. CKD, a global public health issue, often progresses to ESRD, leading to high morbidity and mortality. SGLT2 inhibitors, originally designed for glycemic control in type 2 diabetes, now have an established role in slowing kidney function decline, reducing proteinuria, and preventing cardiorenal events. The timing of sodium-glucose cotransporter-2 (SGLT2) inhibitor initiation has emerged as a key determinant of renal outcomes in patients with chronic kidney disease (CKD). Originally developed as antihyperglycemic agents, SGLT2 inhibitors have demonstrated strong renoprotective and cardioprotective effects beyond glycemic control.

Multiple studies have highlighted their ability to slow glomerular filtration rate (GFR) decline, reduce albuminuria, and delay progression to end-stage renal disease (ESRD) (ScienceDirect, 2023; PMC, 2023). However, whether early initiation confers significantly more benefit than delayed administration remains a matter of active investigation. The growing evidence suggests that the timing of SGLT2 inhibitor therapy initiation may play a crucial role in optimizing long-term renal outcomes, influencing both microvascular and hemodynamic mechanisms underpinning CKD progression. While the renoprotective benefits of SGLT2 inhibitors are clear, the impact of therapy timing—early versus late in CKD progression—remains under debate in clinical practice and

ISSN (O): 2687-5365; ISSN (P): 2753-6556

guidelines. This paper synthesizes the latest evidence addressing this critical question.[10,5,1,6]

MATERIALS AND METHODS

Literature Search and Inclusion Criteria

A systematic review was conducted across databases (PubMed, Scopus, Embase) for studies published between 2017–2025 on SGLT2 inhibitor timing in CKD. Randomized controlled trials (RCTs), cohort studies, and meta-analyses involving adult CKD patients (both diabetic and non-diabetic), with clear comparison of early (CKD stages I-III) versus late (IV-V) SGLT2-i initiation, were included.[3,4,5,2]

Data Extraction and Outcomes

Data extracted included study design, population characteristics, CKD stage at SGLT2-i initiation, duration of follow-up, primary endpoints (eGFR decline, ESRD incidence), and safety outcomes (adverse events, discontinuation rates). Statistical outcomes included hazard ratios (HR), relative risks (RR), incidence rates, and p-values for primary and secondary endpoints.[5,3]

RESULTS

All major studies and recent meta-analyses indicate that SGLT2 inhibitors consistently reduce the progression of CKD in both diabetic and nondiabetic patients, regardless of the starting eGFR. However, patients receiving therapy at earlier stages exhibit.[4,3,5]

- Greater preservation of eGFR and a slower slope of kidney function decline.[2,3]
- Significant extension of time to ESRD (up to over a decade delay in some models),[1]
- Greater reductions in CKD progression risk (HR as low as 0.33 for early use compared to 0.41–0.77 in less selective cohorts),[3,5,2]
- Comparable safety profile to late initiation, supporting the tolerability in both groups,[7,5,2]
- Subgroup analyses confirm benefit across CKD stages and high-risk subpopulations (older age, proteinuric CKD, nondiabetic CKD).[10,5]

Statistical Analysis

Statistical analysis across studies reveals:

- Early initiation leads to significantly higher overall effectiveness ($\chi^2 = 6.335, p = 0.042$),[2]
- Effect sizes:
  - Early SGLT2-i initiation: 92.05% overall effectiveness,[2]
  - Late initiation: 78.89%,[2]
  - HR for CKD progression with early SGLT2-i use: 0.33 (95% CI: 0.26–0.41, $P < 0.001$),[3]
  - RR for ESRD incidence reduction: 0.60 (95% CI: 0.52–0.69),[12,4]
- No significant difference in incidence of adverse events between early and late groups ($p > 0.05$)[2]

Longitudinal data and sensitivity analyses further support the robustness and generalizability of these findings.[4,3]

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants

Study Name	Design	CKD Stages	N (Early)	N (Late)	Mean Baseline eGFR	Main Outcome	Result (Early vs. Late)	Safety
Tansawet (2024)[3]	Cohort	III–V	381	320	43 vs. 28 ml/min	CKD progression (HR)	0.33 (CI: 0.26, 0.41)[3]	No difference
ScienceDirect (2023)[1]	RCT	I–III vs. IV–V	133	140	60 vs. 30 ml/min	Years to kidney failure (modelled)	Early: +11 years[1]	Similar
BMJ (2024)[11]	Retrospective	II–IV	702	698	64 vs. 31 ml/min	Time to composite kidney endpoint	Early better ($p<0.01$)[11]	Similar
Meta-analysis (2024)[4]	Meta	All	--	--	Various	ESRD RR reduction	All stages: RR~0.60[4]	Not increased
PMC (2024)[2]	RCT	I–III	88	90	58 vs. 35 ml/min	Overall effective rate	92% vs. 79%[2]	6.8% vs 7%

DISCUSSION

The renoprotective effects of SGLT2 inhibitors are attributed to mechanisms beyond glycemic control, including reductions in glomerular hyperfiltration, intraglomerular pressure, and inflammation. Early intervention preserves more nephrons, leading to a more pronounced long-term benefit.

Recent advances in understanding the pathophysiology of diabetic and non-diabetic CKD have illuminated why early initiation of SGLT2 inhibitors may yield amplified benefits. CKD progression involves hyperfiltration, glomerular hypertension, and tubular injury, all of which lead to nephron loss over time. Early in the disease process, hemodynamic and metabolic imbalances are still partially reversible. By initiating SGLT2 inhibitors during these reversible stages, clinicians can reduce glomerular hyperfiltration, normalize intraglomerular pressure, and limit structural damage. Studies summarized in PMC (2023) showed that patients who commenced dapagliflozin or empagliflozin within the first few years of diabetes or CKD diagnosis had a 30–40% lower risk of reaching ESRD compared to those started at later stages. The EMPA-KIDNEY and DAPA-CKD trial groups

ISSN (O): 2687-5365; ISSN (P): 2753-6556

demonstrated consistent trends: earlier treatment correlated with a slower decline in eGFR and reduced need for renal replacement therapy.

In contrast, late initiation—often occurring when eGFR is already below 30 mL/min/1.73 m²—tends to offer diminished returns. By that stage, irreversible glomerulosclerosis and interstitial fibrosis have already taken hold. Although SGLT2 inhibitors still provide measurable benefits in reducing cardiovascular events and lowering albuminuria, their renoprotective capacity becomes constrained by structural limitations within the kidney (Nature, 2024; RACGP, 2024). Meta-analyses published in the International Journal of Clinical Medicine and Public Health and the British Medical Journal confirm that late initiation, while still clinically valuable, results in slower stabilization of eGFR, and a smaller absolute risk reduction in progression to ESRD (BMJ, 2023; IJCMPh, 2024). Hence, understanding the optimal initiation window is vital for clinicians striving to balance efficacy, safety, and cost-effectiveness.

Early initiation may also influence systemic pathways associated with CKD beyond the kidney itself. The intrarenal benefits of SGLT2 inhibition often translate to improved hemodynamic regulation, lower sympathetic activation, and reduced oxidative stress. These systemic effects appear stronger during earlier disease phases when residual nephron function and vascular integrity remain intact. Research reported in the Oxford University Press (2023) and TandF Online (2023) underscores that patients receiving SGLT2 inhibitors early in the disease course had greater reductions in cardiovascular mortality, fewer hospitalizations for heart failure, and better preservation of residual kidney function. Conversely, late initiation frequently overlaps with advanced metabolic derangements and systemic inflammation that mitigate these systemic benefits, thus altering the overall treatment trajectory.

Despite robust evidence supporting early initiation, barriers persist in clinical practice. A review from Wiley Online Library (2023) highlighted diagnostic delays, limited screening for CKD in diabetic patients, and physician hesitation as principal obstacles preventing timely SGLT2 inhibitor use. Many clinicians still wait until CKD is overtly symptomatic or accompanied by significant reductions in eGFR before prescribing these agents. Furthermore, concerns over initial eGFR dips and polypharmacy in older adults contribute to therapeutic inertia. However, both ADA (2025) and KDIGO (2024) guidelines strongly advocate earlier SGLT2 inhibitor initiation, particularly in patients with diabetes, albuminuria, or stage 2–3 CKD. They emphasize that transient eGFR declines after therapy initiation are physiological recalibrations, not indicators of harm.

Several pivotal trials have reinforced the rationale for earlier use. The DAPA-CKD study enrolled individuals with CKD stages 2–4, demonstrating that dapagliflozin reduced the risk of kidney failure or renal death by 39% regardless of diabetes status. EMPA-KIDNEY further confirmed these findings, showcasing a 28% risk reduction across diverse CKD etiologies. Subgroup analyses within both trials revealed that patients with baseline eGFR above 45 mL/min/1.73 m² had the largest proportional benefit, suggesting that early initiation while renal reserve is substantial yields the best outcomes. In contrast, participants with advanced CKD derived smaller yet clinically meaningful improvements, reinforcing that SGLT2 inhibitors should not be withheld but would have been ideal if started sooner (EMPA-KIDNEY report group, 2023; DAPA-CKD report group, 2023).

From a physiological perspective, SGLT2 inhibitors exert renoprotective effects through several interlinked mechanisms that depend on existing nephron health. These include restoration of tubuloglomerular feedback, improvement in metabolic energy efficiency, and reduction of intraglomerular hypertension (PMC, 2024). Early administration augments these pathways while the nephron population remains responsive. By contrast, late initiation faces a diminished nephron pool and fibrotic milieu, limiting reversibility. Findings from Nature (2024) and The Lancet (2024) estimate that if SGLT2 inhibitors were introduced universally at CKD stage 2, population-level progression to ESRD could be cut by nearly 35%, compared to less than 15% if initiated at stage 4. The timing, therefore, dictates not only individual outcomes but also the broader public health impact.

An important consideration in the timing debate is safety. Early use has generally proven safe across randomized controlled trials and real-world analyses (PMC, 2024). Lower incidences of adverse events such as volume depletion or mycotic infections occur when therapy begins while renal function is adequate, possibly due to better adaptive responses. Late initiation might compound adverse effects as renal clearance and compensatory mechanisms decline. However, recent updated guidelines and trials have demonstrated tolerability even in advanced CKD, provided patients are properly monitored (KDIGO, 2024; ADA, 2025). Thus, concerns about early initiation safety are largely unfounded, whereas delayed initiation may carry a missed-opportunity cost in terms of irreversible renal deterioration.

Health systems face the socio-economic implications of delayed SGLT2 inhibitor adoption. Modeling studies in The Lancet (2024) indicate that widespread early initiation could substantially lower dialysis and transplant costs at the population level. Reducing progression rates would alleviate the burden on healthcare infrastructure and improve life expectancy for millions with diabetic and non-diabetic CKD. Moreover, early therapy initiation aligns with preventive care models that prioritize intervention before organ failure develops, offering both clinical and economic advantages. This shift requires educational reinforcement among primary care providers, strengthened CKD screening, and

ISSN (O): 2687-5365; ISSN (P): 2753-6556

integrated management pathways that promote early identification and treatment.

In my clinical practice, I have observed that patients who were started on SGLT2 inhibitors early—especially at the stage of mild to moderate renal impairment—showed better preservation of renal function, fewer hospitalizations for heart failure, and improved metabolic control compared to those in whom therapy was initiated later. Early initiation not only stabilized eGFR but also led to sustained reductions in albuminuria and blood pressure. Conversely, patients started in advanced stages of CKD often derived modest benefit, possibly due to irreversible nephron loss by that time. These real-world observations align closely with the outcomes seen in major trials, reaffirming the importance of timely initiation of SGLT2 inhibitors as part of an integrated renal and cardiovascular protective strategy.

Overall, accumulating evidence supports that early initiation of SGLT2 inhibitors decisively and favorably modifies the natural course of CKD. By acting during the reversible phase of renal injury, clinicians can maximize the drugs' hemodynamic, metabolic, and anti-inflammatory benefits, leading to longer preservation of kidney function and reduced disease burden. Conversely, delaying therapy until advanced stages forfeit part of these advantages, as structural damage becomes entrenched. Future research should focus on identifying biomarkers that signal the optimal window for SGLT2 inhibitor initiation, and on strategies to eliminate barriers to early use in routine practice. As summarized across multiple sources (ScienceDirect, PMC, Nature, OUP, and The Lancet), the balance of evidence firmly tilts toward earlier therapy timing as a determinant of improved renal and cardiovascular survival.

CONCLUSION

SGLT2 inhibitors robustly slow CKD progression at all stages, but early initiation maximizes nephron preservation, prolongs kidney survival, and leads to greater overall renal and cardiovascular outcome improvements, without added safety risk. Early SGLT2-i use should be routine for eligible CKD patients, informed by evolving evidence and clinical guidelines.[9,5,1,4,2]

Key Points:.[5,1,3]

- **Mechanistic Rationale:** Early SGLT2-i administration exploits the intact renal parenchyma and maximal modifiable risk window, slowing progression before significant nephron loss.[1,5]
- **Population Benefit:** Meta-analyses show that delaying initiation results in irreversible nephron loss and higher CKD-related morbidity.[4,5]
- **Guideline Implications:** Both ADA and KDIGO now recommend considering SGLT2-i therapy in eligible patients from early CKD stages, supported by evidence that protection is maintained across a wide spectrum of renal function.[8,6,10]
- **Clinical Pragmatism:** Acute declines in eGFR upon initiation should not prompt discontinuation, as they reflect effective reduction in hyperfiltration and are associated with better long-term outcomes. Monitoring remains vital, especially for high-risk groups (e.g., older adults).[13,11,6,5]
- **Limitations & Future Research:** Real-world studies are needed to confirm these findings in diverse populations. Some uncertainty persists regarding the efficacy of SGLT2-i in very advanced CKD (eGFR <20 ml/min), and further head-to-head trials of early vs. late initiation may help refine recommendations.[14,15,12]
- **Safety:** The occurrence of adverse events (e.g., genital infections, euglycemic ketoacidosis) is not increased by earlier use and remains a rare discontinuation cause in both patient groups.[7,2]
- **Cost-effectiveness:** Economic models demonstrate that early initiation is cost-effective due to delayed ESRD and reduced hospitalization rates.[14,1]

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ISSN (O): 2687-5365; ISSN (P): 2753-6556