J Nephropharmacol. 2027; 16(1): e12899.

https://jnephropharmacology.com DOI: 10.34172/npj.12899

Journal of Nephropharmacology

The clinical paradox of SGLT2 inhibition in patients with chronic kidney disease; evaluating the spectrum of toxicity and the dangers of overzealous therapeutic use

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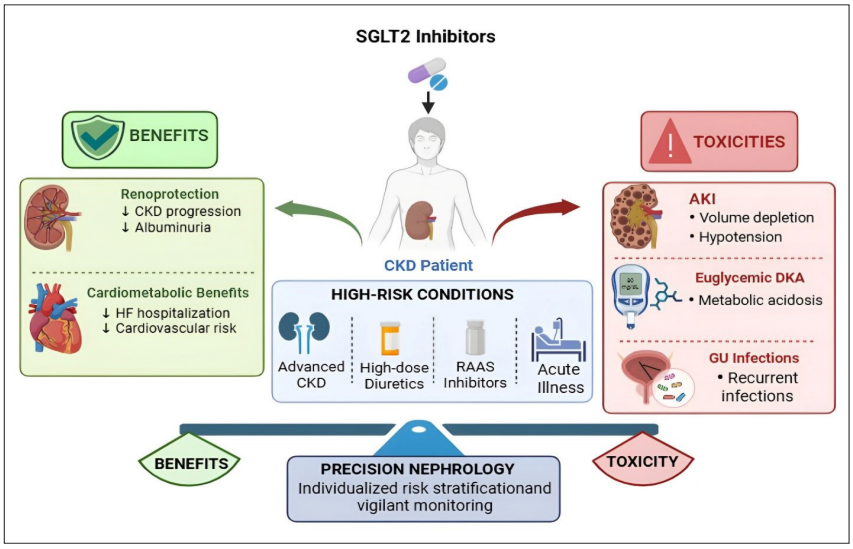
ARTICLE INFO

Article Type:
Review

Article History:
Received: 26 Jul. 2026
Revised: 8 Sep. 2026
Accepted: 14 Sep. 2026
ePublished: 27 Sep. 2026

Keywords:
Chronic kidney disease,
SGLT2 inhibition
Tubuloglomerular feedback
End-stage kidney disease
Glomerular filtration rate
Acute kidney injury
Diabetic ketoacidosis

ABSTRACT



Sodium-glucose cotransporter-2 (SGLT2) inhibitors have revolutionized the management of chronic kidney disease (CKD), offering unprecedented renoprotective and cardiometabolic benefits. However, a clinical paradox has emerged wherein the very agents designed to preserve renal function can precipitate significant toxicity when deployed overzealously or without meticulous patient selection. This overview considers the spectrum of adverse effects associated with SGLT2 inhibition in the CKD population, emphasizing the fine line between therapeutic efficacy and iatrogenic harm. Though robust clinical trials demonstrate profound long-term benefits, real-world application reveals distinct vulnerabilities, particularly concerning volume depletion-induced acute kidney injury, euglycemic diabetic ketoacidosis, and severe, recurrent genitourinary infections. The dangers of overzealous therapeutic use are magnified in patients with advanced CKD, those on concurrent high-dose diuretics or renin-angiotensin-aldosterone system inhibitors, and individuals failing to adhere to essential sick day protocols during acute illness. Furthermore, the aggressive continuation of SGLT2 inhibitors below established estimated glomerular filtration rate thresholds risks exacerbating hemodynamic instability and electrolyte derangements without conferring additional renoprotective advantages. By synthesizing recent pharmacovigilance data, case reports, and clinical trial subgroup analyses, this paper underscores the absolute necessity of individualized risk stratification. Clinicians should know this paradox by balancing the undeniable long-term organ-preserving potential of SGLT2 inhibitors with vigilant, proactive monitoring for acute toxicities. Finally, optimizing outcomes in CKD requires a paradigm shift from blanket, protocol-driven prescribing to precision nephrology, ensuring that the well-intentioned pursuit of renal preservation does not inadvertently accelerate clinical decline through unchecked therapeutic enthusiasm and inadequate physiological surveillance.

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Implication for health policy/practice/research/medical education:
The clinical paradox of sodium-glucose cotransporter-2 (SGLT2) inhibition in chronic kidney disease (CKD) lies in its dual nature; since, these agents offer profound long-term renoprotection by reducing intraglomerular pressure, their overzealous application risks precipitating acute iatrogenic harm. The spectrum of toxicity ranges from predictable, manageable adverse effects like volume depletion and genital mycotic infections to rare, life-threatening complications such as euglycemic diabetic ketoacidosis and Fournier's gangrene. In advanced CKD, the initial hemodynamically mediated dip in estimated glomerular filtration rate can be misinterpreted as true nephrotoxicity, prompting inappropriate discontinuation or, conversely, dangerous continuation in hypovolemic states. Overzealous therapeutic use, particularly without meticulous patient selection and volume status monitoring, transforms a cornerstone renoprotective therapy into a catalyst for acute kidney injury and metabolic derangement. Consequently, clinicians should manage a delicate equilibrium, recognizing that the profound benefits of SGLT2 inhibitors are inextricably linked to vigilant, individualized risk assessment to prevent therapeutic excess from overshadowing renal preservation.

Please cite this paper as: Hajian S, Zahedi Far A. The clinical paradox of SGLT2 inhibition in patients with chronic kidney disease; evaluating the spectrum of toxicity and the dangers of overzealous therapeutic use. J Nephropharmacol. 2027;16(1):e12899. DOI: 10.34172/npj.12899.

Introduction

The advent of sodium-glucose cotransporter-2 (SGLT2) inhibitors has undeniably represented one of the most profound paradigm shifts in modern nephrology and cardiometabolic medicine (1). Initially developed as a novel class of glucose-lowering agents for patients with type 2 diabetes, these medications have rapidly transcended their original indication to become foundational, disease-modifying therapies for heart failure and chronic kidney disease (CKD), regardless of diabetic status (2). Previous clinical trials have consistently demonstrated their capacity to significantly slow the progression of renal decline, reduce the risk of end-stage kidney disease, and lower cardiovascular mortality (3). However, this meteoric rise in therapeutic prominence has simultaneously unveiled a complex clinical paradox (4). The mechanisms that confer profound renoprotection can, under specific circumstances or when applied indiscriminately, precipitate a distinct spectrum of toxicities (5). As guideline recommendations have aggressively expanded, a concerning trend of overzealous therapeutic use has emerged, wherein the enthusiasm for prescribing these agents occasionally outpaces careful patient stratification, physiological monitoring, and individualized risk assessment (6-8). Evaluating this paradox requires an exact understanding of both the pharmacological elegance of SGLT2 inhibition and the very real, sometimes severe, adverse consequences that arise when these powerful agents are deployed without adequate clinical vigilance in vulnerable populations with CKD (9).

Search strategy

For this narrative review, we performed a literature search across multiple databases, including PubMed, Google Scholar, the Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, and Embase. The search strategy employed a variety of relevant keywords, such as chronic kidney disease, SGLT2 inhibition, tubuloglomerular feedback, SGLT2 inhibitors, end-stage kidney disease, glomerular filtration rate, acute kidney injury and diabetic ketoacidosis.

Pathophysiology of SGLT2 inhibition

To fully appreciate this clinical paradox, one must first examine the fundamental pathophysiology of SGLT2 inhibition and how it intersects with the compromised renal architecture of CKD (2). Under normal physiological conditions, SGLT2 proteins in the proximal convoluted tubule are responsible for reabsorbing the vast majority of filtered glucose (10). In states of hyperglycemia, this system is often upregulated, contributing to sustained high blood glucose levels (11). By inhibiting this transporter, SGLT2 inhibitors induce profound glucosuria, which in turn delivers a high sodium and glucose load to the macula densa. This restored delivery activates tubuloglomerular feedback, leading to afferent arteriolar vasoconstriction (12). In the context of CKD, particularly diabetic nephropathy, the afferent arteriole is often pathologically dilated due to hyperfiltration, a state that drives progressive glomerular damage and proteinuria (13). The SGLT2 inhibitor-induced vasoconstriction effectively normalizes this intraglomerular pressure, reducing hyperfiltration and providing a powerful renoprotective shield. However, this hemodynamic alteration is a double-edged sword (4,14). The immediate consequence of this afferent constriction is a predictable, initial decline in the estimated glomerular filtration rate (eGFR). While this initial dip is generally considered a benign, physiological marker of effective target engagement and long-term renal protection, it exists on a razor-thin margin with pathological acute kidney injury (15,16). In patients with advanced CKD, those who are concurrently volume-depleted, or those receiving maximal doses of concurrent diuretics and renin-angiotensin-aldosterone system inhibitors, this hemodynamic shift can tip from protective autoregulation into overt renal hypoperfusion, precipitating a true acute kidney injury that can accelerate, rather than halt, the journey toward end-stage renal

disease (17). The momentum behind SGLT2 inhibitors has been overwhelmingly positive that it has catalyzed a rapid, guideline-driven expansion of their indications (18). What began as a niche therapy for glycemic control is now universally recommended across a broad spectrum of cardiorenal syndromes (19). While this widespread endorsement is rooted in robust evidence, it has inadvertently fostered an environment ripe for overzealous therapeutic use (4). Overzealous use in this context does not necessarily imply malicious intent or gross negligence; rather, it refers to the application of a powerful therapeutic intervention based on a rigid adherence to population-level guidelines, without sufficient adaptation to the complex, heterogeneous reality of individual patients (4). This phenomenon is exacerbated by the halo effect of the drug class, where the overwhelming potency of benefit can unconsciously minimize the perceived risk of adverse events (20). Clinicians, excited to provide state-of-the-art care and mindful of quality metrics, may initiate SGLT2 inhibitors in patients with CKD who possess multiple, compounding risk factors for toxicity, such as advanced age, frailty, recurrent genitourinary infections, or a history of unreliable oral intake, without implementing the necessary safeguards or concomitant medication adjustments (9,21).

Euglycemic diabetic ketoacidosis by SGLT2i

Beyond the immediate hemodynamic perturbations, the metabolic toxicity of SGLT2 inhibitors presents a particularly insidious challenge, most notably in the form of euglycemic diabetic ketoacidosis (22). This condition is a hallmark paradox of the drug class, as it occurs in the presence of near-normal or only mildly elevated blood glucose levels, frequently leading to delayed diagnosis and treatment (23). The pathophysiology involves a combination of factors; while, the SGLT2 inhibitor-induced glucosuria lowers blood glucose, which in turn suppresses endogenous insulin secretion while simultaneously stimulating glucagon release (24). This altered insulin-to-glucagon ratio promotes lipolysis and hepatic ketogenesis (24). In patients with CKD, the risk of euglycemic ketoacidosis is compounded by several factors (25). These patients often have baseline metabolic derangements, including a reduced capacity to excrete acid loads, making them more susceptible to metabolic acidosis (25). Furthermore, the symptoms of early ketoacidosis, such as nausea, vomiting, and fatigue, are frequently non-specific and can be easily misattributed to uremia or other common comorbidities of CKD (26). The danger is magnified during periods of physiological stress, such as acute intercurrent illness, fasting, or perioperative states, which are common in this population (25). Overzealous therapeutic use manifests here when clinicians fail to educate patients on sick day rules, neglect to temporarily withhold the medication during acute illness or prior to surgery, or fail to maintain a high index of suspicion for ketosis when a CKD patient presents with non-specific malaise and a normal blood glucose reading (27).

Genital mycotic infections by SGLT2i

In parallel with these metabolic concerns, the genitourinary tract represents another primary locus of SGLT2 inhibitor toxicity, directly resulting from the drug's intended mechanism of action (28). The deliberate induction of glucosuria creates a nutrient-rich, warm, and moist environment in the lower urinary tract and genitalia, which serves as an ideal culture medium for fungal and bacterial proliferation (29). Genital mycotic infections are the most frequently reported adverse event associated with this drug class (30). While often mild and easily treatable in the general population, the implications for patients with CKD can be far more severe. This population frequently exhibits localized or systemic immune dysfunction, and many have pre-existing urological abnormalities, such as neurogenic bladder, benign prostatic hyperplasia, or a history of recurrent urinary tract infections (4). The introduction of an SGLT2 inhibitor can transform a manageable, intermittent issue into a chronic, debilitating, and recurrent source of morbidity (31). In severe cases, this glucosuria-driven infectious risk can culminate in complicated pyelonephritis, urosepsis, or the rare but catastrophic necrotizing fasciitis of the perineum, known as Fournier's gangrene (32). Overzealous prescribing ignores these critical historical factors, initiating therapy in patients with a known predisposition to severe genitourinary infections without adequate prophylactic counseling, hygiene education, or a low threshold for discontinuation at the first sign of recurrent infection (33).

Administration of SGLT2i in elderly

Furthermore, the cardiovascular and volumetric consequences of SGLT2 inhibition warrant careful scrutiny, particularly in the fragile demographic of advanced CKD (34). The osmotic diuresis caused by glucosuria leads to a modest but consistent reduction in intravascular volume and blood pressure. While this is highly beneficial for patients with volume overload and hypertension, it poses a significant hazard for those who are euvolemic or hypovolemic (35). Patients with CKD are frequently managed with loop or thiazide diuretics to control blood pressure or manage edema. The concurrent use of SGLT2 inhibitors and traditional diuretics can have an additive, sometimes synergistic, volume-depleting effect (36,37). In elderly or frail patients with CKD, this iatrogenic volume contraction can precipitate symptomatic orthostatic hypotension, dizziness, syncope, and subsequent falls (35). The morbidity associated with a fall in an elderly patient with CKD, potentially leading to fractures, head trauma, or a cascade of hospitalizations, can entirely negate the long-term renoprotective benefits of the SGLT2 inhibitor (38). Overzealous therapeutic use is glaringly evident when a

clinician initiates an SGLT2 inhibitor without proactively down-titrating or discontinuing concomitant diuretic therapy, or when the drug is continued despite clear clinical signs of volume depletion and declining blood pressure (39). The aggregation of these diverse toxicities brings into sharp focus the dangers of overzealous therapeutic use, which is frequently characterized by a failure to recognize the boundaries of clinical trial data (40). The landmark trials that established the efficacy of SGLT2 inhibitors in CKD, such as CREDENCE, DAPA-CKD, and EMPA-KIDNEY, were meticulously designed with specific inclusion and exclusion criteria (41). While these trials included patients with a wide range of eGFRs, they generally excluded individuals with the most advanced stages of kidney disease, those with a high burden of competing risks, or those with a history of recurrent, severe adverse events related to the drug class (21). In the real world, however, the boundaries of these trials are often blurred (21). Overzealous use occurs when clinicians extrapolate trial benefits to patients who closely resemble the excluded populations, such as those with an eGFR persistently below 20 mL/min/1.73 m^2, those with a history of recurrent severe genital infections, or those with profound frailty and limited life expectancy (42). In these scenarios, the probability of experiencing a severe adverse event may outweigh the potential for long-term renal preservation, transforming a life-saving medication into a source of iatrogenic harm (42).

The concept of reverse clinical inertia

This overzealous approach is frequently compounded by the phenomenon of reverse clinical inertia (42,43). While clinical inertia traditionally refers to the failure to intensify therapy when indicated, reverse clinical inertia in the context of SGLT2 inhibitors refers to the reluctance to de-prescribe or modify therapy in the face of emerging toxicity or changing clinical circumstances (43). Once an SGLT2 inhibitor is added to a patient's regimen, it is often viewed as a permanent, untouchable pillar of their care, much like a statin or an ACE inhibitor (44,45). Consequently, when a patient with CKD develops acute gastroenteritis, undergoes a surgical procedure, or experiences a significant decline in oral intake, the SGLT2 inhibitor is frequently left active (4,46). This failure to dynamically adjust the medication regimen in response to acute physiological stressors is a primary driver of preventable toxicities, such as euglycemic ketoacidosis and acute kidney injury (47,48). The overzealous prescriber focuses on the long-term guideline mandate, losing sight of the patient's immediate, short-term physiological vulnerability. Moreover, the danger of overzealous therapeutic use is inextricably linked to the broader challenge of polypharmacy in CKD. Patients with impaired renal function are inherently susceptible to drug accumulation and altered pharmacokinetics (44,49). While SGLT2 inhibitors themselves do not typically require dose adjustment based on renal function for their glucose-lowering effect, their hemodynamic and metabolic effects are profoundly influenced by the renal milieu and concurrent medications (41). The simultaneous administration of SGLT2 inhibitors, high-dose RAAS (renin–angiotensin–aldosterone system) blockade, mineralocorticoid receptor antagonists, and loop diuretics creates a complex pharmacological web (50). Overzealous use fails to account for this intricate web, treating the addition of an SGLT2 inhibitor as a simple, isolated intervention rather than a significant perturbation of a delicate, pre-existing physiological equilibrium (28,43). This lack of holistic medication review can lead to a cascade of adverse events, where the treatment of one drug-induced complication inadvertently exacerbates another, ultimately destabilizing the patient's overall clinical status (20). Navigating this clinical paradox requires a fundamental shift from rigid, protocol-driven prescribing to a model of highly individualized, vigilant medicine (44,51). Recognizing the potential for toxicity is not an argument for abandoning SGLT2 inhibitors in CKD; rather, it is a mandate for smarter, more cautious implementation. Safe utilization begins with meticulous patient selection (9,21). Clinicians must actively screen for contraindications and high-risk features, such as a history of recurrent genitourinary infections, severe frailty, or a propensity for volume depletion (30). Prior to initiation, a comprehensive review of the patient's concurrent medications is essential, with a proactive plan to reduce the dosage of loop or thiazide diuretics to mitigate the risk of hypotension and acute kidney injury (30,52). Furthermore, robust patient education is a non-negotiable component of therapy (52). Patients must be thoroughly counseled on the signs and symptoms of genital infections, the importance of maintaining adequate hydration, and the critical "sick day rules" that dictate the temporary suspension of the medication during periods of acute illness, fasting, or prior to surgical interventions (33,53).

Monitoring of individuals treated by SGLT2i

Ongoing monitoring is equally critical to mitigating the dangers of overzealous use. Following the initiation of an SGLT2 inhibitor, clinicians should anticipate and accept a modest initial decline in the eGFR, recognizing it as a physiological response (54,55). However, they must also establish clear parameters for when this dip becomes pathological (55). A decline in eGFR exceeding thirty percent from baseline, or a concurrent rise in serum potassium or creatinine accompanied by symptoms of volume depletion, should trigger an immediate clinical reassessment and potential temporary discontinuation of the drug (55). Similarly, in any patient with CKD presenting with non-specific symptoms such as nausea, abdominal pain, or fatigue, a low threshold for checking serum or urine ketones is essential to rule out euglycemic diabetic ketoacidosis, regardless of the patient's concurrent blood

glucose level (25,56). This proactive, dynamic approach to monitoring ensures that the therapy remains beneficial and is swiftly modified at the first sign of harm. The role of the healthcare system and institutional guidelines in curbing overzealous use cannot be overstated (45,57). While clinical guidelines are invaluable for synthesizing evidence and directing standard care, they must be interpreted as flexible frameworks rather than rigid mandates (9). Quality improvement metrics that heavily penalize the non-prescription of SGLT2 inhibitors in eligible patients with CKD, without providing nuanced exceptions for high-risk individuals, can inadvertently incentivize overzealous prescribing (3,58). Healthcare systems must foster a culture that values thoughtful clinical judgment and shared decision-making over blind adherence to checklist medicine (44,59). This involves empowering both clinicians and patients to openly discuss the potential risks and benefits of the therapy, ensuring that the decision to initiate an SGLT2 inhibitor is aligned with the patient's overall goals of care, life expectancy, and personal tolerance for risk (44,60). Finally, the clinical paradox of SGLT2 inhibition in patients with CKD serves as a powerful reminder of the inherent complexities of modern pharmacotherapy. These agents are undeniably transformative, offering a level of organ protection that was previously unattainable (21,61). They have rightfully earned their place at the forefront of nephrology and cardiology guidelines. However, their potency demands profound respect (21). The spectrum of toxicity associated with SGLT2 inhibitors, ranging from hemodynamic instability and acute kidney injury to euglycemic ketoacidosis and severe genitourinary infections, is not a rare anomaly but an intrinsic feature of their mechanism of action (62). When these drugs are deployed with overzealous therapeutic intent, divorced from careful patient selection, vigilant monitoring, and dynamic medication management, the potential for harm escalates dramatically (63,64). The true art of medicine lies not in the blind application of powerful new therapies, but in the discerning, individualized orchestration of those therapies. By acknowledging and actively managing the paradox of SGLT2 inhibition, clinicians can harness its remarkable renoprotective benefits while steadfastly guarding their patients with CKD against the very real dangers of overzealous therapeutic use (41,61,65).

Conclusion

Sodium-glucose cotransporter-2 inhibitors represent a monumental therapeutic advancement in CKD, offering unprecedented renoprotection and cardiovascular benefits. However, this clinical effectiveness is shadowed by a profound paradox; since, the very hemodynamic and metabolic mechanisms that confer long-term organ protection can precipitate a distinct spectrum of toxicity when applied without meticulous clinical judgment. The dangers of overzealous therapeutic use lie not in the inherent failure of the drug class, but in the misapplication of its physiological effects. Aggressive SGLT2 inhibition can induce significant intravascular volume contraction, leading to symptomatic hypotension, acute kidney injury, and the insidious, life-threatening risk of euglycemic diabetic ketoacidosis, particularly in vulnerable populations with advanced renal impairment, poor oral intake, or concurrent diuretic therapy. Furthermore, the cumulative burden of recurrent genitourinary infections and potential electrolyte derangements underscores that, these agents are not universally benign. Overprescribing, or failing to individualize therapy by neglecting to down-titrate concomitant medications or ignoring dynamically evolving GFRs, transforms a life-saving intervention into a catalyst for iatrogenic harm. Finally, navigating this paradox demands a paradigm shift from blanket, protocol-driven prescribing to highly individualized, vigilant patient management. Clinicians should continuously balance the profound long-term renoprotective gains against the immediate risks of toxicity through rigorous laboratory monitoring, proactive patient education, and timely dose adjustments. The future of SGLT2 inhibitor therapy in CKD contribute not on abandoning these transformative drugs, but on mastering the delicate equilibrium between therapeutic efficacy and iatrogenic risk, ensuring that the noble pursuit of renal preservation does not inadvertently compromise patient safety.

Authors' contribution

Conceptualization: Sepideh Hajian.
Data curation: Sepideh Hajian.
Investigation: Both authors.
Resources: Sepideh Hajian.
Supervision: Both authors.
Validation: Azadeh Zahedi Far
Visualization: Both authors.
Writing–original draft: Both authors.
Writing–review and editing: Both authors.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Funding/Support

None.

References

1. Checa-Ros A, Okojie OJ, D'Marco L. SGLT2 Inhibitors: Multifaceted Therapeutic Agents in Cardiometabolic and Renal Diseases. Metabolites. 2025;15:536. doi: 10.3390/metabo15080536.

2. Skrabic R, Kumric M, Vrdoljak J, Rusic D, Skrabic I, Vilovic M, et al. SGLT2 Inhibitors in Chronic Kidney Disease: From Mechanisms to Clinical Practice. Biomedicines. 2022;10:2458. doi: 10.3390/biomedicines10102458.
3. Madero M, Chertow GM, Mark PB. SGLT2 Inhibitor Use in Chronic Kidney Disease: Supporting Cardiovascular, Kidney, and Metabolic Health. Kidney Med. 2024;6:100851. doi: 10.1016/j.xkme.2024.100851.
4. Gajewska A, Wasiak J, Sapeda N, Młynarska E, Rysz J, Franczyk B. SGLT2 Inhibitors in Kidney Diseases-A Narrative Review. Int J Mol Sci. 2024;25:4959. doi: 10.3390/ijms25094959.
5. Zhang B, Deng L. Application of SGLT-2 inhibitors in non-diabetic CKD: mechanisms, efficacy, and safety. Front Med (Lausanne). 2025;12:1574693. doi: 10.3389/fmed.2025.1574693.
6. Dubrofsky L, Srivastava A, Cherney DZ. Sodium-Glucose Cotransporter-2 Inhibitors in Nephrology Practice: A Narrative Review. Can J Kidney Health Dis. 2020;7:2054358120935701. doi: 10.1177/2054358120935701.
7. Forbes AK, Hinton W, Feher MD, Elson W, Joy M, Ordóñez-Mena JM, et al. Implementation of chronic kidney disease guidelines for sodium-glucose co-transporter-2 inhibitor use in primary care in the UK: a cross-sectional study. EClinicalMedicine. 2024;68:102426. doi: 10.1016/j.eclinm.2024.102426.
8. Hajian S, Zahedi Far A. Remission revolution; redefining CKD management from slowdown to reversal. J Nephropharmacol. 2026;15:e12855-e. doi: 10.34172/npj.2026.12855.
9. Thomas MC, Neuen BL, Twigg SM, Cooper ME, Badve SV. SGLT2 inhibitors for patients with type 2 diabetes and CKD: a narrative review. Endocr Connect. 2023;12:e230005. doi: 10.1530/ec-23-0005.
10. Vallon V. Glucose transporters in the kidney in health and disease. Pflugers Arch. 2020;472:1345-70. doi: 10.1007/s00424-020-02361-w.
11. Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. Diabetologia. 2017;60:215-25. doi: 10.1007/s00125-016-4157-3.
12. Palmer BF, Clegg DJ. Kidney-Protective Effects of SGLT2 Inhibitors. Clin J Am Soc Nephrol. 2023;18:279-89. doi: 10.2215/cjn.09380822.
13. Tonneijck L, Muskiet MH, Smits MM, van Bommel EJ, Heerspink HJ, van Raalte DH, et al. Glomerular Hyperfiltration in Diabetes: Mechanisms, Clinical Significance, and Treatment. J Am Soc Nephrol. 2017;28:1023-39. doi: 10.1681/asn.2016060666.
14. Clemmer JS, Yen TE, Obi Y. Modeling the renoprotective mechanisms of SGLT2 inhibition in hypertensive chronic kidney disease. Physiol Rep. 2023;11:e15836. doi: 10.14814/phy2.15836.
15. Lertdumrongluk P, Tantisattamo E, Obi Y, Nguyen HA, Kovesdy CP, Rhee CM, et al. Estimated glomerular filtration rate at dialysis initiation and subsequent decline in residual kidney function among incident hemodialysis patients. Nephrol Dial Transplant. 2020;35:1786-93. doi: 10.1093/ndt/gfaa055.
16. Collard D, Brouwer TF, Olde Engberink RHG, Zwinderman AH, Vogt L, van den Born BH. Initial Estimated Glomerular Filtration Rate Decline and Long-Term Renal Function During Intensive Antihypertensive Therapy: A Post Hoc Analysis of the SPRINT and ACCORD-BP Randomized Controlled Trials. Hypertension. 2020;75:1205-12. doi: 10.1161/hypertensionaha.119.14659.
17. Bhandari S, Mehta S, Khwaja A, Cleland JGF, Ives N, Brettell E, et al. Renin-Angiotensin System Inhibition in Advanced Chronic Kidney Disease. N Engl J Med. 2022;387:2021-32. doi: 10.1056/NEJMoa2210639.
18. Hu Q, Jin H, Li X, Hu L. Application of SGLT2 inhibitors in kidney diseases: a bibliometric analysis. Front Med (Lausanne). 2026;13:1768225. doi: 10.3389/fmed.2026.1768225.
19. Abdelfadil Elgazzar R, Ramadan M. Sodium-Glucose Cotransporter-2 Inhibitors Across the Glycemic Spectrum: Cardiovascular and Renal Outcomes With Mechanistic Insights. Cureus. 2026;18:e105114. doi: 10.7759/cureus.105114.
20. Falsetti L, Tarquinio N, Mucci L, Santini S, Guerrieri E, Giovenali L, et al. Beyond safety: adverse events and unanticipated advantages of SGLT2 inhibitors. Eur J Clin Pharmacol. 2026;8:93. doi: 10.1007/s00228-026-04023-9.
21. Yau K, Dharia A, Alrowiyti I, Cherney DZI. Prescribing SGLT2 Inhibitors in Patients With CKD: Expanding Indications and Practical Considerations. Kidney Int Rep. 2022;7:1463-76. doi: 10.1016/j.ekir.2022.04.094.
22. Bobba SS, Campbell E, Bril F. Risk of Euglycemic Diabetic Ketoacidosis Can Persist After Discontinuation of Sodium-glucose Cotransporter-2 Inhibitors. JCEM Case Rep. 2025;3:luaf268. doi: 10.1210/jcemcr/luaf268.
23. Mistry S, Eschler DC. Euglycemic Diabetic Ketoacidosis Caused by SGLT2 Inhibitors and a Ketogenic Diet: A Case Series and Review of Literature. AACE Clin Case Rep. 2021;7:17-9. doi: 10.1016/j.aace.2020.11.009.
24. Młynarska E, Czarnik W, Dzieża N, Jędraszak W, Majchrowicz G, Prusinowski F, et al. Type 2 Diabetes Mellitus: New Pathogenetic Mechanisms, Treatment and the Most Important Complications. Int J Mol Sci. 2025;26:1094. doi: 10.3390/ijms26031094.
25. Palmer BF, Clegg DJ. Euglycemic Ketoacidosis as a Complication of SGLT2 Inhibitor Therapy. Clin J Am Soc Nephrol. 2021;16:1284-91. doi: 10.2215/cjn.17621120.
26. Elendu C, David JA, Udoyen AO, Egbunu EO, Ogbuiyi-Chima IC, Unakalamba LO, et al. Comprehensive review of diabetic ketoacidosis: an update. Ann Med Surg (Lond). 2023;85:2802-7. doi: 10.1097/ms9.0000000000000894.
27. Milder TY, Stocker SL, Day RO, Greenfield JR. Potential Safety Issues with Use of Sodium-Glucose Cotransporter 2 Inhibitors, Particularly in People with Type 2 Diabetes and Chronic Kidney Disease. Drug Saf. 2020;43:1211-21. doi: 10.1007/s40264-020-01010-6.
28. Vallon V. State-of-the-Art-Review: Mechanisms of Action of SGLT2 Inhibitors and Clinical Implications. Am J Hypertens. 2024;37:841-52. doi: 10.1093/ajh/hpae092.
29. Geerlings S, Fonseca V, Castro-Diaz D, List J, Parikh S. Genital and urinary tract infections in diabetes: impact of pharmacologically-induced glucosuria. Diabetes Res Clin Pract. 2014;103:373-81. doi: 10.1016/j.diabres.2013.12.052.
30. Confederat LG, Dragostin OM, Condurache MI. SGLT2 Inhibitors and the Risk of Urogenital Infections: A Concise Review. J Clin Med. 2025;14:1960. doi: 10.3390/jcm14061960.
31. Priya, Kumar A, Khatri G, Hasan MM. SGLT2 inhibitors: An answer to diabetes or a question to its complications? Ann Med Surg (Lond). 2022;79:103992. doi: 10.1016/j.amsu.2022.103992.
32. Kaur H, Chauhan S, Yadav M. SGLT2 Inhibitors and Complicated Urinary Tract Infections: A Rare Case of Emphysematous Pyelonephritis and Subsequent Recurrence Associated With Dapagliflozin Use. Clin Case Rep. 2025;13:e71320. doi: 10.1002/ccr3.71320.
33. McGovern AP, Hogg M, Shields BM, Sattar NA, Holman RR, Pearson ER, et al. Risk factors for genital infections in people initiating SGLT2 inhibitors and their impact on discontinuation. BMJ Open Diabetes Res Care. 2020;8: e001238. doi: 10.1136/bmjdrc-2020-001238.
34. Chen X, Wang J, Lin Y, Yao K, Xie Y, Zhou T. Cardiovascular

outcomes and safety of SGLT2 inhibitors in chronic kidney disease patients. Front Endocrinol (Lausanne). 2023;14:1236404. doi: 10.3389/fendo.2023.1236404.
35. Fathi A, Vickneson K, Singh JS. SGLT2-inhibitors; more than just glycosuria and diuresis. Heart Fail Rev. 2021;26:623-42. doi: 10.1007/s10741-020-10038-w.
36. Ali S, Navaneethan SD, Virani SS, Gregg LP. Revisiting diuretic choice in chronic kidney disease. Curr Opin Nephrol Hypertens. 2022;31:406-13. doi: 10.1097/mnh.0000000000000814.
37. Gérard AO, Laurain A, Sicard A, Merino D, Pathak A, Drici MD, et al. New Strategies for Volume Control in Patients with Diabetes Mellitus, a Narrative Review. Pharmaceutics. 2022;14:1569. doi: 10.3390/pharmaceutics14081569.
38. Carriazo S, Ortiz A. Stopping kidney protection in the elderly following acute kidney injury: think mortality. Clin Kidney J. 2022;15:1037-40. doi: 10.1093/ckj/sfac024.
39. Packer M, Wilcox CS, Testani JM. Critical Analysis of the Effects of SGLT2 Inhibitors on Renal Tubular Sodium, Water and Chloride Homeostasis and Their Role in Influencing Heart Failure Outcomes. Circulation. 2023;148:354-72. doi: 10.1161/circulationaha.123.064346.
40. Kimura T, Kaku K. A decade of SGLT2 inhibitors: Lessons learned and the road ahead in type 2 diabetes. J Diabetes Investig. 2025;16:2142-4. doi: 10.1111/jdi.70187.
41. Nespoux J, Vallon V. Renal effects of SGLT2 inhibitors: an update. Curr Opin Nephrol Hypertens. 2020;29:190-8. doi: 10.1097/mnh.0000000000000584.
42. Duni A, Tsavourelou P, Triantafyllidou M, Gkika L, Georgopoulos C, Stamellou E, et al. Benefits of SGLT2 inhibitors in patients with diabetes and advanced chronic kidney disease - where have we gone so far? Front Clin Diabetes Healthc. 2025;6:1759340. doi: 10.3389/fcdhc.2025.1759340.
43. Greene SJ, Pierce JB. Overcoming Barriers to Use of SGLT2 Inhibitor Therapy: The Battle Against Clinical Inertia. JACC Heart Fail. 2023;11:943-5. doi: 10.1016/j.jchf.2023.05.006.
44. Seidu S, Alabraba V, Davies S, Newland-Jones P, Fernando K, Bain SC, et al. SGLT2 Inhibitors - The New Standard of Care for Cardiovascular, Renal and Metabolic Protection in Type 2 Diabetes: A Narrative Review. Diabetes Ther. 2024;15:1099-124. doi: 10.1007/s13300-024-01550-5.
45. Padda IS, Mahtani AU, Parmar M. Sodium-Glucose Transport 2 (SGLT2) Inhibitors. Treasure Island (FL): StatPearls Publishing LLC.; 2026.
46. Bailey CJ, Day C, Bellary S. Renal Protection with SGLT2 Inhibitors: Effects in Acute and Chronic Kidney Disease. Curr Diab Rep. 2022;22:39-52. doi: 10.1007/s11892-021-01442-z.
47. Yau K, Dharia A, Alrowiyti I, Cherney DZI. Prescribing SGLT2 Inhibitors in Patients With CKD: Expanding Indications and Practical Considerations. Kidney Int Rep. 2022;7:2546-7. doi: 10.1016/j.ekir.2022.08.016.
48. Chang J, Kim C, Choi H, Park RW, Lee S. Renal and Safety Outcomes of SGLT2 Inhibitors in Patients with Type 2 Diabetes: A Nationwide Observational Cohort Study. J Clin Med. 2025;14:3349. doi: 10.3390/jcm14103349.
49. Chan JCH, Chan MCY. SGLT2 Inhibitors: The Next Blockbuster Multifaceted Drug? Medicina (Kaunas). 2023;59:388. doi: 10.3390/medicina59020388.
50. Murakami Y, Kiuchi S, Hisatake S, Ikeda T. Combination of SGLT2 Inhibitors and Loop Diuretics in the Treatment of Heart Failure. J Pers Med. 2025;15. doi: 10.3390/jpm15030099.
51. Tilinca MC, Tiuca RA, Tilea I, Varga A. The SGLT-2 Inhibitors in Personalized Therapy of Diabetes Mellitus Patients. J Pers Med. 2021;11:1249. doi: 10.3390/jpm11121249.
52. Gomez-Peralta F, Abreu C, Lecube A, Bellido D, Soto A, Morales C, et al. Practical Approach to Initiating SGLT2 Inhibitors in Type 2 Diabetes. Diabetes Ther. 2017;8:953-62. doi: 10.1007/s13300-017-0277-0.
53. Gorgojo-Martínez JJ, Górriz JL, Cebrián-Cuenca A, Castro Conde A, Velasco Arribas M. Clinical Recommendations for Managing Genitourinary Adverse Effects in Patients Treated with SGLT-2 Inhibitors: A Multidisciplinary Expert Consensus. J Clin Med. 2024;13:6509. doi: 10.3390/jcm13216509.
54. Vallon V, Verma S. Effects of SGLT2 Inhibitors on Kidney and Cardiovascular Function. Annu Rev Physiol. 2021;83:503-28. doi: 10.1146/annurev-physiol-031620-095920.
55. Kao YW, Chao TF, Chen SW, Cheng YW, Chan YH, Chu PH. Initial eGFR Changes with SGLT2 Inhibitor in Patients With Type 2 Diabetes and Associations With the Risk of Abnormal Serum Potassium Level. J Am Heart Assoc. 2024;13:e033236. doi: 10.1161/jaha.123.033236.
56. Ali E, Kamran S, Cheema AAA. SGLT2 inhibitors and the underrecognized risk of euglycemic diabetic ketoacidosis: a clinical call for vigilance. Ann Med Surg (Lond). 2025;87:7795-6. doi: 10.1097/ms9.0000000000003890.
57. Sakai C, Tamaru S, Sugai K, Takeuchi H, Suzuki R. Clinical use and monitoring of adverse effects of sodium-glucose cotransporter-2 inhibitors in persons with type 1 diabetes mellitus. J Diabetes Investig. 2025;16:1420-9. doi: 10.1111/jdi.70085.
58. Romagnani P. SGLT2 inhibitors in CKD: are they really effective in all patients? Nephrol Dial Transplant. 2025;40:1838-42. doi: 10.1093/ndt/gfaf051.
59. MacDonald BJ, McCormack JP, Turgeon RD. Shared decision-making approach to type 2 diabetes management. Can Fam Physician. 2024;70:310-5. doi: 10.46747/cfp.7005310.
60. Recommendations on the Proper Use of SGLT2 Inhibitors. J Diabetes Investig. 2020;11:257-61. doi: 10.1111/jdi.13160.
61. Di Costanzo A, Esposito G, Indolfi C, Spaccarotella CAM. SGLT2 Inhibitors: A New Therapeutical Strategy to Improve Clinical Outcomes in Patients with Chronic Kidney Diseases. Int J Mol Sci. 2023;24:8732. doi: 10.3390/ijms24108732.
62. Morace C, Lorello G, Bellone F, Quartarone C, Ruggeri D, Giandalia A, et al. Ketoacidosis and SGLT2 Inhibitors: A Narrative Review. Metabolites. 2024;14:264. doi: 10.3390/metabo14050264.
63. Singh M, Kumar A. Risks Associated with SGLT2 Inhibitors: An Overview. Curr Drug Saf. 2018;13:84-91. doi: 10.2174/1574886313666180226103408.
64. Pittampalli S, Upadyayula S, Mekala HM, Lippmann S. Risks vs Benefits for SGLT2 Inhibitor Medications. Fed Pract. 2018;35:45-8.
65. Soliman AR, Elkhatib M, El-Khashab S, Darwish RA, Fayed A, Abdelaziz TS, et al. Dual-faced guardians: SGLT2 inhibitors' kidney protection and health challenges: a position statement by Kasralainy nephrology group (KANG). Diabetol Metab Syndr. 2025;17:214. doi: 10.1186/s13098-025-01790-w.