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Paradox of an early decline in estimated glomerular filtration rate during initiation of sodium-glucose cotransporter 2 inhibitors: A literature review of mechanisms, safety, clinical significance, and management strategies

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ABSTRACT

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a fundamental part of the therapeutic approach for patients with type 2 diabetes mellitus (T2DM), heart failure (HF), or chronic kidney disease (CKD), and the phenomena observed during their initiation are increasingly well understood. There is one such phenomenon, a transient decrease in estimated glomerular filtration rate (eGFR), known as the eGFR dip or initial eGFR decline. The eGFR dip, in medical understanding, has evolved from a potential adverse event to a positive pharmacodynamic marker (bioassay), reflecting the activation of a nephroprotective mechanism. This paper summarizes the mechanism, safety, management, and prognostic significance of this effect, based mainly on scientific articles searched in the PubMed database published in the past 10 years, with a particular focus on meta-analyses, randomized controlled trials (RCTs), post hoc analyses, real-world evidence (RWE), and retrospective observational studies. This dip, with the mean decrease of 3–5 ml/min/1.73 m², occurs in most patients within the first 2–4 weeks of SGLT2i initiation. The dip's cause is fully reversible tubuloglomerular feedback (TGF) activation, unrelated to increased biomarkers of structural damage. Clinical guidelines actually promote a shift from reactive monitoring to "strategic tolerance", accepting an eGFR dip up to 30% without interrupting treatment. Modern SGLT2i monitoring strategies require a combination with research aimed at personalizing recommendations for various groups to minimize unnecessary discontinuation and maximize the nephroprotective benefits of treatment.

Keywords: SGLT2 inhibitors, initial eGFR decline, eGFR dip, tubulogromerular feedback (TGF), cardionephroprotection

1. INTRODUCTION

Evolution of indications and historical background

Sodium-glucose cotransporter 2 inhibitors (SGLT2i), also known as "flozins", represent one of the most significant pharmacological innovations of the past decade in diabetology, cardiology, and nephrology. Although SGLT2i initially emerged for glycemic control in type 2 diabetes mellitus (T2DM), their role has rapidly evolved as key trials demonstrated their capacity to decelerate the trajectory of chronic kidney disease (CKD) (Wanner et al., 2016). A contemporary analysis of these benefits reinterprets the phenomenon of early renal function decline. Paradoxically, this initial eGFR decrement presages long-term cardiorenal durability, extending to a significant reduction in cardiovascular events (Neal et al., 2017).

Breakthrough in cardiorenal care

The clinical management of heart failure (HF), even across the full spectrum of ejection fraction, has transformed over the last few years thanks to the newest clinical trials with SGLT2i (McMurray et al., 2019; Anker et al., 2021). At the same time, these drugs established nephrology standards by significantly slowing CKD progression (Perkovic et al., 2019; Heerspink et al., 2020). Importantly, these clinical benefits persist even in advanced stages of CKD, independently of the baseline estimated glomerular filtration rate (eGFR) (Herrington et al., 2023).

The hemodynamic mechanism and the phenomenon of eGFR dip

SGLT2i inhibits sodium-glucose cotransporters, reducing the reabsorption of these molecules in the proximal tubule of the nephron. This process leads to glucosuria and natriuresis, which, in turn, result in decreased blood glucose levels, reduced intravascular volume, and decreased blood pressure. However, the increased sodium influx into the macula densa restores physiological tubuloglomerular feedback (TGF) (Heerspink et al., 2016). TGF activation causes constriction of the afferent arteriole and a reduction in detrimental hyperfiltration, exerting a nephroprotective effect ultimately (Cherney et al., 2022).

A consequence of these changes is a characteristic phenomenon: an early decline in eGFR, which occurs in most patients within 2–4 weeks of starting SGLT2i therapy and is referred to in the medical literature as the "eGFR dip". The interpretation of this process currently tends to the "bioassay" hypothesis, which suggests that the dip should not be considered an adverse drug event but rather an early marker of the drug's hemodynamic efficacy (Kraus et al., 2021). Although a pronounced initial eGFR dip may mimic acute kidney injury (AKI), it is – unlike true AKI - fully reversible and occurs without structural changes, as confirmed by stable tubular injury biomarker levels (Jongs et al., 2022). Furthermore, such an effect acts as a desirable marker of functional nephron unloading, which paradoxically correlates with better long-term nephroprotection (Oshima et al., 2021).

Current guidelines and clinical dilemmas

A breakthrough class of drugs, SGLT2i, has redefined the clinical management of the most common chronic diseases (such as T2DM, HF, and CKD) and the less common cardiovascular-kidney-metabolic (CKM) syndrome. Latest recommendations on the issue of an initial eGFR reduction promote a transition from reactive toward more passive vigilance (McDonagh et al., 2023; KDIGO CKD Work Group, 2024; ADA Professional Practice Committee for Diabetes, 2026). Nevertheless, concerns about the difficulty of interpreting eGFR dips appear to be a significant barrier to better treatment optimization, often leading to premature therapy discontinuation (Weir, 2025). The study analyzes the current knowledge about the mechanism, safety, and prognostic significance of the eGFR dip phenomenon during initiation of SGLT2i, as well as the evolution of the approach to monitoring the eGFR dip over the past decade - from a fear of AKI toward "strategic tolerance". This paper also describes the relationship between initial filtration changes and long-term nephroprotection, differentiating the physiological eGFR dip from pathological AKI. Furthermore, it examines how the magnitude of this decline varies between patient groups, providing a rationale for personalized therapy with flozin.

2. REVIEW METHODS

We have searched the PubMed database for scientific articles published between January 2016 and January 2026 using the different combinations of the following keywords: SGLT2 inhibitors, initial eGFR decline, eGFR dip, tubuloglomerular feedback, cardiorenal protection. We selected meta-analyses, systematic reviews, and randomized controlled trials (RCTs). Inclusion criteria also included

prespecified and post hoc RCT subanalyses, real-world evidence (RWE), retrospective observational studies, current guidelines, and one peer-reviewed expert commentary.

During the selection of searched articles, we excluded narrative reviews, case reports, animal model studies, papers without full-text access, papers in languages other than English, small-sample-size studies, and papers without relevant data on early changes in eGFR. Finally, we enrolled 32 papers in the final analysis. The article screening process followed the PRISMA guidelines (Figure 1).

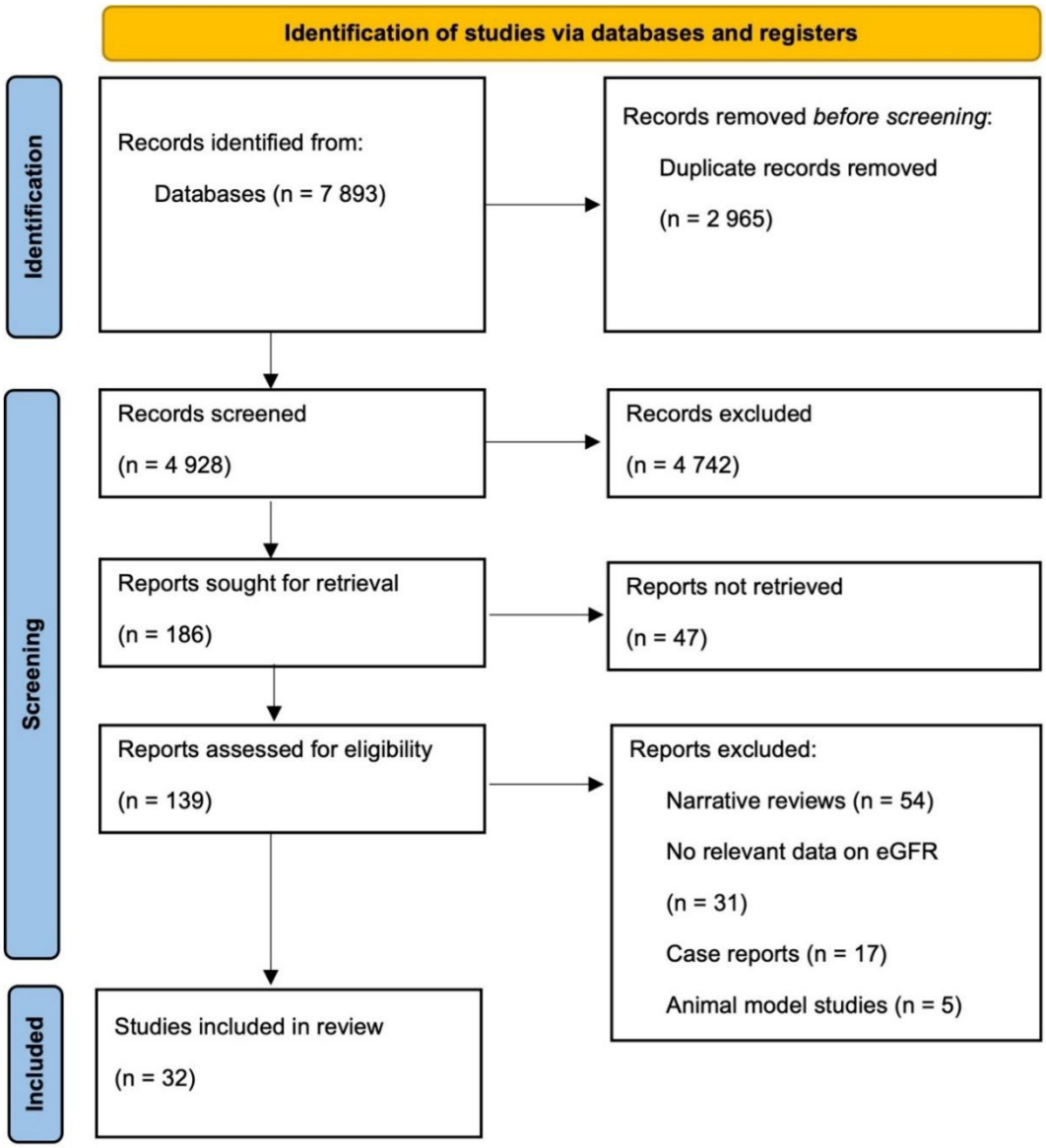

Figure 1. PRISMA flow diagram.

3. RESULTS & DISCUSSION

Characteristics and versatility of the eGFR dip phenomenon

The first reports of the initial eGFR fluctuation phenomenon appeared in early studies of SGLT2 inhibitors. Yet, pivotal trials over the past decade have expanded our understanding of these filtration dynamics. The EMPA-REG OUTCOME trial was the first to highlight the eGFR dip as a key prognostic parameter. It demonstrated a characteristic "crossing of the curves" in filtration rates compared to placebo - despite an initial decline during the first weeks of treatment in the empagliflozin group, long-term follow-up revealed more favorable stabilization of renal function in the study group. In the chronic phase (from week 4 to the end of treatment), the rate of decline in renal function averaged 0.19 ± 0.11 ml/min/1.73 m²/year ($P < 0.001$) for empagliflozin compared with 1.67 ± 0.13 ml/min/1.73

m²/year (P<0.001) in the placebo group (Wanner et al., 2016). In post-hoc analysis of this study a population of 6,668 patients with T2DM and high cardiovascular (CV) risk, the median initial decline in eGFR at week 4 of empagliflozin treatment was -2.69 mL/min/1.73 m² (Interquartile Range [IQR]: –7.87 to –1.30) compared with –0.05 mL/min/1.73 m² (IQR: –4.04, –4.27) between participants receiving placebo (Kraus et al., 2021).

The CANVAS program, involving a total of 10,142 patients with T2DM and high CV risk receiving canagliflozin, demonstrated a 14% reduction (Hazard Ratio [HR] = 0.86; 95% Confidence Interval [CI]: 0.75–0.97) in the risk of a composite endpoint, which included death from cardiovascular causes, non-fatal myocardial infarction, and non-fatal stroke (Neal et al., 2017). In a dedicated post-hoc analysis, the mean early eGFR dip of -3.1 ml/min/1.73 m² (Standard Error [SE]: -3.2 to -3.0) in the canagliflozin group versus -0.7 ml/min/1.73 m² (SE: -0.9 to -0.5) in the placebo group during the first 13 weeks. In the long term, however, stabilization was observed in the treated group, i.e., eGFR +0.3 ml/min/1.73 m²/year (SE: 0.2 to 0.4) compared to a decline of -0.9 ml/min/1.73 m²/year (SE: -1.0 to -0.8) in the placebo group (Perkovic et al., 2018).

The CREDENCE trial (canagliflozin in T2DM and CKD) confirmed that this effect is consistent even in a population with advanced kidney disease. The canagliflozin-treated group achieved a 30% lower risk of end-stage renal disease (HR: 0.70; 95% CI, 0.59 to 0.82; P=0.00001) compared to placebo, despite an initial filtration decline. After 3 weeks, the reduction in eGFR was significantly greater in the study group (-3.72 ± 0.25 mL/min/1.73 m² versus -0.55 ± 0.25 mL/min/1.73 m²; 95% CI; SE: -3.87 to -2.47) than in the placebo group (Perkovic et al., 2019). Additionally, a post-hoc analysis revealed that the mean eGFR change from baseline was -7.0% (SE: 0.4%) in the canagliflozin group and +0.3% (SE: 0.4%) in the placebo group. Nearly 50% participants in the treatment group experienced an eGFR dip >10%, compared with 21% in the placebo group (P<0.001). Predictors of a greater decline were also identified, including higher baseline eGFR, greater baseline albuminuria, and the use of loop diuretics (Oshima et al., 2021).

The DAPA-CKD trial (CKD with or without T2DM) showed that 9.2% of participants in the dapagliflozin group experienced primary outcomes, what means at least 50% decline in eGFR, end-stage renal disease, or death from renal or cardiovascular causes; whereas in the placebo group it was 14.5%(HR: 0.61; 95% CI: 0.51 to 0.67) (Heerspink et al., 2020). A detailed analysis of this population showed a median decline in eGFR of -4.0 mL/min/1.73 m² in the treatment group versus -0.8 mL/min/1.73 m² in the placebo cohort at week 2 of therapy. Importantly, patients with a greater eGFR decline (>10%) paradoxically experienced less long-term CKD progression, with an annual eGFR decline of -1.58 mL/min/1.73 m² compared to -2.44 mL/min/1.73 m² (<10%) (Jongs et al., 2022).

The DAPA-HF trial (dapagliflozin in HF with reduced ejection fraction [HFrEF] without T2DM) confirmed the universality of the eGFR dip phenomenon (McMurray et al., 2019). In the DAPA-HF post-hoc analysis, the median eGFR decline was -4.24 mL/min/1.73 m² (IQR: -9, 1) in the treated cohort versus -1.11 mL/min/1.73 m² (IQR: -5, 3) in the placebo group during the first 14 days of SGLT2i initiation. At the same time, this decline does not negatively impact subsequent cardiovascular and renal benefits. On the contrary, a larger initial decline in eGFR correlates with greater long-term clinical benefits (Adamson et al., 2022).

The EMPEROR-Reduced and EMPEROR-Preserved trials established the consistency of the previously observed early eGFR decline followed by long-term stabilization of renal function across the full HF spectrum treated with empagliflozin (Packer et al., 2020; Anker et al., 2021). Both studies' subanalyses confirmed the safety and assessed the value of early eGFR decline (Zannad et al., 2022; Rastogi et al., 2024). Next, the DELIVER trial confirmed the safety profile of dapagliflozin in HF with mildly reduced (HFmrEF) or preserved ejection fraction (HFpEF) (Solomon et al., 2022). A prespecified subanalysis showed that a dip of >10% at month 1 occurred in nearly 40% (1140 of 2892) of patients, compared with 25% in the placebo arm (OR: 1.9; 95% CI: 1.7-2.1). A drop of>10% was not associated with primary cardiovascular (aHR: 0.90; 95% CI: 0.74-1.09; P for interaction = 0.01) or subsequent kidney composite (aHR: 0.94; 95% CI: 0.49-1.82) outcomes, so the dip did not have a detrimental effect on efficacy. Furthermore, the long-term trend of the average adjusted chronic decline (4-36 months) shows that the difference between the group with >10% dip (-1.2 mL/min/1.73 m²/year) and non-dippers (-0.9 mL/min/1.73 m²/year) was not significant (P for interaction = 0.68) (McCausland et al., 2024).

The latest and largest EMPA-KIDNEY trial, involving 6,609 patients with a wide spectrum of CKD taking empagliflozin - including patients with baseline eGFR ranging from 20 to 45 mL/min/1.73 m² - demonstrated a 28% (HR: 0.72) reduction in the risk of CKD progression or cardiovascular death (Herrington et al., 2023). Subanalysis of early eGFR changes in this study confirmed its safety (Staplin et al., 2024). In the VERTIS CV trial (ertugliflozin, participants: 100% with T2DM, 100% with advanced atherosclerotic cardiovascular disease, 24% with HF), an initial decline in eGFR of approximately -3.0 mL/min/1.73 m² was observed over 6 weeks after drug initiation. Crucially, the therapy nearly double (OR: 1.90; 95% CI: 1.71-2.11) the probability of occurence of a pronounced dip ≥6.0 mL/min/1.73 m² at week 6, what significantly correlated (P for interaction <0.05) with baseline clinical parameters, including advanced CKD (eGFR <60 mL/min/1.73 m²), raised systolic blood pressure (SBP; ≥133.3 mmHg), older age (≥65 years old), and insulin use

(Cherney et al., 2022). In summary, this early decline is a reversible, class-wide effect observed across all patient profiles, which serves as a marker of long-term renal protection, characterized by a significantly slower rate of renal function loss. Table 1 presents a summary of this section.

Table 1. Summary of initial and long-term changes in estimated glomerular filtration rate (eGFR) in major clinical trials of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and their subanalyses.

Study (drug)	Population (N)	Mean (or median) of the early eGFR decline (ml/min/1.73 m²)	Evaluation period of the early eGFR decline (from randomisation)	Long-term effect on eGFR: drug vs. placebo (mL/min/1.73 m²/year)	References
EMPA-REG OUTCOME (empagliflozin)	T2DM + high CV risk (n=7020)	-2,69 (median)	4 weeks	-0,19±0,11 vs -1,67±0,13	Wanner et al., 2016; Kraus et al., 2021
CANVAS Program (canagliflozin)	T2DM + high CV risk (n=10142)	-3,1	13 weeks	+0,3 vs -0,9	Neal et al., 2017; Perkovic et al., 2018
CREDENCE (canagliflozin)	T2DM + CKD (n=4401)	-3,72± 0,25 (median)	3 weeks	–1,85±0,13 vs –4,59±0,14	Perkovic et al., 2019; Oshima et al., 2021
DAPA-CKD (dapagliflozin)	CKD ± T2DM (n=4304)	-4,0	2 weeks	-1,58 vs -3,27 (>10% eGFR dip) -2,44 vs -3,84 (<10% eGFR dip)	Heerspink et al., 2020; Jongs et al., 2022
DAPA-HF (dapagliflozin)	HFrEF ± T2DM (n=4744)	-4,24 (median)	2 weeks	-0,7 vs -2,3 (>10% eGFR dip) -1,7 vs -3,5 (<10% eGFR dip)	McMurray et al., 2019; Adamson et al., 2022
DELIVER (dapagliflozin)	HFmrEF/HFpEF (n=6263)	-4,0 (median)	1 month	-1,2 (>10% eGFR dip) -0,9 (<10% eGFR dip)	Solomon et al., 2022; McCausland et al., 2024
EMPEROR – Reduced (empagliflozin)	HFrEF (n=3730)	-2,5	4 weeks	-0,55 vs -2,28	Packer et al., 2020 Zannad et al., 2022
EMPEROR – Preserved (empagliflozin)	HFpEF (n=5988)	-3,2	4 weeks	-1,25 vs -2,62	Anker et al., 2021 Rastogi et al., 2024
EMPA-KIDNEY (empagliflozin)	CKD ± T2DM (n=6609)	-3,39	2 months	-1,37 vs -2,75	Herrington et al., 2023 Staplin et al., 2024

Mechanism and differentiation of AKI

Understanding the mechanism of early eGFR decline following initiation of SGLT2i therapy allows for proper clinical interpretation and differentiation from AKI. The mechanism of action of SGLT2i involves inhibition of the proximal tubular SGLT2 cotransporter in the limiting sodium reabsorption and increasing its delivery to the macula densa, a region of the distal nephron duct and a part of the juxtaglomerular apparatus (Heerspink et al., 2016). Then, an intensified sodium influx triggers TGF activation, leading to selective vasoconstriction of afferent arterioles to alleviate baseline glomerular hyperfiltration (Cherney et al., 2022). Such an immediate reduction in intraglomerular pressure manifests by an initial acute eGFR dip and, in the long term, it effectively slows CKD progression, as demonstrated by a 39% (HR: 0.61; 95% CI: 0.51-0.72) risk reduction in hard renal composite endpoints, regardless of the presence or absence of diabetes (Heerspink et al., 2020).

A key factor in distinguishing hemodynamic decline in eGFR from structural AKI is the absence of molecular markers of tissue injury. Biomarker analyses from a 6-week randomized, double-blind, placebo-controlled crossover trial confirm that the initial eGFR dip of 5.2 ml/min/1.73 m² (95% CI: 2.5-7.8) induced by dapagliflozin does not indicate tubular injury. In fact, compared to placebo,

flozin significantly decreased urinary Kidney Injury Molecule-1 (KIM-1) excretion by 22.6% (95% CI: 0.3-39.8%; P=0.05) and caused a non-significant change in Neutrophil Gelatinase-Associated Lipocalin (NGAL, P=0.33), with no correlation observed between individual eGFr variations and alterations in any kidney injury markers (Dekkers et al., 2018). Furthermore, a post-hoc analysis of the EMPA-REG OUTCOME trial provided important data on the reversibility of the initial eGFR decline after discontinuation of empagliflozin - eGFR returned to baseline within 2–4 weeks of stopping therapy, regardless of the depth of the dip (Heerspink et al., 2016; Kraus et al., 2021). Notably, the absence of such reversibility or an excessive dip (>30%) may indicate the need to investigate other causes of renal function deterioration (Urban et al., 2025).

In the CREDENCE trial, the risk of an acute drop in eGFR (>10% over 3 weeks) was significantly increased in the canagliflozin group compared with placebo, with an odds ratio of 3.03 (95% CI: 2.65–3.47; P<0.001). Moreover, multivariable analysis in this study indicates that specific clinical parameters are associated with a greater decline in renal filtration (Oshima et al., 2021). Identified key prognostic factors correlated with a higher risk of acute eGFR dip (≥10%), including older age, especially ≥ 75 years old (OR: 4.64; 95% CI: 3.01 - 7.14), male sex (OR: 3.26; 95% CI: 2.76-3.85), black and asian race (OR: 3.73; 95% CI: 2.03-6.86 and OR: 3.69; 95% CI: 2.71-5.03), history of hypertension (OR: 3.06; 95% CI: 2.67-3.51), lack of history of HF (OR: 3.21; 95% CI: 2.78-3.72), body mass index (BMI) ≥30kg/m² (OR: 3.10; 95% CI: 2.58-3.72), SBP higher than median (OR: 3.12; 95% CI: 2.56-3.79), HBA1c <8% (OR:3.28; 95% CI: 2.70-4.00), screening eGFR 45-59 ml/min/1.73 m² (OR: 3.58; 95% CI: 2.78-4.60), 300-3000 mg/g UACR level (OR: 3.34; 95% CI:2.86-3.89), no history of use of insulin (OR: 3.37; 95% CI: 2.66-4.26) (Oshima et al., 2021). On the other hand, there was OR lover than overall <3.03 in age <55 years, female sex, white race, no current smokers, lack of the history of hypertension and cardiovascular disease, history of HF, BMI <30 kg/m², SBP ≤ median, HBA1c ≥8%, screening eGFR 30-44 ml/min/1.73 m² and 60-89 ml/min/1.73 m², UACR level <300 mg/g and ≥3000 mg/g, use of insulin. Importantly, all comparisons of the risk of acute eGFR decline (>10%) between the above and the opposite options were numerically significant but not statistically significant (P for interaction > 0.05), except for the presence or absence of HF history (P for interaction = 0.04). Additionally, in this study, the difference between diuretic use and non-use in the occurrence of a pronounced eGFR decline (>10%). The above predictors are important for distinguishing threatening from hemodynamic eGFR dips (Oshima et al., 2021).

Paradoxically, a greater value of initial eGFR dip may correlate with a more effective correction of hyperfiltration, suggesting a stronger hemodynamic response. As prespecified analysis of DAPA CKD shows an initial dip >10% in eGFR was associated with a milder long-lasting slope trajectory of filtration -1.58 mL/min/1.73 m²/year (95% CI: −2.07, −1.08), compared with -2.44 mL/min/1.73 m²/year (CI: −3.09, −1.80) in <10% acute decline group (P for interaction=0.04) (Jongs et al., 2022). Moving to HF question, patients with HFrEF exhibit low blood pressure and fluctuations in intravascular volume, so monitoring of hydration status is crucial, as changes in hydration can partially mimic an eGFR dip in this patient group (Adamson et al., 2022). Despite an initial eGFR decline and concerns about renal safety, meta-analyses indicate that flozins paradoxically reduce the risk of AKI by 27% (HR: 0.73; 95% CI: 0.63–0.85) and by 20% (HR: 0.80; 95% CI: 0.72– 0.88) relative to laboratory marker (increase ≥50% in serum creatinine). A transient filtration drop should not be considered a risk but rather a marker of a mechanism that protects the kidney from more severe forms of injury in the future (Herrington et al., 2025). As mentioned, such a protective effect results from reduced hyperfiltration, which decreases metabolic stress in the renal tubules and improves intrarenal hemodynamics. (Urban et al., 2025).

In clinical practice, distinguishing hemodynamic eGFR decline following SGLT2i from AKI requires evidence of dynamic changes in filtration. Firstly, about the first one, which is commonly predictable: it usually occurs within 2–4 weeks of treatment initiation and subsequently stabilizes (Kraus et al., 2021). Data from a meta-analysis (n: 23340) indicate that, in the long term, CV and renal benefits are maintained regardless of the magnitude of the initial eGFR decline (Herrington et al., 2025). Although a dip is usually a protective marker, a dip >30% (1.4% on empagliflozin vs. 0.9% on placebo) - especially a persistent one - warrants vigilance, as it may be associated with a higher risk of cardio-renal events (Kraus et al., 2021).

The 2024 KDIGO Clinical Practice Guideline is consistent with the research that an initial decline in eGFR is a functional and acceptable response to the initiation of hemodynamically active therapies, including SGLT2i, in patients with CKD. Within this recommendation, an isolated dip of up to 30% should not automatically trigger discontinuation of therapy in the absence of clinical signs. On the other hand, in the event of an eGFR decline of≥30%, especially accompanied by clinical symptoms, guidelines recommend temporarily stopping SGLT2i therapy until the clinical condition stabilizes, and a differential diagnosis (including causes of AKI such as hypovolemia, inappropriate diuretic dose, or nephrotoxic medications e.g., NSAIDs) will be completed (KDIGO CKD Work Group, 2024). Table 2 presents a summary of this section.

Table 2. Comparison of a hemodynamic-related early decline in estimated glomerular filtration rate (eGFR) with pathological acute kidney injury (AKI).

Feature	Haemodynamic decline in eGFR following SGLT2i	Acute kidney injury (AKI)	References
Time of occurrence	Predictable, usually 2–4 weeks after initiation.	Unpredictable, triggered by a specific factor (e.g., an infection).	Heerspink et al., 2016; KDIGO, 2024
Magnitude of the drop	Moderate: average 3–5 mL/min/1.73 m² (usually <30% of baseline).	Variable, often rapid, ≥30% of baseline eGFR.	Kraus et al., 2021; Oshima et al., 2021; KDIGO, 2024
The dynamics of change	A spontaneous stabilization following an initial decline.	Progressive; deterioration without intervention.	Kraus et al., 2021; Oshima et al., 2021; KDIGO, 2024
Reversibility	Complete after discontinuation of the medication.	Variable, depends on the cause and severity.	Kraus et al., 2021; Oshima et al., 2021; KDIGO, 2024
Markers for structural damage of renal tubules	Absent, reduction in KIM-1 and stable NGAL level versus placebo.	Current, significantly higher.	Dekkers et al., 2018; KDIGO, 2024
Associated symptoms	None; clinical condition stable; mild diuretic effect possible.	Common symptoms: oliguria, signs of dehydration, and nausea.	Heerspink et al., 2016; Adamson et al., 2022; KDIGO, 2024
Long-term prognosis	Beneficial, associated with a slower progression of CKD (nephroprotection).	Unfavorable, progression of CKD, risk of permanent loss of kidney function and death	Oshima et al., 2021; KDIGO, 2024; Herrington et al., 2025
Procedure	Dip <30%: continue treatment, routine monitoring (2–4 weeks after initiation).	Discontinuation of the medication, treatment of the underlying cause.	Adamson et al., 2022 KDIGO, 2024

The "bioassay" hypothesis and the "dip paradox" - does early decline in kidney function predict long-term treatment success?

In the field of SGLT2i in recent years, there has been the observation that a greater transient decline in eGFR following the initiation of SGLT2i therapy is not only harmless but, in certain situations, may paradoxically be associated with better long-term renal protection outcomes, leading to the formulation of the so-called "bioassay" hypothesis. According to this hypothesis, the initial dip in eGFR does not represent an adverse event but indicates that the drug has reached the nephron and effectively activated hemodynamic mechanisms (glomerular unloading via TGF) (Zannad et al., 2022).

One of the strongest data regarding the above issue came from the DAPA-CKD post-hoc study. This analysis demonstrated that participants with a more pronounced dip (>10%) had a significantly slower rate of chronic kidney function loss than those with a dip ≤10% (respectively: -1.58 vs. -2.44 ml/min/1.73 m²/year). Patients with the greatest decline in eGFR (>7.3 ml/min/1.73 m²) exhibited the most stable chronic slope of the filtration curve compared with those without an initial decline (Jongs et al., 2022). In the DAPA-HF trial, among HFrEF patients, a greater dip was associated with a more favorable trend in clinical outcomes, including a lower risk of hospitalized heart failure (HHF) and CV death (Adamson et al., 2022).

The above-described association between the depth of initial eGFR and long-term outcomes has not been confirmed across all studies, as shown by the prespecified DELIVER analysis (HFmrEF/HFpEF). In the mentioned study, long-term filtration decline was -0.9 mL/min/1.73 m2/year in the group with a modest (<10%) initial eGFR dip, while in the group with a larger (>10%) initial eGFR dip, it was -1.2 mL/min/1.73 m2/year. Such results lead us to conclude that the initial dip reflects more acute hemodynamic unloading than long-term protection; however, although the correlation was numerically visible, it was not statistically significant (P for interaction = 0.68) (McCausland et al., 2024).

Although there is ongoing debate in the literature regarding an optimal range for the decline (10 – 30%), recent reports from the RWE suggest that even a severe early dip in eGFR (≥5 ml/min/1.73 m²) in patients with HF correlates with favorable, long-term stabilization of renal function (Ogata et al., 2025). Furthermore, another RWE plays a critical role in delineating permissible ''safe allowance'' thresholds, thereby expanding the clinical framework for treatment continuation. It demonstrated that patients who do not discontinue therapy despite the occurrence of a dip - including a deep one (>30%) - achieve a significantly lower risk of death and CKD progression compared to those who discontinue treatment. Consequently, even a marked eGFR decline exceeding 30% does not warrant premature deescalation of therapy, instead, continuity of SGLT2i under careful monitoring and with optimized fluid balance yields significant clinical benefits, reducing a risk of all-cause mortality by 46% (HR: 0.54; 95% CI:0.42-0.71) and the risk of the primary composite kidney outcome by 49% (HR: 0.51; 95% CI: 0.35-0.76) compared to those who stopping the drug (Xie et al., 2021).

From "reactive monitoring" to "strategic tolerance": a care paradigm shift

The 'reactive monitoring' paradigm was a traditional approach to monitoring kidney function, beginning at the start of SGLT2i treatment, in which any decline in eGFR was considered a warning requiring immediate intervention, such as a drug dose reduction or discontinuation. In recent years, however, modern standards for monitoring patients treated with SGLT2i have evolved toward a much greater tolerance (up to a 30% decline from baseline eGFR) for early changes in glomerular filtration. Nevertheless, an excessive dip (>30%), although rare (approx. 3% of patients), is associated with a higher risk of cardio-renal events (Weir, 2025).

A recent meta-analysis of individual-level data from 23,340 patients has provided landmark evidence of the benefits of SGLT2i even in high-risk groups. Empagliflozin reduced the risk of kidney failure by as much as 34% (HR: 0.66; 95% CI: 0.55–0.79), and this renal effect was consistent even in the subgroup with the lowest, baseline eGFR <30 mL/min/1.73 m2, which accounted for 12.1% (n=2,826) of the study population (Herrington et al., 2025). Moreover, regarding the geriatric population, RWE data fully support the safety profile of SGLT2i in this group as well. Although an initial eGFR dip exceeding 14% occurs significantly more frequently among octogenarians than younger patients < 50 years old (38.7% vs. 10.0%; P<0.001) and is notably deeper (mean -15.5% vs. -7.9%; P<0.001), this phenomenon remains strictly functional. Moreover, the best confirmation of the hemodynamic, non-injurious nature of the initial drop remains virtually unchanged between 3 and 12 months (57.7 ml/min/1.73 m² versus 57.2 ml/min/1.73 m²; P > 0.672), suggesting sustained renal function stabilization. These data demonstrate that the treatment is safe, efficacious, and that there is no need to discontinue therapy solely on the basis of early eGFR decline in the elderly population (An et al., 2024).

In the point of mineral metabolism, strict potassium monitoring is essential, whereas a dip above 30% increases the risk of both hyperkalemia ≥5.5 (aHR: 4.59; 95% CI: 2.28-9.26) and hypokalemia <3.0 mmol/L (aHR: 3.21; 95% CI: 1.90-5.42), while an early eGFR decline below 30% has a negligible impact on the electrolyte profile. Potassium assessment is particularly important among patients with baseline kidney disease or those using RAAS inhibitors or diuretics concurrently (Kao et al., 2024).

To prevent premature discontinuation of this life prolongin therapy, current ESC recommendations state that concerns about renal stability should not delay the introduction of fundamental SGLT2i therapy across the entire spectrum of HF phenotypes, this proactive cardiological approach must be strictly balanced with precise monitoring of the patient's volume status, to preventively mitigate the risk of severe hypovolemia (McDonagh et al., 2023; Chuang et al., 2024).

The latest ADA guidelines establish a strategic framework for routine eGFR monitoring within 1 to 3 months post-initiation for clinically stable patients (ADA Professional Practice Committee for Diabetes, 2026). On the other hand, high-risk cohorts, specifically characterized by advanced age (≥80 years), advanced CKD (baseline eGFR <30 mL/min/1.73 m2), baseline anemia, or concurrent RAAS inhibitors and on diuretic therapy - require earlier surveillance at 1–2 weeks following flozin initiation to keep adherence in group, which chas chance to achieve the greatest long-term benefits (ADA Professional Practice Committee for Diabetes, 2026; An et al., 2024; Herrington et al., 2025; Weir, 2025).

The cardiorenal paradigm shift from ''reactive monitoring" toward "strategic tolerance", accepting a transient early decline up to 30% as an expected, hemodynamic response rather than a kidney structural injury (Weir, 2025; Urban et al., 2025). Short-term, early fluctuations in eGFR resulting from the restoration of TGF mechanisms are a necessary ''price to pay'' for long-term organ stability (Weir, 2025; KDIGO CKD Work Group, 2024). The optimized approach described above maximizes the protective potential of flozin, even in the highest-risk population. Additionally, in this group, the 34% reduction in acute renal events is independent of the magnitude of the initial eGFR dip (Herrington et al., 2025). Table 3 represents a summary of this section.

Table 3. Overview of key clinical assumptions with scientific evidence and source materials.

Key clinical assumption	Scientific rationale (evidence synthesis)	References
Overcoming decision-making barriers	Historical concerns between healthcare professionals regarding early declines in eGFR have limited the use of hemodynamically active drugs (including SGLT2i), which may have delayed the implementation of therapies with proven efficacy in improving prognosis.	Weir, 2025
Safe fluctuation margin (30%)	A decrease in eGFR of no greater than 30% from baseline, in the absence of symptoms of clinical instability, is considered an acceptable and predictable hemodynamic effect that does not require dose adjustment or discontinuation of nephroprotective therapy.	Weir, 2025
Prioritization of clinical assessment	Patient management should shift toward monitoring hemodynamic stability (blood volume, blood pressure) and critical parameters such as serum potassium levels (especially when the dip is >30%), prioritizing overall condition over isolated eGFR values.	ADA, 2026; Kao et al., 2024
The independence of benefits from the level of the early dip	A long-term reduction in the risk of kidney failure (by approximately 34%) and a slowing of CKD progression are achieved in patients, regardless of the occurrence and severity of the initial decline in glomerular filtration rate.	Herrington et al., 2025
The protective nature of early eGFR changes	The onset of a decline in eGFR following initiation of the drug correlates with subsequent stabilization of kidney function and a gentler slope of the chronic kidney function decline curve over time.	Weir, 2025
The physiological mechanism of the response	The initial decrease in filtration is due to the restoration of tubulo-glomerular feedback (TGF), which leads to a beneficial reduction in intraglomerular pressure, thereby protecting the nephron from damage.	An et al., 2024; KDIGO, 2024

4. CONCLUSION

An initial eGFR decline following the start of SGLT2i therapy is a predictable and reversible hemodynamic paradox resulting from the restoration of tubuloglomerular feedback. Nowadays, this initial dip is considered a positive bioassay marker, indicating effective glomerular unloading. Although a more pronounced decline often correlates with stronger long-term protection, a decline >30% warrant careful clinical evaluation to exclude concurrent structural damage. The latest evidence supports a shift away from "reactive monitoring" toward "strategic tolerance," which avoids unjustified treatment interruption and allows for the full utilization of the cardio-nephroprotective potential of valsartan in the treatment of cardiovascular-kidney-metabolic syndrome. This review emphasizes that accepting short-term fluctuations in filtration is a prerequisite for achieving long-term, spectacular benefits, making the individualization of monitoring the foundation of modern medicine and highlighting the need for further research into strategies for its personalization.

List of Abbreviations

ADA – American Diabetes Association

AKI – Acute Kidney Injury

BMI – Body Mass Index
CI – Confidence Interval
CKD – chronic kidney disease
CKM – Cardiovascular-Kidney-Metabolic
CV – Cardiovascular
eGFR – Estimated Glomerular Filtration Rate
HF – Heart Failure
HFmrEF – Heart Failure with Mildly Reduced Ejection Fraction
HFpEF – Heart Failure with Preserved Ejection Fraction
HFrEF – Heart Failure with Reduced Ejection Fraction
HHF – Hospitalized Heart Failure
HR – Hazard Ratio
IQR – Interquartile Range
KDIGO – kidney disease: Improving Global Outcomes
KIM-1 – Kidney Injury Molecule-1
NGAL – Neutrophil Gelatinase-Associated Lipocalin
RAAS – Renin-Angiotensin-Aldosterone System
RCTs – Randomized Controlled Trials
RWE – Real-World Evidence
SBP – Systolic Blood Pressure
SE – Standard Error
SGLT2i – Sodium-Glucose Cotransporter 2 inhibitors
T2DM – Type 2 Diabetes Mellitus
TGF – Tubuloglomerular Feedback

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Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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