eGFR decline after SGLT2 inhibitor initiation: the tortoise and the hare reimagined

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Sodium-glucose transporter 2 inhibitors (SGLT2i) have emerged as an effective class of medications to treat chronic kidney disease and heart failure. SGLT2i improve cardiovascular outcomes in patients with type 2 diabetes mellitus (1–3) and those with heart failure with reduced ejection fraction (4–7). Moreover, they have been shown to attenuate kidney disease progression in patients with proteinuric chronic kidney disease, irrespective of diabetes status (8,9). The rapid uptake of SGLT2i into practice necessitates a careful understanding of their risks. Furthermore, clinicians need to know what to expect when prescribing these agents, including an early decline in estimated glomerular filtration rate (eGFR) following initiation. We aim to put this observation into context while providing clinicians with a practical approach to managing this scenario.

The suggested mechanism of action of the SGLT2is has previously been described (10). These drugs inhibit sodium and glucose reabsorption in the proximal tubule, leading to increased sodium and chloride delivery to the macula densa. This results in afferent arteriolar vasoconstriction secondary to adenosine-mediated myogenic activation, leading to a reduction in the intraglomerular pressure and the glomerular filtration rate (10). Therefore, it is not surprising that the major SGLT2i outcome trials have reported an early decline in eGFR (around 3 to 6 ml/min/1.73m²) shortly after initiating these drugs compared to placebo controls (5,8,9,11,12). These early declines or dips were typically observed at 2-4 weeks after initiation of the SGLT2i, with subsequent partial recovery of the eGFR curve by week 12, and ultimately followed by an attenuation of the slope of eGFR decline compared to placebo controls after 52 weeks (Table 1).

How can we reconcile early dips in eGFR with long-term nephroprotection? Maladaptive glomerular hemodynamics play a central role in kidney disease progression (13). Single nephron hyperfiltration and increased glomerular capillary pressure occur in response to a diminished number of functional nephrons regardless of the cause. The resulting proteinuria and glomerulosclerosis are the common final pathway for various kidney diseases (13). Hyperfiltration is frequently seen in diabetic kidney disease and often precedes the development of overt albuminuria (14,15). Mitigation of pathologic hyperfiltration may therefore be therapeutic, even at the cost of an acute eGFR decline. These data lend credence to the somewhat counterintuitive notion that agents that cause initial decrements in eGFR have long-term therapeutic benefits for patients with proteinuric kidney disease.

In clinical practice, SGLT2i prescribers, who will frequently be non-nephrologists (16), maybe uncomfortable watching the serum creatinine rise in response to initiating these agents. This anxiety may have been inadvertently heightened by a sensitivity to "causing" acute kidney injury (AKI). The Kidney Disease Improving Global Outcomes Clinical Practice Guidelines define AKI as an acute rise in serum creatinine from baseline of ≥ 0.3 mg/dL in 48hrs or ≥ 1.5x within one week (17). Therefore, it is conceivable that a newly started SGLT2i could potentially induce a rise in serum creatinine that would meet AKI criteria. However, one has to question whether a SGLT2i-driven drop in eGFR is genuinely representative of AKI. Contemporary thresholds for defining AKI were guided by data from hospitalized patients in whom relatively modest increments in serum creatinine were found to be associated with adverse outcomes (18).
Serum creatinine rises of similar magnitude are unlikely to have the same significance in an otherwise stable outpatient who initiated a SGLT2i.

In a post hoc analysis of the EMPA-REG trial, which showed that empagliflozin reduced the risk of major adverse cardiovascular events in patients with Type II diabetes mellitus, Kraus et al. performed a granular analysis of eGFR decrements following the initiation of study drugs (19). A post-initiation eGFR decline of ≥10% was considered significant "dipping" and was observed in 28% of participants in the empagliflozin arm vs 13% in the placebo arm. Reassuringly, the patients with an early dip in eGFR partially recovered some of their "lost" GFR by week 12 with a net eGFR decline of 4 to 6 ml/min/1.73m$^2$. However, it is unclear if this ostensible recovery resulted from medication adjustments in response to the initial dip. Most importantly, the presence of a post-drug initiation eGFR dip did not seem to diminish the protective effect of empagliflozin on cardiovascular outcomes. It remains to be seen if these findings will extend to patients with lower baseline eGFR and significant albuminuria, such as those enrolled in the CREDECNCE and DAPA-CKD trials (8,9). A theoretical extrapolation of the CREDECNCE trial data would suggest that a typical trial participant may delay ESKD for 15 years even when accounting for the initial eGFR dip (Figure 1).

The seemingly paradoxical coexistence of GFR declines and long-term clinical benefits has precedent in nephrology. This phenomenon is well described with renin-angiotensin-aldosterone system inhibitors (20,21). A reanalysis of the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial showed that acute increases in serum creatinine after commencing perindopril-indapamide were associated with more significant short-term risks of major macrovascular events, new or worsening nephropathy, and all-cause mortality. However, perindopril's continuation reduced the long-term risk of major clinical outcomes, irrespective of the acute increase in serum creatinine, compared with patients who stopped the drug. (22).

In a post hoc analysis of the Systolic Blood Pressure Intervention Trial (SPRINT), 10.3% of patients randomized to the intensive blood pressure control arm had an early decline (first six months) in eGFR ≥ 20%. This decline did not have a negative impact on the overall benefits of intensive blood pressure control (23). In the recently published Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes (FIDELIO) trial, patients randomized to finerenone experienced a steeper decline in eGFR that persisted until month 24, when the slope of eGFR crossed over that of the placebo group. At the end of follow up, patients in the finerenone group had better kidney outcomes (HR 0.82, 95% CI 0.73-0.93 for the composite outcome of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes) (24).

Conversely, maneuvers that increase kidney blood flow and eGFR have not been associated with better outcomes. A vivid example is bardoxolone, where an improvement in eGFR occurred, but this did not translate into a reduction in the risk of ESKD or death from cardiovascular causes (25,26). Collectively, these data support the notion of "permissive hypercreatinemia," which broadly highlights the need to consciously accept a modest decline in
eGFR as the cost of initiating and maintaining medications that have long-term benefits that are meaningful for patients (27).

How does a clinician respond when faced with an abrupt rise in serum creatinine after initiation of a SGLT2i? Though the data cited above would suggest that most such dips are merely expected hemodynamic changes of limited clinical relevance, it is essential to recognize that in some cases, this may signal systemic illness (i.e., infection, occult bleeding) with bona fide kidney injury. Traditionally, a 30% increase in serum creatinine has prompted clinicians to reevaluate renin-angiotensin-aldosterone system blockade, and we believe that the same approach may be reasonable for SGLT2i (28,29). A significant increase in serum creatinine (>30% from baseline) should prompt a detailed clinical review to verify if the patient has suffered a volume-contracting illness (which may justify temporarily holding the SGLT2i and other medications that affect kidney hemodynamics), initiated new medications that may affect kidney function or has another reason for AKI. In Figure 2, we propose an approach to navigating abrupt eGFR declines in a patient commencing a SGLT2i. The overarching goal is to maintain patients on therapy by addressing non-SGLT2i related factors that may have precipitated the acute GFR decline and by adjusting the cardiorenal drug regimen to enable the safe continued use of the SGLT2i as well as other therapies that have an established impact on patient-relevant outcomes.

*The Tortoise and the Hare* is perhaps the most famous of Aesop's fables. It tells the story of a tenacious tortoise who defeated an overconfident hare in a race, demonstrating that enthusiasm and perseverance can prevail over hastiness and overconfidence. The race against end-stage kidney disease is a marathon, not a sprint. We ought to be patient and persistent, much like the tortoise in Aesop's fable, and set our eyes on the critical clinical outcomes, most notably preventing ESKD and preventing cardiovascular events. We thus advocate resisting the urge of stopping SGLT2i when faced with an early modest dip in eGFR. More often than not, this acute dip will be mild, and even if not reversible, clinicians should avoid the urge to discontinue the SGLT2i. Ultimately, the prevention of kidney failure and cardiovascular events should take precedence over excursions in serum creatinine.
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R Wald: Supervision; Writing - review and editing
Bibliography


Table 1. Randomized controlled trials reporting an initial dip of eGFR

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Agent studied</th>
<th>Primary Outcomes</th>
<th>Observed early drop in eGFR</th>
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<tbody>
<tr>
<td>CREDENCE (8)</td>
<td>Canagliflozin</td>
<td>Reduction in the composite risk of ESKD, doubling serum creatinine level, or death from renal or cardiovascular causes (HR 0.70, 95% CI 0.59, 0.82), compared with placebo.</td>
<td>5 ml/min/1.73m²</td>
</tr>
<tr>
<td>DAPA-CKD (9)</td>
<td>Dapagliflozin</td>
<td>Reduction in the risk of 50% GFR decline, ESKD, or death from renal or cardiovascular causes (HR 0.61 95% CI 0.51, 0.72), compared with placebo.</td>
<td>4 ml/min/1.73m²</td>
</tr>
<tr>
<td>EMPEROR Reduced (5)</td>
<td>Empagliflozin</td>
<td>Reduction of the risk of cardiovascular death or hospitalization for worsening heart failure (HR 0.75, 95% CI 0.65, 0.86), compared with placebo.</td>
<td>4 ml/min/1.73m²</td>
</tr>
<tr>
<td>EMPA-REG Outcome (11)</td>
<td>Empagliflozin</td>
<td>Canagliflozin decreased the risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (HR 0.86, 95% CI 0.74, 0.99), compared with placebo.</td>
<td>3-4 ml/min/1.73m²</td>
</tr>
<tr>
<td>CANTATA-SU (12)</td>
<td>Canagliflozin</td>
<td>Canagliflozin slowed the progression of kidney disease compared with glimepiride in patients with type 2 DM (P &lt; 0.01 for each canagliflozin group versus glimepiride).</td>
<td>3-6 ml/min/1.73m²</td>
</tr>
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CI: 95% Confidence intervals. CKD: Chronic Kidney Disease. DM: Diabetes Mellitus, ESKD: End Stage Kidney Disease, HR: Hazard Ratio,
Figure 1

A typical patient included in CREDENCE would lose 4.6 ml/min/year of eGFR if treated with RAASi only, reaching ESKD in 10 years. However, if canagliflozin is added to his treatment, he would only lose 1.85 ml/min/year of eGFR, delaying ESKD by 15 years. eGFR = estimated Glomerular Filtration Rate. ESKD: End-Stage Kidney Disease. RAASi = Renin-Angiotensin-Aldosterone System inhibitors.

Figure 2. Proposed algorithm for initiation of treatment with SGLT2i
Figure 1.

- **Crossover of eGFR slopes (1 year)**
- **Initial eGFR dip (4 weeks)**
- **Additional 15 years freedom from ESKD**

**eGFR ml/min/1.73m²**

**CREDENCE patient**
- AGE = 63
- eGFR = 56

**RAASi**
- AGE = 73
- eGFR = 10

**SGLT2i + RAASi**
- AGE = 88
- eGFR = 10