Clinical Implications of an Acute Dip in eGFR after SGLT2 Inhibitor Initiation

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Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a relatively new class of drugs that are cardiovascula
receptor is pharmacologically antagonized, the acute
Glomerular hyperfiltration is one of the earliest mecha-
tivity and weight loss, or to simultaneous inhibition of
proximal tubular sodium reabsorption (3). This leads
to augmented distal nephron sodium delivery, an effect
linked with macula densa sodium uptake, which
generates adenosine from ATP breakdown (3). Aden-
osine binds to the adenosine type 1 receptor at the
afferent arteriole, leading to vasoconstriction (3,6). As
a result, this proximal natriuresis causes vasoconstric-
tion and a reduction in glomerular hyperperfusion and
hyperfiltration. In this model, when the adenosine

The fact that SGLT2 inhibitors induce an acute dip in
eGFR has been known for more than 8 years. Less
clear, however, was the relevance of the eGFR dip, and
whether it represented potential signals around kid-
ney safety or, conversely, clinical benefit. It is for this
reason that three recent analyses—one from Empagli-
flozin Cardiovascular Outcome Event Trial in Type 2
Diabetes Mellitus Patients (EMPA-REG OUTCOME),
one from Evaluation of Ertugliflozin Efficacy and
Safety Cardiovascular Outcomes Trial (VERTIS-CV),
and one from Canagliflozin and Renal Events in Di-
abetes with Established Nephropathy Clinical Evalua-
tion (CREDO)—are of importance. The first report
was a post-hoc analysis from EMPA-REG OUTCOME in
participants with type 2 diabetes and cardiovascular
disease. The analysis showed that after 4 weeks, 28% of
empagliflozin-treated participants versus 13% placebo-
treated participants experienced an acute dip in eGFR
≥10% (odds ratio, 2.7; 95% confidence interval, 2.3 to
3.0). Diuretic use at baseline and a higher Kidney
Function Category were associated with higher likelihood of eGFR dipping. Importantly, long-term eGFR trajectories and safety outcomes, including AKI, were similar regardless of the initial dip in eGFR with empagliflozin treatment (Figure 1) (7). A third analysis from the VERTIS-CV randomized controlled trial in patients with type 2 diabetes and cardiovascular disease, pre-

Fortunately, new experimental and clinical studies
have provided important insights into the mechanisms
and clinical relevance of the eGFR dip. SGLT2 inhibitors
exert a variety of physiologic effects that are either
attributable to glucosuria, such as HbA1c reduction
and weight loss, or to simultaneous inhibition of
the glomerular filtration rate (GFR), which is often
referred to as the GFR “dip.” This response pattern suggests these agents
reduce glomerular hypertension—an effect that is
reminiscent of ACE inhibitors/ARBs. The clinical
implications of the acute eGFR dip were unknown
and led to concerns about the safety of SGLT2 inhibitors
because observational reports suggested an increase in
the risk of AKI with these therapies (4). Given the clear
cardiorenal protective effects of SGLT2 inhibitors, it is
important to resolve uncertainty around the safety
and long-term consequences of eGFR dipping to avoid
clinical inertia with these therapies (5).

In conclusion, clinical inertia with these therapies (5).

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subgroup, the risk for kidney-related adverse events was slightly increased compared with nondippers. In this rare circumstance, the SGLT2 inhibitor should be temporarily held so eGFR can return to baseline. Collectively, these data confirm SGLT2 inhibitors preserve kidney function, regardless of the initial dip in eGFR.

These new data are reassuring and confirm the dip in eGFR is not associated with progressive long-term kidney function loss or AKI. Meta-analyses have also demonstrated SGLT2 inhibitors do not cause AKI, and in fact may even reduce the likelihood of it occurring (10). With the concern about AKI risk no longer significant on the basis of contemporary trials, clinicians still grapple with how to monitor patients after SGLT2 inhibitor initiation, and what to do in response to the eGFR dip when it occurs. On the basis of the new data from EMPA-REG OUTCOME, VERTIS-CV, and CREDENCE, and consistent safety data in real-world evidence studies (11), it seems reasonable to conclude that in the majority of patients, there is no need to have a routine monitoring strategy to check kidney function or electrolytes, unless there is a clinical concern about volume depletion in specific individuals, such as in patients with BP <120/70 mm Hg, sign/symptoms of volume depletion (e.g., orthostatic symptoms), in patients taking high-dose diuretics, and perhaps

Figure 1. eGFR change over time during empagliflozin treatment in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG-Outcome) trial and canagliflozin treatment in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial by category of percentage change in eGFR from baseline to week 4 in EMPAREG-Outcome and from baseline to week 3 in CREDENCE. In both the EMPAREG-Outcome (A) and CREDENCE trial (B), the long-term eGFR trajectories remained stable in all dipping categories. In the CREDENCE trial, long-term annual eGFR decline was slightly but statistically significantly less in patients with an acute eGFR dip (2.0 ml/min per 1.73 m² per year) compared with patients with an acute eGFR increase (2.1 ml/min per 1.73 m²; P=0.04).
in the elderly. This is predicated on the concepts that: (1) AKI risk is not increased; (2) eGFR dipping is not associated with kidney injury; (3) even in the event of dipping, this should not affect management or continuation of therapy; (4) SGLT2 inhibitors do not cause electrolyte abnormalities, so there is no need to check potassium after initiation (i.e., as with ACE inhibitors, ARBs). Therefore, patients can safely have the next set of blood work at subsequent scheduled appointment to avoid additional cost and concerns from clinicians or patients around the eGFR dip. This streamlined approach is also appropriate to remove unnecessary clinical barriers to initiation of therapy, including in primary care.

In conclusion, SGLT2 inhibitors reduced the risk of kidney failure and cardiovascular outcomes in two independent large kidney outcome trials in patients with CKD, including individuals with and without type 2 diabetes. Clinical practice guidelines are evolving and recommend the use of SGLT2 inhibitors for kidney protection. The dip in eGFR observed soon after SGLT2 inhibitor initiation likely reflects their protective mechanism of action and should not lead to safety concerns and/or barriers for their widespread implementation.

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References


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