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EDITORIAL

"Dip" in eGFR: Stay the Course With SGLT-2 Inhibition

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During the past 5 to 7 years, the SGLT-2 inhibitors (SGLT2i) have been shown to improve cardiovascular outcomes in patients with and without diabetes,[1,2] forestall kidney disease progression in patients with and without diabetes,[3] and improve mortality in patients with heart failure.[4] Balancing the long-term benefits of a suite of drugs including renin-angiotensin-aldosterone system inhibitors (RAASi), diuretics, and now SGLT2i against potential short-term changes in renal hemodynamics and kidney function can be vexing for even the most astute clinician. It is therefore critical to understand predictable changes in kidney function, as assessed by serum creatinine and estimated glomerular filtration rate (eGFR).

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The long-term benefits of RAASi on kidney function are felt to be secondary to their ability to lower both systemic and intraglomerular pressure.[5] The inhibition of the renin-angiotensin-aldosterone axis induces vasodilation of the efferent arteriole that leads to a reduction in intraglomerular pressure and potentially single nephron GFR. Numerous studies across diverse kidney diseases demonstrated a mean decrease or "dip" in eGFR in patients randomized to RAASi in the first 1 to 3 months followed by a less steep fall in eGFR compared with placebo, preserving kidney function with decreased end-stage kidney disease and doubling of serum creatinine.[6,7] This led to the advice to clinicians to tolerate up to a 30% increase in the serum creatinine on initiation of a RAASi. In addition, several studies in varied settings (heart failure, kidney disease) have demonstrated that patients who have an acute drop or "dip" in GFR have a slower decline in kidney function over time compared with those who do not have a "dip."[8–10] Initial studies with SGLT2i noted a similar early decrease in eGFR, stimulating interest in the potential mechanism for this decrease and its potential prognostic significance.

In this issue of *Circulation*, Adamson et al[11] report on initial eGFR changes on initiation of dapagliflozin in the DAPA-HF trial (DAPA-Heart Failure). The overall results of the trial showed a reduction in mortality and heart failure events in participants with heart failure and reduced ejection fraction.[4] The results of this trial population level analysis demonstrated an average decrease of 4.2 mL/min/1.73 m^2 (95% CI, −4.64 to −3.85) of eGFR within the first 14 days of treatment with dapagliflozin followed by a less steep decline in eGFR compared with placebo. The authors also noted that 38.2% of the 2309 participants randomized to dapagliflozin had a >10% decline in eGFR 14 days after initiation of therapy. Only 3.4% had a decline in eGFR of >30%. The authors noted that older age, lower eGFR, type 2 diabetes, and higher ejection fraction were associated with a >10% decline in eGFR. It is important that patients experiencing a >10% early decrease in eGFR on dapagliflozin had significantly better clinical outcomes, including cardiovascular outcomes as well as a slower chronic rate of decline in eGFR, than among participants assigned to dapagliflozin with an eGFR decline of ≤10%. Conversely, those experiencing the same initial decline in eGFR during treatment with placebo had worse outcomes than those with an eGFR decline of ≤10% on placebo.

Key Words: Editorials ■ heart failure ■ kidney failure

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The analysis and characterization of initial eGFR "dip" in patients with heart failure treated with dapagliflozin reported by Adamson et al[11] is consistent with data reported from the analysis of other large kidney and heart trials involving SGLT2i. The results of an analysis of the EMPA-REG OUTCOME trial reported the median reduction in eGFR at 4 weeks was 2.69 mL/min/1.73 m^2 and that a >10% eGFR decline occurred in 28.3% of empagliflozin-treated participants.[12] These results also noted that participants with type 2 diabetes and more advanced kidney disease were more likely to experience a >10% decline in eGFR on initiation of SGLT2i. A post hoc analysis of the CREDENCE kidney trial data showed 45% of canagliflozin-treated participants experienced an acute eGFR drop of >10% and a neutral effect on the subsequent decline in eGFR compared with participants who did not "dip" on canagliflozin. A >30% drop in eGFR was noted in only 4% of participants in the canagliflozin group.[13]

Adamson et al[11] also noted that more advanced kidney disease was an independent predictor for the initial decline in eGFR. This may reflect that this independent predictor has some mechanistic probability. It may also be confounded by simple mathematics. For example, participants with an eGFR in the 60s would need to drop their eGFR by 6 mL/min/1.73 m^2 to reach the 10% decline threshold, whereas those with eGFRs in the 30s would need to decline by only 3 mL/min/1.73 m^2.

Multiple mechanisms are postulated to drive the physiologic and metabolic changes, including the initial decline in eGFR seen with initiation of SGLT2i. Changes in tubuloglomerular feedback have been postulated to explain both the short-term ("dip") and long-term (GFR preservation) effects. This hypothesis holds that SGLT-2 inhibition reduces sodium and glucose reabsorption in the proximal tubule, which thereby increases sodium delivery to the distal nephron (macular densa) leading to constriction of the afferent renal arteriole and resulting in a reduction of GFR and intraglomerular pressure. However, there are reasons to question whether this is the primary explanation because tubuloglomerular feedback resets during the long term and the benefits also are apparent in people without diabetes where the SGLT2i effect on proximal sodium reabsorption should be less pronounced. In this issue of *Circulation*, this mechanistic hypothesis is explored meticulously by Lytvyn and colleagues[14] in patients with type 1 diabetes on angoitensin converting enzyme inhibitor and SGLT2i alone and in combination.

Lytvyn et al[14] recruited a sample of 30 volunteers with type 1 diabetes and relatively intact kidney function (mean eGFR of 121 mL/min/1.73 m^2) and performed detailed physiologic studies under euglycemic clamp conditions including direct measurement of GFR (inulin clearance), estimated renal plasma flow (para-aminohippurate), urine studies to assess renal sodium handling, and a suite of noninvasive assessments of cardiovascular function. It included a run-in period in which participants were established on background ramipril therapy, and a placebo-controlled cross-over phase in which each participant received either placebo or empagliflozin for a period of 4 weeks. At baseline, these participants had normal blood pressure (mean systolic blood pressure, 112 mm Hg) and measured GFR (mGFR) of 116 mL/min. There was a slight drop in systolic blood pressure and in renal vascular resistance with initiation of ramipril but no change in mGFR. The change in renal vascular resistance is in line with the known physiology of both afferent and efferent arteriolar dilation. The absence of a detectable change in mGFR may stem from the fact that systolic blood pressure declined minimally, and thus the reduction in intraglomerular pressures, and thereby glomerular filtration, is less than expected in a hypertensive population, or it may reflect the relatively small sample size. Subsequently, the addition of empagliflozin on background ramipril therapy revealed a drop in mGFR of 5 mL/min as well as large decreases in absolute proximal fluid and sodium resorption rates. The addition of empagliflozin reduced blood pressure and total peripheral resistance further but otherwise did not generate any significant changes in hemodynamic parameters. Among metabolic changes noted, 8-isoprostane and cGMP decreased significantly with empagliflozin.

The mechanistic study by Lytvyn et al[14] illustrates a modest drop in mGFR with the addition of an SGLT2i to background RAASi therapy. The mGFR data are somewhat limited because of the lack of expected response to RAASi therapy alone. This may be a result of acknowledged sample size/power issues with the study or physiologic differences in the subject pool (type 1 diabetes, young age, relatively normal baseline blood pressure and mGFR). More interesting is the reduction in urinary 8-isoprostane levels, which is a known marker of renal oxidative stress. The reduction in oxidative stress suggested by the reduction in urinary 8-isoprostane levels is intriguing and may give a clue to mechanisms other than changes in tubuloglomerular feedback.

The mechanistic and clinical trial data are consistent. Initiation of an SGLT2i in a population of patients with heart failure results in a "dip" in eGFR of >10% in fewer than half of the patients within the first month of therapy, with an average for the population a modest 3 to 5 mL/min/1.73 m^2 reduction in eGFR. This "dip," if it occurs at all, is generally small and may actually be associated with long-term benefit, certainly not harm. Thus, the fear of a large acute decline in kidney function should *not* be a prominent factor in the decision to start (or hold) a SGLT2i. Given the increasingly documented clinical benefits of SGLT2i, clinicians should anticipate this early decline and stay the course by continuing therapy. Because RAASi or over diuresis can also cause a "dip" eGFR, when starting SGLT2i, it is prudent to maintain

stable doses of diuretics and RAASi to avoid inadvertently attributing a larger "dip" of eGFR to the SGLT2i. Given that larger declines (>30% worsening in eGFR or >0.5 mg/dL increase in serum creatinine) are uncommon with SGLT2i initiation, a large creatinine increase should prompt evaluation for other factors contributing to the change in creatinine such as volume depletion or nephrotoxin exposure. Most patients started on SGLT2i will experience either no change or minor changes in kidney function, and thus staying the course on SGLT2i is the right course of action.

ARTICLE INFORMATION

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