Sodium-glucose cotransporter 2 inhibitors (SGLT2is) have emerged as an effective class of medications to treat CKD and heart failure. SGLT2is improve cardiovascular outcomes in patients with type 2 diabetes mellitus (1–3) and in those with heart failure with reduced ejection fraction (4–7). Moreover, they have been shown to attenuate kidney disease progression in patients with proteinuric CKD, irrespective of diabetes status (8,9). The rapid uptake of SGLT2is 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 eGFR after 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 GFR (10). Moreover, they have been shown to attenuate kidney disease progression in patients with proteinuric CKD, irrespective of diabetes status (8,9). The rapid uptake of SGLT2is 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 eGFR after 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 GFR (10). Moreover, they have been shown to attenuate kidney disease progression in patients with proteinuric CKD, irrespective of diabetes status (8,9). The rapid uptake of SGLT2is 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 eGFR after 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 GFR (10). Moreover, they have been shown to attenuate kidney disease progression in patients with proteinuric CKD, irrespective of diabetes status (8,9). The rapid uptake of SGLT2is 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 eGFR after 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 GFR (10). Moreover, they have been shown to attenuate kidney disease progression in patients with proteinuric CKD, irrespective of diabetes status (8,9). The rapid uptake of SGLT2is 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 eGFR after 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 GFR (10). Moreover, they have been shown to attenuate kidney disease progression in patients with proteinuric CKD, irrespective of diabetes status (8,9). The rapid uptake of SGLT2is 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 eGFR after 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 GFR (10). Moreover, they have been shown to attenuate kidney disease progression in patients with proteinuric CKD, irrespective of diabetes status (8,9). The rapid uptake of SGLT2is 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 eGFR after initiation. We aim to put this observation into context, while providing clinicians with a practical approach to managing this scenario.
| Trial Name               | Agent Studied | Primary Outcomes                                                                                                                                                                                                 | Observed Early Drop in eGFR |
|-------------------------|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| CREDENCE (8)            | Canagliflozin | 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 to 0.82), compared with placebo. | 5 ml/min per 1.73 m²       |
| DAPA-CKD (9)            | Dapagliflozin | Reduction in the risk of 50% eGFR decline, ESKD, or death from renal or cardiovascular causes (HR, 0.61; 95% CI, 0.51 to 0.72), compared with placebo.                                                                     | 4 ml/min per 1.73 m²       |
| EMPEROR-Reduced (5)     | Empagliflozin | Reduction of the risk of cardiovascular death or hospitalization for worsening heart failure (HR, 0.75; 95% CI, 0.65 to 0.86), compared with placebo.                                                                      | 4 ml/min per 1.73 m²       |
| EMPA-REG Outcome (11)   | Empagliflozin | Canagliflozin decreased the risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (HR, 0.86; 95% CI, 0.74 to 0.99), compared with placebo.        | 3–4 ml/min per 1.73 m²    |
| CANTATA-SU (12)         | Canagliflozin | Canagliflozin slowed the progression of kidney disease compared with glimepiride in patients with type 2 DM (P<0.01 for each canagliflozin group versus glimepiride).           | 3–6 ml/min per 1.73 m²    |

CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; HR, hazard ratio; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in CKD; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction; EMPA-REG Outcome, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; CANTATA-SU, Canagliflozin Treatment and Trial Analysis-Sulfonylurea; DM, diabetes mellitus.
significant albuminuria, such as those enrolled in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDEANCE) and Dapagliflozin and Prevention of Adverse Outcomes in CKD trials (DAPA-CKD) (8,9). A theoretic extrapolation of the CREDEANCE trial data would suggest that ESKD in a typical trial participant may be delayed by 15 years, even when accounting for the initial eGFR dip (Figure 1).

The seemingly paradoxical coexistence of eGFR 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 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 BP Intervention Trial, 10% of patients randomized to the intensive BP control arm had an early decline (first 6 months) in eGFR of ≥20%. This decline did not have a negative effect on the overall benefits of intensive BP control (23). In the recently published Effect of Finerenone on CKD Outcomes in Type 2 Diabetes 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 (for the composite outcome of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes; hazard ratio, 0.82; 95% CI, 0.73 to 0.93) (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 hypercreatininemia,” 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 an SGLT2i? Although 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 re-evaluate renin-angiotensin-aldosterone system blockade, and we believe the same approach may be reasonable for SGLT2is (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 an SGLT2i. The overarching goal is to maintain patients on therapy by addressing non-SGLT2i–related factors that may have precipitated the acute eGFR decline, and by adjusting the cardiorenal drug

![Figure 1. SGLT2is may delay ESKD by 15 years. A typical patient included in CREDEANCE would lose 4.6 ml/min per 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 per year of eGFR, delaying ESKD by 15 years. RAASi, renin-angiotensin-aldosterone system inhibitors; SGLT2i, sodium-glucose cotransporter 2 inhibitor.](image-url)
regimen to enable the safe, continued use of the SGLT2is and other therapies that have an established effect 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 ESKD 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 SGLT2is 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.

Disclosures
R. Wald reports receiving research funding from Baxter; serving on the editorial board of CJASN, Kidney360, and Kidney Medicine; and having other interests in/relationships with UpToDate as a contributor. J. Weinstein reports having consultancy agreements with, and receiving honoraria from, Amgen, AstraZeneca, Boehringer Ingelheim, Janssen, and Lilly. The remaining author has nothing to disclose.

Funding
None.
Acknowledgments

We would like to thank Dr. Steven Coca for inviting our group to contribute to Kidney360 and to Dr. Aldo R. Jimenez for his help in the conceptualization of Figures 1 and 2.

The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or Kidney360. Responsibility for the information and views expressed herein lies entirely with the author(s).

Author Contributions

A.Y. Meraz-Muñoz conceptualized the study, was responsible for data curation, and wrote the original draft; A.Y. Meraz-Muñoz, R. Wald, and J. Weinstein reviewed and edited the manuscript; and R. Wald and J. Weinstein provided supervision.

References

1. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hanley S, Matthews MJ, DeWitt T, Johansen OE, Wolfe Jr, Bessey LC, Inzucchi SE; EMPA-REG OUTCOME Investigators: Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 373: 2117–2128, 2015 https://doi.org/10.1056/NEn_jmoa1504720

2. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondou N, Shaw W, Law G, Desai M, Matthews D, DR; CANVAS Program Collaborative Group: Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 377: 644–657, 2017 https://doi.org/10.1056/NEn_jmoa1611925

3. Wiiviot SD, Raz I, Bonaca MP, Kotseva K, Silventoinen K, Vlaskin P, Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson RD, Lapuerta P, Steg PG; SCORED Investigators: Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 375: 323–334, 2016 https://doi.org/10.1056/NEn_jmoa1515920

4. McMurray JJV, Solomon SD, Inzucchi SE, Købøl E, Cahn A, Januzzi JL Jr, Scirica BM, Butler J, Cannon CP, Bhatt DL; DAPA-HF Trial Committees and Investigators: Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 380: 347–357, 2019 https://doi.org/10.1056/NEn_jmoa1812389

5. McCrudden J, Solomon SD, Inzucchi SE, Købøl E, Cahn A, Januzzi JL Jr, Scirica BM, Butler J, Cannon CP, Bhatt DL; Prescriber patterns of SGLT2i after expansions of U.S. Food and Drug Administration labeling. J Am Coll Cardiol 72: 3370–3372, 2018 https://doi.org/10.1016/j.jacc.2018.08.2202

6. Mehta RL, Pascual MT, Gruta CG, Zhuang S, Chertow GM: Refining predictive models in critically ill patients with acute renal failure. J Am Soc Nephrol 13: 1350–1357, 2002 https://doi.org/10.1097/01.ASN.0000014692.19351.52

7. Kraus BJ, Weir MR, Bakris GL, Dahlof B, Pitt B, Shibata S, Hester J, Michel T, Chertow GM, Senni M, Scirica BM, Bailey CJ, Díaz R, Ray KK, Udell JA, Lopes DA; EMPA-REG OUTCOME Investigators: Effects of empagliflozin on renal events in patients with diabetes and chronic kidney disease. N Engl J Med 369: 73: 84–91, 2014 https://doi.org/10.1056/NEn_jmoa1314720

8. Perkovic V, Jardine MJ, Neal B, Borns P, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meiringer G, Brenner BM, Mahaffey KW; CREDENCE Trial Investigators: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 380: 2295–2306, 2019 https://doi.org/10.1056/NEn_jmoa1817744

9. Heerspink HJL, Steffanson BV, Correa-Rotter R, Chertow GM, Greene T, Huf F, Mann JFE, McMurray JIV, Lindberg M, Rossing P, Sjöström CD, Toto RD, Langkilde AM, Wheeler DC; DAPA-CKD Trial Committees and Investigators: Dapagliflozin in patients with chronic kidney disease. N Engl J Med 383: 1436–1446, 2020 https://doi.org/10.1056/NEn_jmoa2024816

10. Heerspink HJL, Perkins BA, Fitchett DH, Husain M, Cherney DZI: Sodium-glucose co-transporter 2 inhibitors in the management of diabetes mellitus: Cardiovascular and kidney effects, potential mechanisms, and clinical applications. Circulation 134: 752–772, 2016 https://doi.org/10.1161/CIRCULATIONAHA.116.021887

11. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Matthews M, Johansen OE, Woerle HJ, Broedl UC, Zinman B; EMPA-REG OUTCOME Investigators: Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 375: 323–334, 2016 https://doi.org/10.1056/NEn_jmoa1515920
23. Beddu S, Shen J, Cheung AK, Kimmel PL, Chertow GM, Wei G, Boucher RE, Chonchol M, Arman F, Campbell RC, Contreras G, Dwyer JP, Freedman BI, Ix JH, Kirchner K, Papademetriou V, Pisoni R, Rocco MV, Whelton PK, Greene T: Implications of early decline in eGFR due to intensive BP control for cardiovascular outcomes in SPRINT. *J Am Soc Nephrol* 30: 1523–1533, 2019 https://doi.org/10.1681/ASN.2018121261

24. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, Kolkhof P, Nowack C, Schloemer P, Joseph A, Filippatos G; FIDELIO-DKD Investigators: Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 383: 2219–2229, 2020 https://doi.org/10.1056/NEJMoa2025845

25. Pergola PE, Raskin P, Toto RD, Meyer CJ, Huff JW, Grossman EB, Krauth M, Ruiz S, Audhya P, Christ-Schmidt H, Wittes J, Warnock DG; BEAM Study Investigators: Bardoxolone methyl and kidney function in CKD with type 2 diabetes. *N Engl J Med* 365: 327–336, 2011 https://doi.org/10.1056/NEJMoai1105351

26. de Zeeuw D, Akizawa T, Audhya P, Bakris GL, Chin M, Christ-Schmidt H, Goldsberry A, Houser M, Krauth M, Lambers Heerspink HJ, McMurray JJ, Meyer CJ, Parving HH, Rennuzzi G, Toto RD, Vaziri ND, Wanner C, Wittes J, Wrolstad D, Chertow GM; BEACON Trial Investigators: Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *N Engl J Med* 369: 2492–2503, 2013 https://doi.org/10.1056/NEJMoa1306033

27. Coca SG: Ptolemy and copernicus revisited: The complex interplay between the kidneys and heart failure. *Clin J Am Soc Nephrol* 13: 825–828, 2018 https://doi.org/10.2215/CJN.05090418

28. Bakris GL, Weir MR: Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: Is this a cause for concern? *Arch Intern Med* 160: 685–693, 2000 https://doi.org/10.1001/archinte.160.5.685

29. Bakris GL, Agarwal R: Creatinine bump following antihypertensive therapy. *Hypertension* 72: 1274–1276, 2018 https://doi.org/10.1161/HYPERTENSIONAHA.118.12051

Received: February 24, 2021 Accepted: March 1, 2021