Sodium–Glucose Cotransporter 2 and Kidney Function

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Sodium–glucose cotransporter 2 inhibitors (SGLT2i) are a relatively novel class of molecules named gliflozines that were originally designed to control glycemia, but over and above their effect on the glycemic metabolism, they unexpectedly improved the management of clinical conditions involving the function of the heart and kidneys. Importantly, the benefits of SGLT2i go beyond guideline-directed medical therapy, in that the drug's metabolic effects on the kidneys and heart ameliorate the entire cardio–circulatory outcome.

glucose transport SGLT2 inhibitor diabetic nephropathy heart failure chronic kidney disease

1. Sodium–Glucose Cotransporter 2 Activity and Sympathetic Drive

1.1. Effects on Sympathetic Activity

In the clinical progression of HF, the renal sympathetic tone is greatly enhanced and the kidneys are the main contributor to the norepinephrine spillover, directly affecting the clinical outcome of HF [1]. The progression of chronic kidney disease (CKD) is also intensively marked by renal sympathetic traffic enhancement, partly related to the activation of α-2 adrenoreceptors and partly to the release of intrarenal AT II. Renally synthesized AT II regulates organ function in a paracrine fashion by modulating Na^+ and water reabsorption within the proximal tubule together with systemic AT II [2]; consistently with this, renal sympathetic denervation abrogates the reabsorption of Na^+ in the proximal tubule [3], where active natriuretic peptides are fast degraded by highly concentrated neprilysin, which is also responsible for the degradation of other peptide hormones such as angiotensin I and II, endothelin [4]. As well as direct kidney management of Na^+ reabsorption, the increased sympathetic traffic in the proximal tubule augments the expression of both NHE3 and SGLT2, playing a further role in the avid sodium reabsorption involved in HF progression [5]. SGLT2 inhibitors interfere with both SGLT2 and NHE3 in the proximal tubule [6], yielding short-term increases in the fractional excretion of sodium [7]. On the plus side, SGLT2 inhibition attenuates renal sympathetic activity and reduces the renal norepinephrine content in states of experimental nutrient excess [6][8], while in animals with HF, renal denervation attenuates the magnitude of response to SGLT2 inhibition [5]. These observations place SGLT2 inhibitors as functional antagonists to renal

sympathetic nerve hyperactivity in HF, which is the main contributor to norepinephrine spillover [9] and is closely linked to outcome in HF patients [10].

1.2. Sodium–Glucose Cotransporter 2 and Sodium Glucose Cotransporter 1 Synergy and "Off Target" Implications

In renal physiology, glucose reabsorption is based on a highly efficient architecture placing SGLT2 in the early proximal tubule to perform the bulk of glucose reabsorption (~80–90%) and positioning sodium glucose cotransporter 1 (SGLT1) in the late proximal tubule, where it reabsorbs the amount of glucose that escapes SGLT2. In the final section of the tubule, the fluid in the glucose concentration falls below the line of stoichiometric reabsorption of 1 glucose molecule to 1 Na^+ performed by SGLT2. As Na^{+-}glucose cotransport is electrogenic, in the later section of the tubule, glucose reabsorption requires SGLT1 to increase its sugar concentration strength, exploiting the electrical power provided by 2 Na^+ ion, so as to transfer 1 glucose molecule from the filtrate into the bloodstream, thereby doubling the energy expense of reabsorption.

As the normal daily glomerular filtrate contains ~1 mol of glucose (~180 g) and the combined action of cotransporters has the capacity to reabsorb ~2.5 mol glucose per day (~450 gr per day), this suggests that in nature, the function of SGLT2 has been dimensioned to cater to broad variations in the glucose concentration that can greatly affect Na^+ reabsorption, with implications for renal O_2 consumption [11]. Persistentent augmenting of Na^+ glucose reabsorption leads to proximal tubule hypertrophy, a primary cause and effect of glomerular hypertrophy driven by hyperfiltration [12][13][14].

The peculiar extensibility of SGLT2 and SGLT1 action has important "off-target" effects that stem from their effect on proximal tubular Na^+ transport, where bicarbonate accounts for approximately 80% of Na^+ reabsorption in this portion of the nephron. The rise in sodium–glucose reabsorption may affect body fluid retention such as sodium bicarbonate, driving additional passive sodium chloride reabsorption. Note that in diabetics, the effect of SGLT2 pharmacologic inhibition is partially offset by enhanced SGLT1 activation, while investigation in animals has provided conclusive evidence that SGLT1 can reabsorb ~30% of filtered glucose, explaining why SGLT2 inhibitors never produce the amount of glucosuria expected if SGLT2 were completely inhibited (preventing 80–90% reabsorption of the filtered glucose load) [15]. This point focuses on the peculiar role SGLT1 plays in the kidney, as SGLT1 engagement can prevent or just limit glucose loss in the urine, at the cost of high energy expenditure by the kidneys.

Intriguingly, two studies performed in Akita mice support the role of SGLT1, expressed in the membrane of the tubuloglomerular apparatus, in increasing nitric oxide (NO) S1-dependent NO formation by sensing the glucose concentration reaching the macula densa, thereafter reducing the vasoconstrictor tone set by TGF and contributing to glomerular hyperfiltration [16]. In Akita mice, the absence of SGLT1 in the tubuloglomerular apparatus not only lowers glomerular hyperfiltration, but also reduces kidney weight, glomerular size, and albuminuria [17]. These findings suggest that SGLT1 may have implications for renal structure and performance besides the reabsorption of glucose.

The inhibition of SGLT2 can reduce glycemia and insulin resistance, and can lower the availability of cellular glucose, while regardless of basal hyperglycemia, it can stimulate a starvation-like response. The response includes SIRT1/AMPK (Sirtuin1/adenosine monophosphate-activated protein kinase) activation and inhibition of the protein kinase b/mTOR1 (mammalian Target Of Rapamycin) pathway [18]. This specific activation, in inducing autophagy, promotes cellular defense and pro-survival mechanisms that counteract the primary pathophysiological mechanism of proximal tubule hypertrophy in diabetes and in conditions involving insulin resistance [6][14][19]. In experimental models and in patients with T2DM, urine metabolomics have indicated that the inhibition of SGLT2 induces a metabolic shift from glycolysis to more mitochondrial oxidation [19][20].

Studies in non-diabetic mice suggest that the kidney's metabolic response to SGLT2 inhibition compensates (a) for the partial inhibition of tubular NHE3 and the glucose uptake/urinary glucose loss, including renal gluconeogenesis upregulation, and (b) urinary Na^+ loss, by inducing tubular secretion of the tricarboxylic acid cycle intermediate, alpha-ketoglutarate, which communicates to the distal nephron the need for compensatory Na^+ reabsorption [21].

SGLT2 inhibition shifts some of the glucose, Na^+, and fluid reabsorption downstream, providing a more equal distribution of transport work and mimicking systemic hypoxia to the renal oxygen sensor, triggering the upregulation of renal NHE3. This effect in HF and on the remaining nephrons in CKD could enhance the natriuretic efficacy and renal hemodynamic effect of SGLT2 inhibition and thereby contribute to kidney and cardio protection in nondiabetic patients.

The inhibition of SGLT2 lowers body weight by coupling the initial natriuretic effect with renal glucose loss, which shifts substrate utilization from carbohydrates to lipids and reduces body fat, lessening visceral and subcutaneous adiposity [22]. This effect also augments the release of free fatty acids, leading to ketone body formation, which can be used as an additional more efficient energy substrate both in the kidneys and failing heart [23]. At the same time, the transport shift to the straight proximal tubule and thick ascending limb in the renal outer medulla could reduce the O_2 availability, endangering medullary structures, as mentioned above [24][25][26].

As gliflozins are the only class of hypoglycemic drugs combining glycosuric and natriuretic actions, they play a joint role in vascular fluid restriction and hemoconcentration. By inhibiting glucose renal reuptake, this class of drug induces significant osmotic diuresis, which selectively decreases the volume of the interstitial space between cells (known as the third space) and affects body weight beyond what nutrient loss can provide [6][12][19]. Osmotic diuresis obtained with SGLT2i has been proven in humans through a double-blind randomized study conducted on 59 type 2 diabetics [22]. It has been postulated that SGLT2i may regulate both the volume between the interstitial space and the vascular bed (interstitial > intravascular) in HF, thus reducing the neurohumoral stimulation generated by the signal denoting decreased vascular filling activated by the baroreceptors [22]. Note that, unlike loop diuretics that promote natriuresis by inhibiting carbonic anhydrase in the thick ascending limb, SGLT2 inhibition halts Na^+ and glucose reabsorption driven by the activation of the Na^+/K^+ pump in the brush border, curbing the O_2 consumption rate in the critical cortex area, without any impact on the electrolyte balance. The peculiarity and sequence of pharmacologic mechanisms activated by SGLT2 inhibitors and by loop diuretics

suggests a reason their combined action generates reciprocal potentiation of natriuresis [23] and supports their combined use in acute decompensated HF.

1.3. Other Implications of Sodium–Glucose Cotransporter 2 Inhibition and Renin–Angiotensin–Aldosterone System Interaction

One should note that a significant increase in kidney sensitivity to adenosine-induced vasoconstrictive action is caused by inhibiting the synthesis of local vasodilatory molecules such as NO or prostaglandins [11][19][27], so that non-steroidal anti-inflammatory drugs (NSAIDs) are among the substances that can lead to acute kidney injury through the potentiation of ADO action on A1R.

The inhibition of SGLT2 not only decreases renal cortex O_2 consumption, as a consequence of lowering GFR, but through partial functional inhibition of other transporters such as the Na- H- exchanger NHE3 [6][13], in the brush border. The co-inhibition of NHE3 contributes to augmenting natriuresis and to lessening blood pressure, with lower effect of SGLT2 inhibitors in the non-diabetic setting [19][28]. It has to be noted that SGLT2 inhibitors enhance renin levels and vasopressin (or copeptin) levels and reduce renal free-water clearance in animal models and humans [29][30][31][32]. This effect is associated with the increased renal protein expression of vasopressin V2 receptors and phosphorylated aquaporin-2 in rats [30][31], indicating active compensation to counter the diuretic and natriuretic effects and highlighting the intricate check and balance system of the renal emunctory function.

At the same time, the inhibition of SGLT2 also significantly increases urate excretion, bringing about an indirect effect on the urate transporter URAT1 in the proximal tubule brush border [6][33].

2. Sodium–Glucose Cotransporter 2 Activity and Acute Kidney Injury

There have been some concerns about the possible association between SGLT2i and an increased risk of acute kidney injury (AKI). This has been mainly the consequence of the reports of the US Food and Drug Administration Adverse Event Report System (FDAERS) [34][35]. A possible explanation for these events is related to osmotic diuresis, which increases the risk of hyperosmolarity and dehydration. A second hypothesis could be represented by the absorption of the increased tubular glucose by the glucose transporter GLUT 9b, which is present at the level of the proximal tubular cells, in exchange for uric acid. The consequent increased uricosuria could favor AKI through both crystal-dependent and crystal-independent mechanisms, particularly in some clinical conditions such as the use of radiocontrast, rhabdomyolysis, heat stress, and dehydration [35]. Another hypothesis is related to the high glucose concentration expression induced by aldose reductase, which is osmolar sensitive. This induction can, in turn, lead to the generation of sorbitol and fructose, which can be metabolized by fructokinase, leading to the synthesis of uric acid, oxidative stress, the release of chemokines, and local tubular injury and inflammation [36]. Finally, sorbitol and fructose can also cause the depletion of intracellular organic osmolytes, such as myo-inositol and taurine, which could contribute to the occurrence of AKI [37].

Despite FDAERS reports and the possible pathophysiological background, data generated by a randomized, double-blind, placebo-controlled crossover study, performed with magnetic resonance in type 1 diabetic patients, are reassuring. The study was designed to assess the acute effects on kidney tissue oxygenation and perfusion of a single 50 mg dose of dapagliflozin, and displayed improved renal cortical oxygenation without changes in renal perfusion or blood flow. This suggests the improved renal cortical oxygenation was linked to reduced tubular transport workload in the proximal tubules [38]. The improved O_2 consumption in the kidneys may explain the long-term beneficial renal effects seen with SGLT2 inhibitors both in randomized trials and in observational studies, where the risk of AKI was reduced rather than increased after SGLT2 inhibition. Indeed, in a meta-analysis using data from the EMPA-REG OUTCOME, CANVAS, DECLARE TIMI 58, and CREDENCE trials, AKI risk was reduced by 25% [39]. Analogously, a reduced risk of AKI was observed in “real-world analyses” comparing SGLT2 inhibitors with the other hypoglycemic drugs [40][41].

References

1. Florea, V.G.; Cohn, J.N. The autonomic nervous system and heart failure. Circ. Res. 2014, 114, 1815–1826.
2. Quan, A.; Baum, M. Regulation of proximal tubule transport by endogenously produced angiotensin II. Nephron 2000, 84, 103–110.
3. Zheng, H.; Liu, X.; Katsurada, K.; Patel, K.P. Renal denervation improves sodium excretion in rats with chronic heart failure: Effects on expression of renal ENaC and AQP2. Am. J. Physiol. Heart Circ. Physiol. 2019, 317, H958–H968.
4. Bozkurt, B.; Nair, A.P.; Misra, A.; Scott, C.Z.; Mahar, J.H.; Fedson, S. Neprilysin Inhibitors in Heart Failure: The Science, Mechanism of Action, Clinical Studies, and Unanswered Questions. JACC Basic Transl. Sci. 2022, 8, 88–105.
5. Katsurada, K.; Nandi, S.S.; Sharma, N.M.; Patel, K.P. Enhanced expression and function of renal SGLT2 (sodium-glucose cotransporter 2) in heart failure: Role of renal nerves. Circ. Heart Fail 2021, 14, e008365.
6. Vallon, V.; Verma, S. Effects of SGLT2 Inhibitors on Kidney and Cardiovascular Function. Annu. Rev. Physiol. 2021, 83, 503–528.
7. Scholtes, R.A.; Muskiet, M.H.A.; van Baar, M.J.B.; Hesp, A.C.; Greasley, P.J.; Karlsson, C.; Hammarstedt, A.; Arya, N.; van Raalte, D.H.; Heerspink, H.J.L. Natriuretic Effect of Two Weeks of Dapagliflozin Treatment in Patients With Type 2 Diabetes and Preserved Kidney Function During Standardized Sodium Intake: Results of the DAPASALT Trial. Diabetes Care 2021, 44, 440–447.
8. Herat, L.Y.; Magno, A.L.; Rudnicka, C.; Hricova, J.; Carnagarin, R.; Ward, N.C.; Arcambal, A.; Kiuchi, M.G.; Head, G.A.; Schlaich, M.P.; et al. SGLT2 inhibitor-induced sympatho-inhibition: A

novel mechanism for cardiorenal protection. JACC Basic Transl. Sci. 2020, 5, 169–179.

9. Hasking, G.J.; Esler, M.D.; Jennings, G.L.; Burton, D.; Johns, J.A.; Korner, P.I. Norepinephrine spillover to plasma in patients with congestive heart failure: Evidence of increased overall and cardiorenal sympathetic nervous activity. Circulation 1986, 73, 615–621.
10. Petersson, M.; Friberg, P.; Eisenhofer, G.; Lambert, G.; Rundqvist, B. Long-term outcome in relation to renal sympathetic activity in patients with chronic heart failure. Eur. Heart J. 2005, 26, 906–913.
11. Vallon, V.; Mühlbauer, B.; Osswald, H. Adenosine and kidney function. Physiol. Rev. 2006, 86, 901–940.
12. Heerspink, H.J.; Perkins, B.A.; Fitchett, D.H.; Husain, M.; Cherney, D.Z. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: Cardiovascular and kidney effects, potential mechanisms, and clinical applications. Circulation 2016, 134, 752–772.
13. Hansell, P.; Welch, W.J.; Blantz, R.C.; Palm, F. Determinants of kidney oxygen consumption and their relationship to tissue oxygen tension in diabetes and hypertension. Clin. Exp. Pharmacol. Physiol. 2013, 40, 123–137.
14. Ruggenenti, P.; Porrini, E.L.; Gaspari, F.; Motterlini, N.; Cannata, A.; Carrara, F.; Cella, C.; Ferrari, S.; Stucchi, N.; Parvanova, A.; et al. Glomerular hyperfiltration and renal disease progression in type 2 diabetes. Diabetes Care 2012, 35, 2061–2068.
15. Abdul-Ghani, M.A.; DeFronzo, R.A.; Norton, L. Novel hypothesis to explain why SGLT2 inhibitors inhibit only 30-50% of filtered glucose load in humans. Diabetes 2013, 62, 3324–3328.
16. Zhang, J.; Wei, J.; Jiang, S.; Xu, L.; Wang, L.; Cheng, F.; Buggs, J.; Koepsell, H.; Vallon, V.; Liu, R. Macula Densa SGLT1-NOS1-Tubuloglomerular Feedback Pathway, a New Mechanism for Glomerular Hyperfiltration during Hyperglycemia. J. Am. Soc. Nephrol. 2019, 30, 578–593.
17. Song, P.; Huang, W.; Onishi, A.; Patel, R.; Kim, Y.C.; van Ginkel, C.; Fu, Y.; Freeman, B.; Koepsell, H.; Thomson, S.; et al. Knockout of Na+-glucose cotransporter SGLT1 mitigates diabetes-induced upregulation of nitric oxide synthase NOS1 in the macula densa and glomerular hyperfiltration. Am. J. Physiol. Renal Physiol. 2019, 317, F207–F217.
18. Packer, M. Role of Impaired Nutrient and Oxygen Deprivation Signaling and Deficient Autophagic Flux in Diabetic CKD Development: Implications for Understanding the Effects of Sodium-Glucose Cotransporter 2-Inhibitors. J. Am. Soc. Nephrol. 2020, 31, 907–919.
19. Vallon, V. Glucose transporters in the kidney in health and disease. Pflugers. Arch. 2020, 472, 1345–1370.
20. Liu, Z.Z.; Bullen, A.; Li, Y.; Singh, P. Renal Oxygenation in the Pathophysiology of Chronic Kidney Disease. Front. Physiol. 2017, 8, 385.

21. Onishi, A.; Fu, Y.; Patel, R.; Darshi, M.; Crespo-Masip, M.; Huang, W.; Song, P.; Freeman, B.; Kim, Y.C.; Soleimani, M.; et al. A role for tubular Na+/H+ exchanger NHE3 in the natriuretic effect of the SGLT2 inhibitor empagliflozin. Am. J. Physiol. Renal Physiol. 2020, 319, F712–F728.
22. Hallow, K.M.; Helmlinger, G.; Greasley, P.J.; McMurray, J.J.V.; Boulton, D.W. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. Diabetes Obes. Metab. 2018, 20, 479–487.
23. Griffin, M.; Rao, V.S.; Ivey-Miranda, J.; Fleming, J.; Mahoney, D.; Maulion, C.; Suda, N.; Siwakoti, K.; Ahmad, T.; Jacoby, D.; et al. Empagliflozin in Heart Failure: Diuretic and Cardiorenal Effects. Circulation 2020, 142, 1028–1039.
24. Nespoux, J.; Patel, R.; Zhang, H.; Huang, W.; Freeman, B.; Sanders, P.W.; Kim, Y.C.; Vallon, V. Gene knockout of the Na+-glucose cotransporter SGLT2 in a murine model of acute kidney injury induced by ischemia-reperfusion. Am. J. Physiol. Renal Physiol. 2020, 318, F1100–F1112.
25. Darawshi, S.; Yaseen, H.; Gorelik, Y.; Faor, C.; Szalat, A.; Abassi, Z.; Heyman, S.N.; Khamaisi, M. Biomarker evidence for distal tubular damage but cortical sparing in hospitalized diabetic patients with acute kidney injury (AKI) while on SGLT2 inhibitors. Ren. Fail 2020, 42, 836–844.
26. Sano, M.; Takei, M.; Shiraishi, Y.; Suzuki, Y. Increased hematocrit during sodium-glucose cotransporter 2 inhibitor therapy indicates recovery of tubulointerstitial function in diabetic kidneys. J. Clin. Med. Res. 2016, 8, 844–847.
27. Vallon, V.; Miracle, C.; Thomson, S. Adenosine and kidney function: Potential implications in patients with heart failure. Eur. J. Heart Fail 2008, 10, 176–187.
28. Wilcox, C.S.; Shen, W.; Boulton, D.W.; Leslie, B.R.; Griffen, S.C. Interaction Between the Sodium-Glucose-Linked Transporter 2 Inhibitor Dapagliflozin and the Loop Diuretic Bumetanide in Normal Human Subjects. J. Am. Heart Assoc. 2018, 7, e007046.
29. Eickhoff, M.K.; Dekkers, C.C.J.; Kramers, B.J.; Laverman, G.D.; Frimodt-Møller, M.; Jørgensen, N.R.; Faber, J.; Danser, A.H.J.; Gansevoort, R.T.; Rossing, P.; et al. Effects of dapagliflozin on volume status when added to renin angiotensin system inhibitors. J. Clin. Med. 2019, 8, 779.
30. Masuda, T.; Watanabe, Y.; Fukuda, K.; Watanabe, M.; Onishi, A.; Ohara, K.; Imai, T.; Koepsell, H.; Muto, S.; Vallon, V.; et al. Unmasking a sustained negative effect of SGLT2 inhibition on body fluid volume in the rat. Am. J. Physiol. Ren. Physiol. 2018, 315, F653–F664.
31. Masuda, T.; Muto, S.; Fukuda, K.; Watanabe, M.; Ohara, K.; Koepsell, H.; Vallon, V.; Nagata, D. Osmotic diuresis by SGLT2 inhibition stimulates vasopressin-induced water reabsorption to maintain body fluid volume. Physiol. Rep. 2020, 8, e14360.
32. Lytvyn, Y.; Bjornstad, P.; Katz, A.; Singh, S.; Godoy, L.; Chung, L.; Vinovskis, C.; Pyle, L.; Roussel, R.; Perkins, B.; et al. SGLT2 inhibition increases serum copeptin in young adults with type 1 diabetes. Diabetes Metab. 2020, 46, 203–209.

33. Suijk, D.L.S.; van Baar, M.J.B.; van Bommel, E.J.M.; Iqbal, Z.; Krebber, M.M.; Vallon, V.; Touw, D.; Hoorn, E.J.; Nieuwdorp, M.; Kramer, M.M.H.; et al. SGLT2 Inhibition and Uric Acid Excretion in Patients with Type 2 Diabetes and Normal Kidney Function. Clin. J. Am. Soc. Nephrol. 2022, 17, 663–671.
34. Hahn, K.; Ejaz, A.A.; Kanbay, M.; Lanaspa, M.A.; Johnson, R.J. Acute kidney injury from SGLT2 inhibitors: Potential mechanisms. Nat. Rev. Nephrol. 2016, 12, 711–712.
35. Hahn, K.; Kanbay, M.; Lanaspa, M.A.; Johnson RJ Ejaz, A.A. Serum uric acid and acute kidney injury: A mini review. J. Adv. Res. 2017, 8, 529–536.
36. Bjornstad, P.; Lanaspa, M.A.; Ishimoto, T. Fructose and uric acid in diabetic nephropathy. Diabetologia 2015, 58, 1993–2002.
37. Kitamura, H.; Yamauchi, A.; Sugiura, T. Inhibition of myo-inositol transport causes acute renal failure with selective medullary injury in the rat. Kidney Int. 1998, 53, 146–153.
38. Laursen, J.C.; Søndergaard-Heinrich, N.; de Melo, J.M.L.; Haddock, B.; Rasmussen, I.K.B.; Safavimanesh, F.; Hansen, C.S.; Størling, J.; Larsson, H.B.W.; Groop, P.-H.; et al. Acute effects of dapagliflozin on renal oxygenation and perfusion in type 1 diabetes with albuminuria: A randomised, double-blind, placebo-controlled crossover trial. EClinicalMedicine 2021, 37, 100895.
39. Neuen, B.L.; Young, T.; Heerspink, H.J.L.; Neal, B.; Perkovic, V.; Billot, L.; Mahaffey, K.W.; Charytan, D.M.; Wheeler, D.C.; Arnott, C.; et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: A systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2019, 7, 845–854.
40. Cahn, A.; Melzer-Cohen, C.; Pollack, R.; Chodick, G.; Shalev, V. Acute renal outcomes with sodium-glucose co-transporter-2 inhibitors: Real-world data analysis. Diabetes Obes. Metab. 2019, 21, 340–348.
41. Iskander, C.; Cherney, D.Z.; Clemens, K.K.; Dixon, S.N.; Harel, Z.; Jeyakumar, N.; McArthur, E.; Muanda, F.T.; Parikh, C.R.; Paterson, J.M.; et al. Use of sodium-glucose cotransporter-2 inhibitors and risk of acute kidney injury in older adults with diabetes: A population-based cohort study. CMAJ 2020, 192, E351–E360.