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Critical Analysis of the Effects of SGLT2 Inhibitors on Renal Tubular Sodium, Water and Chloride Homeostasis and Their Role in Influencing Heart Failure Outcomes

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ABSTRACT: SGLT2 (sodium-glucose cotransporter 2) inhibitors interfere with the reabsorption of glucose and sodium in the early proximal renal tubule, but the magnitude and duration of any ensuing natriuretic or diuretic effect are the result of an interplay between the degree of upregulation of SGLT2 and sodium-hydrogen exchanger 3, the extent to which downstream compensatory tubular mechanisms are activated, and (potentially) the volume set point in individual patients. A comprehensive review and synthesis of available studies reveals several renal response patterns with substantial variation across studies and clinical settings. However, the common observation is an absence of a large acute or chronic diuresis or natriuresis with these agents, either when given alone or combined with other diuretics. This limited response results from the fact that renal compensation to these drugs is rapid and nearly complete within a few days or weeks, preventing progressive volume losses. Nevertheless, the finding that fractional excretion of glucose and lithium (the latter being a marker of proximal sodium reabsorption) persists during long-term treatment with SGLT2 inhibitors indicates that pharmacological tolerance to the effects of these drugs at the level of the proximal tubule does not meaningfully occur. This persistent proximal tubular effect of SGLT2 inhibitors can be hypothesized to produce a durable improvement in the internal set point for volume homeostasis, which may become clinically important during times of fluid expansion. However, it is difficult to know whether a treatment-related change in the volume set point actually occurs or contributes to the effect of these drugs to reduce the risk of major heart failure events. SGLT2 inhibitors exert cardioprotective effects by a direct effect on cardiomyocytes that is independent of the presence of or binding to SGLT2 or the actions of these drugs on the proximal renal tubule. Nevertheless, changes in the volume set point mediated by SGLT2 inhibitors might potentially act cooperatively with the direct favorable molecular and cellular effects of these drugs on cardiomyocytes to mediate their benefits on the development and clinical course of heart failure.

Key Words: diuresis ■ heart failure ■ natriuresis ■ proximal renal tubule ■ SGLT2 inhibitors

SGLT2 (sodium-glucose cotransporter 2) inhibitors reduce the risk of heart failure hospitalizations by ≈30% in large-scale trials of patients with type 2 diabetes, chronic heart failure, and chronic kidney disease, an effect that is independent of glycemic status, ejection fraction, or renal function.[1] Although myriad hypotheses have been proposed, 2 broad mechanisms are considered likely to underlie this benefit. First, SGLT2 inhibitors act on the kidney to promote changes in urinary electrolyte and water excretion. The resulting shift in the volume of circulating and noncirculating fluid compartments, in conjunction with potential modulation of renal salt sensing, reduces the likelihood of volume expansion that often precedes hospitalization for heart failure.[2] Second, SGLT2 inhibitors act directly on the heart to induce nutrient deprivation signaling and promote autophagy, which reduces oxidative and endoplasmic reticulum stress and enhances cellular function and viability.[3,4]

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Nonstandard Abbreviations and Acronyms

EMPAG-HF	Empagliflozin in Acute Decompensated Heart Failure
EMPA-RESPONSE-AHF	Empagliflozin Response Acute Heart Failure
EMPULSE	Empagliflozin in Patients Hospitalized for Acute Heart Failure
NHE3	sodium-hydrogen exchanger isoform 3
NT-proBNP	N-terminal pro-B-type natriuretic peptide
SGLT2	sodium-glucose cotransporter 2
WNK4	with no lysine 4

This direct action on cardiomyocytes is independent of the presence, binding, or inhibition of SGLT2,[3,5] and the effects on cellular health can be negated by genetic or pharmacological interventions that silence sirtuin-1 or AMP-activated protein kinase or interfere with autophagic flux.[3]

Recent reviews have focused on the direct cardiac effects of SGLT2 inhibitors mediated by the modulation of nutrient transport and nutrient deprivation signaling,[3,4] whereas the current overview provides a comprehensive and critical analysis of the direct effects of SGLT2 inhibitors on the urinary handling of electrolytes and water.

EFFECTS OF SGLT2 INHIBITION IN THE PROXIMAL RENAL TUBULE AND IMPORTANCE OF COUNTERBALANCING RESPONSES IN DOWNSTREAM NEPHRON SEGMENTS

Diabetes and heart failure lead to upregulation of SGLT2 in the proximal renal tubule, enhancing its sensitivity to SGLT2 inhibition.[6–8] The expression of SGLT2 is enhanced by renal sympathetic hyperactivity;[7,9] consequently, renal denervation reduces glycosuria, and it attenuates the glycosuric effect of SGLT2 inhibitors.[7,9,10] Renal sympathetic nerve activity is heightened particularly in acutely decompensated heart failure,[11] potentially augmenting the glycosuric effect of SGLT2 inhibitors; accordingly, the magnitude of glycosuria appears to wane as the acuity of the episode subsides.[12]

SGLT2 in the S1 and S2 segments of the proximal tubule is responsible for the overwhelming majority of glucose reabsorption in the kidney (Figure 1).[13] In micropuncture studies, SGLT2 inhibition produces a glycosuria-dependent osmotic diuresis, which increases tubular fluid osmolality sufficiently to dilute proximal tubular sodium and induce a back leak of sodium into the lumen by passive paracellular pathways;[13,14] thus, an osmotic diuresis yields an increase in urine volume accompanied by a modest reduction in proximal tubular sodium reabsorption.[13] The magnitude of SGLT2 inhibitor–mediated glycosuria is reduced in chronic kidney disease.[14,15]

Two-thirds of the filtered sodium is absorbed in the proximal tubule,[16] primarily through the action of NHE3 (sodium-hydrogen exchanger 3). NHE3 is colocalized with and structurally interlinked with SGLT2 in the brush border.[17,18] As a result, SGLT2 inhibitors modulate the functionality of NHE3 (even in the absence of luminal glucose), and this action likely underlies the effects of these drugs on renal sodium handling. Experimental silencing of NHE3 abrogates the effects of SGLT2 inhibition on proximal tubular sodium reabsorption.[8,17,19] Inhibition of NHE3 also promotes bicarbonate excretion,[8,16,17,19–21] contributing to the small decrease in serum bicarbonate observed in clinical trials.[22,23]

Activation of Counterbalancing Renal Tubular Mechanisms

If the effects of SGLT2 inhibitors were determined entirely by their actions on SGLT2 and NHE3 in the proximal renal tubule, their administration would result in a massive loss of sodium, water, and bicarbonate, leading to intravascular and extracellular volume depletion and marked acidosis.[24] Although hypovolemic euglycemic acidosis can occur in patients receiving SGLT2 inhibitors, it is typically associated with ketosis resulting from calorie restriction or insulinopenia.[25] In most circumstances, the lack of hypovolemia and acidosis is related to compensatory nephron mechanisms that counteract the effects of SGLT2 and NHE3 inhibition.

Specifically, SGLT2 inhibition is followed by marked enhancement of sodium reabsorption in downstream nephron segments, including the S3 segment of the proximal tubule, the loop of Henle, and the distal nephron (Figure 1).[13,26,27] Clinical trial proteomic analyses suggest that SGLT2 inhibition is accompanied by upregulation of carbonic anhydrase and uromodulin.[28] Activation of carbonic anhydrase promotes sodium and bicarbonate reabsorption in the proximal tubule and in the cortical collecting duct,[29,30] and uromodulin activates the Na^+,K^+,$2Cl^-$ cotransporter in the loop of Henle.[31] SGLT2 inhibition elevates circulating levels of aldosterone in some studies,[32] and increased glucose delivery to the distal convoluted tubule activates sodium reabsorption by the Na-Cl cotransporter.[33] In addition, SGLT2 inhibitors increase the proximal tubular levels of α-ketoglutarate,[19] which promotes sodium and chloride reabsorption by facilitating chloride-bicarbonate exchanger–related reabsorption pathways, while enhancing ammoniagenesis to achieve renal acid excretion.[19,34,35] These compensatory mechanisms, acting in concert, enhance sodium chloride reabsorption in the

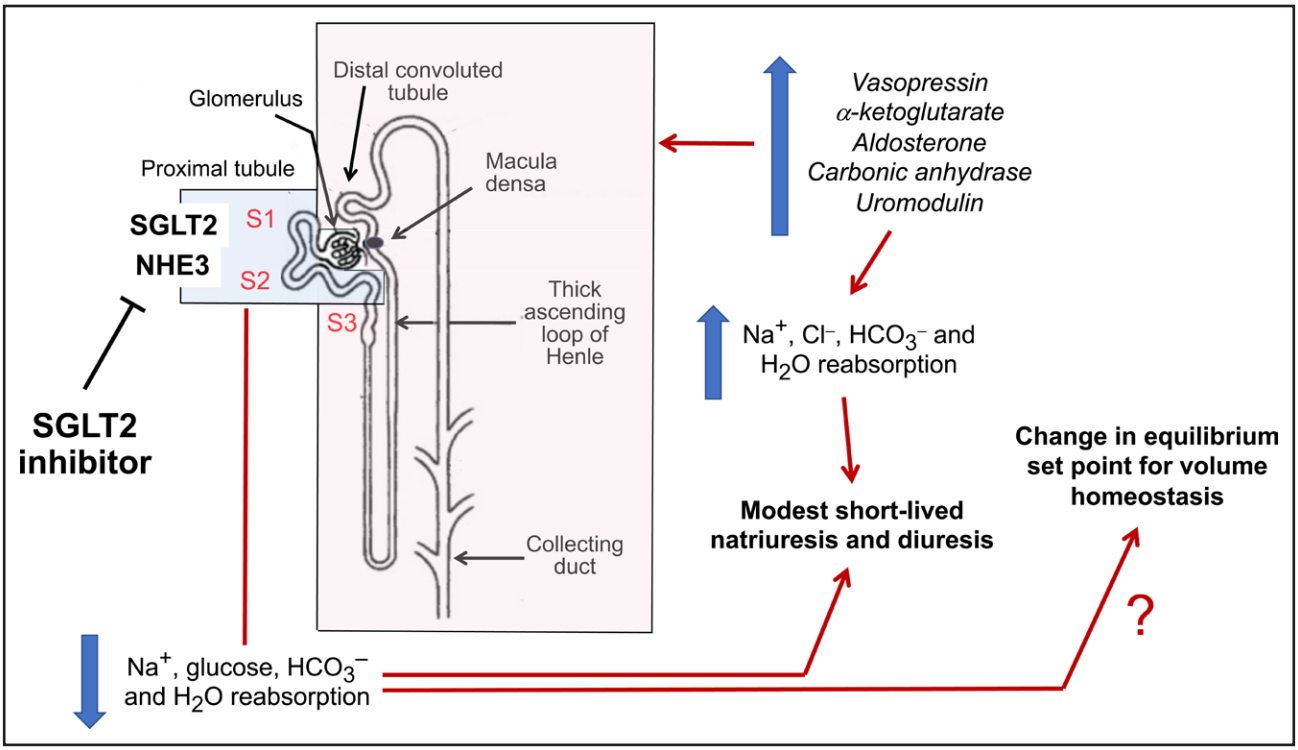

Figure 1. Direct and compensatory actions of SGLT2 inhibitors on the proximal renal tubule and distal nephron segments. SGLT2 (sodium glucose cotransporter 2) inhibitors directly interfere with the actions of SGLT2 and NHE3 (sodium hydrogen exchanger 3) in the S1 and S2 segments of the proximal tubule, thus inhibiting the reabsorption of sodium, glucose, bicarbonate, and water. These effects are counteracted by upregulation of electrolyte and water reabsorptive pathways in downstream nephron segments, mediated by vasopressin, aldosterone, α-ketoglurate, carbonic anhydrase, and uromodulin. The net result is a modest short-lived natriuresis and diuresis, and potentially, a change in the equilibrium set point for volume homeostasis. Segments in blue are sites of sodium, glucose, bicarbonate and water reabsorption that are attenuated by SGLT2 inhibitors; segments in red are sites of sodium, chloride, bicarbonate, and water reabsorption that are potentiated by SGLT2 inhibitors.

loop of Henle and more distal segments of the nephron, while simultaneously preventing the development of severe metabolic acidosis.

The mild osmotic diuresis that occurs with the tubular glucose load induced by SGLT2 inhibitors is easily compensated for by normal osmoregulatory mechanisms, primarily vasopressin.[36–39] The magnitude of the reactive antiaquaretic effect can be sufficiently marked to paradoxically cause a decrease in free water clearance in clinical studies of SGLT2 inhibitors,[37,40] explaining why plasma osmolarity increases only slightly during the water diuresis induced by glycosuria[18,39,40] and why serum sodium concentration can decline after initiation of treatment.[41] An increase in electrolyte-free water clearance becomes apparent if vasopressin is suppressed by water loading.[42] Vasopressin also increases sodium reabsorption in the loop of Henle and distal segments.[43]

Consequences of SGLT2 Inhibitor–Mediated Increases in Distal Chloride Delivery

In micropuncture studies, inhibition of SGLT2 and NHE3 in the proximal tubule enhances the delivery of chloride to downstream segments,[20] with several potential consequences.

Activation of Downstream Sodium Avidity and Mitigation of Hyperkalemia

As noted earlier, after SGLT2 inhibition, the reabsorption of sodium and chloride is enhanced in downstream nephron sites[20,33] as a result of upregulation of vasopressin, uromodulin, aldosterone, and α-ketoglutarate.[20,28,32,36–38,44–46] Increases in aldosterone may in part explain the effect of SGLT2 inhibitors to mitigate the risk of hyperkalemia (without inducing hypokalemia) in patients with diabetes or heart failure.[47,48]

Activation of Tubuloglomerular Feedback

Increased delivery of chloride to the macula densa after SGLT2 inhibition activates tubuloglomerular feedback, leading to afferent arteriolar vasoconstriction or efferent arteriolar vasodilation and a decline in glomerular filtration pressure.[20,49–51] Tubuloglomerular feedback becomes saturated, and single-nephron glomerular filtration falls dramatically, but with time, there is partial adaptation caused by increased sodium reabsorption in the loop of Henle, in conjunction with resetting of tubuloglomerular feedback.[20] Tubuloglomerular feedback has been hypothesized to contribute to the early dip in glomerular filtration rate after initiation of SGLT2 inhibitors, although this link has been challenged.[52]

Alleviation of Resistance to Loop Diuretics

Hypochloremia is a hallmark of diuretic resistance.[53,54] A reduction in filtered chloride combined with cellular chloride depletion activates WNK4 (with no lysine 4), thus increasing the activity of the Na^+,K^+,2Cl^- cotransporter,[55] the site of action of loop diuretics. Efforts to enhance chloride delivery (by dietary chloride[53] or acetazolamide[56]) may inhibit WNK4 and restore responsiveness to loop diuretics.[53,57] SGLT2 inhibitors can increase serum chloride[58–60] and enhance the effects of loop diuretics,[61] presumably because the increased delivery of sodium chloride to the loop of Henle enlarges the drug target.[62]

Therefore, the net effect of SGLT2 inhibitors on the urinary sodium and water excretion may depend on (1) the activation of SGLT2 and NHE3; (2) the magnitude of glycosuria, which is limited in patients with impaired renal function; (3) the effect to promote downstream chloride delivery; and (4) the degree of upregulation of counterregulatory antinatriuretic and antiaquaretic mechanisms at downstream nephron sites.

EVALUATION OF SODIUM AND WATER EXCRETION IN CLINICAL STUDIES OF SGLT2 INHIBITORS

From our comprehensive review, we identified 27 studies that evaluated the effects of SGLT2 inhibitors on urinary sodium and water excretion in healthy volunteers or patients with type 2 diabetes, heart failure, or chronic kidney disease, for periods ranging from 3 days to 3 months (Table 1).[12,32,37,39,40,42,44,46,58,61,63–81] Typically, dietary sodium and use of diuretics were not controlled; sodium balance was not achieved; and some studies analyzed spot (rather than 24-hour) urine collections.[12,46,67,81] Trials that were double-blind and placebo-controlled are less subject to these confounding factors.

Body weight was reported in many studies, but decreases in body weight during SGLT2 inhibition can be caused by the excretion of fluid or the loss of calories due to glycosuria.[82] It is noteworthy that Zanchi et al[32] and Sha et al[64] (who studied healthy volunteers and patients with diabetes) reported a reduction in body weight in the absence of a diuresis, but paradoxically, Mordi et al,[42] Kolwelter et al,[79] Boorsma et al,[12,77] Tamaki et al,[78] and Schulze et al[80] (who studied patients with heart failure) did not observe decreases in weight, despite increased urine volume. These observations suggest that changes in body weight after SGLT2 inhibitors do not reliably reflect pretreatment fluid retention or the diuretic response to these drugs.

As shown in Table 1, the effect of SGLT2 inhibitors on sodium and water excretion varies with the clinical setting or study design (Figure 2).

Healthy Volunteers and Patients With Type 2 Diabetes

In 18 studies of healthy individuals or patients with type 2 diabetes (none of whom were reportedly receiving diuretics), SGLT2 inhibition was typically (but not invariably) accompanied by immediate increases in the fractional excretion of lithium (indicative of inhibited proximal tubular sodium reabsorption), total urinary sodium excretion, and urinary volume (Table 1). However, after 5 to 7 days, although fractional lithium excretion was maintained and glycosuria persisted, the drugs had no significant effect on total urinary sodium excretion or volume. Several studies[37,39,40,44,46,72] have noted a decrease in free water clearance, accompanied by vasopressin activation; such an antiaquaretic counterregulatory response may be particularly likely in patients with diabetes.[83]

Heart Failure With and Without Recent Acute Decompensation

In patients with chronic heart failure receiving low doses of loop diuretics, the response to SGLT2 inhibition was characterized primarily by an increase in electrolyte-free water clearance. Four double-blind, placebo-controlled trials reported on the effects of SGLT2 inhibitors in patients who were treated with and responsive to furosemide equivalent doses <40 to 80 mg/d;[12,42,79,80] 2 of the 4 trials evaluated patients with acutely decompensated heart failure. In all 4 trials, SGLT2 inhibition produced an immediate and persistent increase in urinary volume, which was not accompanied by significant changes in urinary sodium excretion and was attributed to an osmotic diuresis produced by glycosuria. Counterregulatory downstream sodium reabsorptive mechanisms may be particularly active in the sodium-avid state of heart failure. A water diuretic effect may be especially evident in patients with acutely decompensated heart failure, possibly because renal sympathetic nerve hyperactivity in this setting enhances the glycosuric effect of SGLT2 inhibitors.[7–12] However, any water diuresis that follows a tubular glucose load would be rapidly opposed by normal osmoregulatory mechanisms, such as thirst and the release of vasopressin, thus minimizing the durability and clinical importance of an osmotic effect.

Chronic Heart Failure With Diuretic Resistance

Two studies evaluated in the effect of SGLT2 inhibition in patients with heart failure who were diuretic-resistant. Yeoh et al[81] evaluated 61 patients with heart failure who had fluid retention while receiving mean furosemide equivalent doses of ≈250 mg/d, who were randomized to dapagliflozin 10 mg/d or metolazone 5 to 10 mg/d; metolazone (but not dapagliflozin) potentiated the natriuretic effect of loop diuretics. Griffin et al[74] randomized 20 patients with diabetes and chronic heart failure who were clinically euvolemic while receiving mean furosemide equivalent doses of 244 mg/d. Patients received

Table 1. Studies Reporting Effect of SGLT2 Inhibitors on Urinary Sodium and Water Excretion

Study	Study participants	Trial design	Major findings
Healthy adults			
Wilcox et al (2018)[61]	42 healthy adults on fixed sodium diet	Open-label, randomized, parallel-group trial; bumetanide 1 mg daily or dapagliflozin 10 mg daily for 7 days, followed by combination for 7 days.	Increase in urinary sodium excretion with first dose of SGLT2 inhibitor (given alone), but attenuated after 1 week. SGLT2 inhibition potentiated response to bumetanide. SGLT2 inhibition increased serum osmolarity. Weight not reported.
Blau et al (2018)[63]	29 healthy adults on fixed sodium diet	Single-blind, randomized, placebo-controlled crossover trial; canagliflozin 300 mg daily vs placebo, for 5 days.	When compared with placebo, urinary sodium excretion increased with first dose of SGLT2 inhibitor, but no longer apparent after 5 days. Weight not reported.
Zanchi et al (2020)[32]	45 healthy adults; dietary sodium not controlled	Double-blind, randomized, parallel-group trial; empagliflozin 10 mg daily (n=30) or placebo (n=15) for 1 month.	SGLT2 inhibition produced increases in fractional lithium excretion on day 1 and after 1 month of treatment. SGLT2 inhibition caused a decline in 24-hour sodium excretion, as aldosterone increased. Weight loss with SGLT2 inhibition was significant after 1 week, but not after 4 weeks.
Type 2 diabetes			
Sha et al (2014)[64]	36 patients with type 2 diabetes	Double-blind, randomized, placebo-controlled trial; canagliflozin 300 mg daily or placebo, for 12 weeks.	No increase in fractional sodium excretion or total urinary sodium excretion after 1 week or 12 weeks of SGLT2 inhibition. Weight loss with SGLT2 inhibition at week 1 and week 12.
Heise et al (2016)[65]	22 patients with type 2 diabetes, on controlled sodium intake	Open-label, single-arm, case series study; empagliflozin 25 mg daily for 5 days.	Increase in urinary sodium excretion and urinary volume with SGLT2 inhibition after first day, but these changes were no longer apparent after 5 days. Body weight did not decrease on day 1, but decreased on day 5.
Heise et al (2016)[66]	22 patients with type 2 diabetes, on controlled sodium intake	Open-label, randomized, crossover trial; empagliflozin 25 mg/d for 5 days vs hydrochlorothiazide 25 mg daily or torsemide 5 mg for 4 days, followed by the addition of empagliflozin 25 daily for 5 days.	No increase in urinary sodium excretion or urinary volume with SGLT2 inhibition alone, but increased urinary sodium and volume and decreased body weight when SGLT2 inhibitor was combined with other diuretic. Increased in serum osmolarity with SGLT2 inhibition, without effect on serum sodium.
Hirose et al (2016)[67]	20 patients with type 2 diabetes; dietary sodium not controlled	Open-label, single-arm case series; tofogliflozin 20 daily for 8 weeks.	SGLT2 inhibition increased fractional excretion of sodium at 8 weeks, which was accompanied by modest decrease in body weight.
Tanaka et al (2017)[68]	13 patients with type 2 diabetes	Open-label single-arm case series; canagliflozin 100 mg daily for 6 days, no control group.	SGLT2 inhibition increased urinary sodium excretion and volume on day 1, but not maintained after 5 days, despite persistent glycosuria. No effect on body weight.
Solini et al (2017)[69]	26 patients with type 2 diabetes, on standardized sodium diet	Open-label single-arm study of dapagliflozin 10 mg daily for 2 days (n=16) or hydrochlorothiazide 12.5 mg daily for 2 days (n=10).	SGLT2 inhibition increased urinary volume (accompanied by increase in urinary glucose) without any change in urinary sodium or fractional sodium excretion. Free water clearance decreased. Weight not measured.
Kawasoe et al (2017)[70]	20 patients with type 2 diabetes	Open-label, single-arm case series using several different SGLT2 inhibitors for 6 months.	SGLT2 inhibition increased urinary sodium and glucose excretion and urinary volume and decreased body weight at 2 weeks and at 6 months
Eickhoff et al (2019)[40]	69 patients with type 2 diabetes and albuminuria receiving inhibitors of the renin-angiotensin system	Pooled data from 2 double-blind placebo-controlled crossover trials, with treatment periods of 6 weeks and 12 weeks	SGLT2 inhibition increased fractional lithium excretion without change in urinary sodium excretion at 6 and 12 weeks. Decrease in free water clearance with increase in copeptin, with increase in serum sodium concentration at end of treatment.
Opingari et al (2020)[71]	78 patients with type 2 diabetes	Double-blind, randomized, placebo-controlled trial; empagliflozin 10 mg daily or placebo, for 6 months.	SGLT2 inhibition produced persistent increase in urine glucose but without change in fractional urinary sodium excretion at 6 months.
van Bommel et al (2020)[58]	44 patients with type 2 diabetes	Double-blind, randomized, parallel-group trial; dapagliflozin 10 mg daily (n=24) vs gliclazide 30 mg daily (n=20) for 12 weeks.	SGLT2 inhibition increased urinary volume without increasing urinary sodium excretion, and increased serum chloride without changing serum sodium concentration.
Scholtes et al (2021)[37,72]	14 patients with type 2 diabetes, with controlled dietary sodium	Open-label single-arm case series; dapagliflozin 10 mg daily for 14 days.	After SGLT2 inhibition, modest change in fractional lithium excretion on day 1, but without change in urinary volume or sodium excretion. No increase in urinary sodium excretion or urinary volume by day 14, despite persistent glycosuria. Decrease in free water clearance with increase in copeptin. Body weight decreased at day 1 and day 14.

(*Continued*)

Table 1. Continued

Study	Study participants	Trial design	Major findings
van Ruiten et al (2022)[73]	66 patients with type 2 diabetes	Double-blind, randomized, placebo-controlled, comparing dapagliflozin 10 mg daily, exenatide 10 mg twice daily, combination or placebo for 16 weeks.	SGLT2 inhibition produced modest increase in urinary volume at 10 days, but not after 16 weeks. No increase in urinary sodium excretion at either time point.
Lytvyn et al (2022)[52]	31 patients with type 1 diabetes	Double-blind, placebo-controlled crossover trial; periods of no treatment, ramipril alone (4 weeks), ramipril combined with empagliflozin (25 mg/d) for 4 weeks, and off treatment.	SGLT2 inhibition decreased absolute proximal sodium and fluid reabsorption rate and increased fractional sodium and lithium excretion after 4 weeks
Berton et al (2023)[46]	36 patients with type 2 diabetes	Open-label randomization to empagliflozin 10 or 25 mg/d (n=24) or dapagliflozin (n=12) for 3 months	SGLT2 inhibition increased fractional sodium excretion and urine osmolarity after 1 and 3 months. Decrease in body weight after 1 month.
Chronic kidney disease			
Sen et al (2022)[44]	6 nondiabetic patients with chronic kidney disease, sodium-controlled diet, not receiving diuretics	Open-label, single-arm case series; dapagliflozin 10 mg daily for 14 days.	SGLT2 inhibition increased urinary glucose excretion, but did not increase urinary volume, fractional lithium or 24-hour urinary sodium excretion, initially or after 4 or 14 days. Weight not reported.
Chronic or acutely decompensated heart failure			
Mordi et al (2020)[42]	23 patients with diabetes and stable heart failure, 70% with EF <45%, (NT-proBNP ≈2400 pg/mL), all receiving loop diuretics, generally ≤40 mg/d)	Double-blind, randomized, placebo-controlled crossover trial; empagliflozin 25 mg daily vs placebo, each for 6 weeks. Studies performed using an overhydration protocol.	When compared with placebo, SGLT2 inhibition produced increases in urinary volume at day 3 and after 6 weeks due to increase in electrolyte-free water clearance. No short-term or long-term changes in fractional sodium or 24-hour urinary sodium excretion. No change in NT-proBNP at any time. Significant change in body weight at week 6, but not after 3 days.
Griffin et al (2020)[74]	20 patients with diabetes and euvolemic heart failure, NT-proBNP ≈400, all receiving loop diuretics and diuretic resistant (furosemide equivalents, 244 mg daily)	Double-blind, randomized, placebo-controlled crossover trial; empagliflozin 10 mg daily vs placebo, each for 14 days.	SGLT2 inhibition produced increase in fractional sodium excretion after day 1, which was still apparent after 14 days, and was potentiated by a loop diuretic. Natriuresis was unrelated to magnitude of glycosuria or baseline glomerular filtration rate. Decrease in body weight at 14 days, but no change in NT-proBNP.
Fukuoka et al (2020)[75]	40 patients with type 2 diabetes, stable after hospitalization for heart failure, EF ≈41%, 95% on loop diuretic	Open-label, single-arm case series; ipragliflozin 50 mg daily for 4 days.	SGLT2 inhibition produced modest increases in urinary volume and 24-hour urinary sodium excretion for 3 days, accompanied by decrease in body weight. Greater effect if high baseline furosemide dose.
Ikeda et al (2021)[76]	56 patients with type 2 diabetes, stable after hospitalization for heart failure; EF ≈44%; BNP ≈480 pg/mL; furosemide equivalent dose, 12 mg daily	Open-label, single-arm case series; empagliflozin 10 mg daily (n=29), dapagliflozin 5 mg daily (n=17) or canagliflozin 100 mg daily (n=100) for 4 days.	SGLT2 inhibition produced modest increase in urine volume, which became attenuated after 4 days. No increase in urinary sodium excretion after 4 days. Body weight decreased at 4 days.
Boorsma et al (2021)[12,77]	79 patients with acutely decompensated heart failure, NT-proBNP 5200, EF ≈36%; within 24 hours of admission, all on loop diuretic, ≈40 mg furosemide equivalent dose	Double-blind, randomized, placebo-controlled trial; empagliflozin 10 mg daily or placebo, for 30 days.	SGLT2 inhibition increased urine volume for 4 days, but no increase in the fractional excretion of sodium or 24-hour urinary sodium excretion at 4 or 30 days, despite immediate and persistent glycosuria. No change in body weight after 4 days. Increase in plasma osmolality with empagliflozin at 72 hours. No change in NT-proBNP at any time point.
Tamaki et al (2021)[78]	59 patients with type 2 diabetes, within 96 hours of acute heart failure decompensation, 80% class IV, EF ≈44%, NT-proBNP 3200), loop diuretic in 50%, furosemide equivalent dose ≈20–25 mg daily	Open-label randomized trial; empagliflozin 10 mg daily or other diabetic therapy for 7 days.	SGLT2 inhibition produced increases in urinary volume and urinary sodium excretion at 24 hours. No change in body weight after day 1 or day 7. Lower NT-proBNP at day 7.
Schulze et al (2022)[80]	60 patients with acutely decompensated heart failure, within 12 hours of admission, EF ≈45%, NT-proBNP 3400, 40% no previous loop diuretic; received furosemide equivalent ≈60 mg/d	Double-blind, randomized, placebo-controlled trial; empagliflozin 25 mg daily vs placebo for 5 days.	SGLT2 inhibition produced greater increase in urine volume over 5-day study period, but without change in total urinary sodium excretion or fractional sodium excretion. Decrease in NT-proBNP at 5 days, but no reduction in body weight.
Kolwelter et al (2023)[79]	74 patients with stable euvolemic heart failure, EF ≈41%, NT-proBNP ≈450 pg/mL, 40% receiving loop diuretics (not >80 mg daily)	Double-blind, randomized, placebo-controlled parallel-group trial; empagliflozin 10 mg daily vs placebo, for 3 months.	When compared with placebo, SGLT2 inhibition produced increases in urinary volume and decreases in body weight (but no between-group difference in urinary sodium) after 1 month. No between-group differences in urinary volume, urinary sodium, or NT-proBNP after 3 months. Weight loss at 3 months.

(*Continued*)

Table 1. Continued

Study	Study participants	Trial design	Major findings
Yeoh et al (2023)[81]	61 hospitalized patients with fluid retention resistant to loop diuretics, EF 45%, NT-proBNP ≈4000 pg/mL	Open-label, randomized, parallel-group trial; dapagliflozin 10 mg daily vs metolazone 5–10 mg daily, for 3 days.	No change in spot urinary sodium concentration with SGLT2 inhibition during 3-day treatment period. Less natriuresis, lower loop diuretic efficiency and less weight loss with dapagliflozin than metolazone.

BNP indicates B-type natriuretic peptide; EF, ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SGLT2, sodium-glucose cotransporter 2.

empagliflozin 10 mg/d or placebo (double blind), each for 14 days, followed by crossover to the alternative treatment. SGLT2 inhibition produced an immediate increase in the fractional sodium excretion, which was still discerned after 14 days, and the natriuresis was enhanced by bumetanide but was unrelated to the magnitude of glycosuria. Wilcox et al[61] and Heise et al[66] also observed that SGLT2 inhibitors could potentiate the natriuretic effects of loop diuretics. Such potentiation may be related to the action of SGLT2 inhibitors to increase distal chloride delivery, thus sensitizing the $Na^+,K^+,2Cl^-$ cotransporter to pharmacological antagonism,[84] yet potentiation of natriuresis was not observed in the patients with diuretic resistance and fluid retention who were studied by Yeoh et al.[81]

It is understood that the initial natriuretic response to any diuretic is typically attenuated as euvolemia is achieved as a result of the activation of counterregulatory mechanisms. The finding that fractional lithium clearance and glucose excretion persists during long-term SGLT2 inhibition indicates that pharmacological tolerance to the effects of these drugs on the proximal tubule does not develop.

EVALUATION OF PLASMA AND BLOOD VOLUME IN CLINICAL STUDIES OF SGLT2 INHIBITORS

Loop diuretics produce pulmonary decongestion in patients with heart failure by decreasing circulating plasma and blood volume, thus reducing cardiac filling pressures. Therefore, in characterizing the diuretic properties of SGLT2 inhibitors, studies of their effects on plasma volume are relevant.

Challenges in the Assessment of Plasma Volume During SGLT2 Inhibition

Plasma volumes can be measured using indicator dilution methods based on agents that bind to albumin. However, in most reports, plasma volume has been estimated indirectly, relying on formulae developed by Kaplan and Hakim for single assessments and by Strauss et al for paired assessments.[85] The Kaplan formula is based on hematocrit and body weight, whereas the Strauss formula focuses on the ratios of hemoglobin and hematocrit. These formulas yield poor estimates of directly measured values[86]—often deviating by >1 liter[87]—and provide unreliable metrics of clinical congestion[88] or decongestion.[89] Furthermore, the Strauss formula assumes that red blood cell mass in the central circulation does not change between paired assessments.[86,87] Because SGLT2 inhibitors stimulate erythropoietin and reticulocytosis within 7 days,[90–92] the Strauss formula cannot be applied for the estimation of changes in plasma volume with these drugs. Even if there were no erythropoiesis, estimation of plasma volume by the Strauss formula can be distorted by shifts in the distribution of red blood cells from intravascular pools, as is commonly seen during the clinical course of patients with acutely decompensated heart failure.[86–88,93]

Even if measured accurately, decreases in plasma volume do not reliably reflect intravascular or total body decongestion. Diuretics may have little effect on or even increase plasma volume in heart failure, if they mobilize fluid from the interstitial space.[89,93–95] Furthermore, any expansion of red blood cell mass triggers an adaptive reduction in plasma volume, because if plasma volume were to remain constant, erythrocytosis would result in intolerable hypervolemia. This principle explains why physiological or pharmacologically induced increases in hematocrit (regardless of cause) lead to decreases in plasma volume.[96,97]

Effect of SGLT2 Inhibitors on Plasma and Blood Volume in Clinical Studies

On the basis of a comprehensive review, we identified 15 studies that evaluated the effect of SGLT2 inhibitors on plasma volume (Table 2).[64,72–74,78,98–109] Unfortunately, most studies estimated changes in plasma volume using the Kaplan-Hakim and Strauss formulae, which cannot be applied to the evaluation of changes produced by SGLT2 inhibitors. Four reports[64,72,74,109] used indicator dilution methods, and of these, 3 were double blind and placebo controlled. In patients with type 2 diabetes, SGLT2 inhibition for 12 weeks reduced plasma volume in 1 trial,[109] but not in another.[64] In the third trial,[74] SGLT2 inhibition decreased plasma volume in diuretic-resistant patients with heart failure after 2 weeks.

Decreases in the serum albumin concentration may reflect a dilution that occurs when plasma volume expands during sodium-avid states.[110] SGLT2 inhibitors increase serum albumin in mechanistic studies and large-scale trials; the effects are seen after a few weeks

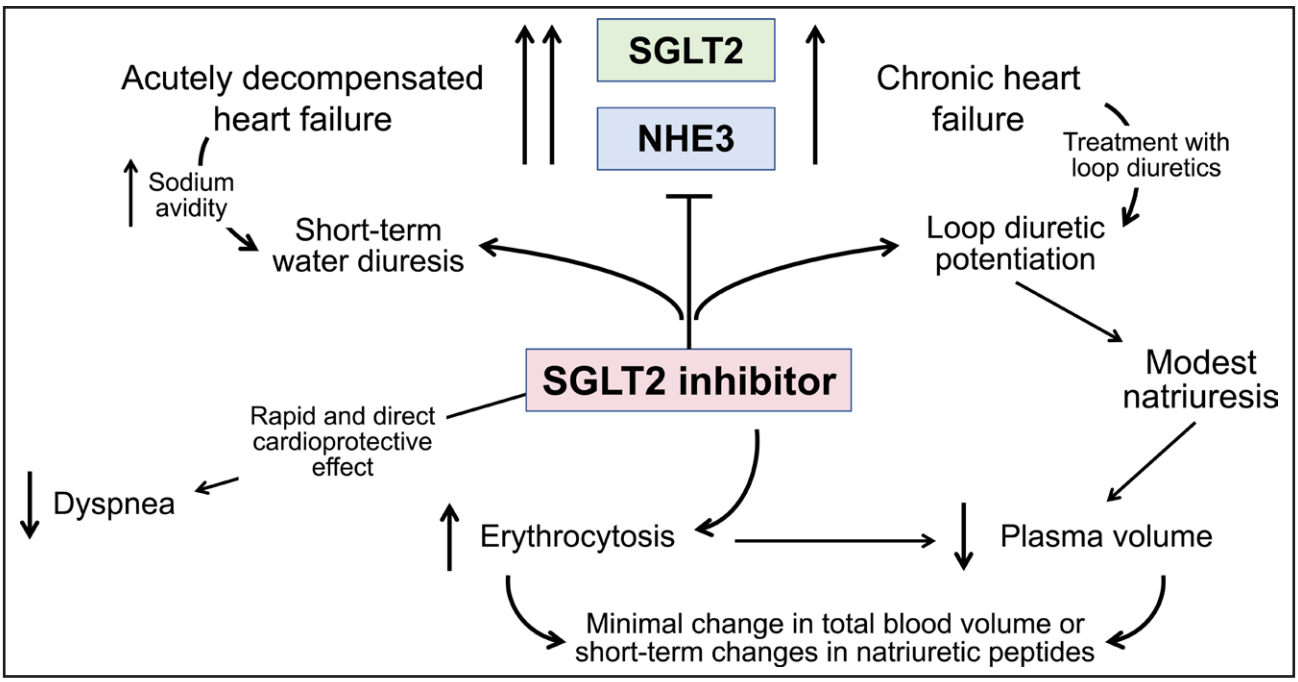

Figure 2. Effects of SGLT2 inhibitors on urinary sodium and water excretion in chronic heart failure and acutely decompensated heart failure.

The administration of an SGLT2 (sodium glucose cotransporter 2) inhibitor to patients with acutely decompensated heart failure is often accompanied by a short-term water diuresis, but clinical improvement may be related primarily to a rapid and direct cardioprotective effect similar to that seen during the first 2 to 4 weeks of treatment in clinical trials of patients with chronic heart failure. The administration of an SGLT2 inhibitor to patients with chronic heart failure who are receiving loop diuretics can be accompanied by potentiation of the effect of the loop diuretic, resulting in a modest diuresis and a reduction in plasma volume. However, because of their erythropoietic effect, these drugs produce minimal changes in total blood volume or decreases in circulating natriuretic peptides, and thus, short-term changes in urinary sodium or water excretion do not explain the short- and long-term decrease in the risk of heart failure events. Intriguingly, these events are not reduced in randomized controlled trials of short-term intensification of other diuretic drugs. NHE3 indicates sodium hydrogen exchanger 3.

and persist for the duration of treatment.[23,103,108,110] When SGLT2 inhibitors are discontinued after long-term therapy, serum albumin falls within 7 days.[111]

These observations indicate that SGLT2 inhibitors likely lead to a short- and long-term decrease in plasma volume (Figure 2). However, it is not clear whether this effect is related to the action of these drugs to promote a diuresis or an erythrocytosis. Regardless, as a result of SGLT2 inhibitor–stimulated erythropoiesis, the increase in red blood cell mass offsets any ability of a decrease in plasma volume to be translated into a change in total circulating blood volume during long-term therapy. SGLT2 inhibition reduced estimated total blood volume by only 1% in the only study in which it was evaluated.[112]

The lack of a meaningful effect on total blood volume may explain why SGLT2 inhibition did not reduce NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels in the 5 placebo-controlled trials in patients with heart failure summarized in Table 1, whereas NT-proBNP levels are reduced by loop diuretics.[113,114] In large-scale heart failure trials, SGLT2 inhibition for 3 months produces only modest changes in natriuretic peptides and left ventricular filling pressures (even in patients with volume overload), with little correlation between changes in natriuretic peptides and metrics of decongestion.[105,115–117] Even in acutely decompensated heart failure, changes in NT-proBNP are not apparent[79] or are modest and not sustained.[118]

EVALUATION OF EXTRACELLULAR FLUID IN CLINICAL STUDIES OF SGLT2 INHIBITORS

Most of the excess fluid in sodium-avid states is retained in the interstitial compartment, where it is manifested as edema.[119] Diuretics alleviate fluid retention by reducing intravascular volume, which promotes the movement of sodium and water from the interstitial space into the circulation, followed by excretion through the kidneys. Interstitial fluid is mobilized through both plasma transcapillary refill and the action of lymphatics, which drain the interstitial space, moving fluid into the great veins.[120] Lymphatic mobilization is gradient-dependent, and increases in right-sided filling pressures can impair both plasma transcapillary refill and lymphatic fluid uptake and duct flow;[120,121] lymphatic congestion within the kidney may also impair sodium excretion.[122] Therefore, by reducing right-sided filling pressures, loop diuretics

Table 2. Studies Reporting Effect of SGLT2 Inhibitors on Plasma Volume

Study	Study participants	Trial design	Major findings
Estimation of plasma volume by hematocrit-based formulae			
Dekkers et al (2019)[98]	4533 patients with type 2 diabetes	Pooled analysis of double-blind, randomized, placebo-controlled trials, dapagliflozin 10 mg daily or placebo, up to 24 weeks.	SGLT2 inhibition reduced estimated plasma volume, with effect apparent at 4 weeks and persistent for 24 weeks, but estimations inappropriately based on Strauss formula. Attempted validation of estimates did not involve sequential measurements.
Matsuba et al (2021)[99]	107 patients with type 2 diabetes	Single-arm, open-label case series of canagliflozin 100 mg daily for 12 months.	SGLT2 inhibition decreased plasma volume at 1 month with persistent effect for 1 year, but estimations inappropriately based on Strauss formula. Weight loss attributed to decreased fat mass.
Tanaka et al (2021)[100]	105 patients with type 2 diabetes	Double-blind, randomized, placebo-controlled trial; empagliflozin 10 mg daily or placebo for 24 weeks.	SGLT2 inhibition decrease estimated plasma volume at 12 weeks through 24 weeks, but estimations inappropriately based on Strauss formula. No weight loss with empagliflozin vs placebo.
Matsubayashi et al (2021)[101]	157 patients with type 2 diabetes	Single-arm, open-label case series, treated with tofogliflozin 20–40 mg daily for 52 weeks.	SGLT2 inhibition decreased in estimated plasma volume and body weight at study end, with increase after drug discontinuation. Parallel changes in hemoglobin, but no associations with body weight. Estimations inappropriately based on Strauss formula.
Hoshika et al (2021)[102]	96 patients with type 2 diabetes and acute myocardial infarction	Double-blind, randomized, placebo-controlled trial; empagliflozin 10 mg daily or placebo for 24 weeks.	SGLT2 inhibition decrease estimated plasma volume at 12 weeks through 24 weeks, but estimations inappropriately based on Kaplan-Hakim formula. Decrease in body weight vs placebo at week 12 and week 24, but not at week 4.
Jensen et al (2021)[103–105]	120 patients with stable heart failure, EF ≈31%, NT-proBNP ≈600 pg/mL, loop diuretic in 60%	Double-blind, randomized, placebo controlled trial; empagliflozin 10 mg daily or placebo for 12 weeks.	When compared with placebo, SGLT2 inhibition decreased body weight and estimated plasma volume (by 7%), but did not decrease NT-proBNP or pulmonary wedge pressure. Estimations inappropriately based on Kaplan-Hakim and on Strauss formulae. SGLT2 inhibition increased serum albumin.
Tamaki et al (2021)[78]	59 patients with diabetes, after acute heart failure decompensation, 80% class IV, EF ≈44%, (NT-proBNP 320), 50% loop diuretic, furosemide equivalent dose ≈20–25 mg/d	Open-label randomized trial; empagliflozin 10 mg daily or other diabetic therapy for 7 days.	SGLT2 inhibition decreased estimated plasma volume at 7 days, but estimations inappropriately based on Strauss formula. No change in body weight after 7 days.
van Ruiten et al (2022)[73]	66 patients with type 2 diabetes	Double-blind, randomized, placebo-controlled, comparing dapagliflozin 10 mg daily, exenatide 10 mg twice daily, combination or placebo for 16 weeks.	Modest decrease in plasma volume in dapagliflozin group at 10 days, but not at 16 weeks; however, estimations inappropriately based on Strauss formula. No change in urinary volume. Body weight measured, but results not shown.
Fujiki et al (2023)[106]	233 patients with heart failure and type 2 diabetes	Open-label, randomized, parallel-group design, canagliflozin 100 mg daily or glimepiride for 24 weeks.	Modest decrease in estimated plasma volume in canagliflozin group at 12 weeks, but estimations inappropriately based on Strauss formula.
Nakashima et al (2022)[107]	165 patients with heart failure and preserved ejection fraction and type 2 diabetes	Open-label, randomized, parallel-group design; luseogliflozin (2.5 mg/d, n=83) vs voglibose (n=82) for 24 weeks.	Decrease in estimated plasma volume at 4, 12, and 24 weeks, shown to be driven primarily by increases in hemoglobin. Estimations inappropriately using Strauss formula.
Scholtes et al (2023)[108]	24 patients with type 2 diabetes	Double-blind, randomized, crossover, empagliflozin 10 mg daily, losartan 50 mg daily, the combination or placebo, each for 1 week with 4-week washout periods.	After 1 week of SGLT2 inhibition, body weight declined, but no change in urinary volume or plasma volume. Estimations inappropriately based on Strauss formula. SGLT2 inhibition increased serum albumin.
Measurement of plasma volume by indicator dilution methods			
Heerspink et al (2013)[109]	75 patients with type 2 diabetes	Double-blind, randomized, placebo controlled, parallel-group trial; dapagliflozin 10 mg daily, hydrochlorothiazide 25 mg daily, or placebo for 12 weeks.	Decrease in plasma volume accompanied by increased in red blood cell mass with dapagliflozin, and not with hydrochlorothiazide. Plasma volume and red cell mass were measured with ^{51}Cr-labelled erythrocytes and ^{125}I-labeled albumin. NT-proBNP increased with dapagliflozin. Similar decrease in body weight with 2 active treatments.

(*Continued*)

Table 2. Continued

Study	Study participants	Trial design	Major findings
Sha et al (2014)[64]	36 patients with type 2 diabetes	Double-blind, randomized, placebo-controlled, parallel-group trial; canagliflozin 300 mg daily or placebo for 12 weeks.	SGLT2 inhibition increase urinary volume and decreased plasma volume after 1 week, but these effects were no longer apparent after 12 weeks. Plasma volume measured by indocyanine green indicator dilution method.
Griffin et al (2020)[74]	20 patients with diabetes and euvolemic heart failure, NT-pro BNP ≈400, all receiving loop diuretics and were diuretic resistant (furosemide equivalents, 244 mg/d)	Double-blind, randomized, placebo-controlled crossover trial; empagliflozin 10 mg daily vs placebo, each for 14 days.	SGLT2 inhibition produced decreases in plasma volume vs placebo at 14 days. Plasma volume measured by radiolabeled I-131 albumin. Expected increases in hemoglobin with SGLT2 inhibition prevented by intensive phlebotomy required by study protocol. Empagliflozin reduced body weight, but had no effect on NT-proBNP.
Scholtes et al (2021)[72]	14 patients with type 2 diabetes, with controlled dietary sodium	Single-arm, open-label administration of dapagliflozin 10 mg daily for 14 days.	SGLT2 inhibition produced no change in plasma volume at 2–4 days or after 14 days. Plasma volume measured by indocyanine green indicator dilution method.

EF indicates ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and SGLT2, sodium-glucose cotransporter 2.

not only enhance plasma transcapillary refill but also markedly increase lymphatic flows and drainage of the interstitial space,[123] allowing a reduction in total body extracellular water and edema.[89]

Effect of SGLT2 Inhibitors on Extracellular Fluid in Clinical Studies

On the basis of a comprehensive review, we identified 13 studies that evaluated the effects of SGLT2 inhibitors on extracellular water (Table 3).[44,46,67,72,73,79,99,103,108,124–128] These reports performed measurements using diverse methods, typically without a control group, making it difficult to reliably discern a treatment effect. In 5 trials that were double blind and placebo controlled, SGLT2 inhibition modestly decreased extracellular fluid in patients with diabetes or heart failure after 1 to 2 weeks, but with little effect after 1 to 3 months. Meaningful responses were noted only in patients with pretreatment fluid retention,[46,127,128] but these reports were not double blind or placebo controlled.

Some investigators have used computer modeling to project the effect of SGLT2 inhibitors on interstitial fluid and concluded that these drugs deplete extracellular water more profoundly than conventional diuretics.[2] These models assumed that SGLT2 inhibitors act primarily as aquaretics to increase serum osmolarity, a finding not confirmed by clinical studies,[2,129] and the models also did not consider the effect of enhanced erythropoiesis to maintain total blood volume. The conclusions of these models are inconsistent with the efficacy of conventional diuretics in edematous states.[89,130]

It has been hypothesized that the interstitium contains nonosmotically active sodium, which has adverse effects on vascular function.[131] SGLT2 inhibitors may reduce skin (but not muscle) sodium content after 1 and 3 months of treatment,[79,124] but it is not clear that these measurements reflect nonosmotic stores of the ion.[132] Nonosmotic stores of sodium might be a determinant of vascular resistance, but not of edema.[132,133]

EFFECT OF SGLT2 INHIBITORS ON EDEMA AND CONGESTION

The primary end point for the regulatory approval of diuretics is the alleviation of edema in sodium-avid states. Thiazide and loop diuretics, mineralocorticoid receptor antagonists, and vasopressin antagonists ameliorate fluid retention in heart failure, hepatic cirrhosis, and nephrotic syndrome.[134–137] In contrast, there are no reports of a favorable effect of SGLT2 inhibitors to reduce the edema of heart failure or the ascites of hepatic cirrhosis. Observations about decongestion are difficult to interpret when patients are being concurrently treated with an intensified regimen of loop diuretics.[81]

It is interesting that in patients hospitalized for heart failure, there may be little relationship between the magnitude of natriuresis and the relief of symptoms. Intensive intravenous loop diuretics produce a greater diuresis but not greater effects on pulmonary congestion.[138] The addition of hydrochlorothiazide to a loop diuretic yields a modest diuretic effect, but no incremental benefit on dyspnea.[139] Acetazolamide potentiates the natriuretic response to loop diuretics but without a reported benefit on symptoms.[140] Conventional diuretics may preferentially act to remove excess fluid from the interstitial space, with little change in total blood volume, cardiac filling pressures, or symptoms.[89]

Effect of SGLT2 Inhibitors on Congestion in Acutely Decompensated Heart Failure

Three double-blind, placebo-controlled trials have evaluated the effects of SGLT2 inhibitors in patients with acutely decompensated heart failure, treated for ≤90 days: EMPAG-HF (Empagliflozin in Acute Decompensated Heart Failure),[80] EMPA-RESPONSE-AHF (Empagliflozin Response Acute Heart Failure),[12,77] and EMPULSE (Empagliflozin in Patients Hospitalized for Acute Heart Failure).[118,141] The largest trial (EMPULSE [Empagliflozin in Patients Hospitalized for Acute Heart Failure])

Table 3. Studies Reporting Effect of SGLT2 Inhibitors on Extracellular Water

Study	Study participants	Trial design	Major findings
Type 2 diabetes			
Hirose et al (2016)[67]	17 patients with type 2 diabetes	Open-label, single-arm case series; tofogliflozin 20 daily for 8 weeks.	Measurements by bioimpedance analysis (Biospace). SGLT2 inhibition decreased extracellular water by 0.4 L after 8 weeks.
Karg et al (2018)[124]	59 patients with type 2 diabetes	Double-blind, randomized, placebo-controlled, crossover trial; dapagliflozin 10 mg daily or placebo, each for 6 weeks.	Tissue water content by ^{23}Na magnetic resonance imaging. No change in muscle or skin water content, but decrease in skin sodium content, at 6 weeks.
Schork et al (2019)[125]	27 patients with type 2 diabetes	Open-label administration of empagliflozin (n=18) or dapagliflozin (n=9) for 6 months.	Measurements by bioimpedance spectroscopy (Fresenius Body Composition Monitor). SGLT2 inhibition led to decrease of 0.3 L by day 3 with loss of effect after 3 and 6 months.
Matsuba et al (2021)[99]	107 patients with type 2 diabetes	Open-label, single-arm case series of canagliflozin 100 mg daily for 12 months.	Measurements by bioimpedance analysis (T-SCAN PLUS). No decrease in extracellular water at 1 and 3 months, but 0.5 L decrease at 12 months.
Scholtes et al (2021)[72]	14 patients with diabetes	Open-label, single-arm administration of dapagliflozin 10 mg daily for 14 days.	Measurements by bioimpedance spectroscopy (Impedimed). SGLT2 inhibition decreased extracellular volume by 0.7 L after 3 days, but no change after 14 days.
Zeng et al (2022)[126]	24 patients with type 2 diabetes, treated with insulin	Open-label, randomized, parallel-group trial; empagliflozin 25 mg daily vs linagliptin for 24 weeks.	Measurements by bioimpedance analysis (X-Scan Plus II). Decrease in extracellular fluid by 0.6 L in SGLT2 inhibitor group, as compared with control.
van Ruiten et al (2022)[73]	66 patients with type 2 diabetes	Double-blind, randomized, placebo-controlled trial; comparing- dapagliflozin 10 mg/d, exenatide 10 mg twice daily, combination or placebo for 16 weeks	Measurements by bioimpedance spectroscopy (Impedimed). SGLT2 inhibition decreased extracellular volume by 1.1 L after 10 days, but attenuated by 16 weeks
Scholtes et al (2023)[108]	24 patients with type 2 diabetes	Double-blind, randomized, crossover, empagliflozin 10 mg/d, losartan 50 mg/d, the combination or placebo, each for 1 week with 4-week washout periods.	Measurements by bioimpedance spectroscopy (Impedimed). Decrease in extracellular fluid by 0.5 L, when compared with placebo, after 1 week.
Berton et al (2023)[46]	36 patients with type 2 diabetes	Open-label randomization to empagliflozin 10 or 25 mg/d (n=24) or dapagliflozin (n=12) for 3 months; no untreated control group.	Measurements by bioimpedance vector analyzer (BIA101BIVA). SGLT2 inhibition decreased extracellular fluid by 1.0 L after 3 months, with notable response only in patients with increased pretreatment values.
Chronic kidney disease			
Ohara et al (2019)[127,128]	40 patients with diabetic kidney disease and fluid retention; 67% on loop diuretic, ≈BNP 70 pg/mL	Open-label, single-arm case series study; dapagliflozin 5 mg daily (n=14), furosemide 54.6 mg daily (n=14), and tolvaptan 6.8 mg daily (n=12) for 7 days.	Measurements by bioimpedance analysis (InBody). Changes in extracellular water were ≈2.1 L with furosemide, ≈1.5 L with dapagliflozin, and ≈1.2 L with tolvaptan; changes closely paralleled changes in body weight. Larger effect seen in those with higher pretreatment levels of extracellular water.
Sen et al (2022)[44]	6 nondiabetic patients with chronic kidney disease on sodium-controlled diet	Open-label, single-arm study of dapagliflozin 10 mg daily for 14 days.	Measurements by bioimpedance spectroscopy (Im-pedimed). Decrease in extracellular fluid by 0.6 L after 4 days, but returned to baseline after 14 days.
Chronic heart failure			
Jensen et al (2021)[103]	120 patients with stable heart failure, EF ≈31%, NT-proBNP ≈600 pg/mL, loop diuretic in 60%	Double-blind, randomized, placebo-controlled trial; empagliflozin 10 mg daily or placebo for 12 weeks.	Measurement of extracellular volume by ^{51}Cr-EDTA. SGLT2 inhibition decreased estimated extracellular volume by 0.1 L, as compared with placebo, at 12 weeks.
Kolwelter et al (2023)[79]	74 patients with stable euvolemic heart failure with a reduced ejection fraction (NT-proBNP 450), 40% receiving loop diuretics (none >80 mg daily)	Double-blind, randomized, placebo-controlled parallel-group trial; empagliflozin 10 mg daily vs placebo, for 3 months.	Measurements by bioimpedance spectroscopy (Fresenius Body Composition Monitor). Tissue water content by ^{23}Na magnetic resonance imaging. No difference in extracellular water or in skin or muscle water content at 1 or 3 months. Decrease in skin sodium content at 3 months, but not at 1 month.

Studies that estimated extracellular fluid by body surface area equations are not included. BNP indicates B-type natriuretic peptide; EF, ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and SGLT2, sodium-glucose cotransporter 2.

enrolled 530 patients (NT-proBNP ≈3200 pg/mL) who (after in-hospital stabilization) were randomized to placebo or empagliflozin (10 mg/d) for 3 months. Empagliflozin reduced a composite symptom score, with benefits seen as early as 15 days, but with modest changes in NT-proBNP. Although patients were required to have pulmonary congestion or peripheral edema at randomization, the effects of empagliflozin on signs of fluid retention were

not reported. Treatment with empagliflozin did not spare the use of loop diuretics; the number of patients receiving furosemide (>40 mg/d) was numerically more frequent in the empagliflozin group. Changes in body weight and hematocrit could not be ascribed to a diuresis, because they can be influenced by the rapid effects of empagliflozin to induce urinary caloric loss and erythropoiesis.

How did SGLT2 inhibition improve symptoms in patients with acutely decompensated heart failure at 15 days? Although urinary volume and sodium excretion were not measured in the EMPULSE trial, 2 earlier trials performed these assessments in the same clinical setting. In the EMPAG-HF trial,[80] 60 patients were randomized within 12 hours of admission (NT-proBNP ≈4800 pg/mL) to placebo or empagliflozin for 5 days. In the EMPA-RESPONSE-AHF trial,[12,77] 79 patients were randomized within 24 hours of admission (NT-proBNP ≈5200 pg/mL) to placebo or empagliflozin for 30 days. In both studies, SGLT2 inhibition increased urinary volume without an effect on fractional sodium excretion, total urinary sodium excretion, body weight, or NT-proBNP. Neither trial reported changes in edema or in signs of pulmonary congestion. These findings suggest that the water diuresis produced by SGLT2 inhibitors in patients with acutely decompensated heart failure is insufficiently durable to reduce body weight or NT-proBNP. Similarly, although urinary assessments were not performed, it seems unlikely that a water diuresis contributed to the findings in the EMPULSE trial, because empagliflozin reduced serum sodium concentration in that study, an effect that is inconsistent with an increase in free water clearance.[141]

Early Effects of SGLT2 Inhibitors in Chronic Heart Failure

Rather than reflecting a diuresis, the effect of SGLT2 inhibitors to improve symptoms at 15 days in the EMPULSE trial parallels a similar early reduction in symptoms and in the risk of hospitalization for heart failure in large-scale trials, which reaches nominal levels of statistical significance within 2 to 4 weeks.[142,143] Some investigators have proposed that this statistical event supports an action of SGLT2 inhibitors to promote a diuresis.[143] However, a similar early statistical event on heart failure hospitalizations is seen after the initiation of sacubitril/valsartan,[144] although the drug does not produce a natriuretic effect, even when combined with loop diuretics.[145,146] Early-onset statistical significance is also seen with β-blockers,[147] although these drugs typically promote early sodium retention. Because the benefits of SGLT2 inhibitors in heart failure are not time dependent,[148] the achievement of early statistical significance is merely a function of the duration of follow-up required to accrue a sufficient number of events rather than an indicator of a mechanism of action. It is therefore noteworthy that the effect of SGLT2 inhibitors to induce nutrient deprivation signaling and promote autophagy emerges rapidly[3,4] and are poised to make a meaningful difference in patients who are acutely ill or on the brink of decompensation at the time of randomization.

Additional analyses of the large-scale trials of SGLT2 inhibitors provide further evidence against a significant early diuretic effect of these drugs. In the EMPEROR-Reduced trial, 40% of the patients had recent volume overload before study enrollment and received larger doses of loop diuretics at baseline.[117] However, those with recent volume overload were not more likely to show a reduction in cardiovascular death or hospitalization for heart failure with empagliflozin. The incidence plots separated immediately in patients without recent volume overload, but this separation occurred after 30 to 45 days in those with recent volume overload. Patients with recent volume overload were not more likely to show an improvement in functional class, decreases in body weight or natriuretic peptides, or increases in hematocrit during the first 4 weeks of treatment.

Some might ascribe a diuretic effect to SGLT2 inhibitors if these drugs were to influence the dose requirements of concurrently administered loop diuretics. In a 3-day randomized controlled trial of diuretic-resistant individuals, patients receiving dapagliflozin required more furosemide to achieve a smaller diuresis than those receiving metolazone.[81] In the large-scale landmark trials with dapagliflozin and empagliflozin in patients with chronic heart failure, the dose of prescribed diuretics did not change in most patients.[117,149] Although SGLT2 inhibition reduced the need for diuretic intensification and increased the likelihood of diuretic dose reduction during long-term therapy,[117,149] only ≈5% of randomized patients experienced a change in diuretic dose that was attributable to SGLT2 inhibition, and drug-induced changes in diuretic dosing were not seen during the first 90 days.[150] Long-term changes in the doses of prescribed diuretics do not imply a diuretic action, because the use of diuretics (and the prevention of new-onset edema[150]) is influenced by an effect of SGLT2 inhibitors to slow the progression of heart failure. A similar pattern of reduced intensification and greater dose reduction has been observed in large-scale trials with angiotensin receptor blockers and sacubitril/valsartan, which do not exert a diuretic effect in chronic heart failure.[151,152]

It is noteworthy that treatments that produce short-term increases in sodium or water excretion do not generally reduce the subsequent risk of cardiovascular death or heart failure hospitalization. Although intensive short-term diuresis to achieve hemoconcentration in hospitalized patients is associated with lower cardiac filling pressures,[153] early decongestion has not been associated with improved outcomes in observational studies or clinical trials.[138–141,154,155] More intensive treatment with intravenous loop diuretics yields a greater short-term

diuresis, but does not reduce heart failure events at 60 days.[138] The addition of hydrochlorothiazide to a loop diuretic yields a modest diuretic effect, but no effect on death or rehospitalization at 90 days.[139] Acetazolamide potentiates the natriuretic response to loop diuretics, but has no effect on morbidity and mortality at 3 months.[141] In a trial comparing short-term therapy with low or high doses of spironolactone, there was no between-group difference in major heart failure events after 30 to 60 days.[156] Last, in a large-scale trial in patients hospitalized for heart failure, vasopressin antagonism induced a short-term diuretic effect, but continued treatment for a median of 10 months did not reduce the risk of cardiovascular death or hospitalization for heart failure.[136,157]

These observations, taken collectively, suggest that a short-term diuretic effect of SGLT2 inhibitors does not contribute meaningfully to the early or long-term ability of these drugs to reduce the risk of major heart failure events.

Effect of SGLT2 Inhibitors on the Risk of Volume Depletion

As a result of their potent natriuretic effects, loop diuretics can produce volume depletion (hypotension and worsening renal function), especially in patients receiving inhibitors of the renin-angiotensin system.[158] Because SGLT2 inhibitors are frequently coadministered with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, the risk of volume depletion has been prospectively evaluated in large-scale trials.

In a meta-analysis[159] of 8 major cardiovascular outcomes trials, volume depletion was reported in 4.4% of the placebo group and in 4.5% of the SGLT2 inhibitor group. The DAPA-HF trial noted an excess of volume depletion, but only in patients taking furosemide-equivalent doses ≥40 mg daily.[149] In patients not taking a loop diuretic, volume depletion was seen in 8.5% in the placebo group and 4.3% in the dapagliflozin group, whereas in patients receiving a furosemide-equivalent dose ≥40 mg daily, volume depletion was seen in 6.8% of placebo-treated patients and 9.0% of dapagliflozin-treated patients (treatment-by-furosemide dose interaction, P=0.012). A similar pattern of diuretic potentiation was seen in a pooled analysis of double-blind trials in type 2 diabetes.[160]

Summary and Conclusions

SGLT2 inhibitors block proximal tubular sodium and glucose reabsorption, but the nature and duration of any natriuretic or osmotic diuretic effect are the result of an interplay of the degree of SGLT2 and NHE3 upregulation, the extent to which downstream nephron mechanisms are activated in a compensatory manner, and the volume status and set point in individual patients. In euvolemic patients, counterregulatory sodium- and water-retaining downstream mechanisms are activated rapidly, thus truncating the duration of any observable diuresis. In fluid overloaded patients with acutely decompensated heart failure, the net early effect of SGLT2 inhibition is a water diuresis, but this aquaresis does not contribute to the early clinical improvement in these patients. The magnitude of any glycosuria-dependent effect is markedly attenuated in patients with a glomerular filtration rate <45 mL/min per 1.73 m^2,[15] and yet these patients still show a robust reduction in the risk of heart failure hospitalizations with SGLT2 inhibitors.[161,162] In patients with chronic heart failure, SGLT2 inhibitors may potentiate the natriuretic effect of loop diuretics, but in the short term, in patients with fluid retention, the effect of SGLT2 inhibitors to enhance the effect of loop diuretics appears to be smaller than with metolazone.[81] There is little evidence that SGLT2 inhibitors alleviate edema or physical signs of congestion.

It should be noted that attenuation of the initial urinary response is an expected finding with any diuretic, because compensatory mechanisms must be activated to prevent volume depletion as patients approach euvolemia. Once volume overload is alleviated by loop diuretics, a new equilibrium is achieved, with sodium excretion matching intake. The goal of diuretic therapy is to change the internal set point, so that salt and water homeostasis is maintained at steady-state conditions characterized by diminished total body sodium and water stores.[163] The actions of SGLT2 inhibitors to increase fractional lithium excretion and promote glycosuria persist during long-term therapy, even when the volume status of patients is not changing, suggesting that SGLT2 inhibitors are poised to exert a durable effect to modulate the set point for volume homeostasis. If aberrations of sodium or water intake were to occur during long-term treatment, the activation of downstream counterregulatory mechanisms diminishes, and a net diuretic effect of the drugs would become clinically evident until the set point for volume homeostasis is reachieved.[42] Studies evaluating the volume responses after salt loading or discontinuation of long-term therapy with SGLT2 inhibitors are needed to confirm this hypothesis. Yet, assuming that the effect of SGLT2 inhibitor on volume homeostasis occur and are durable, it is difficult to know if treatment-mediated changes in the volume set point (if any) contribute to the effect of these drugs to reduce the risk of major heart failure events. Short- or long-term use of many conventional natriuretic and aquaretic drugs has not reduced cardiovascular death or hospitalizations for heart failure,[136,138–140,157] demonstrating that immediate changes in urinary sodium or water excretion do not yield long-term clinical benefits. It is possible that the effects of SGLT2 inhibitors on sodium avidity may differ from other agents, but the volume effect of these drugs is small. In

contrast, the cardioprotective effects of SGLT2 inhibitors represent a direct beneficial effect to reduce cardiomyocyte stress and injury, which is independent of the binding to SGLT2 in the heart or the presence or actions of these drugs on SGLT2 in the proximal renal tubule.[3–5] Nevertheless, any durable changes in the volume set point produced by SGLT2 inhibitors might potentially act cooperatively with the direct favorable molecular and cellular cardiac effects of these drugs to mediate their benefits on the clinical course of heart failure.

ARTICLE INFORMATION

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