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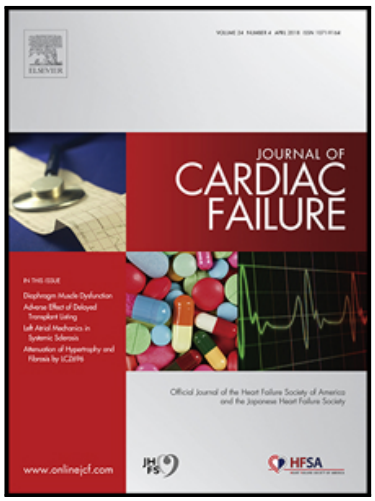

The potential roles of osmotic and non-osmotic sodium handling in mediating effects of SGLT2 inhibitors on heart failure

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June 7, 2021

Title: The potential roles of osmotic and non-osmotic sodium handling in mediating effects of SGLT2 inhibitors on heart failure

Short title: *Sodium & HF outcomes of SGLT2i*

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June 7, 2021

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Highlights

- SGLT2 inhibitors (SGLT2i) mitigate CKD progression and HF hospitalization
- Sodium regulation may contribute to SGLT2i's cardioprotective mechanisms
- SGLT2i might mitigate HF via effects on non-osmotic sodium storage

Abstract word count: 199~~200~~

Manuscript word count: 4074~~3649~~

Abbreviations

AKI, acute kidney injury; BP, blood pressure; CKD, chronic kidney disease; ECV, extracellular volume; ESL, endothelial surface layer; GFR, glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRI, magnetic resonance imaging; NHE3, Na^+/H^+ exchanger isoform 3; PWV, pulse wave velocity; RAAS, renin–angiotensin–aldosterone system; SGLT1, sodium-glucose cotransporter 1; SGLT2, sodium-glucose cotransporter 2; T2D, type 2 diabetes.

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Abstract [limit 200 words, current 199~~200~~]:

Concomitant type 2 diabetes and chronic kidney disease (CKD) increases the risk of ~~cardiovascular disease (CVD), including~~ heart failure (HF). ~~Renoprotective agents, while decreasing fluid overload and blood pressure and improving endothelial function and vascular tone, may protect against CVD and HF. Conversely, glucose-lowering drugs modestly ameliorate CVD risk and possibly even worsen HF outcomes.~~ Recent studies demonstrate beneficial effects of sodium-glucose cotransporter 2 inhibitors (SGLT2i) on CKD progression and~~,~~ HF hospitalization~~, and other cardiovascular outcomes,~~ in patients ~~±~~with and without diabetes. ~~The underlying mechanisms are incompletely explained by modest improvements in blood pressure, glycemic control, body weight, and serum urate.~~ In addition to inhibiting glucose reabsorption, SGLT2i reduce proximal tubular sodium reabsorption, possibly leading to transient natriuresis. We review the hypothesis that SGLT2i's~~the~~ natriuretic and osmotic diuretic effects ~~of SGLT2i~~ mediate their cardio-protective effects. The degree to which these benefits are related to changes in sodium, independent of the kidney, is currently unknown. Aside from effects on osmotically active sodium, we explore the intriguing possibility that SGLT2i could also modulate non-osmotic sodium storage. This alternative hypothesis is based on emerging literature that challenges the traditional two-compartment model of sodium balance to provide support for a three-compartment model that includes the binding of sodium to glycosaminoglycans, such as those in muscles and skin. This ~~R~~recent research on non-osmotic sodium storage, as well as ~~and~~ direct cardiac effects of SGLT2i, provides possibilities for other ways in which SGLT2i ~~inhibitors~~ might ~~contribute to their benefits in~~mitigate HF risk. Overall, w~~W~~e review~~explore~~ the effects of SGLT2i on sodium balance and sensitivity, cardiac tissue, interstitial fluid and plasma volume, and non-osmotic sodium storage.

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Keywords: Heart failure, Natriuresis, Non-osmotic sodium, SGLT2 inhibitors

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Introduction

Type 2 diabetes (T2D) is an established risk factor for ischemic cardiovascular disease (CVD) and heart failure (HF).(1) The risks of ischemic CVD and HF are increased with albuminuria and/or impaired kidney function. Although in recent decades cardiovascular outcomes have improved for adults with or without T2D, reducing the burden associated with HF by treating classical cardiovascular risk factors has proven to be difficult and thus remains a major public health priority.(2) Accordingly, the introduction of sodium-glucose cotransporter (SGLT) 2 inhibitors offers promise to mitigate cardiorenal disease in people with or without T2D. However, to better understand the role of these drugs in the cardiovascular system, it is important to define their mechanism of action on the cardiorenal axis.

The kidney contributes to glucose homeostasis by actively reabsorbing nearly all of the filtered glucose in the proximal tubule. Although the kinetics of renal glucose reabsorption were first described nearly 90 years ago, it took until the early 1970s to demonstrate that glucose reabsorption occurs in the proximal tubule through two distinct sodium-glucose cotransport systems. Shortly thereafter, two sodium-glucose cotransporters (SGLT1 and SGLT2) were discovered.(3) SGLT1 is a high-affinity, low-capacity transporter responsible for approximately 10% of the renal glucose reabsorption; SGLT2 is a low-affinity, high-capacity transporter responsible for approximately 90% of the renal glucose reabsorption.(4, 5) Together, these transporters are thought to be responsible for total renal glucose reabsorption. In addition to glucose reabsorption, SGLT1 and SGLT2 also facilitate concomitant sodium reabsorption. Approximately two-thirds of the total kidney sodium reabsorption occurs in the proximal tubule, although the extent to which this reabsorption is mediated by SGLT1 and SGLT2 presently remains unknown.(6)

SGLT2 inhibitors were granted marketing authorization in 2014 as glucose-lowering drugs, and work by inducing glucosuria. Through their mechanism of action, the

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glucose-lowering effects of SGLT2 inhibitors in patients with chronic kidney disease (CKD) are modest.(7) However, these drugs have recently received considerable attention in large cardiovascular safety trials owing to favorable HF and renal benefits ~~(Figure 1).~~ For example, in patients with T2D and high CVD risk, the EMPA-REG OUTCOME trial demonstrated a 35% relative risk reduction in hospitalization for HF for empagliflozin versus placebo,(8) while the CANVAS Program with canagliflozin demonstrated beneficial cardiovascular and renal outcomes.(9) The CREDENCE trial, which studied the effects of canagliflozin in patients with T2D and diabetic kidney disease,(10) reported a reduction in HF hospitalization by 39% (95% CI 20%–53%), in addition to attenuating loss of kidney function. ~~Given the strong link between CKD and HF, this further emphasizes the importance of the cardiorenal axis.(10)~~ By comparison, studies assessing the cardiovascular effects of glucose lowering *per se*, when mediated by other agents, had not demonstrated similar benefits, while HF outcomes may even be worsened by some glucose-lowering drugs.(11, 12)

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Since publication of the results of ~~several~~ these and other cardiovascular safety trials (Figure 1), as well as real-world effectiveness studies (e.g., CVD-REAL(13)), investigators and clinicians have considered a variety of potential mechanisms underlying the cardiorenal benefits of SGLT2 inhibition. It is generally agreed that (modest) reductions in blood pressure (BP), glucose concentrations, body weight, and serum urate concentrations do not fully explain the observed cardiovascular benefits.(14, 15) Although the exact pathways are not fully understood, the purpose of this article is to describe the effects of SGLT2 inhibitors on sodium handling beyond diuresis and natriuresis *per se*, and to discuss the proposed cardiovascular consequences of changes in sodium sensitivity and balance, including direct sodium-related cardiac effects, effects on interstitial fluid and plasma volume, and changes in non-osmotic sodium storage.

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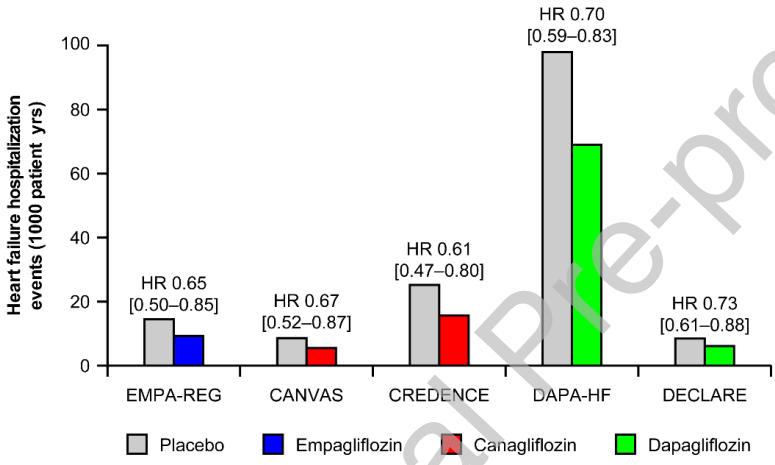
Figure 1 Summary of hospitalization for heart failure results from recent cardiovascular safety trials of SGLT2 inhibitors.



Values in brackets are 95% confidence intervals. Values were derived from the trials' publications; slightly different terminology was used in the trials to describe heart failure hospitalization: EMPA-REG and DECLARE used –rate per 1000 pt-yrs‖, CANVAS used –number of participants per 1000 pt-yrs‖, and CREDENCE and DAPA-HF used –events per 1000 [or 100 for DAPA-HF] pt-yrs‖.

CANVAS, CANagliflozin cardioVascular Assessment Study; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DECLARE, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; EMPA-REG, EMPAgliflozin

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cardiovascular outcome event trial in type 2 diabetes mellitus patients—Removing Excess Glucose;

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HR, hazard ratio; SGLT2, sodium-glucose cotransporter 2; yrs, years.

Sodium balance, sodium sensitivity, and cardiovascular health

Given the well-known role of sodium in cardiovascular health, we next address recent research that challenges traditional views about sodium homeostasis, with potential implications for the pathophysiology and treatment of HF, including~~, including~~ the pathophysiological role of interstitial sodium in HF, as reviewed elsewhere.(16) In most adult populations, the average salt intake well exceeds the ~5-g daily limit recommended by the World Health Organization.(17) Excessive salt intake has been linked to hypertension, CVD,(18) and CKD. Although the pathogenesis underlying the relationship between excessive salt intake and cardiorenal complications remains debated, the leading hypothesis for decades has been that—in so-called salt-sensitive individuals—excess sodium intake with concomitant impaired renal sodium excretion results in extracellular volume (ECV) expansion and hypertension.(19) ~~Particularly i~~In patients with CKD, lower glomerular filtration rate (GFR) ~~reduces the rate of sodium and fluid excretion, possibly leading to~~and activation of the renin–angiotensin–aldosterone system (RAAS) result in ~~and, consequently, through various mechanisms, leads to reduced cardiac output,~~ elevated venous pressure, reduced renal perfusion, reduced cardiac output, and ultimately HF. The net results of these pathophysiological changes include further sodium and water retention with activation of the RAAS and the sympathetic nervous system. However, carefully designed sodium-balance studies in so-called ‗salt-resistant' participants, i.e., individuals in whom increased salt intake does not increase BP or body water/weight, show that much of the ingested sodium excess is in fact not excreted in the urine.(20) Rather, these studies have proposed that sodium may be stored non-osmotically (i.e., without altering ECV) at extrarenal locations, which serve to act as an osmotic sodium buffer. For example, daily rhythmic fluctuations in total body sodium

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